# STUDY OF POLYMERS AND ADVANCES IN COATING CHEMISTRY

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**PHARMACY**


***By***

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# CERTIFICATE

This is to certify that the Ph.D thesis entitled **"STUDY OF POLYMERS AND ADVANCES IN COATING CHEMISTRY",** is a bonafied record of the original work done by **Mr. Rajesh Suresh Parab**, under my guidance and supervision and the same has not been previously formed the basis for the award of any degree, diploma or certificate or similar title of this or any other University.

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## DECLARATION

I, Mr. RAJESH SURESH PARAB, do hereby declare that this thesis for Ph.D. Degree in Pharmacy entitled "**STUDY OF POLYMERS AND ADVANCES IN COATING CHEMISTRY**" is a bonafide record of original research work done by me under the guidance and supervision of **Prof. Dr Gopal Krishna Rao**, Principal, Goa College of Pharmacy, Goa University.

I also declare that the same has not been previously formed the basis for the award of any degree, diploma or certificate or similar title of this or any other University. I have duly acknowledged all the sources used by me in the preparation of this thesis.

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*……. Rajesh S. Parab*

*This work is dedicated to my beloved family members.*

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| | |
|---|---|
| PVA | Polyvinyl alcohol |
| PVA-PEG | Polyvinyl alcohol - Polyethylene glycol graft copolymer |
| Sodium CMC | Carboxymethyl Cellulose Sodium |
| HPC | Hydroxypropyl cellulose |
| MCT | Medium-chain triglycerides |
| HPLC | High Performance Liquid Chromatography |
| SDA | Sabouraud Dextrose Agar |
| SCDA | Soyabean Casein Digest Agar |
| HPMC | Hydroxypropyl methylcellulose |
| $TiO_2$ | Titanium dioxide |
| FD&C | Food Drug & Cosmetics |
| TEC | Triethyl citrate |
| QbD | Quality by Design |
| Cp | Centipoise |
| BCS | Biopharmaceutical Classification System |
| API | Active Pharmaceutical Ingredient |
| BOD | Bio- Oxygen Demand |
| RPM | Revolutions per Minute |
| w/w | Weight by weight |
| µ | Micron |
| RH | Relative Humidity |
| kPa | Kilo Pascals |
| Kg | Kilogram |
| % w/w | Percentage weight by weight |
| g/min | Gram per minute |
| Cm | Centimeter |
| ˚C | Degree Celsius |
| DSC | Differential Scanning Calorimeter |

| | |
|---|---|
| mg | Milligram |
| BSS | British Standard Specifications |
| µm | Micrometer |
| g/mL | Gram per milliliter |
| mm | Millimeter |
| NLT | Not Less Than |
| NMT | Not more than |
| USP | United States Pharmacopoeia |
| IP | Indian Pharmacopoeia |
| CQA | Critical quality attributes |
| CPP | Critical process parameters |
| DT | Disintegration time |
| GU | Gloss units |
| CPVC | Critical pigment volume concentration |
| $T_g$ | Glass transition temperature |
| SOD | Solid Oral Dosage |
| TRI | Toxics Release Inventory |
| MC | Methylcellulose |
| FDA | Food and Drug Administration |
| GMS | Glyceryl monostearate |
| $T_c$ | Crystallization temperature |
| $T_m$ | Melting temperature |
| TGA | Thermogravimetric Analysis |
| OOT | Out of Trend |
| ICH | International Conference for Harmonization. |
| PCA | Principal Component Analysis. |
| PLSR | Partial Least Square Regression. |
| FTIR | Fourier Transform Infrared Spectrophotometer. |
| DSC | Differential Scanning Calorimetry. |

# *ABSTRACT*

# ABSTRACT

Oral solid dosage forms are the most commonly used in medicine for advantage they offer. They are more convenient to administer compared to injections and liquids, provide accuracy of dose, has scope to target delivery to specific sites, has ability to control dosing.

Coating of Solid oral dosage forms was always considered as enhancing overall properties of the dosage forms. Among different types of coatings, Film Coating using polymeric films are most preferred based on advantages offered by them.

Distinct benefits offered by Film Coating are improved patient compliance through odor and taste masking, swallowability, bioavailability by controlling duration and site of release, safety and stability of dosage units, anticounterfeiting or branding of a product and others.

Present project focused on evaluation of various water soluble polymers and study their synergies when combined as blends in fully formulated coating systems. Objective was of using latest polymers systems that offer productivity advantage, provide a robust formulations which behave consistently even when wide range of processing conditions are applied, support green initiatives by reducing requirement of organic solvents, process energy & time and offer greater flexibility.

Mechanical strength (of casted film) and viscosity (in aqueous media) parameters have been assessed using various polymer blends before finalizing two best combinations of natural polymer like Hypromellose and synthetic polymer like poly vinyl alcohol. The initial evaluation was using parameters that define chemical and mechanical strength of blends as well as casted films and these include tensile strength, Youngs Modulus, Extension at break, etc. Effect of different plasticizers and other key additives used in typical Film Coating formulation was also studied using similar parameters. Molecular effect of plasticizers was evaluated using Differential Scanning Calorimetric (DSC) technique.

These formulations were designed using final application by coating on placebo tablets as well as model active pharmaceutical ingredients carefully selected using Biochemical Classification System (BCS). These coated formulations were subjected for through evaluation and accelerated stability conditions for six months. All these formulations demonstrated excellent performance as well as withstanding the stress conditions of accelerated stability study. They demonstrated acceptable performance over range of process parameters tested using Quality by Design concept (QbD) involving level of defects generated, impact to disintegration time as well as gloss level of coated film.

Optimised formulations were further subjected to surface profile studies using Raman microscopy equipped with Atomic Force Microscopy and laser light to guide the microscope through an optical fibre. The objective of this study was to unravel the impact of variables and understand the interplay between coating formulation and type of polymer blend by focusing on measurement of surface roughness of coated tablets.

Objective of project were met in effectively designing the polymer blend based coating systems in two robust formulations on active dosage forms containing Aspirin and Ranitidine HCL. Both formulations met the official standards in terms of disintegration time, dissolution, assay, stability and other physiochemical parameters. Polymer blends so designed may be effectively extended to other formulations containing different active pharmaceutical ingredients.

***Key Words:*** *Water Soluble Polymers, Film Strength, Youngs Modulus, Extension at Break, Differential Scanning Calorimetry**,** Aspirin, Ranitidine HCL, QbD, Stability, Surface Profilometry*,

# *CHAPTER - 1*

# *INTRODUCTION*

## 1. Introduction

Pharmaceutical dosage forms are designed to meet various requirement administering medicines to patient, this include indication, drug absorption and elimination pattern, bioavailability consideration, patient compliance (taste, swallowability etc) and to address other specific needs. One of the most common dosage forms that serves majority of these requirements is in form of Solid Oral Dosage forms.
Solid Oral Dosage forms includes tablets, Capsules, powders and modification of these dosages like films, sprinkles etc.

Coating of Solid Oral Dosage (SOD) forms is desired to meet various requirements including taste making, odor masking, ease of swallowing, protection from light, oxygen, moisture as well as ease of identification.

**Tablet Formulation:**

The major solid oral dosage form is the tablet, and these can range from relatively simple, single, immediate-release dosage forms to complex modified-release system (Table 1.1).

**Table 1.1:** Different types of Tablet Dosage Form[1]

| Formulation type | Description |
|---|---|
| **Immediate-release tablet** | Intended to release the drug immediately after administration. |
| **Delayed-release tablet** | Drug is not released until a physical event has occurred e.g. change in Ph |
| **Sutained-release tablet** | Drug is released slowly over extended time |
| **Soluble tablet** | Tablet is dissolved in water prior to administration |
| **Dispersible tablet** | Tablet is added to water to form a suspension prior to administration |
| **Effervescent tablet** | Tablet is added to water, releasing carbon dioxide to form a efferevescent solution |

| | |
|---|---|
| **Chewable tablet** | Tablet is chewed and swallowed |
| **Chewable gum** | Formulation is chewed and removed from the mouth after a directed time |
| **Buccal and subligual tablet** | Tablet is placed in the oral cavity for local or systemic action |
| **Orally disintegrating tablet** | Tablet dissolves or disintegrates in the mouth without the need for water |

**Advantages and Disadvantages of Tablet Formulation:**

Tablets are a popular dosage forms due to their simplicity and economy of manufacture, relative stability, and convinience in packaging, shipping and storage. For the patient, uniformity of dose, blandness of taste, and ease of administration ensure their popularity. The following may cited as the primary potential advantages of tablets[2] .

- Tablets are unit dosage form, and they offer the greatest capabilities of all oral dosage forms for the greast dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are th lightest and most compact of all oral dosage forms.
- They are in general the easist and cheapeast to package and ship of all oral dosage forms.
- Product identification is simplest and cheapest requiring no additional processing steps when employing an embossed or monogrammed punch face.
- Easy to administer with least tendency for “hang-up” above stomach, espectially when coated.
- Tablets are better suited to large-scale production than other unit oral forms.
- Tablets have the best combined properties of chemical, mechanical and microbiologic stability of all the oral forms.

A well-designed tablet formulation usually contain the some excipients in additiona to the active ingradients, which are functioning as a diluent (lactose, microcrystalline cellulose), a binder or an adhesive (starch, polyvinyl pyrrolidone, cellulose derivatives), a disintegrant (sodium starch glycolate, starch), and a lubricant (magnesium stearate, stearic acid) which enables effortlessness of overall tablet compression process as well as release the active ingredients at the intended rate and site upon administration[1].

The disadvantages of tablets include the following[2]:

- Some drugs resist compression into dense compact owing to their amorphous nature or flocculent, low-density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, or any combination of these features may be defficult to formulate and manufacture as a tablet.

Bitter-tasting drugs, drugs with an objectionable odor, or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation, or the tablets may require coating. Coating of SOD's can be carried out by using Sugar (Sugar Coatings, Sugar Film Coating) or use of different polymers to give thin Film Coating.

Film coating is defined as a process by which a polymer base is applied on the surface of solid[3]. There are two types of film coating processes, one of which is aqueous film coating (using water as carrier) and the other type is non-aqueous film coating (using organic solvents). The non-aqueous film coating process has number of disadvantages which include safety of employees (flammability, toxicity etc and hence not a desired exposure environment). This also poses damage to environment if the solvent vapors are not trapped using scrubber. Aqueous film coating process is preferred in modern world for overcoming the safety, high cost, potential toxicity and environmental concerns associated with use of organic polymer solutions. The film coated on surface of SOD must be smooth, should form uniform even coat and satisfactorily adhere to

the surface of substrate and provide stable drug[4] . These films are very thin and typical thickness of such coating is usually less than 100 μm.

Film coatings are applied for several reasons[5]:

- To mask the odor and taste.
- Improve mechanical resistance of coated product (e.g. reduce friability)
- Reduction in processing time compared to Sugar Coating.
- Increase shelf life though protection from moisture, light and oxygen.
- Increase process efficiency and output.
- Provide immediate release, enteric release, sustain release, controlled release etc.
- To enhance the brand image of a drug products which may provide a significant marketing advantage over competitive products.

**Advantages of Film Coating:**

Film coating is a process which involves the deposition of a thin polymeric film (typically in the range of 10 – 100 μm thick) onto the surfaces of a pharmaceutical dosage units (typically tablets, mini-tablets, pellets, granules or particles). Coating is an additional step in the manufacturing of dosage form. Therefore, it is time-consuming, requires special equipment, and increase production costs. Nevertheless, such a coated formulation can have several advantages (Table 1.2). The coating is also important for patient compliance. Bitter taste or unpleasent odor can be covered through coating. Coated tablets have a more aesthetic appreance than uncoated ones and a smoother surface, which may facilate swallowing. Coloured coating make it easier for the patient to identify the right tablet, which is of special interest for multi-morbid patient who take several different medications.

The coating liquid that is used in the process cab either be an orgnic solution or an aqueous solution or dispersion. Aqueous-based coating have several advantages over organic solutions, which inclueds regulatory, environmental, safety and helath issues.

**Table 1.2:** Advantages of coated solid dosage forms[6-11]

| Parameters | Adavantage |
|---|---|
| **Chemical stability** | Proecion aainst light, humidity, moisture, pH, and/or oxygen; avoidance of interaction between ingredients |
| **Mechanical stability** | Protection against attrition during processing and handling |
| **Drug release** | Modified release (control release); delayed release (taste masking, gastro-resistant, colon delivery), pulsatile release, prolonged release (extended release, sustained release) |
| **Compliance** | Taste masking, odor masking, aesthetic appearance, identification, facilitating swallowing |

When organic solvents are used, a test on residual solvent is necessory, and the requirements of the pharmacopoeia have to be meet. On the other hand, aqueous liquids have a few drawbacks. The heat of evaporation is higher than for organic liquids. This leads to longer drying times and/or higher drying temperatures, which both result in higher energy costs. A second drawback is the more complex film formation from aqueous dispersions than from solutions, which makes it often necessary to add a final curing step at the end of the process[12,13].

**Green Chemistry Application:**

Use of aqueous-based coating formulation has an additional advantage in maintaining green chemistry in pharmaceutical industries for decreasing the amount of chemical waste released to the air, water and land. As per data released by EPA's (US Environmental Protection Agency) Toxics Release Inventory (TRI), between 2004 and 2013, the amount of chemical waste release to land, air and water has decreased by 7%. These data show that releases for some chemicals, including hydrochloric acid,

trichloroethylene, and methyl isobutyl ketone, have decreased by more than 60% over that time. The releases reported by the pharmaceutical industry, which has long generated the most chemical waste per kilogram of product to produce complex molecules of high purity, have been dropped by half.

Pharmaceutical companies are also selecting less hazardus reagents, reducing reaction steps, and developing better catalyst. In the similar line, for coating on solid oral dosage forms, also prefereed to use aqueous-based coating formulation having benefits of environmental, safety and helath.

Film coating formulations are typically formulated with following components such as:

- Polymer
- Plasticizer
- Pigment/ Opacifier
- Additives
- Solvent or Water as vehicle.

Functionality wise Film Coatings are further divided into:

- Immediate release coating
- Sustained release or modified release coating
- Enteric release coating

Immediate-release film coating (also known as ‘non-functional’ film coating or conventional film coating) is used to describe film coatings that are designed to improve product appearance, perhaps improve handling and stability of the dosage form, but has no measurable effect on biopharmaceutical properties of the dosage form. Polymers used in immediate-release coating formulations fall into the following categories: Cellulosic polymers (HPMC, HPC, MC), Vinyl derivatives (PVA, PVP), and glycols (PEG).

The patient compliance is strongly decreasing in such cases, when multiple daily administrations are necessary to maintain constant blood levels of the drug. Therefore, extended release polymers were developed, which can provide a sustained action by a controlled release over time. Polymers (cellulose acetate, ethyl cellulose, methacrylic acid copolymers- Eudragit RS, RL) for extended release are in general insoluble in water over the entire pH-range. The drug released is thus controlled by diffusion through the hydrated polymers or through cracks or water -filled pores. Combinations of ethyl cellulose with water-soluble or enteric polymers were investigated to achieve desired drug release profile.

Enteric coatings are prepared from gastric resistant polymers. The coatings prepared from such polymers remain intact in acidic environment but dissolve readily at the elevated pH of small intestine. Example of enteric polymers include; natural polymer (shellac), synthetic polymer (cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, methacrylate copolymers – Eudragit L and Eudragit S).

**Polymer:** Polymers are large molecule of high molecular weight called macromolecule, made up of many repeated subunits to form a long chain. Polymer derives from the Greek word *poly means* "many, much" and *mers means* "parts"[14].

The term "polymer" was coined in 1833 by Jöns Jakob Berzelius, though Berzelius did little that would be considered polymer science in the modern sense[15]. In 1920 the German organic chemist, Hermann Staudinger was demonstrated the presence of macromolecules, which he characterized as polymers[16]. The only difference between the two terms is that *polymers are made of repeating units called monomers*, whereas *macromolecules are generally used to refer to any large molecule not just those made of repeating units*. Thus, polymers can be considered as subset of macromolecules which are widely used in pharmaceutical industry from centuries due to wide range of application and advantages offered by them in modern medicine[17]. Most predominantly used group of polymers are the cellulose ethers, which includes

hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyvinyl alcohol (PVA), acrylates and methylcellulose (MC).

Polymers are important especially in the field of drug delivery. Polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions[18]; also used to protect the dosage form against environmental conditions and for hiding a bad taste, odor or appearance.

For application point of view, polymer may be classified as protective or functional coating. Based on their origin or preparation, natural, semi-synthetic or synthetic polymers are distinguished. Natural polymers are mostly subjected to several purification steps, but without chemical modification. Usually, related to their origin, they are mixtures of different compounds, subjected to certain variability of their composition and thus the resulting performance. Semi-synthetic polymers are derived from a natural substance, receiving its specific property after certain chemical modifications. The cellulose derivatives used for coating are one example of such materials. Synthetic polymers in contrast are fully chemically-synthesized, as for example the methacrylic acid copolymers.

Polymers used in conventional film coating formulations are typically water-soluble ingredients, so that the applied coating does not interfere with dissolution characteristics. Sometimes water insoluble polymers are used for specific purpose like rate controlling modified release dosage forms[19]. The estimation of physical and mechanical properties of polymeric films provides important information for the development of film coating system by expressing their performance in pharmaceutical dosage forms[20]. Commercial film coating system also contains other ingredients to promote processing or to improve performance and appearance of pharmaceutical dosage form. The addition of other ingredients influences the mechanical properties of polymeric films[21-24] like pigments to enhance product appearance, talc to reduce tackiness of the coating and lubricants to prevent

agglomeration of the coated substrates. Inclusion of these ingredients reduces tensile strength and extensibility while increases Young's modulus of HPMC films[25,26].
Factors to be considered while selecting polymer for coating application are as follows[27]:

**Polymers Used For Aqueous-Based Coating**

Polymers are large molecule of high molecular weight called macromolecule, made up of many repeated subunits to form a long chain. Polymer derives from the Greek word poly means "many, much" and mers means "parts"[14]. The term "polymer" was coined in 1833 by Jöns Jakob Berzelius, though Berzelius did little that would be considered polymer science in the modern sense[15]. In 1920 the German organic chemist, Hermann Staudinger was demonstrated the presence of macromolecules, which he characterized as polymers[16]. The only difference between the two terms is that polymers are made of repeating units called monomers, whereas macromolecules are generally used to refer to any large molecule not just those made of repeating units. Thus, polymers can be considered as subset of macromolecules.

The polymers used in aqueous-based coating can be classified under various aspects. In Table 1.3, the mostcommon polymers are devided by their chemical structure, its solubility in aqueous media. The solubility is not only responsible for the type of resulting liquid (solution or dispersion); it is also important for the functionality of the resulting coating[28].
A dosage form coated with water-based film coating, for example, Hypromellose, will act as a protecting film with good handling properties and an attractive appearance, and the release of the API will be largely unaffected. Therefore, such films are sometimes refered to as nonfunctional.

Water-insoluble polymers with acidic carboxylate group (e.g. methacrylic acid-methyl methacrylate copolymer, Eudragit L/S) show a pH- dependent solubility due to ionizationof the functional group at higher pH values. Depending on the amount of

acidic groups in the polymerchain, they are insoluble at pH values below 6 (Eudragit®L with 50% methacrylic acid units) or 7 (Eudragit® S with about 30% methacrylic acid units) and soluble in slightly alkaline media. These films are called enteric coatings because they are insoluble in the acidic gastric fluid and can protect the API against the acidic environment and/or the gastric mucosa from an irritant API.in the more-or-less neutral pH in the small intestine, the polymers dissolve, and the API is released. Polymers with basic amino grpoup (e.g. amino methacrylate copolymer, Eudragit® E) are only soluble in acidic media. With such polymer coatings, taste masking can be achieved[29].

The water-insoluble polymers (e.g. ethylcellulose, Eudragit RL/RS) can be applied for controlled drug delivery, especially for prolonged and sustained release. They are insoluble in the entire gastrointestinal tract and act as a diffusion barrier as long as the coating remains intact. The API is released by a diffusion-controlled mechanisam through the polymer film itself (often after swelling) or through pores.

The release rate of the drug can mainly be influenced by the type of polymer, the thickness of the film[30], and the addition of excipients, such as pore formers[31,32].

**Table 1.3**: Polymers used for aqueous-based coating as solution or dispersion

| **Type** | **Example** | **Solubility** | **Trade Names, Example** |
|---|---|---|---|
| Cellulose derivatives | Hypromellose (Hydroxypropyl methylcellulose) HPMC | Water soluble | METHOCEL ™, Opadry® PHARMACOAT® Aqoat®, AquaSolve® |
| | Hypromellose acetate succinate (HPMCAS) | Enteric coating | Aquacoat®CPD |

| | | | |
|---|---|---|---|
| | Hypromellose phthalate (HPMCP) | Enteric coating | |
| | Cellulose acetate phthalate (CAP) | Enteric coating | Eastman®C-A-P |
| | Hydroxypropylcellulose (HPC) | Water soluble | Klucel® HPC, L-HPC Aqualon® , Blanose® |
| | Carboxymethylcellulose sodium (CMC Na) | Water soluble | Opagloss® II |
| | Ethylcellulose (EC) | Water insoluble | Surelease® Aquacoat®ECD |
| Acrylic resin, poly(meth) acrylates | Ethyl acrylate-methyl methacrylate copolymer (PMMA) | Water insoluble | Eudragit®NE/ NM; Kollicoat® EMM |
| | Ammonio methacrylate copolymer type A/ type B | Water insoluble | Eudragit® RS/RL |
| | Methacrylic acid-methyl methacrylate copolymer 1:1/ 1:2 (PMMA) | Enteric coating | Eudragit® L/S |
| | Methacrylic acid-ethyl acrylate copolymer (PMMA) | Enteric coating | Eudragit®L100-55; Kollicoat® MAE |

| | | | |
|---|---|---|---|
| | Basic butylated methacrylate copolymer (PMMA) | Taste masking | Eudragit® E |
| Polyvinyl derivatives | Polyvinyl alcohol (PVA)<br><br>Polyethylene glycol-polyvinyl alcohol graft polymer (PVA-PEG) | Water soluble<br><br>Water soluble | Opadry® amb; amb II<br><br>Kollicoat® IR |

**Hydroxypropyl methylcellulose (HPMC):**

Classical film coating systems typically employed hypromellose [HPMC, hydroxypropyl methylcellulose] as the film forming polymer. Chemically, hypromellose [Hydroxypropyl methylcellulose (HPMC)] is mixed-alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. A general structure of cellulose ether polymers is shown in Fig.. 1.1, where the R group can be a single or a combination of substituents.

HPMC was first synthesized in the laboratories of the Dow Chemical Company in the late 1930s. HPMC is the principal cellulosic ethers used in film coating and its usage dates back to the early days of film coatings. The first reported application of HPMC for film coating was by Singiser[33] of Abbott Laboratories. Film coatings with HPMC soon became popular replacing conventional sugar coating of tablets because of several reasons viz;

- It is soluble in both aqueous media and the organic solvent systems normally used for film coating.
- HPMC films can be used with pigments (for colored coatings) or used without pigments to form clear transparent coated products.

- It affords relatively easy processing due to its non-tacky nature and forms transparent, tough and flexible films from organic/ aqueous solutions. The films are soluble in the gastrointestinal tract at any physiological pH. HPMC being surface active also helps in enhancing wettability and bioavailability of certain active pharmaceutical ingredients.
- HPMC is non-ionic water-soluble polymer, and hence the possibility of ionic interaction or complexation with other formulation components or active pharmaceutical ingredient is greatly reduced. HPMC coatings do not show any impact of pH of dissolution media on drug release profile which is essential for wide array of pharmaceuticals administered as immediate release dosage forms.
- Aqueous solutions of HPMC are stable over a wide pH range (pH 3–11) and are resistant to enzymatic degradation.
- From the regulatory aspect, in addition to its use in pharmaceutical products globally, HPMC has a long history of safe use as a thickener and emulsifier in the food industry and has been classified by FDA as a GRAS excipient (generally regarded as safe).

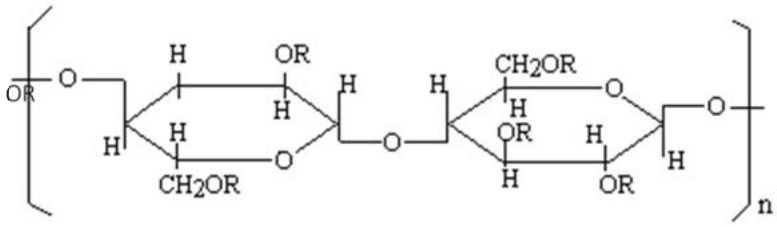



**Fig.. 1.1**: General structure of cellulose with three possible substitution sites indicated by R (not all are substituted) (hydroxyl groups) on each d-anhydroglucose monomer. Hydroxypropyl methylcellulose (HPMC) contains methoxyl (CH3–O) and hydroxypropoxyl (CH3CHOHCH2–O) substituents.

HPMC is classified according to the content of substituents and its viscosity. Commercially available HPMC includes several substitution types such as HPMC 2208, 2906, and 2910. This USP classification code is based on the substitution type

with the first two digits representing the mean % methoxyl substitution and the last two digits representing the mean % hydroxypropyl substitution. Commercially HPMC is available from Dow Chemical Company under the trade name of Methocel™. Methocel is available in four different chemistries (A, E, F and K) depending on the degree of hydroxypropoxyl and methoxyl group substitutions. Historically, Methocel E (hypromellose 2910 USP) chemistry has been widely used in film coating applications because of its better solubility in organic solvents, which was important attribute in earlier days when organic coatings were popular. Although aqueous coatings have mostly replaced organic coatings and the solubility in organic solvents therefore of less importance, the 2910 grade is still widely used. Other substitution grades such as 2208 and 22906 could also be used in film coating applications; however there are very few suitable commercial products available with low viscosity. Methocel grades for film coating applications include E3, E5, E6, E15 and E50LV CR. The viscosity of a 2% aqueous solution of these polymers ranges from 3 to 50 cPs at 20°C. Similar grades of HPMC are also available from other suppliers such as ShinEtsu Chemical Co. Ltd., Japan and Samsung Fine Chemicals, Korea under brand names of Pharmacoat® and AnyCoat® respectively.

In general as the HPMC viscosity decreases, mechanical properties of the films such as tensile strength and elongation also decrease. HPMC with viscosity of 3 cP or less is capable of providing high-concentration polymer solutions and thus seems to be more economical, however films from such low viscosity HPMC are quite inferior and peeling may occur during the coating operation if friable tablets are used or if the pigment load is high in the coating formulation. There is also a possibility of crack formation in the film after coating. Thus, the use of such low viscosity HPMC (≤ 3 cP) is limited to special cases e.g., coating of small pellets to prevent pellets from sticking during the coating operation or use in conjugation with other polymers/ viscosities. In recent study it was shown that the incidence of edge splitting and peeling on tablet coated with Hydroxyproyl methyl cellulose could be decreased on increasing the viscosity grade or molecular weight of the polymer[34]. Viscosity grades of 5 or 6 cP are more popular for film coating applications, providing adequate balance

of productivity and film mechanical properties for most of the applications. When using HPMC with viscosities of greater than 15 cP, it is difficult to achieve high concentration of polymer suitable for spraying and hence not economical. These high viscosity HPMC grades are used only in cases where higher tensile strength of the film is desired to overcome defects such as edge splitting or cracking.

**Poly Vinyl Alcohol (PVA):**

Poly vinyl alcohol has recently gained popularity as a film coating polymer of choice because of following reasons[35-40]:

- Good film properties from the polymeric solutions and global regulatory acceptance for pharmaceuticals and nutritionals.
- Relatively low viscosity of coating solutions made with this polymer typically ≥ 25% solids, enabling higher concentration of the polymer to be used, thus rending it more economical and productive.
- Use of PVA in film coatings results in strong films that can adhere strongly to tablet surfaces and thus enable excellent logo definition even with challenging designs
- Use of PVA as film coating material improves bulk tablet flow properties when compared with HPMC coated thus enhancing packaging speed and time savings.
- The films have very good barrier properties, especially with respect to moisture and oxygen.
- Polyvinyl alcohol contains significantly lower levels of formic acid and formaldehyde impurities than the three commonly used low viscosity grades of hypromellose (3 cPs, 5, cPs and 15 cPs), thus reducing the possibility of interactions with some APIs that could otherwise lead to adduct formation and color change with these impurities.

Poly vinyl alcohol (PVA) has a simple chemical structure with pendant hydroxyl groups. The monomer unit is vinyl alcohol. Commercial PVA is typically made by

the hydrolysis of poly (vinyl acetate) or PVAC. In this chemical reaction not all acetate groups are substituted by OH radicals; consequently polymers with different hydrolysis degree will be obtained. The chemical structure for a 100% hydrolyzed polymer and partially hydrolyzed polymer is presented in Fig.. 1.2. The value of n for commercially available materials is in between 50 and 5000, equivalent to a molecular weight range of approximately 20000- 200000 and correspondingly PVA grades are classified as low viscosity (molecular weight ~ 20000), medium viscosity (molecular weight ~ 130000) and high viscosity (molecular weight ~ 200 000). The degree of polymerization and the degree of hydrolysis are the two determinants of their physical and solution properties.

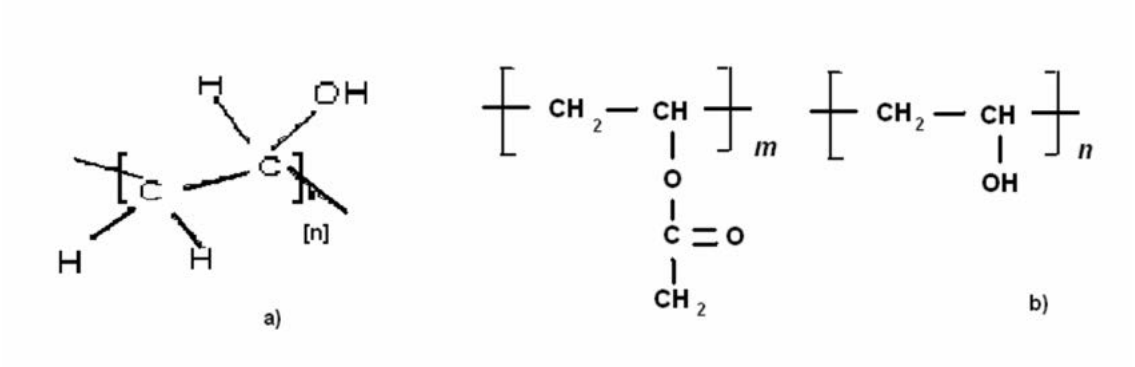



**Fig.. 1.2:** Chemical structure for: a) 100% hydrolyzed polymer and b) partially hydrolyzed polymer

The percentage of acetate groups converted to alcohol groups determines the hydrolysis level of PVA, which affects the degree of polymer crystallinity, solution properties including viscosity, surface tension and physical and mechanical properties of the films. The PVA melting temperature is 230 °C for 100% hydrolyzed polymer and 180 – 190 °C for partial hydrolyzed polymer The glass transition temperature is 85°C for highly hydrolyzed PVA and 58°C for partially hydrolyzed (87%-89%) grade.

The degree of hydrolysis influences the polymer behavior in the solution. In aqueous PVA solutions, a part of the inter-chain hydrogen bonding remains, in addition to the hydrogen bonding between the PVA chains and the water molecules formed during

the dissolution process. The extent of both inter and intra chain hydrogen bonding and solute–solvent hydrogen bonding is mainly determined by molecular weight, the degree of hydrolysis and the temperature of the solution. Despite the fact that PVA is essentially atactic, due to the small size of the hydroxyl group, the molecular chains of PVA can fold up easily in an organized manner leading to crystallinity. The crystallinity of PVA tends to decrease with increasing molecular weight and decreasing hydrolysis. Long molecular chains involve restricted segmental motion and thus make it more difficult for the molecules to fold up into crystalline structures. As the degree of hydrolysis decrease, the number of residual acetate group in the molecules increases. The bulky size of the pendent acetate group prevents the molecular chains to closely fold up to form crystalline structure. Thus partially hydrolyzed grades of PVA have less degree of crystallinity. Because of the same reason, the solubility of partially-hydrolyzed PVA is high at room temperature while fully-hydrolyzed PVA is essentially insoluble in water at the same situation. Reverse is however true at higher temperatures i.e. the solubility decreases as the temperature increases and/or the percentage of hydrolysis decreases. For this reason, pharmaceutical grades are partially hydrolyzed materials and these grades and are named according to a nomenclature, where first number following the a trade name refers to the degree of hydrolysis and the second set of numbers indicate the approximate viscosity (dynamic) in mPa s, of a 4% aqueous solution at 20◦C. For film coating applications, partially hydrolyzed low viscosity grades are used and are available commercially from Astro Chemicals Inc., Celanese, Penta Manufacturing Co and Nippon Gohesi Ltd.

The role of possible hydrogen bonding of the -COOH groups of acrylic acid with –OH group of the PVA is proposed as the mechanism for enhanced moisture barrier properties of this system, similar to those observed in polyvinyl alcohol/ acrylic acid/ methyl methacrylate copolymer[41].

**Polyethylene Glycol-Polyvinyl Alcohol (PEG-PVA) Graft Copolymer**:

PEG-PVA is a hydrophilic freely water-soluble polymer, comprised of 25% PEG and 75% PVA, wherein the vinyl alcohol moieties are grafted on a polyethylene glycol backbone, as shown in Fig. 1.3.

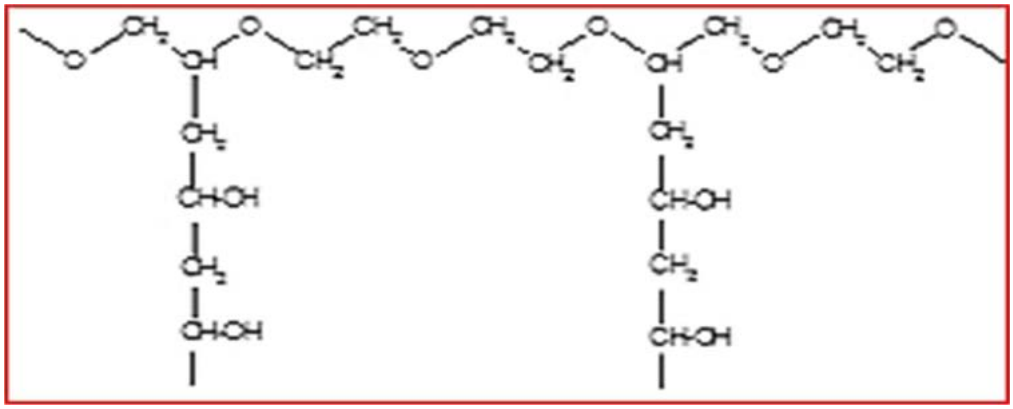


**Fig. 1.3:** Structure of PEG-PVA copolymer

The manufacturing of PVA-PEG graft co-polymer involves a 2-step reaction process[42]:

- A polymerization reaction, whereby PEG and PVA are reacted together in the presence of a polymerization initiator (tert-butyl peroctoate in methanol) to form polyethylene glycol-graftpoly(vinyl acetate) co-polymer [PEG-graft-poly(vinyl acetate) co-polymer];
- A reaction whereby PEG-graft-poly(vinyl acetate) co-polymer is further reacted with sodium methoxide (MeONa) in methanol to form PEG-graft-poly(vinyl alcohol) co-polymer (PEGgraft-PVA co-polymer) and methyl acetate. No additional catalysts, other than tert-butyl peroctoate, are used

PEG-PVA is a spray dried powder of a high flowability recognizable by an angle of repose below 30°. The grafted PEG acts as a plasticizer, and hence provides a greater flexibility of films without additional plasticizers. Due to the low peroxide level PEG-PVA is highly suitable for oxygen sensitive drugs[43]. PEG-PVA films with iron oxide

red pigment are effective against transmission of light and meets the European pharmacopeia's requirement of colored light protecting glass containers[44]. The low viscosity of PEG-PVA even at higher solid contents in aqueous solutions, improves processing time and saves cost.

**Solubility:** For conventional film coating the polymer should have good solubility in aqueous fluids to facilitate the dissolution of active ingredients from the finished dosage form. However, where a modified release action is required then a polymer system of low water solubility or permeability will be chosen. The following have a good solubility in water: HPMC, HPC, MC, PVP plus gastrointestinal fluid and the common organic solvents used in coating.

Where it is proposed to use an aqueous solvent for film coating it is necessary to consider, first, the need to minimize contact between the tablet core and water and, secondly, the need to achieve a reasonable process time. Both can be achieved by using the highest possible polymer concentration (i.e. the lowest possible water content). The limiting factor here is one of coating suspension viscosity.

**Viscosity:** In general polymers should have a low viscosity for a given concentrations. This will permit the easy trouble-free spraying of their solution in industrial film coating equipment. The lower viscosity grade polymer permits a higher solids concentration to be used, with consequent reduction in solvent content of the solution. The practical advantage to be gained is that the lower the solvent content of the solution, the shorter will be the processing time as less solvent has to be removed during the coating process. This beneficial interaction between polymer viscosity and possible coating solids is self-limiting in that very low viscosity polymers will suffer from poor film strength due to low molecular weight composition.

**Permeability:** Film coating used to optimize the shelf life of tablet preparation as some polymers provide efficient barriers against the permeability of water vapor or other atmospheric gases. These properties vary widely between the individual polymers. Usually the moisture permeability of a simple film may be decreased by the incorporation of water-insoluble polymers, however, disintegration and dissolution characteristics of the dosage form must be carefully checked.

Water vapor permeability of polymer is dependent on the relative polarity of polymer. One of the approaches of assessing water vapor permeability is sorption-desorption technique to evaluate the performance of two film forming polymers, example HPMC and PVA. Addition of PVA to the HPMC was seen to enhance very effectively the moisture barrier effect of the HPMC. This behavior is possibly due to potentiation of the crystallinity of the HPMC by the PVA.

**Mechanical properties**: A polymer chosen for a film coat formulation must be having adequate strength to withstand the impact and abrasion encountered in normal handling[45-46]. Insufficient coating strength will be demonstrated by the development of cracks and other imperfections in the coating. It should be mentioned that the polymer chosen must also comply with relevant regulatory and pharmacopoeia requirements current in the intended marketing area.

The mechanical properties of film coat are often determined on polymeric films prepared by casting (free films) or spraying techniques and elucidated in terms of glass transition temperature ($T_g$), tensile strength, toughness, elastic or Young's modulus, minimum film forming temperature (MFT), moisture effect and plasticizer performance. The mechanical properties of free films prepared from polymeric dispersion/ solution provide valuable information to help the pharmaceutical scientist for predicting the stability and drug-release properties of film coated solid dosage forms.

Ideally increasing the tensile strength of the coating reduces the risk of cracking and reducing the elastic modulus decreases the potential of occurrence of bridging and cracking. These properties will be influenced by environmental factors (temperature, humidity, time, and rate of stressing the polymer, pressure, stress and strain amplitude), the chemical composition of the polymer (molecular weight, crosslinking and branching, crystallinity) and the presence of diluent (plasticizer, residual solvent, additives or fillers). The tensile properties of HPMC films is depends on the concentration of pigments (example titanium dioxide), the films became more brittle as the concentration of pigments increased, as evidence by the decrease in elongation and increase in Young's modulus. The addition of titanium dioxide to polyvinyl alcohol also resulted in a decrease in tensile strength. The presence of a plasticizer in the film coating is essential to reduce the brittle properties and to achieve effective coatings of the pellets or tablets without the formation of cracks or defects. Plasticizers also helps to lowers the $T_g$ and helps to increase the coalescence of the colloidal polymeric particles to form a uniform homogenous film over the substrate.

**Plasticizer:** Plasticizers are most critical component among all the ingredients that dictates proper film formation, quality and stability of the resulting film. Plasticizer added to reduce brittleness and helps to improve flow and flexibility of polymeric chains[47,48]. Toughness and strength of polymeric films is also increased by using plasticizer. Plasticizer helps to lower the glass transition temperature by reducing internal stress and a uniform homogenous film formed over the substrate which enhance the coalescence of the colloidal polymeric particles[49]. Change in film mechanical properties may ultimately influence the drug release, stability and the final physicochemical properties of the coated dosage forms[50].

Plasticizers are low molecular weight materials having ability to change the physical properties of polymer which are useful in performing its function as a film-coating material. It is considered that the mechanism of action for a plasticizer is to interpose its molecules between the individual polymer strands thus breaking down polymer-polymer interactions. This polymer-plasticizer interaction is stronger than the

polymer-polymer interaction[50-52]. Therefore, a plasticizer must be able to diffuse into and interact with the polymer and have minimal or no tendency for migration or exudation from the polymer. The commonly used plasticizers were classified as Polyols (glycerin, polyethylene glycol, propylene glycol), Organic esters (acetyl triethyl citrate, acetyl tributyl citrate, dibutyl phthalate, dibutylsebacate, tributyl citrate) and oils/glycerides (castor oil, acetylated monoglycerides, fractionated coconut oil)[53]. These plasticizers are normally added at the minimum effective level (10 to 30 % of the polymer). Excessive amount of plasticizer cause tablet tacking, plasticizer bleeding, color depletion or interaction with active ingredients and may significantly affect drug release[54,55].

The plasticizers triacetin and citrate esters- triethyl citrate (TEC) have the greatest ability to interact with the polymer. In triacetin, the carboxyl oxygens are readily available to interact through hydrogen bonding with the carboxyl hydrogen of the copolymer. This is also true for TEC, but the presence of ethyl group may reduce the accesibility of the carbonyl oxygen for hydrogen bonding (Fig. 1.4). This indicates that water soluble plasticizers have a higher affinity to diffuse into, and interact with the polymer, increasing the molecular mobility of the polymer chains.

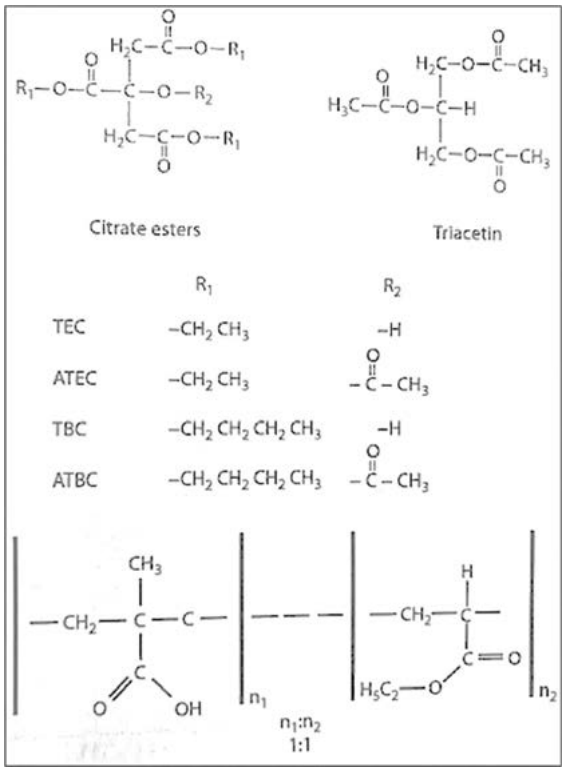



**Fig. 1.4:** Molecular structure of triacetin and citrate ester plasticizers and structural characteristics of poly methacrylic acid ethylacrylate, commercially available as Eudragit ® L30D and L100-55. ATBC, acetyl tributyl citrare; ATEC, acetyl triethyl citrate; TBC, tributyl citrate; TEC, triethyl citrate. (From Gutierrez-Rocca JC, McGinity JW, Int J Pharm 1994; 103:293-301)

Polymer-plasticizer interactions can be studied by determining the intrinsic viscosity of polymer dissolved in the plasticizer solution using the following equation.

$$\frac{\eta sp}{C} = [\eta] + k[\eta]^z c$$

Where $\frac{\eta sp}{C}$ is reduced viscosity, [ŋ] is intrinsic viscosity, defined as the limit of the reduced viscosity ( $\frac{\eta sp}{C}$) as the concentration approaches zero, C is the concentration of solution and ķ is an intrinsic constant also called huggins constant[56].

While formulating a coating dispersion, the selection of plasticizer is important as the plasticizers must remain in the film, showing little or no tendency for migration and

are must be compatible with polymer. While formulating coating dispersion, the addition of a proper amount of plasticizer is also significantly important. The insufficient quantity of plasticizer in the formulation can produce brittle polymeric films.

The ultimate relationship between the polymer and plasticizer can be evaluated by determining the mechanical properties of plasticized polymeric films. On the addition of plasticizer increases the ductility of the film is increases ultimately reduce its tensile strength and modulus of elasticity and produce soft, tough film. In the present work determination of mechanical properties (of casted film) is emphasized on blends of polymers with varying concentration of plasticizers helps to discover the best ratio of plasticized polymer blends that can be used in coating system.

**Pigment/ Opacifier and Additives:** Film coating systems generally contain additives such as plasticizers, pigments, and opacifiers to obtain appropriate end-use properties. To improve the physical appearance of dosage forms, to enhance the stability of photolytic drugs, and to aid in processing insoluble excipients are added to polymeric film coating solutions and dispersions. Also, film coatings which confer a modified release effect on the dosage form need to be mechanically tough in order to prevent damage of coating during normal handling. The esthetic appearance of the final product may be improved by the addition of pigments into a coating formulation[57]. There are three main categories of pigments[7]:

- Synthetic water-soluble organic dyes (sunset yellow, erythrosine),
- Insoluble aluminium lakes (water soluble dyes adsorbed onto small, insoluble particles of alumina) and
- Inorganic pigments (titanium dioxide, talc). To protect photosensitive drugs from exposure to light, titanium dioxide may be used in coatings, thus improving product stability.

The effect of aluminium lakes and inorganic pigments on the properties of both free and applied films is very dissimilar to that of plasticizers and considerably altered the physical, mechanical, adhesive, and drug-release properties of the films[58-60].

As the concentration of pigment increased, result in decrease in elongation and increase in Young's modulus, the cellulosic films became more brittle[61]. Hsu et al[62] showed that there is decrease in tensile strength, as the titanium dioxide added to polyvinyl alcohol. The magnitude of this effect was a function of both filler morphology and of filler-polymer interaction. Ideally, as the concentration of an insoluble pigment is increased, the quantity of polymer required to completely surround the particles increases. At a specific concentration, the polymer present is insufficient to surround all the insoluble particles (known as the **critical pigment volume concentration**), that results in marked changes in the mechanical properties of the film[63]. The quantity of insoluble filler combined with aqueous dispersion must be adjusted without increasing the maximum carrying capacity of the polymer or CPVC. The most commonly used antiadherents in film coating formulations are talc and glyceryl monostearate (GMS)[64]. These fillers, however, are not water soluble, and they have been shown impact on the mechanical and drug-release properties[22,65-67]. Okhamafe and York suggested that the effects of additives used in coating formulations were dependent on the balance between their influence on the internal stress of film coating and the strength of the film-tablet interface[68]. Water soluble additives like lactose, sodium lauryl sulfate is also included in aqueous coating formulations resulted in a decrease of the tensile strength of all the films tested; certainly, some films became too brittle to test[69].

**Solvent or Water as vehicle:** The major classes of solvents used in preparation of coating dispersion/ solution are water, alcohols, ketones, esters, chlorinated hydrocarbons. It is important that selected solvent system should be interacted with a given polymer. Higher the solvent-polymer interaction, permits the film properties such as adhesion and mechanical strength. For safety and health-related issues of people at workplace, it is preferred to use aqueous processing.

**Differential scanning calorimetry**, or **DSC** is a thermo analytical technique where the difference in the amount of heat required for increasing the temperature of a

sample and reference is measured as a function of temperature[70]. E. S. Watson and M. J. O'Neill in 1962, developed this technique[71] and commercially introduced at the 1963 Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy. The term DSC was coined to describe this instrument, which measures energy directly and allows precise measurements of heat capacity.

DSC is mostly used for inspecting polymeric materials to determine their thermal transitions. Important thermal transitions include the glass transition temperature ($T_g$), crystallization temperature ($T_c$), and melting temperature ($T_m$). The observed thermal transitions can be used to compare materials, though the transitions alone do not uniquely identify composition. The composition of unknown materials may be completed using complementary techniques such as FTIR spectroscopy. Melting points and glass transition temperatures for most polymers are available from standard compilations, and the method can show polymer degradation by the lowering of the expected melting temperature. $T_m$ depends on the molecular weight of the polymer and thermal history.

The study of thermal degradation of polymers can be conducted by DSC technique using an approach such as Oxidative Onset Temperature/Time (OOT); however, the user risks contamination of the DSC cell, which can be problematic. For decomposition behavior determination thermogravimetric Analysis (TGA) may be more useful. By examining thermograms, impurities in polymers can be determined for anomalous peaks, and plasticizers can be identified at their characteristic boiling points. In addition, examination of minor events in first heat thermal analysis data can be useful as these apparently "anomalous peaks" can in fact also be representative of process or storage thermal history of the material or polymer physical aging. Evaluation of first and second heat data collected at consistent heating rates can allow the analyst to learn about both polymer processing history and material properties.

Surface profilometry is a simple and fast measurement technique for determining the physical thickness of thin films[72].

**Quality by Design (QbD):** QbD approach can be applied to the current work. The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance. It is beneficial as it makes better understanding of the process with less batch failure and more efficient and effective control of change.

**Stability study:** Stability testing has become an integral part of the formulation development. It generates information on shelf life of drug or dosage forms, or their recommended storage conditions are based. Stability is defined as the capacity of a drug substance or drug product to remain within established specifications to maintain its identity, strength, quality and purity throughout the expiration dating period**.** The main purpose of stability testing studies is to provide evidence on how the quality of drug substance or drug product varies with time under the effect of variety of environmental factors (temperature, humidity and light)[73,74]. Stability of pharmaceutical preparation can be defined as "the capability of particular formulation (dosage form or drug product) in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life". Stability is an important factor of quality, safety and efficacy of a drug substance. A drug substance, which is not of sufficient stability, can result in changes in physical (like appearance, melting point, clarity and color of solution, water, crystal modification, particle size etc.) as well as chemical characteristics (increase in impurities and decrease in assay) and microbiological attributes (total bacterial count, fungal count and for pathogenic microbes). The stability data evaluation and extrapolation are performed using ICH guidelines[75].

Based on ICH Guidelines for Zone IV (Hot humid/ Tropical Zone), stability studies are conducted at two conditions[76]

- Accelerated and intermediate Testing Conditions and
- Long term testing conditions.

Accelerated stability studies under the stressed conditions (at higher temperature and relative humidity) are short term. The purpose of this study is to increase the rate of chemical and physical degradation of the product, so the significant degradation can be observed in a relatively short period.
The long- term studies are conducted under ambient storage conditions. Stability data obtained from long term testing is primary because it is directly used for the shelf life estimation.

**Table 1.4:** Storage conditions for study: General case

| **Study** | **Storage condition** | **Minimum time period covered by data at submission** |
|---|---|---|
| Long term | 30°C ± 2°C/65% RH ± 5% RH | 12 Months |
| Accelerated | 40°C ± 2°C/75% RH ± 5% RH | 6 Months |

**Surface Profilometry**

Surface profilometry study is intended to evaluate film coating performance based on surface roughness and texture developed during the process and also to check robustness of fully formulated coating compositions. This tool was used to add more value to these studies. This was to further challenge the optimized formulations and check which of the two polymer blends (HPMC + PVA:PEG or PVA + PVA:PEG ) performs better and has more consistent outcome. Surface profilometric images were collected using 20X true surface scan.

# *CHAPTER - 2*

# *AIM AND OBJECTIVES*

# *(Scope of Present Work)*

## AIM AND OBJECTIVES

This project envisaged in designing and development of polymer blend based coating systems to understand the effect of components in variable proportion on the physical characteristics of coated films on core tablets.

- Screening and selection of various types of film coating polymers based on solution properties, viscosity below 400cp, microbiological evaluation
- Formulation of the blend with various polymers, plasticizers, and additive ratio and evaluation of effect on film properties.
- Evaluation of mechanical properties of films casted using polymer blends.
- Evaluation of fully formulated polymer blend based coating systems using model drugs selected based on BCS Classification.
- Stability evaluation on placebo as well as tablets containing model active pharmaceutical ingredients (API's).
- Apply Quality by Design (QbD) concept to test for robustness of selected fully formulated film coating systems.
- Use of Surface Profilometry as tool to review performance of the selected formulations of film coating systems on coated tablets.

# *CHAPTER - 3*

# *REVIEW OF LITERATURE*

## 3.1 Background History:

Polymer- large molecule of high molecular weight called macromolecule, made up of many repeated subunits to form a long chain. Polymer derives from the Greek word *poly means* "many, much" and *mers means* "parts"[14]. A structure molecule composed of multiple repeating units is known as polymer, from which originates a characteristic of high relative molecular mass and attendant properties[1].

Hermann Staudinger was demonstrated the presence of macromolecules, which he characterized as polymers[77]. The only difference between the two terms is that *polymers are made of repeating units called monomers*, whereas *macromolecules are generally used to refer to any large molecule not just those made of repeating units*. Thus, polymers can be considered as subset of macromolecules

Polymers are macromolecules which are widely used in pharmaceutical industry from centuries due to wide range of application and advantages offered by them in modern medicine[17].

## 3.2 Polymers used in pharmaceutical applications

Polymers find various applications in pharmaceutical dosage developments and enhancing properties of formulations. Our focus is on polymers used for film coating application[78].

Polymers used in conventional film coating formulations are typically water-soluble ingredients, so that the applied coating does not interfere with dissolution characteristics. Sometimes water insoluble polymers are used for specific purpose like rate controlling modified release dosage form[19].

The first sprayable film coating solvents were formulated for use with organic solvent. As a result of this, there was a requirement that the polymer was soluble both in organic solvents and in gastro-intestinal fluids (i.e. water soluble). To meet this requirement, HPMC was found to be very much an ideal polymer. From the 1970's onwards there has been lot of pressures to eliminate organic solvents from pharmaceutical processing for cost, operator health and environmental reasons. As the polymer HPMC was soluble in both, organic solvents as well as water, the simplest way was to just replace the existing solvent system with aqueous based system. Not much thoughts were given to test, if HPMC was the most suitable polymer for aqueous film coating application[79].

While studies were conducted to find water soluble polymer having moisture barrier properties, Vinyl polymers like Poly Vinyl Alcohol (PVA) was extensively studied and it was found that poly vinyl alcohol was offering many advantages along with its moisture barrier property. This was a more ideal polymer for aqueous film coating when compared to Hypromellose.

Glycols, especially higher molecular weight like PEG20000 were used as polymers in some very early ladled film coating systems but are now used mainly as plasticizers[79].

Most of the acrylic polymers have specific pH/solubility or pH/swellability properties that make them most useful in modified release systems[80].

### 3.3 Solid Oral Dosage Forms

Based on market data (IMS update)[81] Oral solid dosage forms (OSDF) are the most commonly used forms among the other modes of administration of medicines. They are considered as more convenient to administer to patient compared to injections, accuracy in dosing, provide scope for targeting the delivery and controlling the

release of active medication, improved stability compared to liquid formulations and thus these advantages make them more popular forms to be offered in market.

### 3.4 Film Coating of solid dosage forms

Film coating is a process of depositing a thin layer of polymeric film in the range of 20 to 100 micron thickness onto surface of dosage forms like tablets, capsules, pellets, minitablets, powders etc.,[82].

### 3.5 Rationale for film coating[83]

1. **Therapy:**
    a. Improve bioavailability by controlling the duration and site of drug release. (Delayed Release and extended release coatings)
    b. Minimize irritation of the esophagus and stomach by improving esophageal transit performance. This reduces localized mucosal irritation.
    c. Minimize inactivation of active ingredient in the stomach due to acidic environment.
    d. Improve patient compliance e.g. easier to swallow[84], masks unpleasant taste[85].

2. **Technology & Process**
    a. Separate the reactive component in the tablet.
    b. Minimize dust formation and thus cross contamination as well as cleaning issues.
    c. Easily identify a branded product and avoiding mistakes while taking different strengths of same active formulation.
    d. Improve drug stability by protecting from oxygen, moisture and/or light, the three key causes of drug degradation.

e. Improves the resistance of the tablet surface thus reducing damage during packaging & other bulk handling operations

3. **Marketing:**
   a. Improve appearance of dosage forms, mask defects on tablet core.
   b. Improve efficiency of any printing operation resulting in improved print clarity.

4. **Anti-Counterfeiting method**[86] –
   a. Unique color and surface characteristics that can be achieved by coating are an aid to detection. Counterfeit product manufacturers may be more likely to target tablets without pronounced distinguishing characteristics, such as unique logos.

5. **Trademarking & Branding**:
   a. The appearance of a product in terms of color, shape, surface characteristics and printing can all be used as trade-marking elements.

## 3.6 Selection of Model Drugs

Model drugs are used as markers to evaluate performance of selected polymers. This is final step in the evaluation of polymers the models are selected based on dose and solubility parameters similar to BCS classification.

BCS considers three major factors[87]:

1. Solubility,
2. Intestinal permeability and
3. Dissolution rate

It is therefore important to understand effect of polymer based coatings on drug release profile of model drugs.

Examples of leading pharmaceutical formulations coated with polymers:

(a) Pfizer's Lipitor (Atorvastatin) coated using Hypromelose[88] & Caduet (Amlodipine besylate and atorvastatin calcium) coated using Polyvinyl alcohol[89]

*(b)* GSK's Paxil CR (Paroxetin hydrochloride tablets) coated with Methacrylic acid copolymer type C[90]

In this present study we selected below two Model drugs

1. Aspirin low dose formulatiuon representing BCS Class I (high permeability, high Solubility). This also poses stability challenges from the efficiency of aqueous coating process hence becomes an ideal candidate.
2. Ranitidine Hydrochloride representing BCS Class III (low permeability/ high solubility). Additionally is affected by moisture from coating and poses stability challenges hence an ideal candidate challenging evaluation.

This study also focused on review of patents filed for Polymer applications in aqueous film coatings. This is to get overview of what is already studied by leading commercial manufacture or any other research scholar[91-104].

Pharmacopoeia acceptance limit for viscosity range is 75% to 125% of the labeled viscosity value for grades below 600cp[105].

Hypromellose has advantage of being there from early days of film coating. It is soluble in both aqueous media and organic solvents generally used in pharmaceutical industry.

Hypromellose is available in number of viscosity designations defined as the nominal viscosity of a 2% w/w aqueous solution at 20°C. Thus a 3 mPa s grade will have a nominal viscosity of 3mPa s in 2% aqueous solution in water at 20°C and similarly with 6 mPa s and 15 mPa s grades[106].

Effect of solution viscosity on film coating performance. Considering the final solution to be sprayed, a normal HPMC based system would have a viscosity of approximately 500 mPa s. The lower viscosity grade polymer permits higher solids concentration to be used, with consequent reduction in solvent content of the solution. The lower the solvent content in a solution, the shorter will be the processing time as less solvent has to be removed during the coating procedure. However very low viscosity polymers will suffer from poor film strength due to lower molecular weight composition. Delporte (1980) has examined polymer solution viscosities in the 250-300 mPa s range to conclude 5 mPa s gives balance between film strength and solution solids levels[106].

Most widely used polymers are the cellulose ethers, which includes hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) methylcellulose (MC) and acrylates. One of the main applications of these polymer is to prepare film coating system. Physical protection provided to the dosage form by film coating systems which is depending on its mechanical characteristics and this is important to predict the release property and stability of film-coated dosage form. The selection of polymer for coating application is depends on many factors, such as polymer solubility, viscosity, film permeability and mechanical properties of film coat. Estimation of mechanical properties of free films in the development of a film coating system, can readily characterize the fundamental properties of the coating.

The mechanical properties of polymers may range between an almost perfect elastic state (original strain recovers after removal of an applied stress) to an almost Newtonian viscous state (the deformation is permanent, and the original strain is not recovered). Lever & Rhys classify the properties of film coat based on their characteristic stress-strain curves (soft and weak, soft and tough, hard and brittle, hard and strong, hard and tough)[107]. Tobolsky observed in deformational behavior (viscoelasticity behavior), polymers may undergo different regions such as glassy, transition, rubbery, rubbery liquid and liquid[108].

The mechanical properties of such film coat are often determined on polymeric films prepared by casting or spraying techniques[109] and elucidated in terms of glass transition temperature ($T_g$), tensile strength, toughness, elastic or Young's modulus, minimum film forming temperature (MFT), moisture effect and plasticizer performance[110-114]. Ideally increasing the tensile strength of the coating reduces the risk of cracking and reducing the elastic modulus decreases the potential of occurrence of bridging and cracking. These properties will be influenced by environmental factors (temperature, humidity, time, and rate of stressing the polymer, pressure, stress and strain amplitude), the chemical composition of the polymer (molecular weight, crosslinking and branching, crystallinity) and the presence of diluent (plasticizer, residual solvent, additives or fillers)[115-116]. The tensile properties of HPMC films is depends on the concentration of pigments (example titanium dioxide), the films became more brittle as the concentration of pigments increased, as evidence by the decrease in elongation and increase in Young's modulus[24]. Hsu et al, showed the addition of titanium dioxide to polyvinyl alcohol also resulted in a decrease in tensile strength[117]. The presence of a plasticizer in the film coating is essential to reduce the brittle properties and to achieve effective coatings of the pellets or tablets without the formation of cracks or defects. Plasticizers lowers the $T_g$ and enhance the coalescence of the colloidal polymeric particles to form a uniform homogenous film over the substrate.

Rowe noted that, the average molecular weight and molecular weight distribution of polymers are important factors in the coating process since it will influence not only solution viscosity but also the mechanical properties of the final film coat[118]. For a given polymer-solvent system, the viscosity varies with the molecular weight of the polymer. During the film coating process, the film coating formulations are encountering a wide range of shear rates. These values of shear rates range from as low as $300s^{-1}$ to as high as 20000 $s^{-1}$causing a very good velocity, which runs between spray gun and nozzle as high speed atomizing air[119]. Newtonian solutions are likely to exhibit the same rheological behavior at all stages of the coating process

irrespective of the share rate encountered, whereas non-Newtonian behavior may vary in viscosity at various stages during the coating process and different coating conditions.

Most of present scientific work on mechanical properties, rheological profile of film coating system is based on the utilization of different types of polymers either alone or in combination with other additives (plasticizer, pigments and solvent system); also commercially formulated coating system are available with either single polymer or combination of polymers at different ratios along with other additives to enhance the effectiveness of films coat for providing better protection to the pharmaceutical dosage form, however, limited data is available on mechanical properties of film coat formulated using blends of polymer in aqueous system. Therefore, present work of determination of mechanical properties (of casted film) and viscosity (of aqueous solution) is emphasized on blends of polymers to find the best ratio of polymer blends that can be used in coating system.

To protect the dosage form against environmental conditions and for masking a bad taste, odor or appearance polymers plays important role in pharmaceutical formulation. The evaluation of physical- mechanical properties of polymeric films for the development of film coating system, provides an important information to verbalizing their performance in pharmaceutical dosage forms[120]. Commercial film coating system does not consist of polymer alone but also contains other ingredients for a specific reason, either to assist processing or to improve performance and appearance. The addition of other ingredients in film coating formulations such as pigments to enhance product appearance, talc to reduce tackiness of the coating and lubricants to prevent agglomeration of the coated substrates, will influence the mechanical properties of polymeric films[22-24,121]. Normally inclusion of these ingredients (pigments, fillers, talc, titanium dioxide) reduces the tensile strength and extensibility while increasing the Young's modulus of HPMC films[47, 122,].

Among all the ingredients that are incorporated into film coating system, the plasticizer is the most critical component that dictates proper film formation, quality and stability of the resulting film. Plasticizers are added to reduce the brittleness, improve flow, and improve flexibility of polymeric chains[47-48]. In addition, they will also increase toughness and strength of polymeric films, lower the glass transition temperature, decreasing internal stress and enhance the coalescence of the colloidal polymeric particles to form a uniform homogenous film over the substrate[49]. Change in film mechanical properties may ultimately influence the drug release, stability and the final physicochemical properties of the coated dosage forms[50].

Plasticizers are low molecular weight materials having ability to alter the physical properties of polymer to render it more useful in performing its function as a film-coating material. It is generally considered that the mechanism of action for a plasticizer is for the plasticizer molecules to interpose themselves between the individual polymer strands thus breaking down polymer-polymer interactions. This action is facilitated as the polymer-plasticizer interaction which is stronger than the polymer-polymer interaction[51-52]. Therefore, for a plasticizer to be effective, it must be able to diffuse into and interact with the polymer and have minimal or no tendency for migration or exudation from the polymer. The commonly used plasticizers were classified as Polyols (glycerin, polyethylene glycol, propylene glycol), Organic esters (acetyltriethyl citrate, acetyltributyl citrate, dibutyl phthalate, dibutyl sebacate, tributyl citrate) and oils/glycerides (castor oil, acetylated monoglycerides, fractionated coconut oil)[53]. These plasticizers normally added at the minimum effective level (usually 10 to 30% with respect to the polymer), excessive amount may cause tablet tacking, plasticizer bleeding, color depletion or interaction with active ingredients and may significantly affect drug release[54-55].

The selection of plasticizer is of the utmost importance when formulating a coating dispersion. Plasticizers must remain in the film, exhibiting little or no tendency for migration. Moreover, plasticizers must be compatible with polymer. The addition of a proper amount of plasticizer to a coating dispersion is also considerable importance.

The inadequate amount of plasticizer in the formulation can result in polymer films are brittle.

The ultimate relationship between the polymer and plasticizer can be evaluated by determining the mechanical properties of plasticized polymeric films. Generally, the addition of plasticizer increases the ductility of the film, but this is often accompanied by a reduction in its tensile strength and modulus of elasticity. The addition of plasticizer, therefore, results in soft, tough film. Increasing the plasticizer enhancing this effect. Present work of determination of mechanical properties (of casted film) is emphasized on blends of polymers with varying concentration of plasticizers to find the best ratio of plasticized polymer blends that can be used in coating system.

The mechanical properties of free films prepared from aqueous polymeric dispersions provide valuable information to help the pharmaceutical scientist predict the stability and drug-release properties of film coated solid dosage forms. Film coating systems generally contain additives such as plasticizers, pigments, and opacifiers to obtain appropriate end-use properties. Insoluble excipients are added to polymeric film coating solutions and dispersions to improve the physical appearance of dosage forms, enhance the stability of photolytic drugs, and aid in processing. Also, film coatings which confer a modified release effect on the dosage form need to be mechanically tough in order that the coating is not inadvertently damaged during normal handling. Plasticizers are added to reduce the brittleness, improve flow, and improve flexibility of polymeric chains[47-48]. The addition of pigments into a coating formulation may improve the esthetic appearance of the final product[57].

Pigments fall into three main categories:

- synthetic water-soluble organic dyes (sunset yellow, erythrosine),
- their insoluble aluminium lakes (water soluble dyes adsorbed onto small, insoluble particles of alumina) and

- inorganic pigments (titanium dioxide, talc). Titanium dioxide may be used in coatings to protect photosensitive drugs from exposure to light, thus improving product stability[7].

The influence of aluminium lakes and inorganic pigments on the properties of both free and applied films is generally very different to that of plasticizers and significantly affecting the physical, mechanical, adhesive, and drug-release properties of the films[59-61]. The cellulosic films became more brittle as the concentration of pigment increased, as evidenced by the decrease in elongation and increase in Young's modulus[123]. More recently, Hsu et al.[117] showed that the addition of titanium dioxide to polyvinyl alcohol also resulted in a decrease in tensile strength. The magnitude of this effect was a function both of filler morphology and of filler/polymer interaction. Ideally, as the concentration of an insoluble pigment is increased, the amount of polymer necessary to completely surround the particles increases. At a specific concentration, known as the **critical pigment volume concentration** (CPVC), the polymer present is insufficient to surround all the insoluble particles, and marked changes in the mechanical properties of the film will occur[64]. The amount of insoluble filler incorporated in aqueous dispersion must be optimized without exceeding the maximum carrying capacity of the polymer or CPVC. Talc and glyceryl monostearate (GMS) are the most commonly used antiadherents in film coating formulations[65]. These fillers, however, are not water soluble, and they have been shown to influence the mechanical and drug-release properties[22,63,66,67]. Okhamafe and York suggested that the effects of additives in coating formulations were dependent on the balance between their influence on the internal stress of film coating and the strength of the film-tablet interface[70]. Water soluble additives such as lactose, sodium lauryl sulfate is also added in aqueous coating formulations. Their inclusion resulted in a reduction of the tensile strength of all the films tested; indeed, some films became too brittle to test[71].

Present study is focused on the effect of polymeric additives (titanium dioxide and talc) on mechanical properties of polymeric films. Polymeric films prepared using

blends of polymer with fixed concentration of plasticizer (25% of PEG3350 with respect to total quantity of polymers) and varying the concentration of additives. Also in this study, the theories of the interactions between polymer and insoluble additives are addressed.

Plasticizer PEG 3350 (water soluble) was selected for this study. The polymers selected in this study are water soluble, having different chemistry; hence, their interaction with plasticizer/s must be different. Other additives such as $TiO_2$ and talc are also selected for this study, which are water insoluble, thus there would be no interaction between water soluble polymers and these additives. However, presence of these water insoluble additives must have physical interaction on mechanical properties of polymers.

Film coating formulation system also contains other ingredients along with polymer. For aqueous application, blend of polymer with other ingredients are normally added into water under stirring, prior to proceeding for coating on substrate. The addition of other ingredients in film coating formulations have a specific role, such as plasticizers to reduce the brittleness, improve flow, and improve flexibility of polymeric chains[47,48], pigments to enhance product appearance, to provide opacity and therefore protection from light which also greatly aid in identifying the tablets[57], talc to reduce tackiness of the coating and lubricants to prevent agglomeration of the coated substrates, will influence the mechanical properties of polymeric films (example: reduces the tensile strength and extensibility while increasing the Young's modulus of HPMC films)[21-24, 122]. Thus, presence of other ingredients in coating formulation play a significant role to assist the coating process, improve the performance and appearance of coated formulation, barrier properties, and in some cases their film forming characteristics[124].

Overall properties of film coating will depend on four factors; the constitutes and properties of the substrate, the coating formulation applied, the coating process parameters and the environment in which the coated product subsequently stored. It

was reported that presence of film coating defects on coated tablet surface, such as edge splitting, peeling, cracking or bridging of the intagliation or monograms within a batch of tablets[34, 125-126.] It has been shown that these film defects are because of the build-up of stresses within the film coating. This stress arises because the coating applied as a solution by spraying, loses solvent as it dries, and thus it must shrink as the volume of solvent evaporates. Since the coating is applied as a continuous film around a solid tablet core, the amount of shrinkage allowed in the plane of the coating is restricted. When the solvent concentration has been reduced to a certain level, the coating loses its ability to flow and the continued tendency of the film to shrink around the tablet core leads to mechanical stress in the coating. Also, because the coatings are dried above room temperature, a thermal stress arises as the coated tablets cool due to higher thermal expansion coefficient of the polymeric film compared with that of the tablet substrate.

Addition of pigments or insoluble additives can affect the mechanical properties of film coatings causing an increase in the Young's modulus of the film but decrease in tensile strength thus affecting their performance in suit on the tablet surface. It also causes an increase in both internal stresses and thermal stresses within coated film[47,125]. The presence of plasticizer in film coating system play a key role to reduce these film defects. Plasticized film has ability to lower the Young's modulus and tensile strength which resulted in decrease in internal stresses within coated film[34,126,127].

The properties of coating material as well as the process of coating and the underlying mechanisms are nowadays well understood and controlled, but due to the introduction of new polymers/ polymer blends and modern technologies, further investigations and knowledge are necessary in that field.

This work describes the evaluation of coating system formulated using polymer blends along with other ingredients (plasticizer, pigments and anti-tacking agent) and its ease of aqueous application by actual performing coating trial on placebo tablets.

The results are related to the behavior, integrity of these materials and formation of defects (if any) when applied as coatings on an inert tablet substrate.

Two types of polymer blends *viz* “PVA: PVA-PEG (ratio 90:10)” and “HPMC 6Cp: PVA-PEG (ratio 90:10)” were selected to prepare pigmented and non-pigmented coating system along with varying the concentration of other additives (pigment, plasticizer and anti-tacking agent). $TiO_2$ and FD&C Blue#2 (Indigo Carmine) lake as pigment, TEC as a plasticizer and talc as an anti-tacking agent were selected for this study. For pigmented coating system, the ratio of polymer bend to additives of 20:80, 30:70, 40:60, 50:50, 60:40, 70:30 were used along with TEC as a plasticizer (25% with respect to quantity of polymer blend) and 1% FD&C Blue #2 lake, whereas in case of clear (non-pigmented) coating system, the ratio of polymer bend to additives of 80:20, 90:10 were used along with 12.5% and 5.5% of TEC respectively (TEC concentration is with respect to quantity of polymer blend). In pigmented coating system the FD&C Blue #2 lake was added at 1% level whereas the quantity of $TiO_2$ varied from 14 to 44%, this in turn coated tablets will have darker to lighter shade of film coat.

FD&C Blue# 2 lake is known for being sensitive to light and oxidizing agents[128], therefore selected for this study to find its impact on coated tablets surface. The polymers selected in this study are water soluble, having different chemistry, hence, its interaction (physical) with plasticizer (water soluble) must be different in the presence of water insoluble additives ($TiO_2$ and Talc). It may affect mechanical properties of polymer and this can be visually observed (defects if any) when such type of coating system applied on tablet surface.

# *CHAPTER - 4*

# *MATERIALS & METHODS*

# 4. METHODOLOGY

## 4.1 List of Materials

**Sr. No Material Description, Manufacturer, Lot No.**

1. Hypromellose – *Methocel Grades,* Manufacturer : DuPont,
   a. Methocel E3 Premium LV (Lot No.: 3E150124L1)
   b. Methocel E6 Premium LV (Lot No.: 1A290124L1 & D011G4CL02)
   c. Methocel E15 Premium LV (Lot No.: 3E240124L1)
2. Poly Vinyl Alcohol – *Gohsenol GL-05FS*, Manufacturer : Nippon Gohsei (Lot No: 64M52T, Viscosity: 5.3 cP.)
3. Polyvinyl Alcohol – PEG Graft Copolymer - *Kollicoat IR*, Manufacturer: BASF (Lot No.: 38230468E0, Viscosity: 120 cP).
4. Hydroxy propyl Cellulose – *Klucel LF*, Manufacturer: Ashland, (Lot No.: 4673, Viscosity 80 cP of 5% aqueous solution).
5. Carboxy methyl cellulose sodium – *Cellogen HP-8A*, Manufacturer: Montello (Lot No.: 2543B1, Viscosity: 43 cP of 2% aqueous solution).
6. Poly ethylene glycol 400 – *Polyglykol 400*, Manufacturer: Clarient International, (Lot No.: DEG4401829).
7. Poly ethylene glycol 3350 – *Polyglykol 3350*, Manufacturer: Clarient International, (Lot No.: DEA4006020).
8. Medium Chain Triglyceride – *Miglyol*, Manufacturer: IOI Oleochemicals, (Lot No.: 141129-6).
9. Tri ethyl citrate, Manufacturer: Vertellus, (Lot No.: 0000157958).
10. Titanium Dioxide, Manufacturer: Brentag Specialties, (Lot No.: 0001161).
11. Purified Talc, Manufacturer: Luzenac, (Lot No.: S.180/18).

12. FD&C Blue #2 Lake (Indigo Carmine), Manufacturer: Colorcon, (Lot No.: WP781738:AX8281).
13. Aspirin USP, Manufacturer: Alta laboratories, (Lot No.: J99).
14. Partially Pregelatinized Starch (*Starch 1500*), Manufacturer: Colorcon, (Lot No.: IN532309).
15. Microcrystalline Cellulose – *Vivapur 101*, Manufacturer: JRS Pharma, (Lot No.: 6610161210).
16. Stearic Acid, Manufacturer: Oleotec Limited, (Lot No.: GAR476594).
17. Ranitidine hydrochloride (Form II USP), Manufacturer: Orcher India, (Lot No.: R010PD081816CEP).
18. Co-processed mix of maize starch and partially pregelatinzed Starch (*StarCap 1500*), Manufacturer: Colorcon, (Lot No.: IN537449).
19. Microcrystalline Cellulose (*Avicel PH 102*), Manufacturer: FMC Corporation, (Lot No: 71646C).
20. Colloidal silicon dioxide (*Cab-o-Sil*), Manufacturer; Cabot Corporation, (Lot No GAR486516).
21. Magnesium Stearate, Manufacturer: Akcros, (Lot No. : GAR487248).
22. Soyabean Casein digest agar (Tryptic soya agar), SCDA, Hi Media (Lab Reagent).
23. Sabouraud Dextrose Agar – SDA, Hi Media (Lab Reagent).

## 4.2 List of Instruments

### 4.2.1 Specialised Instruments & Software

1. Film Casting Knife – custom make

2. Dog Bone shape cutter 75mm X 10mm – RR/HCP Ray-Ran Test Equipment, UK

3. Tensile Strength Tester – 5942 Instron, UK

4. Leica Microscope – S8 APO

5. Optical Profilometer – WITec alpha 300RA+, WITec GmbH, Ulm, Germany

6. Gloss Meter – Tricor, IL USA

7. Differential Scanning Calorimeter-DSC-I, Mettler Toledo, Switzerland.

8. Software 1: Tensile Strength Testing Software – Bluehill.
9. Software 2: For QbD – Minitab from Minitab Inc, US.

### 4.2.2 Other Laboratory Equipments

1. Viscometer – Brookfield LV Model DV1 with appropriate spindles.
2. pH Meter – Electrolab.
3. Fourier Transform Infra-Red (FTIR) Spectrophotometer – Thermo Fischer Nicolet iS10.
4. Laboratory Incubator - 30°C to 35°C.
5. BOD Incubator - 20°C to 25°C.
6. Tablet Compression Machine – Cadmach CU20 Rotary Press with D type tooling.

7. Coating Machine – Ohara LCM5 Fitted with 8.5" fully perforated pan.
8. Spray Gun – Schlick ABC Type 970 design 7-1-S75, 0.8mm nozzle dia.
9. Peristaltic Pump – Watson Marlow.
10. Laboratory Jar fitted with Propeller Stirrer.
11. Laboratory Balance – various capacities (200g, 1kg, 5kg).
12. Disintegration Test Apparatus – Electrolab ED 2L.
13. Dissolution Test Apparatus – Electrolab EDT – 08 LX.
14. High Performance Liquid Chromatography – Agilent HPLC 1200 infinity series.
15. Small Apparatus – Magnifying Glass Petri plates, beakers etc.

### 4.3 Selection of polymers based on preliminary screening

Primary criteria were to evaluate water soluble polymers that can be used for immediate release film coating application. This is done to support "Green Chemistry" approach of eliminating use of organic solvents from the process.

Different polymers were evaluated in aqueous medium for viscosity, pH and microbial stability over 5 day's period. Based on the results of these studies ideal candidates were evaluated.

Polymers involved in screening process are :

- Hypromellose 3 cp, 6 cp and 15 cp
- Hydroxypropyl Cellulose, low substituted (L-HPC)
- Carboxymethyl Cellulose Sodium (Na-CMC)
- Poly-vinyl alcohol, partially hydrolyzed (PVA)
- Polyvinyl alcohol - Polyethylene glycol graft copolymer (PVA-PEG)

Viscosity Measurements were carried out using Rotational Viscometer Make: Brookfield LV Model DV1 at Temp 24±2°C. pH values were measured using a digital pH meter having auto temperature correction to 25°C. FTIR Scans of pure polymers were recorded using Thermo Fischer Nicolet iS10 model.

In microbial evaluation bacterial count and mold and yeast were carried out on Soyabean Casein Digest Agar (Tryptic soya Agar) -(SCDA) and Sabouraud Dextrose Agar - (SDA) respectively. The bacterial count was carried out in the laboratory incubator at 30° C - 35° C for 3 - 5 days. The fungal count was carried out in BOD incubator 20°C - 25° C for 5 - 7 days.

## 4.4 Formulation and evaluation of blend of selected polymers

### *4.4.1 Preparation of Blends*

Blends were prepared by manual mixing two different polymers in 5 different ratios as given in Table no. 4.1. Solutions of these blends were prepared to contain different solids levels.

**Table 4.1: Polymer ratio for preparation of blends**

| **Polymer Blend** | **90:10** | **80:20** | **70:30** | **60:40** | **50:50** |
|---|---|---|---|---|---|
| **PVA: PVA-PEG**<br>**% Solids in Solution** | 20 | 20 | 20 | 20 | 20 |
| **PVA: Na CMC**<br>**% Solids in Solution** | 20 | 15 | 15 | 15 | 10 |
| **HPMC 6cP : PVA-PEG**<br>**% Solids in Solution** | 15 | 15 | 15 | 15 | 20 |
| **PVA: HPC**<br>**% Solids in Solution** | 15 | 15 | 15 | 15 | 15 |

### *4.4.2 Viscosity determination*

The blends were dispersed into an aqueous solution based on ratio and concentration given in the table no. 4.1. The solution was vortexed for the uniform mixing of the powder blend and later the speed was reduced until gentle mixing to form a uniform viscous solution for 30 minutes. The air bubbles were eliminated by keeping solution overnight. The solution was later checked for viscosity using medium viscosity Brookfield Pro DV II+ Viscometer equipped with Spindle S01. (Except for PVA: Sodium CMC at 50: 50 ratios, viscosity was measured using Spindle S05) and the temperature of the solution were maintained at 25ºC (±0. 5). The RPM of the spindle was maintained at a different speed level during the determination of viscosity.

The viscosity of individual polymers (Sodium CMC, HPMC 6 cP, PVA-PEG, PVA, and HPC) was also determined at different % solids as reference.

### *4.4.3 Film casting and evaluation of mechanical properties*

The solutions prepared were cast into films. Approximately 50 - 70 mL of the solution was poured on to the Teflon plates and drawn down over the sheet to get a film of uniform thickness. The film was allowed to dry at room temperature and strips of films were cut of precise size (5 mm X 55 mm) using the dog bone shape cutter. The film cuts were tested for mechanical properties using the Instron instrument using Bluehill 3 software. A total of 10 films under each combination were evaluated.

## 4.5 Formulation and evaluation of polymer blend with various plasticizers

### *4.5.1 Blend Composition*

Blends were prepared by using laboratory blender in 90:10 ratio polymers followed by addition plasticizer at 10%, 15% and 20% (concentration with respect to polymers) as given in Table 4.2.

**Table 4.2: Various ratios of polymer blend and plasticizer**

| Polymer Blend | Plasticizer | | | |
|---|---|---|---|---|
| | **PEG 400** (% w/w) | **PEG 3350** (% w/w) | **MCT** (% w/w) | **TEC** (% w/w) |
| **PVA: PVA-PEG** (90:10) | 10 | 10 | 10 | 10 |
| | 15 | 15 | 15 | 15 |
| | 20 | 20 | 20 | 20 |
| **HPMC 6cP: PVA-PEG** (90:10) | 10 | 10 | 10 | 10 |
| | 15 | 15 | 15 | 15 |
| | 20 | 20 | 20 | 20 |
| **PVA: HPC** (90:10) | 10 | 10 | 10 | 10 |
| | 15 | 15 | 15 | 15 |
| | 20 | 20 | 20 | 20 |

### 4.5.2 *Film casting and evaluation of mechanical properties*

Purified water was used to prepare solution of polymer blends at 20% solids (PVA: PVA-PEG) and 15% solids (HPMC 6cP: PVA-PEG and PVA: HPC). Films of these solutions were casted at an approximate thickness of 100 µ on glass plates with the help of a film casting knife. Casted films were allowed to dry overnight at room conditions (~ 25±2°C, 65 ± 5% RH). The films were cut into pieces of uniform shape (75 mm x 10 mm) with the help of the Dogbone cutter (RR/HCP, Ray-Ran Test Equipment, UK). The tensile strength of these cast film pieces was determined using Tensile strength tester (5942, Instron, UK) equipped with Bluehill 3 software. A total of 10 films under each combination were evaluated for their mechanical properties (modulus of elasticity, tensile strength).

## 4.6 Preparation of blend with plasticizer and additives

### 4.6.1 *Blend Preparation with plasticizer*

Blends were prepared using laboratory blender in 90:10 ratio polymers followed by the addition of additives at different ratios (Polymer: diluent ratio; 20:80, 30:70, 40:60, 50:50, 60:40 ratio respectively) and plasticizer (PEG 3350), as given in Table 4.3. All polymer blends have a similar quantity of PEG 3350 (25% of the total quantity of polymers).

**Table 4.3: Various ratios of the polymer blend, plasticizer, and additives**

| Polymer blend | Name of Ingredients | Polymer bends to Additives ratio | | | | |
|---|---|---|---|---|---|---|
| | | **20:80** | **30:70** | **40:60** | **50:50** | **60:40** |
| | | **T1** | **T2** | **T3** | **T4** | **T5** |
| | | **Quantities (%)** | | | | |
| **PVA: PVA-PEG (ratio 90:10)** | **PVA** | 18 | 27 | 36 | 45 | 54 |
| | **PVA-PEG** | 2 | 3 | 4 | 5 | 6 |
| | **PEG 3350** | 5 | 7.5 | 10 | 12.5 | 15 |
| | **$TiO_2$** | 45 | 37.5 | 30 | 22.5 | 15 |
| | **Talc** | 30 | 25 | 20 | 15 | 10 |
| | Total (%) | 100 | 100 | 100 | 100 | 100 |
| **HPMC 6Cp: PVA-PEG (ratio 90:10)** | | **T6** | **T7** | **T8** | **T9** | **T10** |
| | **HPMC 6cP** | 18 | 27 | 36 | 45 | 54 |
| | **PVA-PEG** | 2 | 3 | 4 | 5 | 6 |
| | **PEG 3350** | 5 | 7.5 | 10 | 12.5 | 15 |
| | **$TiO_2$** | 45 | 37.5 | 30 | 22.5 | 15 |
| | **Talc** | 30 | 25 | 20 | 15 | 10 |
| | Total (%) | 100 | 100 | 100 | 100 | 100 |

| PVA:HPC (ratio 90:10) | | T11 | T12 | T13 | T14 | T15 |
|---|---|---|---|---|---|---|
| | **PVA** | 18 | 27 | 36 | 45 | 54 |
| | **HPC** | 2 | 3 | 4 | 5 | 6 |
| | **PEG 3350** | 5 | 7.5 | 10 | 12.5 | 15 |
| | **$TiO_2$** | 45 | 37.5 | 30 | 22.5 | 15 |
| | **Talc** | 30 | 25 | 20 | 15 | 10 |
| | Total (%) | 100 | 100 | 100 | 100 | 100 |

### 4.6.2 Film casting and evaluation of mechanical properties:

The solution of polymer blends was prepared in purified water at 20% solids (PVA: PVA-PEG, HPMC: PVA-PEG and PVA: HPC). Films were casted from these solutions at an approximate thickness of 100 µ on glass plates using spray rig system. Films were allowed to dry overnight at conditions (25 ± 2°C, 65 ± 5% RH) and then cut into size 75 mm x 10 mm using Dog-bone cutter (RR/HCP, Ray-Ran Test Equipment). These films were tested using Tensile strength tester (5942, Instron, UK) equipped with Bluehill 3 software. A total of 10 films under each combination were evaluated.

## 4.7 Tablet compression

The tablets were prepared by compressing a standard placebo blend, consisting of lactose monohydrate (69%), Cellulose powder (15%), Starch 1500 (15%), Magnesium stearate (0.5%) and Aerosil 200 (0.5%), using 20 station tablet press (Cadmach, CU-20) fitted with 10.1 mm plain, round, standard concave tooling. Target core weight of 360 mg/tablet and having a hardness of 9 to 11 kP.

## 4.8 Coating Formulation Systems

Coating formulation systems were prepared using laboratory blender in 90:10 ratio polymers followed by the addition of additives at different ratios (Polymer: diluent ratio; 20:80, 30:70, 40:60, 50:50, 60:40, 70:30, 80:20 and 90:10 ratio respectively) $TiO_2$, FD&C Blue# 2 Lake, Talc and plasticizer (triethyl citrate), as given in Table 4.4.

## Details of Coating Equipment

- **Machine** : O'Hara Labcoat LCM 5
- **Pan Diameter** : 8.5" Fully Perforated
- **Number & type of Spray Gun** : single, Schlick ABC 970
- **Gun Nozzle Dia** : 0.8 mm
- **Baffles Type** : 6 no's of Anti-Slide bars

**Table 4.4: Coating Formulation System.**

| Polymer blend | Name of Ingredients | Polymer blends to Additives ratio | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 20:80 | 30:70 | 40:60 | 50:50 | 60:40 | 70:30 | 80:20 | 90:10 |
| | | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 |
| | | Pigmented | | | | | | Non-pigmented | |
| | | Quantities (%) | | | | | | | |
| PVA: PVA-PEG (90:10) | PVA | 18 | 27 | 36 | 45 | 54 | 63 | 72 | 81 |
| | PVA-PEG | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| | TEC | 5 | 7.5 | 10 | 12.5 | 15 | 17.5 | 10 | 5 |
| | $TiO_2$ | 44 | 36.5 | 29 | 21.5 | 14 | 6.5 | 0 | 0 |
| | FD&C Blue#2 lake | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |
| | Talc | 30 | 25 | 20 | 15 | 10 | 5 | 10 | 5 |
| Total (%) | | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| | | T9 | T10 | T11 | T12 | T13 | T14 | T15 | T16 |
| | | Pigmented | | | | | | Non-pigmented | |
| HPMC 6Cp: PVA-PEG (90:10) | HPMC 6cP | 18 | 27 | 36 | 45 | 54 | 63 | 72 | 81 |
| | PVA-PEG | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| | TEC | 5 | 7.5 | 10 | 12.5 | 15 | 17.5 | 10 | 5 |
| | $TiO_2$ | 44 | 36.5 | 29 | 21.5 | 14 | 6.5 | 0 | 0 |
| | FD&C Blue#2 lake | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |
| | Talc | 30 | 25 | 20 | 15 | 10 | 5 | 10 | 5 |
| Total (%) | | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

## 4.9 Coating of Compressed Tablets

Placebo tablets were coated in an O'Hara (8.5-inch side vented coating pan) with a coating formulation (T1 to T16 as given in Table 4) at 3% weight gain. The coating dispersion was used at 20% solids in purified water. Details of coating process parameters are listed in "Table 4.5(a) and Table 4.5(b)".

**Table 4.5 (a): Coating process parameters**

| | Unit | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 |
|---|---|---|---|---|---|---|---|---|---|
| **Polymer blend** | - | PVA: PVA-PEG (90:10) | | | | | | | |
| **Polymers blend to additive ratio** | - | 20:80 | 30:70 | 40:60 | 50:50 | 60:40 | 70:30 | 80:20 | 90:10 |
| **Weight gain** | % w/g | 3 | | | | | | | |
| **% Solids** | % w/w | 20 | | | | | | | |
| **Solvent** | - | Purified water | | | | | | | |
| **Tablet load** | Kg | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| **Atomization pressure** | Bar | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Pattern air pressure** | Bar | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Pan speed** | Rpm | 10 | 10 | 10 | 10 | 15 | 15 | 15 | 15 |
| **Inlet air temperature** | ˚C | 60-62 | 60-62 | 60-62 | 60-62 | 60-62 | 60-62 | 60-62 | 60-62 |
| **Bed temperature** | ˚C | 44-47 | 44-47 | 44-47 | 44-47 | 44-47 | 44-47 | 44-47 | 44-47 |
| **Gun to bed distance** | Cm | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| **Spray rate** | g/min | 3-4 | 3-4 | 3-4 | 3-4 | 3-4 | 3-4 | 3-4 | 3-4 |

**Table 4.5 (b): Coating process parameters**

| | Unit | T9 | T10 | T11 | T12 | T13 | T14 | T15 | T16 |
|---|---|---|---|---|---|---|---|---|---|
| **Polymer blend** | - | HPMC 6cP: PVA-PEG (90:10) | | | | | | | |
| **Polymers blend to additive ratio** | - | 20:80 | 30:70 | 40:60 | 50:50 | 60:40 | 70:30 | 80:20 | 90:10 |
| **Weight gain** | %w/g | 3 | | | | | | | |
| **% Solids** | %w/w | 20 | | | | | | | |
| **Solvent** | - | Purified water | | | | | | | |
| **Tablet load** | Kg | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 |
| **Atomization pressure** | Bar | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Pattern air pressure** | Bar | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Pan speed** | Rpm | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Inlet air temperature** | ˚C | 60-62 | 60-62 | 60-62 | 60-62 | 60-62 | 60-62 | 60-62 | 60-62 |
| **Bed temperature** | ˚C | 44-47 | 44-47 | 44-47 | 44-47 | 44-47 | 44-47 | 44-47 | 44-47 |
| **Gun to bed distance** | Cm | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| **Spray rate** | g/min | 3-4 | 3-4 | 3-4 | 3-4 | 3-4 | 3-4 | 3-4 | 3-4 |

## 4.10 Film casting and determination of Glass Transition Temperature (Tg)

### 4.10.1 *Polymer blend preparation*

Blends were prepared by mixing 90:10 ratio of polymers using blender followed by addition of plasticizer at 10%, 15% and 20% (concentration with respect to polymers) as given in Table 4.6.

**Table 4.6: Combination of the various ratios of polymers with different plasticizers**

| Polymer Blend | Plasticizer | | | |
|---|---|---|---|---|
| | **PEG 400** (% w/w) | **PEG 3350** (% w/w) | **MCT** (% w/w) | **TEC** (% w/w) |
| **PVA: PVA-PEG (90:10)** | 0 | | | |
| | 10 | 10 | 10 | 10 |
| | 15 | 15 | 15 | 15 |
| | 20 | 20 | 20 | 20 |
| **HPMC 6cP : PVA-PEG (90:10)** | 0 | | | |
| | 10 | 10 | 10 | 10 |
| | 15 | 15 | 15 | 15 |
| | 20 | 20 | 20 | 20 |
| **PVA: HPC (90:10)** | 0 | | | |
| | 10 | 10 | 10 | 10 |
| | 15 | 15 | 15 | 15 |
| | 20 | 20 | 20 | 20 |

Plasticizers were selected based on their solubility in water; PEG is soluble in water, TEC is slightly soluble in water whereas MCT is practically insoluble in water. The polymers selected in this study are water-soluble, having different chemistry, hence, its interaction with plasticizer must be different. Polymer blends with and without plasticizers (powder form, physical mixture) were used for determination of Tg, along with as such polymers (HPMC, PVA, HPC, PVA-PEG) were also used for determination of Tg as a control sample to compare the Tg of polymers versus polymer blends (with and without plasticizers). The powder form of polymer blends used for determination of Tg to confirm the penetration of plasticizer in the polymer chain as in these blends, polymer, and plasticizer are physically mixed. To further confirm these findings, casted films of the polymer blend with plasticizer was prepared for

PVA: PVA-PEG (90:10) + 20% TEC and HPMC 6cp: PVA-PEG (90:10) + 20% TEC, followed by determination of Tg.

### *4.10.2 Film Casting*

The solution of polymer blends was prepared with purified water at 20% solids (PVA: PVA-PEG) and 15% solids (HPMC 6cP: PVA-PEG). Films of these solutions were casted at an approximate thickness of 100 μ on glass plates with the help of a film casting knife.

### *4.10.3 Determination of Glass Transition Temperature (Tg)*

The glass transition temperature of the casted film determined using Differential Scanning Calorimeter (Mettler Toledo, DSC-1, Switzerland) with a sample size ~ 3.5 mg and temperature programming 30°C to 300°C with an increment of 10°C per minute.

## 4.11 Coating of Model Formulations (Aspirin tablets and Ranitidine Hcl tablets)

### 4.11.1 *Aspirin 75 mg tablets compression*

The detailed composition of aspirin core tablets is shown in Table 4.7. Tablet formulation (weighing and compression) was carried under control condition at 25 ± 2°C and 40 ± 5% RH which was maintained by using a dehumidifier (Tropical Nortec, Mumbai) Aspirin was used as supplied (granular form; particle size less than 850 microns). Starch1500®, partially pregelatinized maize starch, Vivapur 101 and stearic acid were passed through a British Standard Specifications (BSS) 36mesh (420μm) screen to break up any aggregates. Blending was carried out using the V-blender attachment of the Karnavati all-purpose unit (HD 410AC, Karnavati Engineering). Aspirin tablets were manufactured by direct compression method at a target weight of 85 mg/tablet using 8 station tablet press (Rimek, Mini Press II, Ahmedabad) fitted with 5 mm plain, round, standard concave tablet tooling.

**Table 4.7: Composition of Aspirin Tablets**

| Material | Supplier | % w/w | mg/tablet |
|---|---|---|---|
| Aspirin IP | Alta Lab | 88.235 | 75.000 |
| Partially pregelatinized starch (Starch 1500) | Colorcon | 3.838 | 3.262 |
| Microcrystalline cellulose (Vivapur 101) | JRS Pharma | 7.677 | 6.525 |
| Stearic acid | Oleotec | 0.250 | 0.213 |

### *4.11.2 Ranitidine Hcl 150 mg tablets compression*

The core formulation of Ranitidine Hydrochloride 150 mg tablet is as shown in Table 4.8. Tablet formulation (weighing and compression) was carried under a control condition at 25± 2°C and 40±5% RH which was maintained by using a dehumidifier (Tropical Nortec, Mumbai). Ranitidine Hydrochloride, StarCap 1500 and Microcrystalline cellulose were passed through an ASTM mesh # 40 sieve, Colloidal silicon dioxide was passed through an ASTM mesh # 80 sieve. All the sieved ingredients were weighed accurately and were blended using a DCM blender (Rimek, DCM-5, Ahmedabad) for 10 minutes at 20 rpm. The blend was lubricated by the addition of magnesium stearate (passed through ASTM mesh # 80 sieve) for 2 minutes at 20 rpm by using a DCM blender.

**Table 4.8: Composition of Ranitidine HCl Tablets**

| Material | Supplier | % w/w | mg/tablet |
|---|---|---|---|
| Ranitidine Hcl (Form-II) | Orchev, India | 54.00 | 167.4* |
| Microcrystalline Cellulose | FMC (Avicel 101) | 30.16 | 93.5 |
| StarCap 1500 | Colorcon | 15.09 | 46.8 |
| Cab-o-sil | Cabot | 0.50 | 1.6 |
| Magnesium stearate | Akcros | 0.25 | 0.8 |

*167.4mg of Ranitidine Hydrochloride is equivalent to 150 mg of Ranitidine

Ranitidine tablets were manufactured by direct compression method at a target weight of 310 mg/tablet using 8 station tablet press (Rimek, Mini Press II) fitted with 9.0 mm plain, round, standard concave tablet tooling. Physical parameters (lubricated blend and core tablets) are depicted in Table 4.9.

**Table 4.9: Physical Properties of Aspirin and Ranitidine Hcl tablets**

| Physical Parameters | Aspirin 75 mg Tablets | Ranitidine Hcl 150 mg Tablets |
|---|---|---|
| **Lubricated blend properties** | | |
| **Tapped Density (g/mL)** | 0.91 | 0.69 |
| **Bulk Density (g/mL)** | 0.61 | 0.43 |
| **LOD (% L)** | 1.56 | 1.97 |
| **Powder Flow** | Very Poor | Very Poor |
| **Hausner's Ratio** | 1.50 | 1.59 |
| **Compressibility Index (%)** | 33.33 | 36.95 |
| **Tablet Physical Parameters** | | |
| **Tablet weight (mg)** | 88 ± 3.1 | 307 ± 2.2 |
| **Tablet width (mm)** | 5.00 ± 0.0 | 9.00 ± 2.2 |
| **Tablet thickness (mm)** | 3.70 ± 0.1 | 4.98 ± 0.1 |
| **Hardness (kPa)** | 4.5±0.9 | 7.36±1.6 |
| **Friability (%)** | 0.64 | 0.06 |
| **LOD (% L)** | 1.87 | 2.62 |

## 4.12 Coating Formulation Systems

Coating formulation systems (T3 and T11) were prepared by mixing in domestic blender at 90:10 ratio polymers followed by addition of additives at $TiO_2$, FD&C Blue# 2 Lake, Talc and plasticizer (TEC), as given in below Table 4.10.

**Table 4.10: Coating Formulation System.**

| Polymer blend | Name of Ingredients | Polymer bend to Additives ratio |
|---|---|---|
| | | 40:60 |
| | | T3 |
| | | Quantities (%) |
| PVA: PVA-PEG (90:10) | PVA | 36 |
| | PVA-PEG | 4 |
| | TEC | 10 |
| | $TiO_2$ | 29 |
| | FD&C Blue#2 lake | 1 |
| | Talc | 20 |
| Total (%) | | 100 |
| | | T11 |
| HPMC 6Cp: PVA-PEG (90:10) | HPMC 6cP | 36 |
| | PVA-PEG | 4 |
| | TEC | 10 |
| | $TiO_2$ | 29 |
| | FD&C Blue#2 lake | 1 |
| | Talc | 20 |
| Total (%) | | 100 |

### 4.12.1 *Coating of Aspirin Tablets and Ranitidine HCl Tablets*

The tablets were coated using O'Hara (8.5-inch side vented coating pan) with a coating formulation (T3 and T11 given in Table 4) at 3% weight gain. The coating dispersion was used at 20% solids in purified water. Details of coating equipment are the same as mentioned in section 4.7. Coating process parameters are listed in Table 4.11.

**Table 4.11: Coating process parameters**

| | **Unit** | **Aspirin 75 mg Tablets** | | **Ranitidine Hcl 150 mg Tablets** | |
|---|---|---|---|---|---|
| **Coating Formulation** | - | T3 | T11 | T3 | T11 |
| **Weight gain** | % w/g | 3 | | | |
| **% Solids** | % w/w | 20 | | | |
| **Solvent** | - | Purified water | | | |
| **Tablet load** | G | 300 | | | |
| **Atomization pressure** | bar | 1.5 | 1.5 | 1.5 | 1.5 |
| **Pattern air pressure** | bar | 1.5 | 1.5 | 1.5 | 1.5 |
| **Pan speed** | rpm | 10-12 | 10-12 | 10-12 | 10-12 |
| **Inlet air temperature** | ˚C | 60-62 | 60-62 | 60-62 | 60-62 |
| **Bed temperature** | ˚C | 44 - 47 | 44 – 47 | 44 – 47 | 44 – 47 |
| **Air Flow** | $m^3$/hr | 90-100 | 90-100 | 90-100 | 90-100 |
| **Gun to bed distance** | Cm | 6 | 6 | 6 | 6 |
| **Spray rate** | g/min | 3-4 | 3-4 | 3-4 | 3-4 |

### *4.12.2 Disintegration Testing of coated tablets*

This test was carried out as per general chapter in Indian Pharmacopoeia as this is not part of specific monograph of Aspirin Tablet and Ranitidine Hydrochloride Tablets. All the tablets (core and coated) were tested for disintegration test using tablet disintegration tester (ED 2L, Electrolab) in purified water at 37 ± 2°C without disk.

### *4.12.3 Assay for Coated Aspirin 75 mg tablets*

Assay test of tablets (core and coated) was determined in accordance with the Indian Pharmacopoeia (IP) monograph for Aspirin tablets by HPLC method (Agilent HPLC 1200 Infinity series). The IP specifies that aspirin tablets contain not less than 95.0 percent and not more than 105.0 percent of the stated amount of aspirin, $C_9H_8O_4$.

### *4.12.4 Assay for Coated Ranitidine Hcl 150 mg tablets*

Assay test of tablets (core and coated) was determined in accordance with the Indian Pharmacopoeia (IP) monograph for Ranitidine tablets by HPLC method (Agilent HPLC 1200 Infinity series). The IP specifies that Ranitidine tablets contain not less than 90.0 percent and not more than 110.0 percent of the stated amount of Ranitidine.

### *4.12.5 Dissolution testing of Aspirin 75 mg tablets*

Dissolution testing of tablets (core and coated tablets) was carried out in accordance with the IP monograph for Aspirin tablets. Drug release was determined using an IP compliant dissolution bath (Electrolab, EDT-08LX,Mumbai) in 500 ml of acetate buffer pH 4.5, Apparatus No 2 (baskets) at 50 rpm for the time period of 45 minutes. Sample aliquots were withdrawn at 10, 20, 30 and 45 minutes, and analysed for aspirin dissolved. The specification for the buffer phase is not less than 70% drug dissolved after 45 minutes.

### *4.12.6 Test for free salicylic acid (Aspirin 75 mg tablets core and coated)*

The test was carried out in accordance with the IP monograph for Aspirin tablets by HPLC method. The IP monograph specifies a limit of not more than 3.0% for coated tablets.

### *4.12.7 Dissolution testing of Ranitidine Hcl 150 mg coated tablets*

Dissolution testing of tablets (core and coated) was carried out in accordance with the IP monograph for Ranitidine tablets. Drug release was determined using an IP monograph compliant dissolution bath (Electrolab, EDT-08LX, Mumbai) in 900 ml of purified water using Apparatus No 1 (paddles) at 50 rpm for a time period of 45 minutes. Sample aliquots were withdrawn at 10, 20, 30 and 45 minutes and analysed for Ranitidine dissolved. Dissolution criteria selected was not less than 80% of the drug should be dissolved after 45 minutes.

## 4.13 Stability Evaluation

Coating formulations T3 and T11 were selected and tested for stability as per following plan using conditions as per ICH Guidelines.

### *4.13.1 Stability of Placebo tablets coated using formulation T3 & T11.*

*Placebo tablets were coated at 3% weight gain and below tests were performed during stability study:*

- **Disintegration test**: Coated tablets were tested for disintegration test as per IP Method, without use of disk.
- **Color difference**: Coated tablets were tested for color difference using Datacolor 600 instrument.
- **Appearance of tablets** was observed by cutting tablets in half and as such tablets (uncut).

### *4.13.2 Stability of Ranitidine Hcl 150 mg coated tablets:*

*Tablets were coated using formulation T3 & T11 to 3% Weight gain and below tests were performed during stability study:*

- **Dissolution testing**: Dissolution testing of coated tablets was carried out in accordance with the IP monograph for Ranitidine tablets. Drug release was determined using an IP compliant dissolution bath (Electrolab, EDT-08LX, Mumbai) in 900ml of purified water using Apparatus No 1 (paddles) at 50 rpm for time of 45 minutes. Sample aliquots were withdrawn at 10, 20, 30 and 45 minutes and analyzed for Ranitidine dissolved. Dissolution criteria selected was not less than 80% drug dissolved after 45 minutes.

- **Assay**: Assay of coated tablets was determined in accordance with the IP monograph for Ranitidine tablets by HPLC method (Agilent HPLC 1200 Infinity series). The IP specifies that Ranitidine tablets contain not less than 90.0 percent and not more than 110.0 percent of the stated amount of Ranitidine.

- **Disintegration test**: Coated tablets were tested for disintegration test as per IP Method, without use of disk.

- **Appearance of tablets** was observed by cutting tablets in half and as such tablets (uncut).

### *4.13.3 Stability of Aspirin 75 mg coated tablets:*

*Tablets were coated using formulation T3 & T11 to 3% weight gain and below tests were performed during stability study:*

- **Dissolution testing**: Dissolution testing of tablets (core and coated tablets) were carried out in accordance with the IP monograph for

Aspirin tablets. Drug release was determined using dissolution bath (Electrolab, EDT-08LX, Mumbai). Below are the dissolution parameters as per IP monograph.

Dissolution criteria selected was not less than 70% of the drug released in 45 min.

- **Assay**: (for core and coated tablets) - determined in accordance with the IP monograph for Aspirin tablets by HPLC method (Agilent HPLC 1200 Infinity series). The IP specifies limits between 95.0 percent and 105.0 percent of the labeled amount of aspirin.

**Table 4.12: Dissolution testing parameters of Aspirin tablets as per IP monograph**

| Parameters | IP Monograph |
|---|---|
| **Apparatus** | No 2 (Basket) |
| **Medium** | 500 ml buffer solution pH 4.5 |
| **Rpm** | 50 |
| **Time** | 45 minutes |

- **Test for free salicylic acid**: This test was carried out in accordance with the IP monograph for Aspirin tablets by HPLC method (Limit: NMT 3.0 %).

- **Disintegration test**: Coated tablets were tested for disintegration test as per IP Method, without use of disk.

## 4.14 Applying Quality by design (QbD) concept to Film coating Formulations.

QbD approach used to determine the optimal coating process conditions and robust process design space for newly developed coating formulation (T3 and T11) containing polymer blends. In this study, the critical quality attributes (CQAs) for the film-coated product were identified as lack of coating defects (measured as % defect level), tablet disintegration time, and tablet appearance (gloss), while the critical process parameters (CPPs) were identified as dispersion spray rate, inlet air temperature, airflow and % solids.

In all coating trials, pan speed was maintained to 11 rpm, atomization and pattern air pressure maintained to 1.5 bar. Minitab software (Minitab Inc., PA, USA) was used to develop a coating trial using four input factors. 15 coating trials using each coating formulation (T3 and T11) were conducted to examine the impact of the CPPs on the CQAs. All coating trials were conducted in an 8.5" fully perforated O'Hara Labcoat (LCM 5) coating pan.

In each trial, 300 g of biconvex placebo tablets (10mm) was coated to a 3% weight gain (WG) with coating formulation T3 and T11. Coated tablets from each trial were visually evaluated for defects and tested for gloss, and disintegration time (DT) in purified water using the following methods:

**Table 4.13: Coating Process parameters for QbD Evaluation**

| Trial no. | Inlet temperature °C | Spray rate (g/min) | % Solid | Airflow (m3/hr) |
|---|---|---|---|---|
| **1** | 63 | 4 | 20 | 90 |
| **2** | 75 | 15 | 15 | 85 |
| **3** | 75 | 15 | 25 | 85 |
| **4** | 75 | 3 | 25 | 200 |
| **5** | 50 | 15 | 15 | 85 |
| **6** | 50 | 3 | 15 | 200 |
| **7** | 63 | 9 | 20 | 142 |
| **8** | 50 | 15 | 15 | 200 |
| **9** | 50 | 3 | 25 | 85 |
| **10** | 50 | 15 | 25 | 85 |
| **11** | 50 | 3 | 15 | 85 |
| **12** | 75 | 3 | 15 | 200 |
| **13** | 75 | 3 | 15 | 85 |
| **14** | 50 | 15 | 25 | 200 |
| **15** | 75 | 3 | 25 | 85 |

### *4.14.1 Defects evaluation for QbD*

At the end of each coating trial, samples were collected and assessed for the percentage of tablets having defects. For the purposes of this evaluation, a defect was defined as any instance where the coating was not continuous, and the tablet core was exposed. The number of defects in a batch was determined by visual observation of 50 tablets and the average result reported.

### *4.14.2 Evaluation using Disintegration Time as a parameter.*

Disintegration time was tested in purified water at 37°C, and the average result was determined from 6 tablets per trial.

### *4.14.3 Evaluation using Gloss as a parameter.*

Twenty film-coated tablets with a 3% weight gain of T3 and T11 from each trial were analysed for gloss using a gloss meter (Tricor, IL, USA). Results were reported in gloss units (GU).

## 4.15 Surface Profilometry

### 4.15.1 Surface Roughness Measurement

The instrument used in this study was a Raman microscopy- WITec alpha 300RA+ (WITec GmbH, UIm, Germany). This instrument incorporates the features of the Raman microscopy system alpha300 R for powerful chemical imaging along with Atomic Force Microscopy (alpha300 A) for high-resolution nanoscale surface characterization.

The Tablet samples were placed on glass slide which was fixed using double sided tape. The full tablet images were acquired using 10x (digital image size 13000 x 13000 μm) while using 20x true surface objective the image size was 4000 x 4000 μm. The surface profilometric images were collected using 20x true surface objective. The image size and position of collection of images were fixed which was 400 x 2000 μm acquired from center of the tablet. The sensor probe can resolve an elevation difference of 3 mm with a step size of 120 nm along the z-axis. ~400 x 2000 μm tablet surface was irradiated and was rasterized at a step size of 5 x 5 μm along the x and y-axis using an integration time of 0.05 s with 1 scan accumulations. Post-scan analysis was conducted using the image statistics dialog as a part of the operating software (WITec Project Plus 5.0) to give the common roughness parameters. In this study, the surface roughness amplitude values, Sa, (arithmetic mean height) were used as a measure of contact surface roughness.

### 4.15.2 Statistical Evaluation of Data.

Statistical analytical tools such boxplot, multi-plot analysis, correlogram analysis, multivariant analysis and one way ANOVA test was used based on data generated with optical profilometer to understand the formulation variables (type and concentration of polymer blends, pigment versus non-pigmented formulation and influence of talc) and its impact on surface roughness.

# *CHAPTER - 5*

# *RESULTS & DISCUSSION*

## 5. Result & Discussion:

### 5.1 Selection of polymers based on preliminary screening

The first criteria for the selection was appropriate concentration of different polymer based on viscosity of individual polymers at different solids levels in aqueous medium. Viscosity was measured using rotational viscometer at various concentration levels (5 to 15%) in aqueous media at room temperature (24±2°C).

**VISCOSITY MEASUREMENTS:**

**Table 5.1: Viscosity and pH data for Hypromellose 3 cps.**

Sample: Methocel 3cps Manufacturer: DuPont

| **Concentration** | **5% w/w** | **7.5% w/w** | **10% w/w** | **12.5% w/w** | **15% w/w** |
|---|---|---|---|---|---|
| Viscosity Day 1 | 12.1 | 23.0 | 49.1 | 98.9 | 183.3 |
| Viscosity Day 5 | 12.0 | 22.1 | 45.5 | 87.9 | 197.7 |
| pH Day 1 | 7.01 | 6.63 | 6.91 | 6.89 | 6.79 |
| pH Day 5 | 6.95 | 6.60 | 6.74 | 6.80 | 6.90 |

**Photo of solutions:**

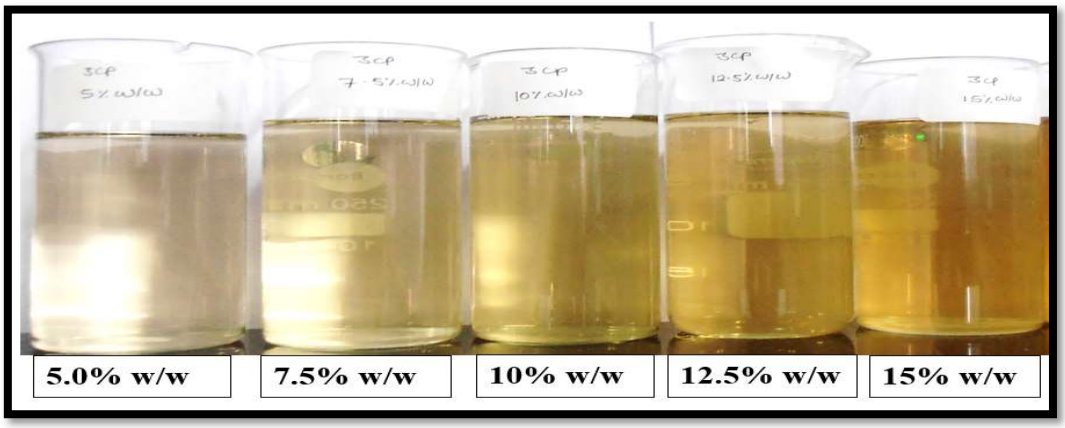


**Table 5.2: Viscosity and pH data for Hypromellose 6 cps.**

Sample: Methocel 6cps Manufacturer: DuPont

| **Concentration** | **5% w/w** | **7.5% w/w** | **10% w/w** | **12.5% w/w** | **15% w/w** |
|---|---|---|---|---|---|
| Viscosity Day 1 | 30.0 | 96.6 | 259.1 | 628.7 | 1,483 |
| Viscosity Day 5 | 26.0 | 86.4 | 229.8 | 554.3 | 1,305 |
| pH Day 1 | 7.40 | 7.07 | 7.30 | 7.42 | 6.75 |
| pH Day 5 | 6.69 | 6.90 | 6.90 | 7.01 | 7.40 |

**Photo of solutions:**

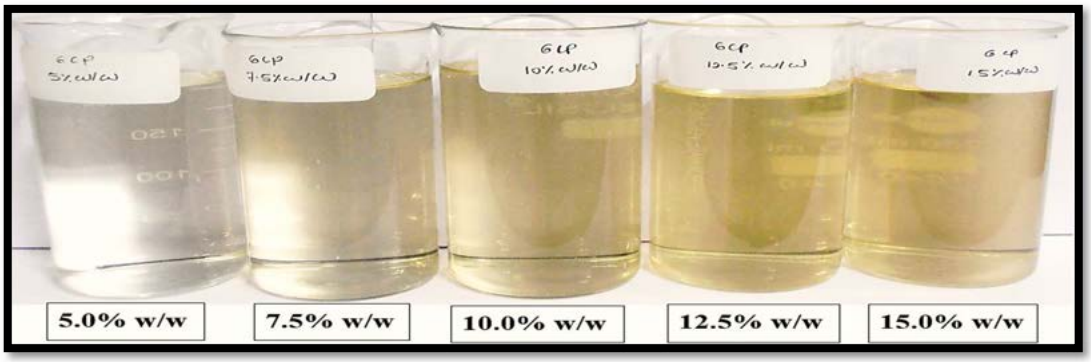


**Table 5.3: Viscosity and pH data for Hypromellose 15 cps.**

Sample: Methocel 15cps Manufacturer: DuPont

| **Concentration** | **2.5% w/w** | **5% w/w** | **7.5% w/w** | **10% w/w** | **12.5% w/w** |
|---|---|---|---|---|---|
| Viscosity Day 1 | 23.9 | 152.1 | 1,073 | 3,010 | 6,579 |
| Viscosity Day 5 | 22.1 | 135.9 | 1,106 | 3,007 | 5,719 |
| pH Day 1 | 6.46 | 6.68 | 7.02 | 6.5 | 7.23 |
| pH Day 5 | 6.82 | 6.74 | 6.23 | 6.15 | 6.38 |

**Photo of solutions:**

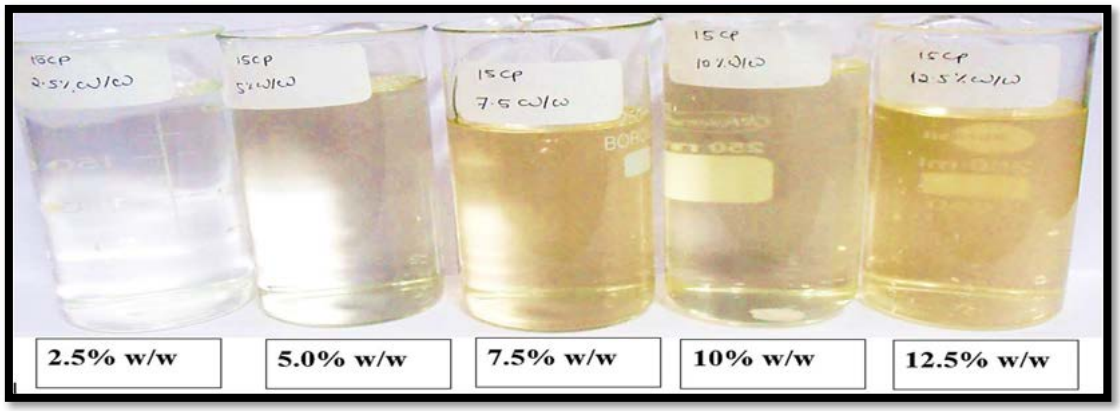


**Table 5.4: Viscosity and pH data for Hydroxypropyl cellulose.**

Sample: Klucel LF Manufacturer: Ashland

| **Concentration** | **5% w/w** | **7.5% w/w** | **10% w/w** | **12.5% w/w** | **15% w/w** |
|---|---|---|---|---|---|
| Viscosity Day 1 | 65.4 | 245.0 | 740.2 | 1,730 | 3,929 |
| Viscosity Day 5 | 64.8 | 241.7 | 739.4 | 1,689 | 3,851 |
| pH Day 1 | 6.64 | 6.81 | 6.81 | 6.87 | 6.88 |
| pH Day 5 | 6.34 | 6.56 | 6.70 | 6.67 | 6.67 |

**Photo of solutions:**

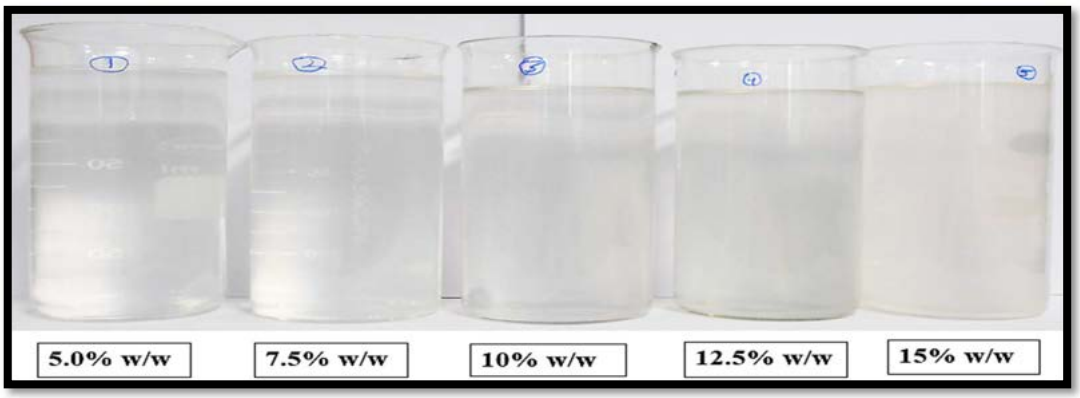


**Table 5.5: Viscosity and pH data for Carboxymethyl Cellulose Sodium.**

Sample: Cellogen HP-8A Manufacturer: Montello

| **Concentration** | **2.5% w/w** | **5% w/w** | **7.5% w/w** | **10% w/w** | **12.5% w/w** |
|---|---|---|---|---|---|
| Viscosity Day 1 | 46.7 | 498.1 | 16,556 | 29,724 | 7,58,000 |
| Viscosity Day 5 | 44.1 | 497.8 | 15,437 | 43,191 | 7,31,000 |
| pH Day 1 | 6.64 | 6.51 | 6.43 | 6.35 | 6.73 |
| pH Day 5 | 6.63 | 6.84 | 6.81 | 6.59 | 6.53 |

**Photo of solutions:**

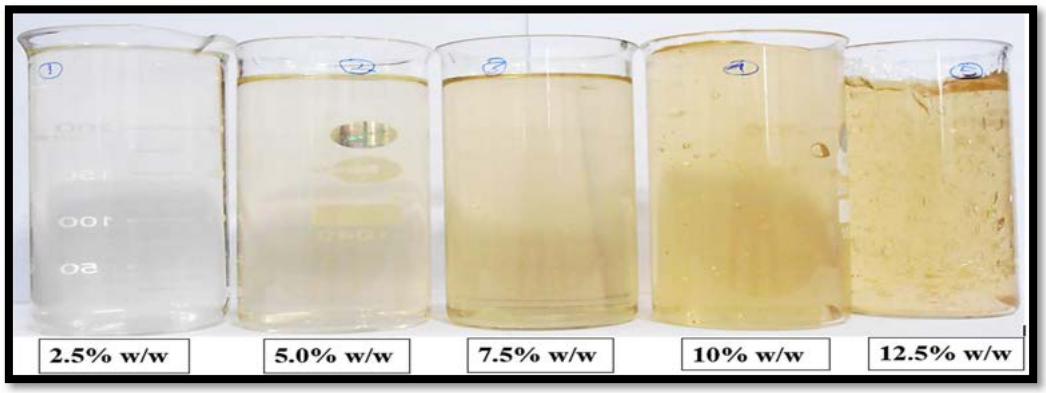


**Table 5.6: Viscosity and pH data for Polyvinyl alcohol (5cp).**

Sample: Poly vinyl alcohol GL-05FS Manufacturer: Nippon Gohsei

| **Concentration** | **5% w/w** | **7.5% w/w** | **10% w/w** | **12.5% w/w** | **15% w/w** |
|---|---|---|---|---|---|
| Viscosity Day 1 | 9.76 | 17.1 | 35.0 | 67.3 | 157.6 |
| Viscosity Day 5 | 9.7 | 17.0 | 33.9 | 67.1 | 156.0 |
| pH Day 1 | 5.50 | 5.49 | 5.47 | 5.49 | 5.50 |
| pH Day 5 | 5.60 | 5.48 | 5.44 | 5.42 | 5.44 |

**Photo of solutions:**

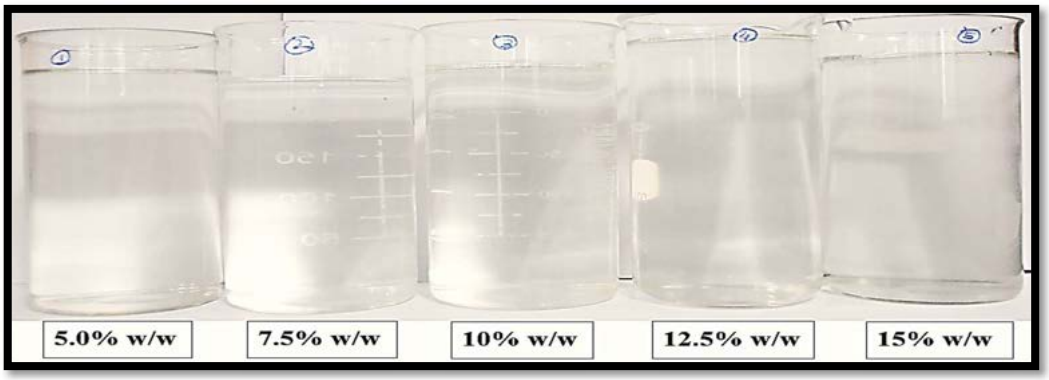
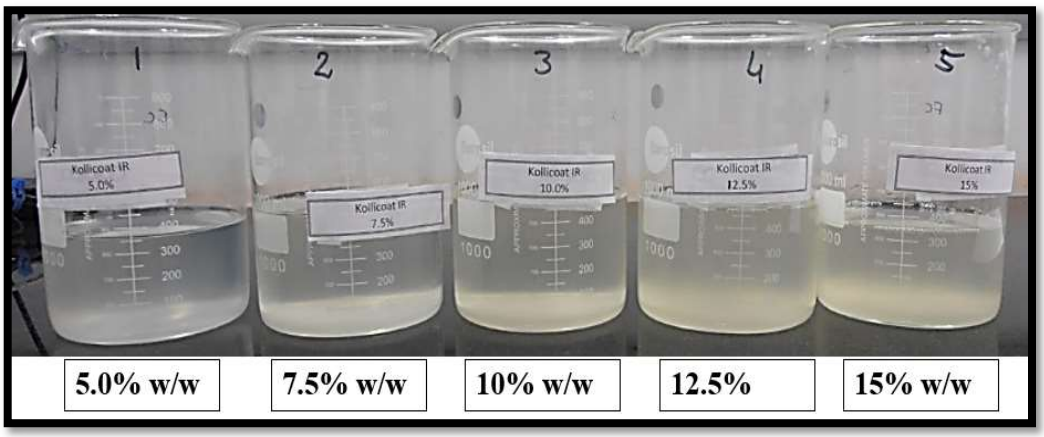


**Table 5.7: Viscosity and pH data for Polyvinyl alcohol and PEG Graft Copolymer.**

Sample: Kollicoat IR Manufacturer: BASF

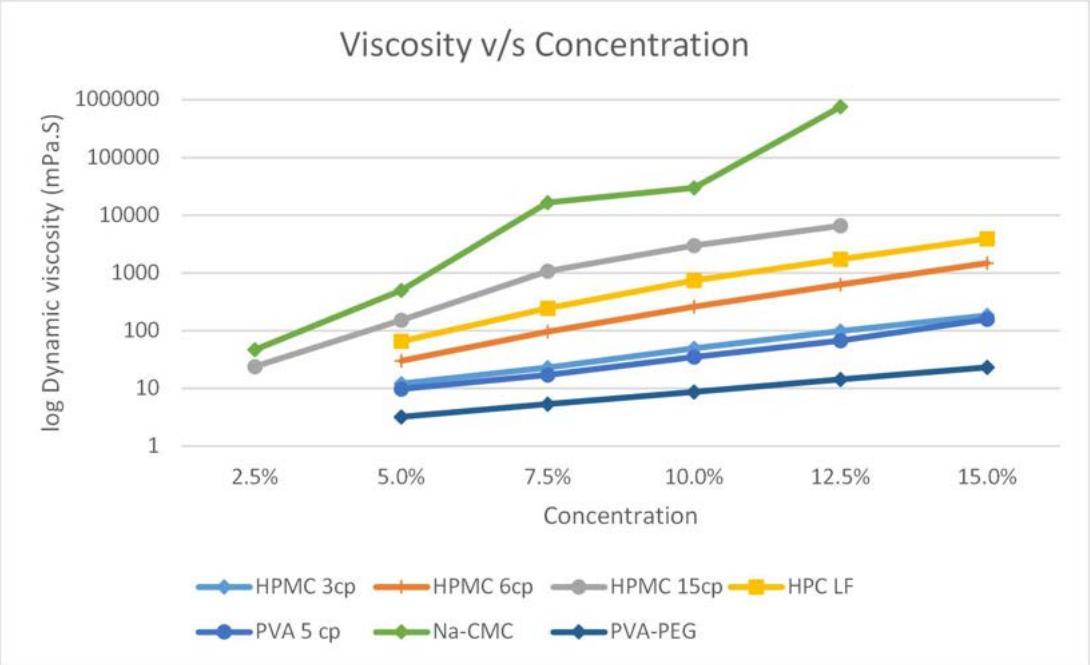
| **Concentration** | **5% w/w** | **7.5% w/w** | **10% w/w** | **12.5% w/w** | **15% w/w** |
|---|---|---|---|---|---|
| Viscosity Day 1 | 3.21 | 5.36 | 8.66 | 14.2 | 23.1 |
| Viscosity Day 5 | 3.02 | 5.30 | 8.54 | 14.1 | 22.9 |
| pH Day 1 | 6.32 | 6.33 | 6.29 | 6.31 | 6.35 |
| pH Day 5 | 6.28 | 6.30 | 6.18 | 6.22 | 6.20 |

**Photo of solutions:**



**Details of viscosity are summarised in below Fig. 5.1.**

**Fig. 5.1: Summary of Viscosity of Water-Soluble Polymers at different concentrations.**




Overall findings of viscosity study indicated that:

- Viscosity increase is directly proportional to concentration of polymer.
- The relationship between concentrations of polymer to viscosity increase is exponential.
- The highest viscosity trend is shown by Carboxymethyl Cellulose Sodium.
- Lowest viscosity plot is seen for PVA-PEG Copolymer.
- Cellulose based polymers are less susceptible to microbial growth in aqueous solutions (shown in Table 5.8 and Table 5.9).

Three low-viscosity grades of Hypromellose 2910 (3cp, 6cp and 15cp) were evaluated and among which, the 15cp grade of Hypromellose data showed that maximum solid levels in solution that meets the less than 500cp criteria was at 5%

level. This indicates that, for a coating solution containing 15cp HPMC will be require to prepare coating solutions at lower solids in aqueous media so that final coating solution will be within the easily sprayable limit of viscosity (less than 500 cP), however, such system will require longer coating time if the intension is to do higher solid deposits on substrate. This will, therefore, expose the core tablets or substrate to tough coating conditions for prolonged period and that in turn may affect the appearance and stability of final finished formulation. Therefore, such type of polymer is not ideal for preparation of coating system.

Hypromellose 6cp shows good balance of viscosity and solids levels (10%w/w Solution showing viscosity below 300cp), hence this presents well to be considered as one of the candidates for further evaluation by blending it with other water-soluble polymers.

Hydroxypropyl cellulose when compared with Hypromellose grades shows that 7.5% w/w solids levels in water giving viscosity values below 250cp. Due to lower solids levels this system is also not considered as ideal option. Lower solids affect the productivity of the system and not preferred for commercial scale operations.

Sodium Carboxymethyl Cellulose solutions in water exhibit exponential changes in viscosity values over narrow range of solids percentage in media and thus yielding to the difficulty in processing of film coating by spray application. This polymer is thus considered not ideal.

PVA and PVA-PEG graft copolymers both are showing very low solution viscosities, below 200cp, even at concentrations of 15% w/w in water. Actually, the PVA-PEG copolymer at 15%w/w aqueous solution is below 50cp. Also, they show good ageing stability after 5-day storage. These two polymers can therefore be considered ideal candidates to meet the expectations of formulators. The low viscosity will help in preparing coating formulations at most optimum solids levels and reduce coating process time.

Based on above experiments and results it is clear that the synthetic polymers like Polyvinyl alcohol (PVA) and PVA-PEG Graft co-polymer has given far more acceptable results at all concentrations ranging from 5% w/w to 15% w/w. This is probably due to no effect of aqueous media, microbial burden or other environmental factors on physical nature of polymer chain. Apart from these two polymers, all others are of natural cellulose backbone and shows behavior totally different from that of PVA and PVA-PEG graft copolymer.

However, these experiments have also prompted us to think of the rationale in combining the synthetic polymers with natural polymers to understand any synergy which will be explored to improve film properties of ready to coat formulations.

Microbiological evaluation of aqueous solutions over period of 5 days storage at ambient temperatures was done to check if the polymers support microbial growth in absence of added preservatives. Based on the results it shows cellulose based polymers do not actively support microbial growth and hence show lower counts. In typical pharmaceutical operations every manufacturer must perform hold time study of coating suspensions to determine maximum time they can use the coating suspension. This data obtained is not static information as number of other factors determine the initial load and subsequent contamination, some of them are equipment cleaning levels, water quality as well as environmental conditions, temperature at which the suspension is kept.

**Table 5.8: Microbial Evaluation of aqueous solutions of various polymers – Day 0.**

| **SAMPLES** polymer-viscosity (%w/w) | **Total Bacterial Count (cfu/ml) Limit – NMT 100 cfu** | | | **Fungal Count (Moulds + Yeast) (cfu/ml) Limit – NMT 10 cfu** | | |
|---|---|---|---|---|---|---|
| | **Plate 1** | **Plate 2** | **Average** | **Plate 1** | **Plate 2** | **Average** |
| Hypromellose 3cp (5%) | 2 | 1 | 2 | <10 | <10 | <10 |
| Hypromellose 3cp (15%) | 0 | 0 | 0 | <10 | <10 | <10 |
| Hypromellose 6cp (5%) | 2 | 2 | 2 | <10 | <10 | <10 |
| Hypromellose 6cp (15%) | 0 | 0 | 0 | <10 | <10 | <10 |
| Hypromellose 15cp (5%) | 0 | 1 | 1 | <10 | <10 | <10 |
| Hypromellose 15cp (12.5%) | 1 | 1 | 1 | <10 | <10 | <10 |
| HPC (5cp) | 24 | 15 | 20 | <10 | <10 | <10 |
| HPC (12.5%) | 17 | 19 | 18 | <10 | <10 | <10 |
| Na-CMC (2.5%) | 59 | 37 | 48 | <10 | <10 | <10 |
| Na-CMC (10%) | 28 | 24 | 26 | <10 | <10 | <10 |
| PVA (5%) | 81 | 54 | 68 | <10 | <10 | <10 |
| PVA (15%} | 22 | 17 | 20 | <10 | <10 | <10 |
| PVA-PEG (5%) | 8 | 12 | 10 | <10 | <10 | <10 |
| PVA-PEG (15%) | 28 | 32 | 30 | <10 | <10 | <10 |

**Table 5.9: Microbial Evaluation of aqueous solutions of various polymers – Day 5.**

| **SAMPLES** polymer-viscosity (%w/w) | **Total Bacterial Count (cfu/ml) Limit – NMT 100 cfu** | | | **Fungal Count (Moulds + Yeast) (cfu/ml) Limit – NMT 10 cfu** | | |
|---|---|---|---|---|---|---|
| | **Plate 1** | **Plate 2** | **Average** | **Plate 1** | **Plate 2** | **Average** |
| Hypromellose 3cp (5%) | 1 | 4 | 3 | <10 | <10 | <10 |
| Hypromellose 3cp (15%) | 0 | 2 | 1 | <10 | <10 | <10 |
| Hypromellose 6cp (5%) | 39 | 43 | 41 | <10 | <10 | <10 |
| Hypromellose 6cp (15%) | 35 | 40 | 38 | <10 | <10 | <10 |
| Hypromellose 15cp (5%) | 1 | 0 | 1 | <10 | <10 | <10 |
| Hypromellose 15cp (12.5%) | 74 | 88 | 81 | <10 | <10 | <10 |
| HPC (5cp) | TNTC | TNTC | TNTC | TNTC | TNTC | TNTC |
| HPC (12.5%) | TNTC | TNTC | TNTC | TNTC | TNTC | TNTC |
| Na-CMC (2.5%) | TNTC | TNTC | TNTC | TNTC | TNTC | TNTC |
| Na-CMC (10%) | TNTC | TNTC | TNTC | TNTC | TNTC | TNTC |
| PVA (5%) | TNTC | TNTC | TNTC | TNTC | TNTC | TNTC |
| PVA (15%} | TNTC | TNTC | TNTC | TNTC | TNTC | TNTC |
| PVA-PEG (5%) | 9 | 11 | 10 | 27 | 53 | 40 |
| PVA-PEG (15%) | 75 | 87 | 81 | 17 | 23 | 20 |

TNTC- Too numerous to count

**FTIR SPECTROSCOPY (**ThermoFischer Nicolet iS10 model)

**Fig. 5.2: Infra-Red Spectrum of Hypromellose**

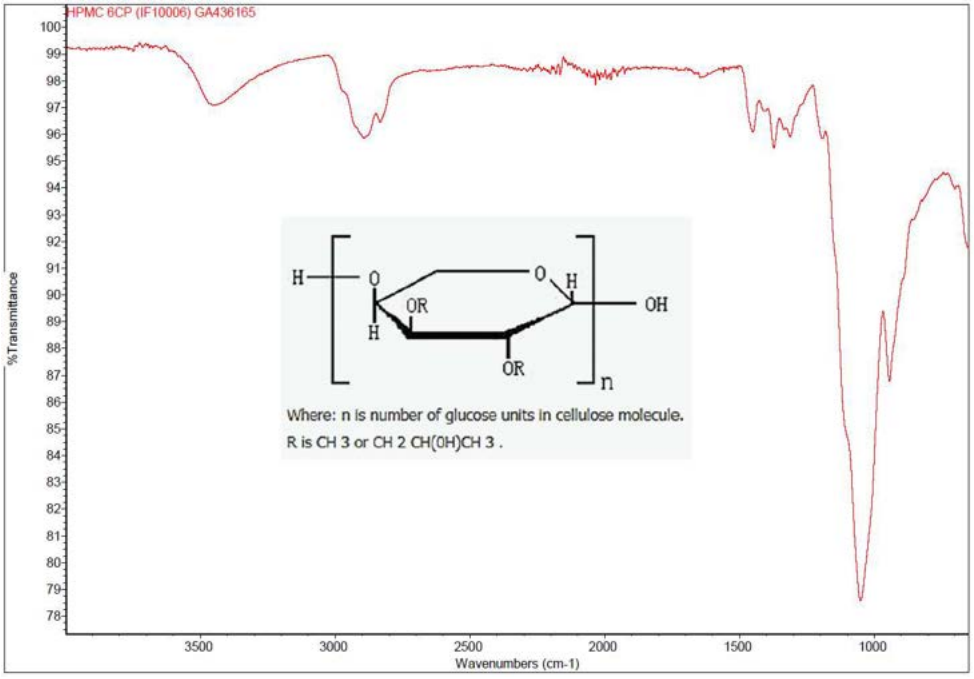



**Fig. 5.3: Infra-Red Spectrum of Hydroxy propyl cellulose.**

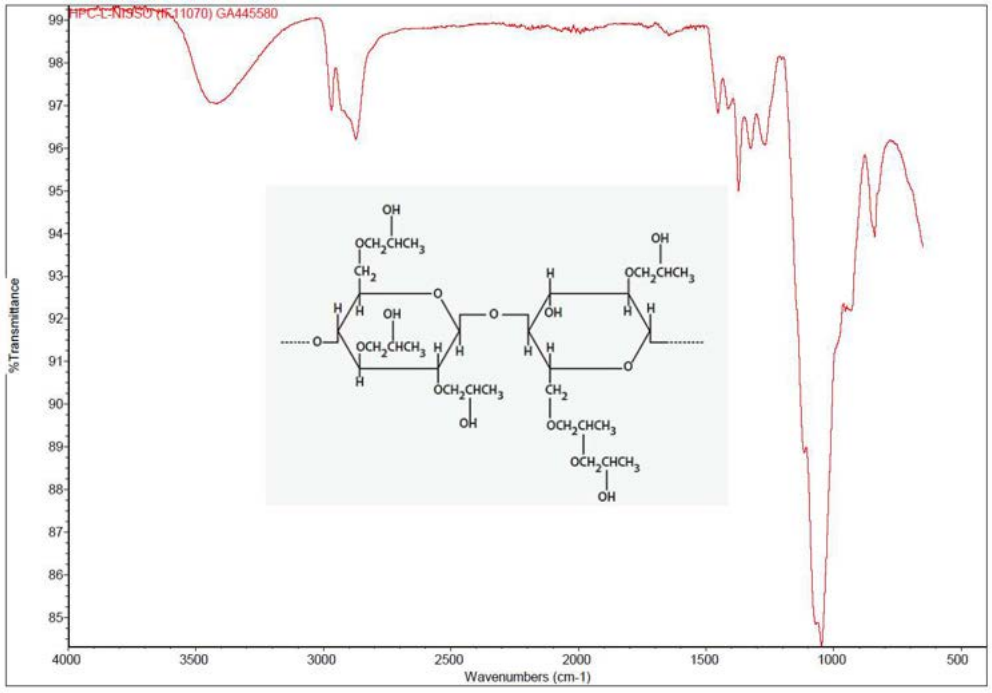


**Fig. 5.4: Infra-Red Spectrum of Carboxymethyl cellulose Sodium.**

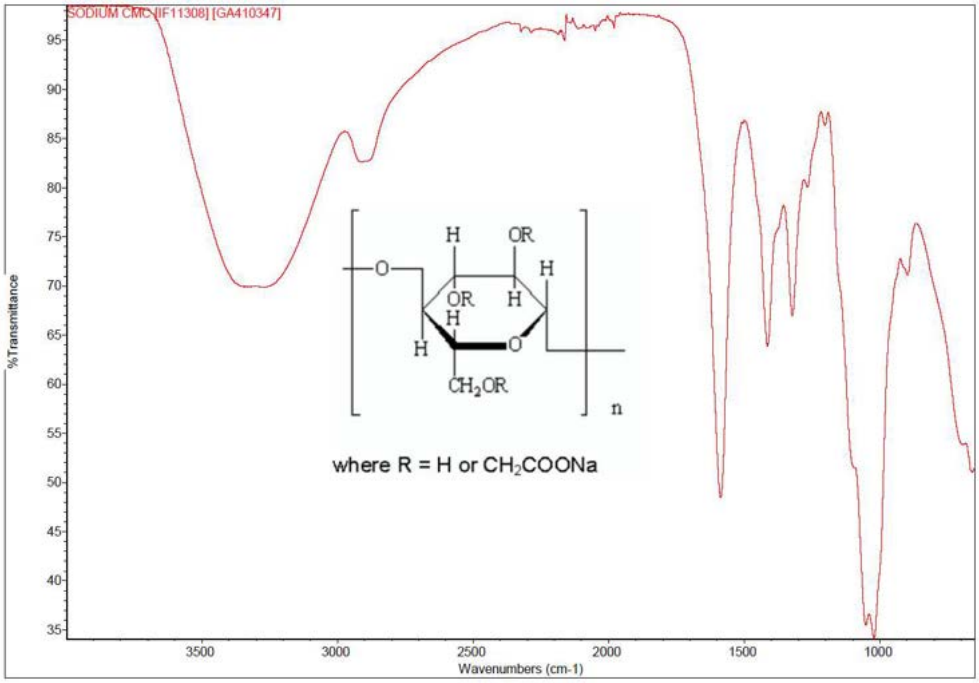



**Fig. 5.5: Infra-Red Spectrum of Poly vinyl alcohol**

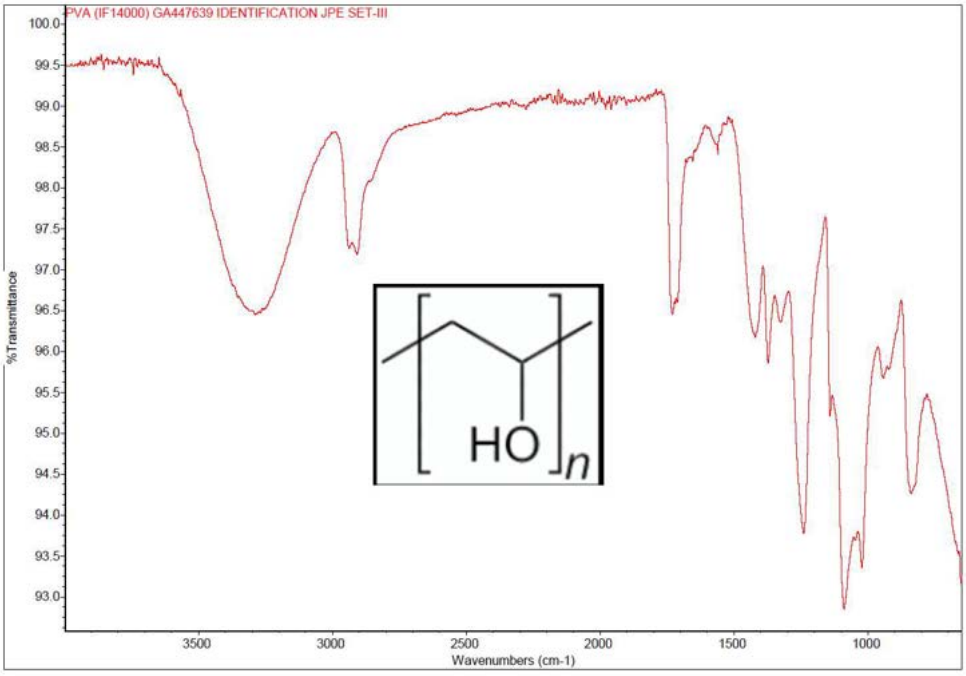
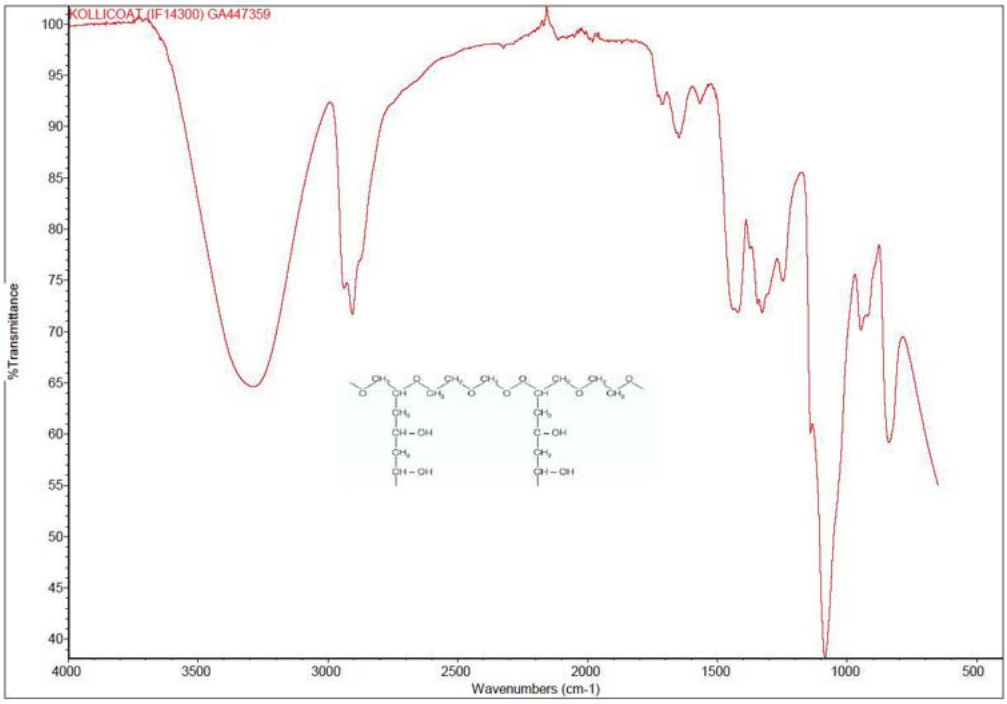


**Fig. 5.6: Infra-Red Spectrum of Poly vinyl alcohol – PEG graft Co-polymer.**




## 5.2 Blend preparation and Evaluation:

### 5.2.1 Determination of Viscosity of polymer blends in aqueous solution

Among all polymer blends, PVA: PVA-PEG Copolymer blend showed lowest viscosity as compared to that of other polymer blends. Solution was prepared at 20% solids levels using PVA: PVA-PEG Copolymer blend as this blend showing very low viscosity at 15% solids, whereas other polymer blends solution was prepared at 15% solids. Also, there is gradual decrease in viscosity for the polymer blend PVA: PVA-PEG Copolymer from the ratio of 90:10 (viscosity: 1360 cP) to 50:50 (Viscosity: 483 cP).

In case of PVA: Sodium CMC polymer blend, lowest viscosity (763 cP) was observed at (90:10 ratio). Other polymer blends HPMC 6cP: PVA-PEG

Copolymer and PVA: HPC showed lowest viscosity at 50: 50 ratios (725 cP) and 90:10 ratios (485 cP) respectively.

Individual polymer viscosity showed lowest viscosity for PVA-PEG Copolymer (155 cP at 20% solids) followed by PVA (1960 cP at 20% solids), HPMC 6cP (2220 cP at 15% solids), HPC (2060 cP at 10% solids) and Sodium CMC (8933 cP at 8% solids). These finding indicates that, the contribution of PVA and PVA-PEG Copolymer resulted in lowering the viscosity of polymer blends in aqueous solution. Additionally, PVA and PVA-PEG copolymers have lower chain mobility when interacting with water molecule and act as surface active agent to reduces the surface tension of aqueous solutions and thus cumulative impact is lowering the viscosity of polymer blend[129-132].

Results of viscosity for individual polymers and polymer blends are depicted in Table 5.10 & 5.11 respectively.

**Table 5.10: Result of viscosity for individual polymer solution in aqueous media.**

| Sr. No. | Blend Details | | Viscosity (cP) | Spindle Number | Spindle Speed (rpm) | Torque (%) |
|---|---|---|---|---|---|---|
| | Polymer | % w/w solids | | | | |
| 1. | PVA-PEG | 20 | 154.6 | S01 | 30.0 | 45.3 |
| 2. | | 25 | 1930 | S01 | 3.0 | 57.9 |
| 3. | | 40 | 32960 | S05 | 5.0 | 41.2 |
| 4. | HPMC 6 cP | 15 | 2220 | S01 | 3.0. | 65.4 |
| 5. | HPC | 10 | 2060 | S01 | 3.0 | 61.8 |
| 6. | | 15 | 6400 | S02 | 3.0 | 48.1 |
| 7. | PVA | 20 | 1960 | S01 | 3.0 | 58.8 |
| 8. | Sodium CMC | 08 | 8933 | S01 | 0.6 | 53.6 |
| 9. | | 15 | 137000 | S07 | 6.0 | 20.7 |

**Table 5.11: Result of viscosity for polymer blends solution in aqueous media.**

| Sr. No. | Blend Details | | | Viscosity (cP) | Spindle Number | Spindle Speed (rpm) | Torque (%) |
|---|---|---|---|---|---|---|---|
| | Polymer blend | % w/w solids | Polymer ratio | | | | |
| 1. | PVA: PVA-PEG | 20 | 90: 10 | 1360 | S01 | 3.0 | 40.8 |
| 2. | | | 80: 20 | 1147 | S01 | 3.0 | 34.4 |
| 3. | | | 70: 30 | 1090 | S01 | 3.0 | 32.7 |
| 4. | | | 60: 40 | 628 | S01 | 6.0 | 37.2 |
| 5. | | | 50: 50 | 483 | S01 | 12.0 | 58.0 |
| 6. | PVA: Sodium CMC | 15 | 90: 10 | 763.3 | S01 | 6.0 | 45.7 |
| 7. | | | 80: 20 | 2647 | S01 | 1.5 | 39.7 |
| 8. | | | 70: 30 | 12383 | S01 | 0.6 | 74.4 |
| 9 | | | 60: 40 | 17640 | S01 | 0.5 | 88.2 |
| 10. | | | 50: 50 | 32800 | S05 | 5.0 | 41.0 |
| 11. | HPMC 6cP: PVA-PEG | 15 | 90: 10 | 2447 | S01 | 3.0 | 73.4 |
| 12. | | | 80: 20 | 1550 | S01 | 3.0 | 46.5 |
| 13. | | | 70: 30 | 1470 | S01 | 3.0 | 44.1 |
| 14. | | | 60: 40 | 1060 | S01 | 3.0 | 31.8 |
| 15. | | | 50: 50 | 725.3 | S01 | 6.0 | 43.3 |
| 16. | PVA: HPC | 15 | 90: 10 | 485 | S01 | 10.0 | 48.3 |
| 17. | | | 80: 20 | 660 | S01 | 10.0 | 66.0 |
| 18. | | | 70: 30 | 720 | S01 | 3.0 | 21.6 |
| 19. | | | 60: 40 | 1387 | S01 | 1.5 | 20.8 |
| 20. | | | 50: 50 | 1607 | S01 | 3.0 | 48.2 |

### 5.2.2 Determination of tensile strength

Tensile strength measurement alone is not useful in predicting the mechanical performance of films, however, higher values of tensile strength are indicative of abrasion resistance[133].

Polymer blend PVA: PVA-PEG Copolymer showed gradual decrease in Young's Modulus from the ratio of 90:10 (1304 MPa) to 50:50 (532 MPa), whereas slight changes in the extension at break value (40 to 60 mm) in all ratios. In case of PVA: Sodium CMC polymer blend, lowest Young's Modulus (858.32 MPa), highest extension at break (23.30 mm) was observed at 90:10 ratios. For HPMC 6cP: PVA-PEG Copolymer polymer blend showed lowest Young's Modulus (1146.64 MPa) with extension at break 1.98 mm at 50: 50 ratios. Highest extension at break (16.22 mm) was observed at 90:10 ratios for PVA: HPC polymer blend with Young's Modulus 1905.15 mPa. Individual polymer showed lowest Young's Modulus for PVA (24.22 MPa) followed by PVA-PEG Copolymer (87.15 MPa), Sodium CMC (2752.88 MPa) and HPMC 6cP (2877.43 MPa). The above findings indicate that the presence of PVA and PVA-PEG Copolymer in polymer blend has great impact on Young's Modulus and extension at break of casted film. PVA has high tensile strength and flexibility[134]. The presence of PVA in polymer blend at higher ratio showed higher Young's Modulus and extension at break (PVA: PVA-PEG Copolymer at 90:10 ratios: 1304.02 MPa Young's Modulus and 59.20 mm Extension at break), (PVA: HPC at 90:10 ratios: 1905.15 MPa Young's Modulus and 16.22 mm Extension at break). However, in case of PVA: Sodium CMC polymer blend, the Young's Modulus increases and Extension at break decreases as the concentration of PVA is decreases in the polymer blend (at 90:10 ratios 858.32 MPa Young's Modulus and 23.30 mm extension at break and at 50:50 ratios Young's modulus increases to 2402.57 MPa and Extension at break decreases to 1.37 mm. Fig. 5.7 and 5.8 represent the relationship between the ratio of polymer blends versus Young's Modulus and Extension at break respectively.

**Fig. 5.7: Graph showing changes in Young's Modulus V/s Ratio of Polymer and Co-polymer used in blend.**

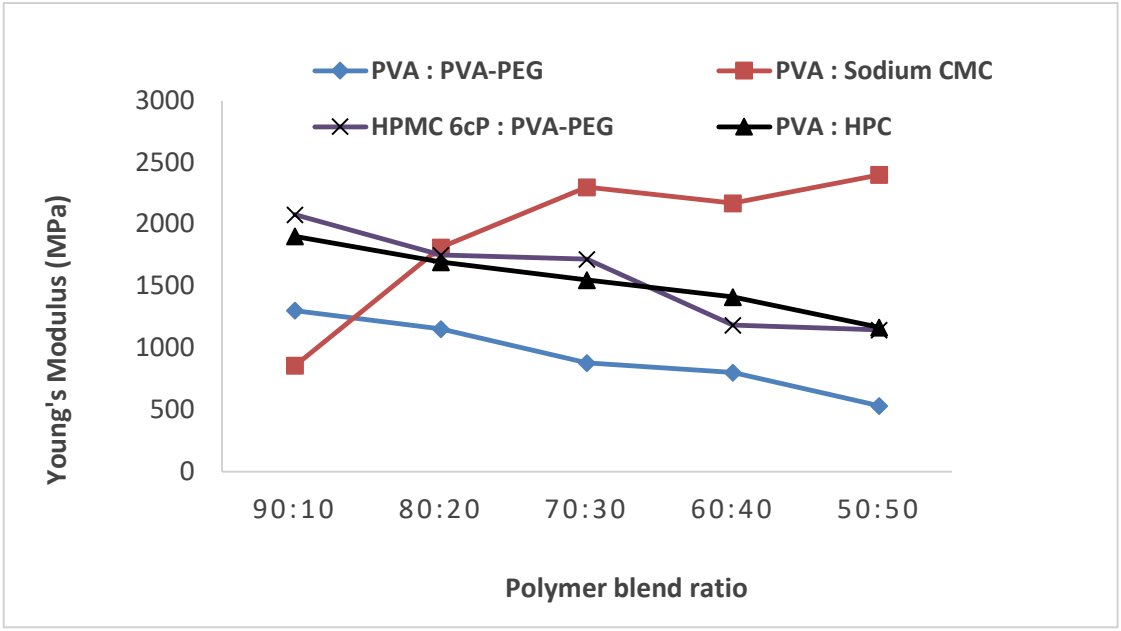
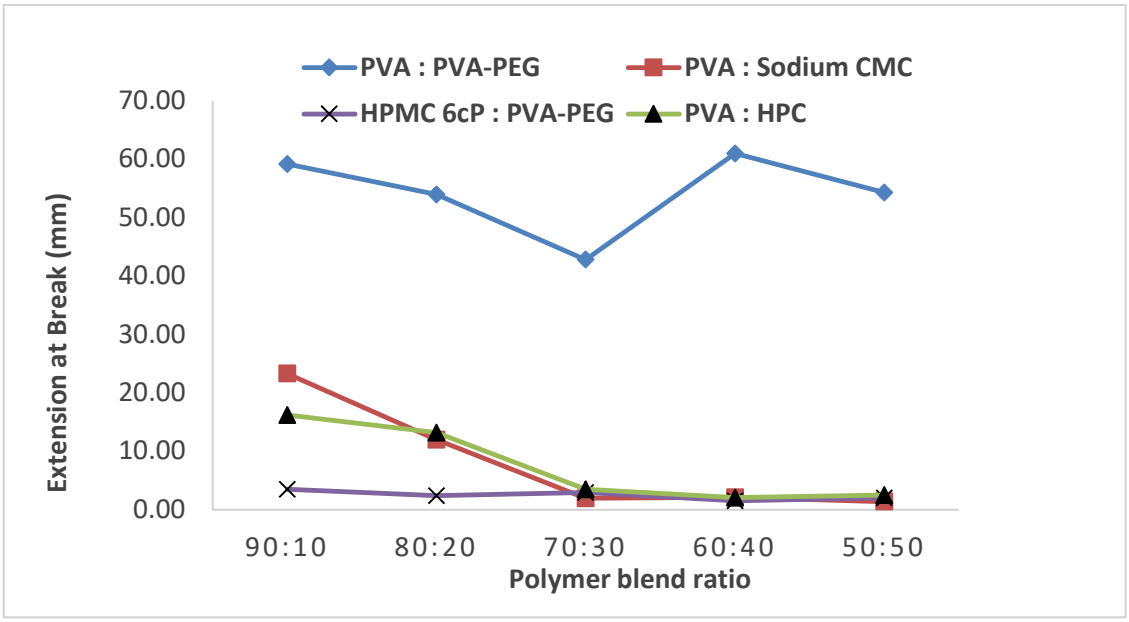



**Fig. 5.8: Graph showing Extension at Break V/s Ratio of Polymer and Co-polymer used in blend.**



Also, presence of PVA-PEG Copolymer in HPMC 6cP, showed slight decrease in Young's Modulus and extension at break as the concentration of PVA increases in the polymer blend. Other tensile testing properties such as Tensile stress at maximum load, Tensile strain at break, Toughness and Energy at Break was also monitored for all polymer blends and respective data represented in Table 5.12 to 5.16.

**Table 5.12: Tensile strength properties of PVA: PVA-PEG Copolymer blends at different ratios.**

| PVA: PVA-PEG combination | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| 90: 10 | 20 | 1304.02 ± 144.52 | 25.79 ± 1.85 | 107.47 ± 16.79 | 0.02002 ± 0.00 | 0.54207 ± 0.15 | 59.20 ± 9.23 |
| 80: 20 | | 1152.87 ± 122.81 | 23.49 ± 1.77 | 97.93 ± 23.21 | 0.02053 ± 0.00 | 0.39712 ± 0.11 | 53.97 ± 12.76 |
| 70: 30 | | 880.53 ± 253.52 | 19.64 ± 3.94 | 77.41 ± 28.27 | 0.02332 ± 0.01 | 0.27854 ± 0.15 | 42.84 ± 15.60 |
| 60: 40 | | 802.56 ± 185.07 | 21.75 ± 2.62 | 110.48 ± 22.22 | 0.02828 ± 0.01 | 0.42261 ± 0.17 | 61.00 ± 12.24 |
| 50: 50 | | 532.65 ± 190.97 | 16.76 ± 2.98 | 98.15 ± 32.06 | 0.03690 ± 0.02 | 0.24669 ± 0.08 | 54.29 ± 17.71 |

**Table 5.13: Tensile strength properties of PVA: Sodium CMC blends at different ratios.**

| PVA: Sodium CMC combination | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| 90: 10 | 15 | 858.32 ± 228.61 | 7.37 ± 2.03 | 41.84 ± 3.49 | 0.00857 ± 0.00 | 0.04005 ± 0.02 | 23.30 ± 1.87 |
| 80: 20 | | 1814.14 ± 473.87 | 21.87 ± 2.81 | 21.56 ± 9.79 | 0.01290 ± 0.00 | 0.09525 ± 0.05 | 11.97 ± 5.45 |
| 70: 30 | | 2302.46 ± 167.51 | 23.86 ± 4.41 | 3.51 ± 1.91 | 0.01043 ± 0.00 | 0.01759 ± 0.01 | 1.94 ± 1.06 |
| 60: 40 | | 2171.68 ± 210.67 | 27.30 ± 1.06 | 3.80 ± 0.79 | 0.01270 ± 0.00 | 0.02007 ± 0.01 | 2.11 ± 0.44 |
| 50: 50 | 10 | 2402.57 ± 109.53 | 30.61 ± 1.58 | 2.48 ± 0.51 | 0.01276 ± 0.00 | 0.01345 ± 0.00 | 1.37 ± 0.28 |

**Table 5.14: Tensile strength properties of HPMC 6cP: PVA-PEG Copolymer blends at different ratios.**

| HPMC 6cP: PVA – PEG combination | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| 90: 10 | 15 | 2079.99 ± 319.05 | 27.18 ± 4.40 | 6.32 ± 1.46 | 0.01308 ± 0.00 | 0.02105 ± 0.01 | 3.48 ± 0.81 |
| 80: 20 | | 1753.74 ± 109.54 | 32.28 ± 2.59 | 4.31 ± 0.91 | 0.01848 ± 0.00 | 0.01779 ± 0.01 | 2.38 ± 0.50 |
| 70: 30 | | 1719.87 ± 111.40 | 35.48 ± 1.59 | 5.33 ± 1.04 | 0.02068 ± 0.00 | 0.02704 ± 0.01 | 2.93 ± 0.57 |
| 60: 40 | | 1185.02 ± 77.51 | 19.00 ± 1.96 | 2.76 ± 0.59 | 0.01605 ± 0.00 | 0.00722 ± 0.00 | 1.52 ± 0.32 |
| 50: 50 | | 1146.64 ± 224.61 | 21.33 ± 5.18 | 3.59 ± 1.17 | 0.01847 ± 0.00 | 0.01221 ± 0.01 | 1.98 ± 0.64 |

**Table 5.15: Tensile strength properties of PVA: HPC blends at different ratios.**

| PVA: HPC combination | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| 90: 10 | 15 | 1905.15 ± 313.40 | 23.77 ± 1.44 | 29.38 ±13.89 | 0.01271 ± 0.00 | 0.16288 ± 0.11 | 16.22 ± 7.67 |
| 80: 20 | | 1696.42 ± 315.29 | 21.19 ± 4.15 | 23.71 ± 22.53 | 0.01266 ± 0.00 | 0.06266 ± 0.04 | 13.15 ± 12.53 |
| 70: 30 | | 1550.31 ± 370.62 | 19.80 ± 5.05 | 6.33 ± 3.25 | 0.01294 ± 0.00 | 0.02760 ± 0.02 | 3.49 ± 1.80 |
| 60: 40 | | 1412.63 ± 277.94 | 15.01 ± 2.52 | 3.72 ± 2.50 | 0.01087 ± 0.00 | 0.00983 ± 0.01 | 2.05 ± 1.37 |
| 50: 50 | | 1168.26 ± 148.45 | 15.40 ± 0.95 | 4.49 ± 1.80 | 0.01335 ± 0.00 | 0.01097 ± 0.01 | 2.48 ± 0.99 |

**Table 5.16: Tensile strength properties of pure polymers (100%)**

| Polymers | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| HPMC 6 cP | 15 | 2877.43 ± 350.99 | 57.47 ± 9.48 | 8.30 ± 2.45 | 0.01882 ± 0.00 | 0.04586 ± 0.02 | 4.59 ± 1.35 |
| Sodium CMC | 8 | 2752.88 ± 793.24 | 50.74 ± 13.68 | 12.96 ± 2.05 | 0.01851 ± 0.00 | 0.09622 ± 0.02 | 7.16 ± 1.13 |
| PVA | 20 | 24.22 ± 9.19 | 16.67 ± 3.06 | 221.77 ± 31.1 | 0.76414 ± 0.24 | 0.94581 ± 0.30 | 125.44 ± 17.7 |
| PVA – PEG | 25 | 87.15 ± 25.46 | 4.23 ± 1.53 | 25.18 ± 16.52 | 0.04832 ± 0.01 | 0.00646 ± 0.00 | 14.64 ± 9.64 |

## 5.3 Evaluation of polymer blends along with plasticizer

It has been reported that the selection of plasticizers in coating formulation has distinct effect on the mechanical properties of the polymeric films in aqueous dispersion[135]. In present study showed that, both type of plasticizer and its concentration have an impact on result of mechanical properties (modulus of elasticity, tensile strength) of casted films. The modulus of elasticity is a measure of the stiffness and rigidity of the film. In case of PEG 400 as a plasticizer, all polymer blend PVA: PVA-PEG Copolymer, HPMC 6cP: PVA-PEG and PVA: HPC at 90:10 ratio showed gradual decrease in Young's Modulus, tensile stress at max load as the concentration of plasticizer increases in the blend, whereas extension at break increases as the concentration of plasticizer increases in polymer blend. In the similar line, there was significant difference in Young's modulus value and extension at break in PEG 400 plasticized polymers blends as compared to that of polymer blends formulated without plasticizer. This increased

extension at break caused by addition of plasticizer was explained by the increase in chain mobility in the presence of plasticizer. Increasing plasticizer content led to an increase in percent elongation and a reduction in strength[136-138]. The above finding indicates that, the introduction of PEG 400 as a plasticizer to the polymer blends promoted increase in viscoelastic behavior of the polymers which resulted in films were more soft and tough. A soft and tough film will possess a low tensile strength but much greater elongation and a higher area under the curve (toughness)[139].

However, opposite scenario was observed with PEG 3350 plasticized films. The polymers blends showed gradual increase in Young's modulus and decrease in extension at break. There was increase in extension at break when the plasticizer was included in the film at the 10% and 15% level. No further increase was found in the extension as the plasticizer increased from 15% to 20%. Similarly, Young's modulus decreases at 10% plasticizer level and further there was slight increase in Young's modulus at 15% plasticizer level. Although, there was significant difference in Young's modulus value and extension at break for the PEG 3350 plasticized polymers bends as compared to that non-plasticized polymer blend. This is mainly due to the plasticizing efficiency of polyethylene glycols decreases with increasing molecular weight. The high-molecular-weight solid PEG additives exhibited phase separation[51]. Similar effects were reported by Aulton with the inclusion of PEGs. Plasticization efficiency increased with decreasing PEG molecular weight and possibly due to the greater number of plasticizer molecule available to interact with the polymer[129]. Rowe reported decrease in elasticity of polymeric film with increasing molecular weight grade of PEG, this was mainly attributed to decrease in mole fraction of the hydroxyl groups[118]. In case of MCT and TEC as a plasticizer polymer blend PVA: PVA-PEG Copolymer, HPMC 6cP: PVA-PEG showed decrease in Young's modulus and increase in extension at break as compared to that of polymer blends formulated without plasticizer. However, in case of polymer blends PVA: HPC showed leaching of plasticizers (for both MCT and TEC) from the polymeric films as well as some

kind of phase separation of polymers were also observed. The leaching was quite rapid from the casted films and increased with increasing level plasticizers.

Although casted films of polymer blends (PVA: HPC; 90:10) with inclusion of plasticizers (MCT and TEC) at 10%, 15% and 20% concentration were successfully formulated, however, stain of liquid plasticizer (MCT and TEC) as well as separation of polymers were visually observed on the surface of casted films indicating that, these plasticizers are not compatible for this polymer blends. Bodmeier and Paeratakul reported the leaching of water-soluble plasticizers (TEC) from polymeric films prepared by casting and drying of plasticized Aquacoat dispersion[140].

Among all plasticizers PEG 400 and PEG 3350 showed significant impact on mechanical properties (modulus of elasticity and tensile strength) of casted films formulated using polymer blends of PVA: PVA-PEG Copolymer and HPMC 6cP: PVA-PEG Copolymer. The tensile strength properties data of different polymer blends with respective concentration of plasticizers are represented Fig. 5.9 and 5.10 represent the relationship between the plasticizer concentration (PEG 400 and PEG 3350) versus Young's Modulus and Extension at break respectively.

**Fig. 5.9: Graph showing effect of Plasticizer Concentration (PEG 400 & PEG 3350) on Young's Modulus.**

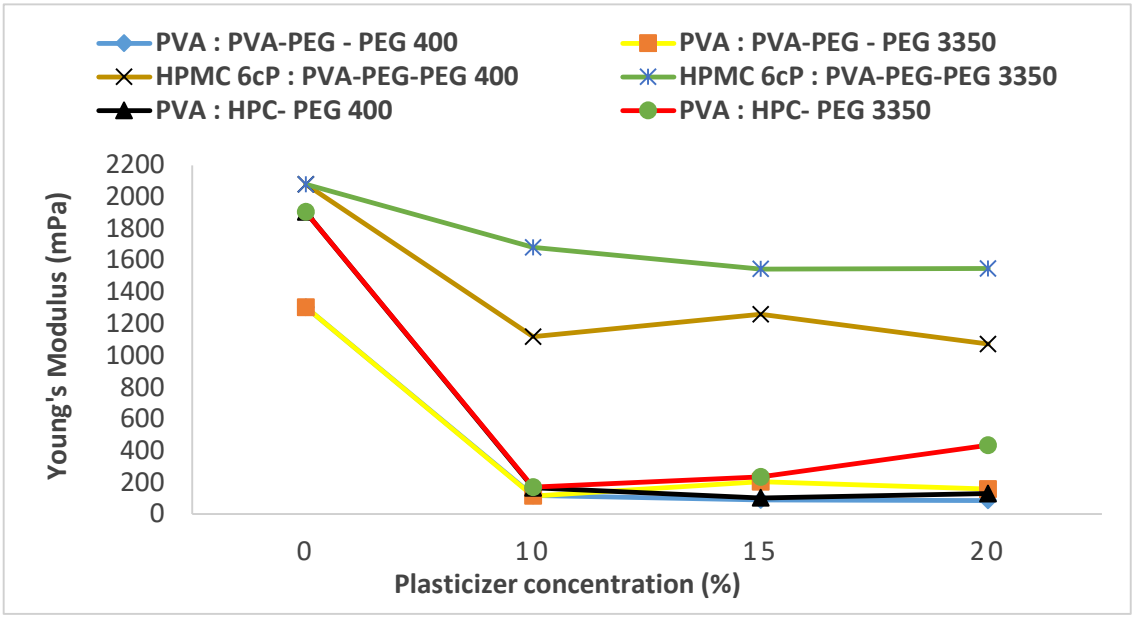



**Fig. 5.10: Graph showing effect of Plasticizer Concentration (PEG 400 & PEG 3350) on Extension at break.**

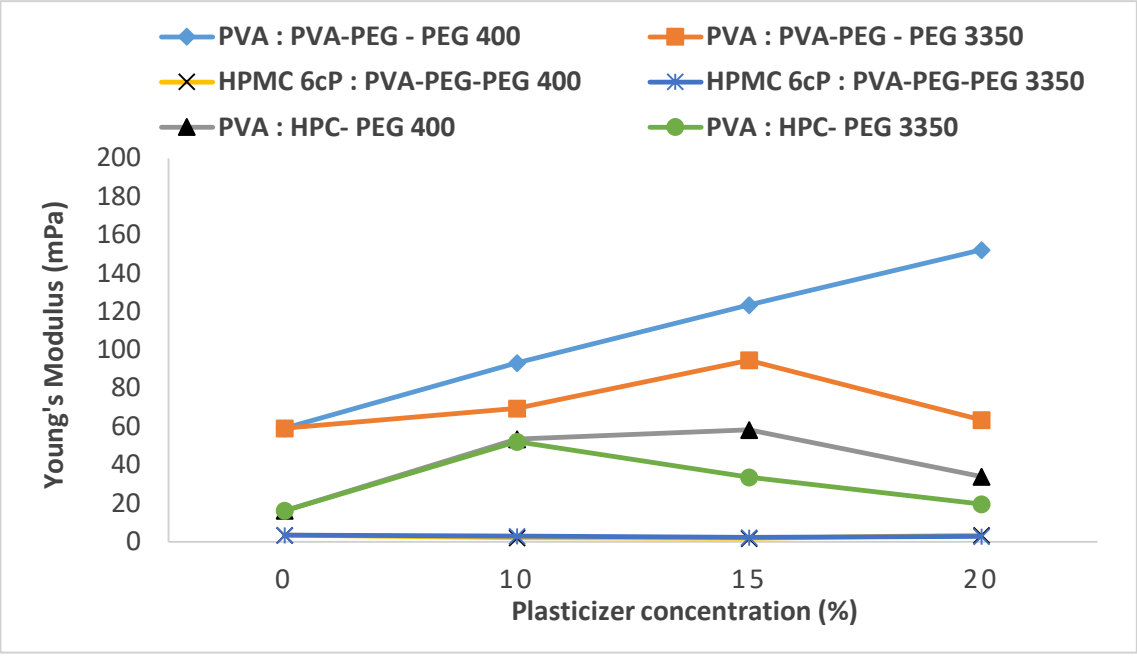


**Table 5.17: Tensile strength properties of PVA: PVA-PEG Copolymer blends with inclusion of different plasticizers**.

| Blend Details | | | **Young's Modulus (MPa)** | **Tensile stress at maximum load (MPa)** | **Tensile strain at break (%)** | **Toughness (Tensile/ modulus)** | **Extension at break (mm)** |
|---|---|---|---|---|---|---|---|
| Polymer blend | Plasticizer concentration (%) | | | | | | |
| PVA: PVA-PEG (90:10); 20% w/w Solids | *0 | | 1304.02 ± 144.52 | 25.79 ± 1.85 | 107.47 ± 16.79 | 0.02 ± 0.00 | 59.20 ± 9.23 |
| | PEG 400 | 10 | 116.99 ± 32.48 | 20.65 ± 6.31 | 1.21 ± 0.28 | 0.18 ± 0.05 | 93.19 ± 21.32 |
| | | 15 | 88.84 ± 16.91 | 16.57 ± 3.41 | 1.61 ± 0.39 | 0.19 ± 0.04 | 123.49 ± 30.26 |
| | | 20 | 85.31 ± 10.68 | 18.02 ± 2.68 | 1.99 ± 0.37 | 0.21 ± 0.04 | 152.18 ± 28.09 |
| | PEG 3350 | 10 | 113.66 ± 25.91 | 13.55 ± 1.69 | 0.92 ± 0.10 | 0.12 ± 0.02 | 69.54 ± 7.86 |
| | | 15 | 203.39 ± 68.86 | 18.89 ± 6.97 | 1.25 ± 0.38 | 0.10 ± 0.04 | 94.68 ± 28.84 |
| | | 20 | 156.56 ± 41.40 | 10.12 ± 0.74 | 0.84 ± 0.16 | 0.07 ± 0.02 | 63.53 ± 12.30 |
| | MCT | 10 | 89.79 ± 28.48 | 14.29 ± 4.92 | 1.20 ± 0.26 | 0.16 ± 0.05 | 91.60 ± 19.59 |
| | | 15 | 152.82 ± 93.05 | 15.78 ± 5.28 | 1.38 ± 0.55 | 0.14 ± 0.09 | 104.93 ± 41.95 |
| | | 20 | 149.17 ± 83.95 | 15.10 ± 2.50 | 1.27 ± 0.37 | 0.14 ± 0.08 | 96.91 ± 28.50 |
| | TEC | 10 | 399.98 ± 153.69 | 13.34 ± 4.05 | 0.61 ± 0.56 | 0.04 ± 0.03 | 46.44 ± 11.79 |
| | | 15 | 168.83 ± 70.80 | 12.67 ± 5.58 | 0.97 ± 0.31 | 0.10 ± 0.07 | 74.27 ± 23.30 |
| | | 20 | 219.19 ± 93.55 | 16.38 ± 2.86 | 1.21 ± 0.28 | 0.09 ± 0.05 | 92.25 ± 21.38 |

*Standard values from literature[171].

**Table 5.18: Tensile strength properties of HPMC 6cP: PVA-PEG Copolymer blends with inclusion of different plasticizers**.

| Blend Details | | | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| Polymer blend | Plasticizer concentration (%) | | | | | | |
| HPMC 6cP: PVA-PEG (90:10); 15% w/w Solids | *0 | | 2079.99 ± 319.05 | 27.18 ± 4.40 | 6.32 ± 1.46 | 0.013 ± 0.00 | 3.48 ± 0.81 |
| | PEG 400 | 10 | 1118.27 ± 174.35 | 14.79 ± 2.33 | 0.027 ± 0.01 | 0.013 ± 0.00 | 2.03 ± 0.39 |
| | | 15 | 1260.53 ± 157.22 | 14.16 ± 2.17 | 0.024 ± 0.00 | 0.011 ± 0.00 | 1.782 ± 0.34 |
| | | 20 | 1072.34 ± 157.77 | 14.19 ± 2.27 | 0.045 ± 0.02 | 0.013 ± 0.00 | 3.371 ± 1.17 |
| | PEG 3350 | 10 | 1681.18 ± 51.32 | 20.83 ± 0.87 | 0.04 ± 0.01 | 0.01 ± 0.00 | 2.93 ± 0.72 |
| | | 15 | 1546.04 ± 123.84 | 18.20 ± 1.36 | 0.03 ± 0.01 | 0.01 ± 0.00 | 2.34 ± 0.56 |
| | | 20 | 1547.67 ± 126.06 | 19.78 ± 2.25 | 0.04 ± 0.01 | 0.01 ± 0.00 | 2.73 ± 0.66 |
| | MCT | 10 | 1334.16 ± 107.78 | 15.61 ± 1.96 | 0.03 ± 0.01 | 0.01 ± 0.00 | 1.90 ± 0.52 |
| | | 15 | 1128.88 ± 180.04 | 14.68 ± 2.97 | 0.02 ± 0.01 | 0.01 ± 0.00 | 1.88 ± 0.58 |
| | | 20 | 964.36 ± 62.54 | 10.75 ± 1.34 | 0.02 ± 0.00 | 0.01 ± 0.00 | 1.22 ± 0.21 |
| | TEC | 10 | 939.67 ± 178.41 | 11.14 ± 2.84 | 0.02 ± 0.01 | 0.01 ± 0.00 | 1.68 ± 0.44 |
| | | 15 | 1028.54 ± 207.33 | 11.97 ± 3.94 | 0.03 ± 0.01 | 0.01 ± 0.00 | 2.061 ± 0.49 |
| | | 20 | 695.13 ± 72.19 | 8.43 ± 1.00 | 0.04 ± 0.01 | 0.01 ± 0.00 | 2.75 ± 0.53 |

*Standard values from literature[171].

**Table 5.19: Tensile strength properties of PVA: HPC blends with inclusion of different plasticizers**.

| Blend Details | | | **Young's Modulus (MPa)** | **Tensile stress at maximum load (MPa)** | **Tensile strain at break (%)** | **Toughness (Tensile/ modulus)** | **Extension at break (mm)** |
|---|---|---|---|---|---|---|---|
| Polymer blend | Plasticizer concentration (%) | | | | | | |
| PVA: HPC (90:10); 15% w/w Solids | *0 | | 1905.15 ± 313.40 | 23.77 ± 1.44 | 29.38 ± 13.89 | 0.0127 ± 0.00 | 16.22 ± 7.67 |
| | PEG 400 | 10 | 164.05 ± 29.87 | 18.01 ± 3.23 | 0.70 ± 0.18 | 0.11 ± 0.02 | 53.48 ± 13.63 |
| | | 15 | 101.73 ± 20.89 | 13.23 ± 4.20 | 0.76 ± 0.24 | 0.13 ± 0.02 | 58.43 ± 18.17 |
| | | 20 | 127.67 ± 48.15 | 11.85 ± 4.09 | 0.44 ± 0.20 | 0.09 ± 0.02 | 34.04 ± 15.61 |
| | PEG 3350 | 10 | 169.85 ± 47.74 | 12.74 ± 3.40 | 0.69 ± 0.19 | 0.08 ± 0.02 | 52.25 ± 14.24 |
| | | 15 | 233.90 ± 46.96 | 9.66 ± 1.46 | 0.44 ± 0.10 | 0.04 ± 0.01 | 33.59 ± 7.56 |
| | | 20 | 433.65 ± 37.87 | 7.62 ± 2.11 | 0.26 ± 0.09 | 0.02 ± 0.01 | 19.61 ± 6.83 |
| | MCT | 10 | Film properties unable to determine due to visual leaching of added plasticizer (MCT and TEC) at all concentration level from the casted films | | | | |
| | | 15 | | | | | |
| | | 20 | | | | | |
| | TEC | 10 | | | | | |
| | | 15 | | | | | |
| | | 20 | | | | | |

*Standard values from literature[171].

The mechanical properties of free films prepared from aqueous dispersion of polymer blends with inclusion of different types of plasticizers (10%, 15% and 20% concentration levels) provide valuable information to predict the best ratio of plasticized polymer blends that can be used in the development of coating formulation. The presence of plasticizers in polymer blends have a significant impact on reduction of modulus of elasticity of polymer. This is most essential for most polymers to reduce the brittle properties and to achieve effective coatings of the pellets or tablets without the formation of cracks and defects. Thus, plasticizers are essential additives for most polymers of pharmaceutical interest. Selection of plasticizer and its concentration play an important role in changing the physical properties of polymer to render it more useful in performing its function as a film-coating material.

## 5.4 Evaluation of polymer blends with plasticizer in the presence of additives

It has been reported that the modulus of elasticity in general practice was found to increase when pigments were added to the polymer systems[70, 132, 141]. Present study showed that, additives at all concentration levels have an impact on result of mechanical properties (modulus of elasticity, tensile strength) of casted films of polymer blends. Although all polymer blends contain similar concentration of plasticizer (PEG 3350 at 25% of total concentration of polymer). All polymer blends showed gradual increase in Young's modulus and decrease in extension at break as the concentration of additives in the casted film increases. The tensile strength properties data of different polymer blends with respective concentration of additives are represented in Table 5.17 to Table 5.19. Among all polymer blends, PVA: PVA-PEG Copolymer (90:10) and PVA: HPC (90:10) showed comparatively higher extension at break as compared to that observed with HPMC: PVA-PEG Copolymer (90:10) at all concentration level of additives. Also, literature survey indicates that, PVA crystallinity was depressed in the presence of the additives[142] which may have further impact on mechanical properties of polymer blends. Casted film of polymer blend HPMC 6CP: PVA-

PEG Copolymer (90:10) and PVA: HPC (90:10) showed harder and brittle at 20:80 ratio of polymers: additives, hence, mechanical properties of this ratio was not determined. However, in case of PVA: PVA-PEG Copolymer (90:10) ratio showed comparatively less brittleness at 20:80 ratio of polymers: additives. Hard and brittle films exhibit a high tensile strength and Young's modulus with little elongation. The presence of brittleness in casted film at high concentration of additives may be due to these insoluble additives (titanium dioxide and talc) acting as stress concentrations, thereby promoting the initiation of cracks in the film and/or the presence of interactions between the additives and the polymer[143]. Ideally these water insoluble additives are defects in the film[125], which enhances film failure and therefore decrease in elongation. Further, this brittleness as well as Young's Modulus of casted film decreases in all polymer blends as the concentration of additives decreases.

The increased Young's modulus may be related to the increased stiffness and brittleness of hybrid composite films by the addition additives in polymer blend. This may be brought about in two ways; first, the mobility of polymer phase may be physically hindered by the presence of the additive particles (this is a hydrodynamic effect). Second, additives-polymer interaction (a reinforcing effect) could stiffen the molecular chains of portions of the polymer matrix at the additives - polymer interface thus reducing segmental mobility. Thus, decrease in extension at break caused by addition of additives can be further explained by the decrease in chain mobility of polymers in the presence of high concentration of additives.

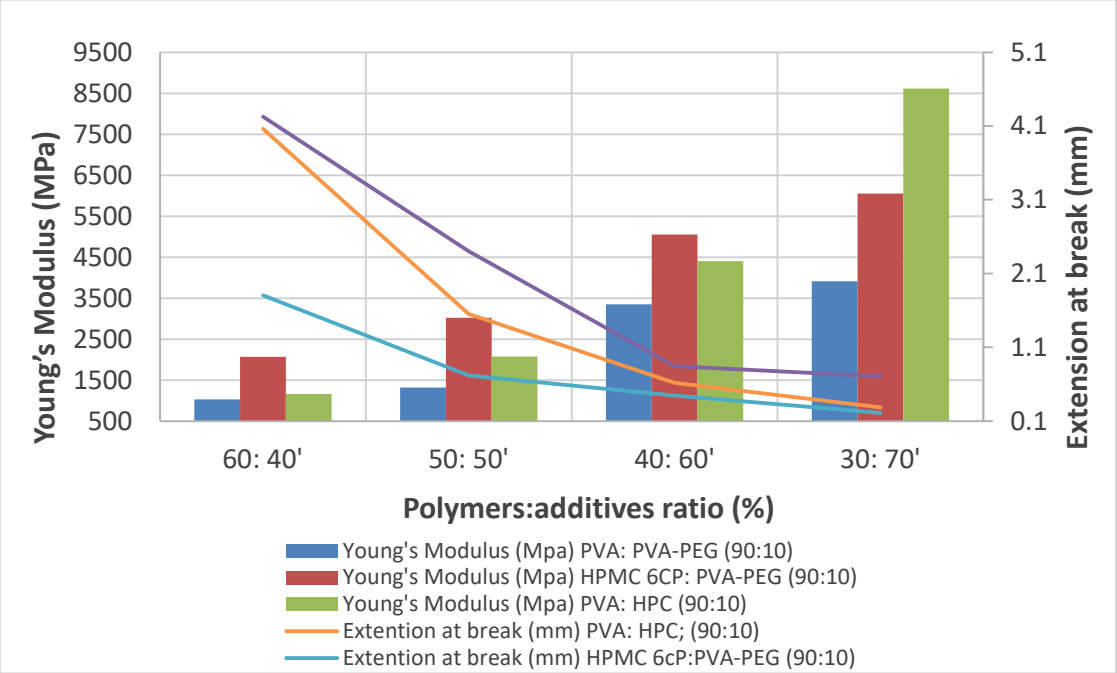
Additives, therefore, reduce intermolecular bonding between polymer molecules and affect the properties of the film (decreasing polymer mobility as well as its elongation). Here elongation has been considered as a measure of the deformation capacity, i.e. the ability to deform under stress, of a film. From the tensile strength data (from Table 5.19 and 5.20), minimum concentration of additives (less than

70%) in polymer blend is recommended, in order to produce continuous film (reduces the brittleness of casted film). Ideally increasing the tensile strength of the coating reduces the risk of cracking and reducing the elastic modulus decreases the potential of occurrence of bridging. Polymers with high additive capacity can be defined as those that can incorporate very high levels of insoluble additives while still retaining their functional characteristics. A more well-defined concept, in this regard, is the CPVC (critical pigment volume concentration)[64,25.144]. According to this theory, below the CPVC, the polymer is able to completely bind and surround the additives particles, forming a dense and continuous film, however, above the CPVC, there is incomplete binding of pigment particles by the polymer, resulting in the formation of voids within the film[145,146]. In present study, continuous film formed with polymer blends having less than 70% of additives. Fig. 5.11 showed graphical presentation of polymers: additives concentration (%) Vs Young's Modulus (mPa) Vs Extension at break (mm).

**Table 5.20: Tensile strength properties of different polymer blends with varying concentration of additives.**

| Blend Details | | | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| Polymer ratio | Polymers: additives ratio | | | | | | |
| PVA: PVA-PEG (90:10) | 20:80 | T1 | 7067.6 ± 1780.66 | 15.697 ± 2.66 | 0.005 ± 0.001 | 0.002 ± 0.0 | 0.355 ± 0.080 |
| | 30:70 | T2 | 3914.7 ± 677.7 | 15.375 ± 2.27 | 0.008 ± 0.003 | 0.003 ± 0.0 | 0.707 ± 0.133 |
| | 40:60 | T3 | 3352.9 ± 946.9 | 10.697 ± 2.90 | 0.011 ± 0.002 | 0.003 ± 0.00 | 0.847 ± 0.140 |
| | 50:50 | T4 | 1316.5 ± 212.7 | 10.962 ± 0.011 | 0.011 ± 0.005 | 0.006 ± 0.00 | 2.402 ± 2.370 |
| | 60:40 | T5 | 1030.8 ± 112.1 | 5.777 ± 0.85 | 0.056 ± 0.016 | 0.005 ± 0.00 | 4.228 ± 1.220 |
| | 100:0 | - | 156.6 ± 41.40 | 10.120 ± 0.74 | 0.840 ± 0.16 | 0.070 ± 0.02 | 63.530 ± 12.30 |
| HPMC 6CP: PVA-PEG (90:10) | 20:80 | T6 | ***Film is brittle, unable to determine film properties*** | | | | |
| | 30:70 | T7 | 6051.3 ± 366.58 | 10.872 ± 1.83 | 0.002 ± 0.001 | 0.002 ± 0.00 | 0.212 ± 0.04 |
| | 40:60 | T8 | 5053.9 ± 440.6 | 14.801 ± 3.33 | 0.005 ± 0.002 | 0.002 ± 0.00 | 0.445 ± 0.17 |
| | 50:50 | T9 | 3018.9 ± 282.7 | 19.134 ± 1.83 | 0.009 ± 0.001 | 0.006 ± 0.00 | 0.719 ± 0.09 |
| | 60:40 | T10 | 2070.8 ± 458.60 | 10.131 ± 1.02 | 0.024 ± 0.006 | 0.005 ± 0.00 | 1.805 ± 0.50 |
| | 100:0 | - | 1547.7 ± 126.06 | 19.780 ± 2.25 | 0.040 ± 0.01 | 0.010 ± 0.00 | 2.730 ± 0.66 |
| PVA: HPC (90:10) | 20:80 | T11 | ***Film is brittle, unable to determine film properties*** | | | | |
| | 30:70 | T12 | 8618.3 ± 735.8 | 14.601 ± 1.78 | 0.003 ± 0.001 | 0.001 ± 0.00 | 0.287 ± 0.07 |
| | 40:60 | T13 | 4402.5 ± 442.7 | 12.141 ± 0.91 | 0.008 ± 0.001 | 0.004 ± 0.00 | 0.618 ± 0.15 |
| | 50:50 | T14 | 2079.6 ± 396.9 | 8.503 ± 1.21 | 0.020 ± 0.006 | 0.004 ± 0.00 | 1.551 ± 0.51 |
| | 60:40 | T15 | 1166.1 ± 94.94 | 6.599 ± 0.67 | 0.054 ± 0.014 | 0.005 ± 0.00 | 4.064 ± 1.09 |
| | 100:0 | - | 433.7± 37.87 | 7.620± 2.11 | 0.260± 0.09 | 0.020± 0.01 | 19.610± 6.83 |

**Fig. 5.11: Graph showing relationship of Polymers: additives concentration (%) to Young's Modulus (mPa) and Extension at break (mm).**




### *5.5 Tablet compression:*

It has been reported that film-coating defects can generally be divided into three groups, depending on the complexity of the resolution[147].

- Defects that can easily be improved by changing one or more of the process conditions (example: air temperature, spray rate). This group includes blistering (wrinkled appearance), chipping (chips and breaks at the edges of tablet), picking (film pull away from the surface when the tablets stick together) and pitting (pits occur in the surface of tablet core without any visible disruption of the film coating).
- Defects that can only be improved by changing a combination of both process condition and film coating formulation. This group includes blooming (dulling of the coating; normally occur after coating if tablets stored at

elevated temperature), blushing (whitish specks or haziness in the film), color variation, mottling (uneven distribution of color within the film coat) and orange peel (roughness, non-glossy film; the appearance of the surface being similar to that of an orange).

- Defects that require a more fundamental approach may also include reformulation of the tablet core in addition to changes in the coating formulation and process conditions. This group includes the defects bridging, cracking/splitting (film crack across the crown of tablet or split around the edges of tablet), peeling/ flaking (film either peeling back or flacking off)- problems associated with high internal stresses within the film coating.

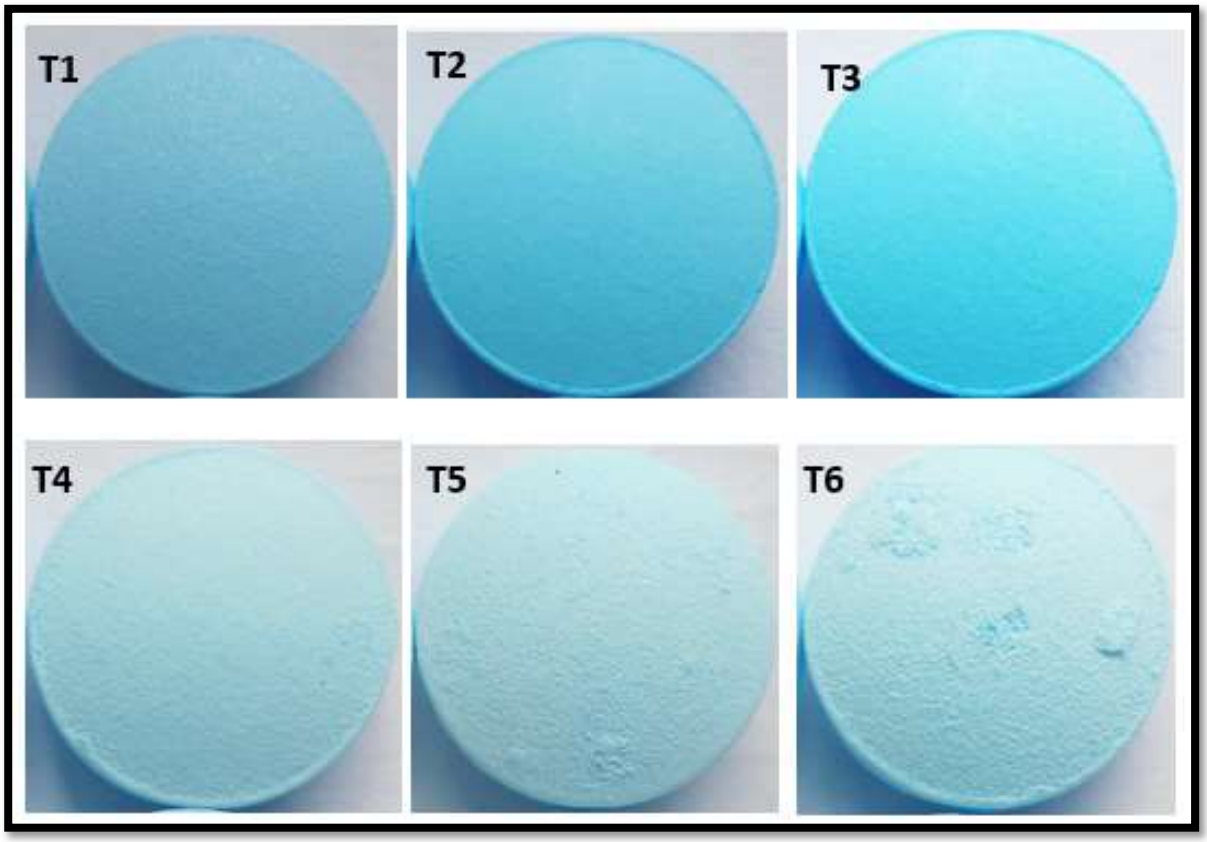
In present work, all coatings were performed using distinct types of coating formulations (T1 to T16) with similar type of coating process parameters and similar type of core tablets, therefore, defects observed on coated tablets are mainly related to either coating formulation and/or coating process parameters.

Literature survey indicated that, other factors which affect the roughness and gloss on film coated tablets include the initial roughness of the tablet core, the film thickness and the concentration and size of any added pigment or fillers[148-150]. It is noticed that increasing particle size of pigments will produce inhomogeneity in coating dispersion which results information of defects in coated film[151].

Pigmented coating formulation (T1, T2 and T3) prepared with polymer blend PVA: PVA-PEG Copolymer (ratio 90:10), coated tablets have smooth surface without any defects. However, in case of other pigmented coating formulation (T4, T5 and T6), coated tablets showed roughness, non-glossy film appearance.

In all pigmented formulation the quantity of FD&C blue #2 is fixed whereas $TiO_2$ quantity is varied, which resulted in shade of coated tablets changes from darker blue to lighter blue as the quantity of $TiO_2$ decreases in the coating formulation (refer to Fig. 5.12).

**Fig. 5.12: Photographs of tablets, coated using pigmented coating formulation (T1 to T6).**




Polymer blend PVA: PVA-PEG Copolymer (ratio 90:10) having maximum proportion of PVA and literature survey showed that PVA has an inherent tackiness[152], therefore, presence of anti-tacking agent (talc) and plasticizer in film coating formulation play a significant role in making smooth and uniform film. The talc is a glidant, and it helps to improve the smoothness of the final coating since the talc facilitates the tumbling of tablets over one another during coating. Coating formulation T1 to T6 contains similar quantity of Plasticizer (TEC) i.e. 15% with respect to quantity of polymer blend. In coating formulation T1, T2 and T3, the quantity of anti-tacking agent (talc) is on higher side as compared to that of present in T4, T5 and T6 whereas the quantity of PVA is on higher side in T4, T5 and T6 as compared to that of present in T1, T2 and T3. This resulted in overall smooth uniform coating happened in T1, T2 and T3 whereas, roughness with

sticking of tablets was observed with T4, T5 and T6. Further, tendency of this roughness on coated tablets is increases in the order of T4<T5<T6 as the quantity of talc decreases and PVA quantity increases respectively. Also, Literature survey indicates that, PVA crystallinity was depressed in the presence of the additives[60] which may have further impact on mechanical properties of coated film.

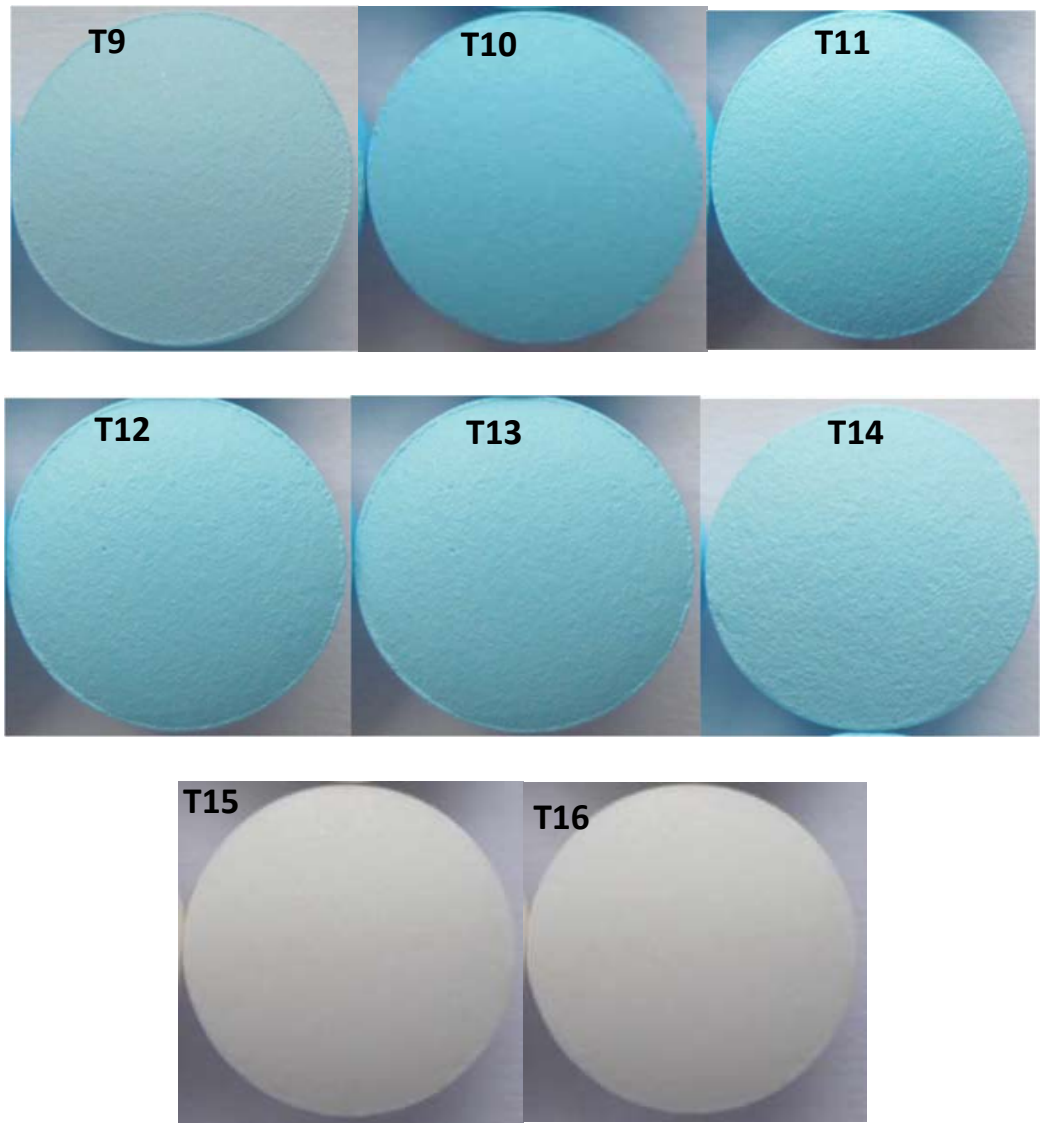
Although, the coating process parameters used in all coatings was similar, coating dispersion at 20% solids having sufficient viscosity to produce relatively small droplets during coating process which resulted in smooth surface on coated tablets (T1 to T3). Whereas, in case of T4, T5 and T6, the quantity of polymer blend in coating formulation is on higher side as compared to that of present in T1, T2 and T3, and having comparatively higher viscosity of coating dispersion at 20% solids and droplets are too viscus to spread when they reach to tablet surface which resulted in rough film formation on tablet surface. High viscosity solutions will result in large droplets with a relatively low surface area for evaporation, whereas for low-viscosity solutions the opposite will occur with the added possibility of spray drying.

Similar argument applicable in case of non-pigmented coating formulation T7 and T8 in which again comparatively polymer content on higher side with lower amount of talc and plasticizer which resulted in coated tablets has very rough surface (refer to Fig. 5.13).

**Fig. 5.13: Photographs of tablets, coated using Non-pigmented coating formulation (T7, T8).**

In case of HPMC based polymer blends (HPMC 6cP: PVA-PEG Copolymer; ratio 90:10) and corresponding their coating formulation systems (T9 to T16) both pigmented and non-pigmented showed coated tablets have overall smooth surface, however, in case of T12 to T16, coated tablets have slight roughness (refer to Fig. 5.14). This slight roughness is mainly due to presence of higher content of polymer blend in these coating formulations which resulted in increase in viscosity of coating dispersion and droplets are too viscus to spread when they reach to tablet surface which resulted in rough film formation on tablet surface. Although in these coating formulations as the quantity of HPMC polymer increases the corresponding quantity of PVA-PEG Copolymer polymer also increases, which have positive impact on minimizing internal stresses created in the coated film as well as reducing the glass transition temperature of the polymers as this coating formulation also contains plasticizer (TEC). Literature survey indicates that, blending of high and low molecular weight grades of a polymer can increase its effective strength and lower the incidence of formation of defects in the coated film[34]. This finding indicates that, the overall physical interaction of HPMC and PVA based polymer blends differs with respect to presence of other additives in coating formulation. HPMC polymer does not have tacking issue like PVA therefore the quantity of talc in coating formulation does not act as an anti-tacking agent, however, here talc has the unique effect of enhancing the ability of films to undergo stress release and hence relieve stress build-up[153]. Although, coating process parameters involves use of higher bed temperature (more than 42˚C), higher atomization air pressure have positive impact to get smaller droplets as well as to avoid sticking tablets during coating process.

**Fig. 5.14: Photographs of tablets, coated using pigmented and non-pigmented coating formulation (T9 to T16).**




Also, in these coating formulation systems (T1 to T16), the lowest amount of plasticizer (5% TEC) present in T8 (PVA: PVA-PEG Copolymer 90:10) and T16 (HPMC: PVA-PEG Copolymer 90:10) coating formulation. However, cross section of tablets coated using T8 coating formulation showed tendency of bridging, film cracking (refer to Fig. 5.15 [T8a]), however, such tendency of bridging, film cracking not observed with tablets coated of T16 coating formulation (refer to Fig. 5.16 [T16a]). Development of internal stress within coated film can contribute the such types of issues. Rowe[47,154] suggested,

magnitude of these stresses can be impacted by both coating process conditions as well as by the nature of the coating formulation employed in a given application. Okhamafe and York[70] suggested that the effect of additives in coating formulations were dependent on the balance between their influence on the internal stress of the film coating and the strength of the film-tablet interface.

Although in both these coatings (T8 and T16) similar coating process used, except, type of polymer blend present in coating system. This indicate that, polymer blend PVA: PVA-PEG Copolymer (90:10) having higher tacking tendency with lower amount of plasticizer in coating system resulted in increase in internal stresses within the film[149,155] causing the coating to pull away from the tablet surface. However, such types of issues are not observed with T1 to T6, as these coating formulations have sufficient amount of both anti-tacking agent (talc) and plasticizer (TEC) except in case of T4 to T6 have roughness issues. This finding indicates that coating formulation should have 20% to 40% concentration of polymer blend (PVA: PVA-PEG Copolymer; 90:10) in-order to get coated tablets with smooth surface without any defects. Further PVA as moisture barrier properties[152,156] so that such types of coating formulation can be utilized for moisture sensitive API, for which higher proportion of polymer (~40%) will have additional advantages.

**Fig. 5.15: Microscopic images of cross section of coated tablets under Leica microscope (12.5X zoom) – Clear formulation with 90% Polymer Blend (PVA: PVA-PEG Copolymer in 90:10 ratio).**

**Fig. 5.16: Microscopic images of cross section of coated tablets under Leica microscope (12.5X zoom) Clear formulation with 90% Polymer Blend (HPMC 6cp: PVA-PEG Copolymer in 90:10 ratio).**


In case of HPMC: PVA-PEG Copolymer (90:10) based coating formulations (T9 to T16), coated tablets have smooth uniform surface, except for T12 to T16 slight roughness observed on coated tablets. These findings indicate that, coating formulation having polymer blend concentration in the range of 20% to 90% can be used for preparation of coating dispersion. Coating formulation T12 to T16 showed slight roughness on coated tablets having polymer concentration 50% to 90% for which it is recommended to reduce the solids level of coating dispersion i.e. to reduce viscosity and thus improve atomization that can reduce roughness on coated tablet[157]. Further in both these type of coating formulations (PVA: PVA-PEG Copolymer 90:10) and (HPMC: PVA-PEG Copolymer 90:10) it is advisable to keep the total polymer concentration more than 20% to provide a better protection and improve the mechanical strength of the substrate. Higher concentration of water insoluble additives in coating formulation acting as stress concentrations, thereby promoting the initiation of cracks in the film[125,143].

## 5.6 *Film casting and determination of glass transition Temperature*

It has been reported that on addition of plasticizer to polymer, plasticizer gets in between the polymer chains and spaces them apart from each other increasing the free volume[158]. This results in polymer chains sliding past each other more easily. As a result, the polymer chains can move around at lower temperatures resulting in decrease in $T_g$ of a polymer[159-162]. $T_g$ value of polymer and polymer blends (powder sample) with and without plasticizers were depicted in below Table 5.18. $T_g$ value of polymer blends in the presence of plasticizers as a casted film were depicted in Table 5.22.

For powder sample of polymer blends in the presence of plasticizer there is no significant reduction in $T_g$ value (Table 5.21), indicating that, no penetration of plasticizer in polymer chain as both polymer and plasticizer are physically mixed. Therefore, DSC of polymer blends with and without plasticizers showed separate $T_g$ / melting value for each polymers and plasticizer (solid). PVA and PVA-PEG Copolymer showed two endothermic peaks. The first broad peak in the range of 78 - 86°C and second peak in the range of 195 to 215°C. As per literature survey, first peak (88.1°C) can be assigned as a thermal effect due to moisture evaporation from sample and may be due to a glass transition with an enthalpy 130.9J/g, whereas second peak due to sharp endothermic melting transition at 209.6°C with an enthalpy 67.4 J/g[163]. The heat required for melting of 100% crystalline PVA, is 138.60J/g[164]. DSC of polymer blend HPMC 6cP: PVA-PEG Copolymer (90:10) showed three $T_g$ values indicating, value close to 81°C (PVA glass phase transition), 200°C (PVA melting phase transition) is for PVA-PEG Copolymer and 178°C is for HPMC 6cP. Peak observed at 200°C is very small, this may be related to small quantity of PVA-PEG Copolymer (10%) present in polymer blend HPMC 6cP: PVA-PEG Copolymer (90:10). Similarly, in case of polymer blends PVA: PVA-PEG Copolymer (90:10) and PVA: HPC (90:10) with and without plasticizer, DSC showed $T_g$ value for PVA (78 - 86°C and 195 to 215°C), however, there is no separate peaks in DSC for PVA and PVA-PEG Copolymer

polymer blend as both the polymers have almost similar chemical structure and individual DSC of these polymers showed $T_g$ at 86°C, 195°C and 81°C, 215°C respectively. Similarly, in case of PVA: HPC polymer blends, DSC thermograms showed one single broad glass transition peak at 83°C and melting transition peak at 195°C. In case of Polymer blend with solid plasticizer showed additional $T_g$ value ~ 60°C is mainly due to PEG 3350.

**Table 5.21: $T_g$ of polymer/ polymer blends (powder sample) with and without plasticizers.**

| **polymer/ polymer blends** | $T_g$ | **polymer/ polymer blends** | $T_g$ |
|---|---|---|---|
| PVA | 86, 196°C | HPMC 6cP: PVA-PEG (90:10) + 20% PEG 3350 | 80, 178, 215°C |
| PVA-PEG | 81, 215°C | HPMC 6cP: PVA-PEG (90:10) + 10% MCT | 76, 175, 215°C |
| PVA: PVA-PEG (90:10) | 81, 195°C | HPMC 6cP: PVA-PEG (90:10) + 15% MCT | 80, 160, 215°C |
| PVA: PVA-PEG (90:10) + 10% PEG 400 | 84, 197°C | HPMC 6cP: PVA-PEG (90:10) + 20% MCT | 81, 160, 200°C |
| PVA: PVA-PEG (90:10) + 15% PEG 400 | 81, 198°C | HPMC 6cP: PVA-PEG (90:10) + 10% TEC | 81, 180, 210°C |
| PVA: PVA-PEG (90:10) + 20% PEG 400 | 84, 197°C | HPMC 6cP: PVA-PEG (90:10) + 15% TEC | 76, 180, 205°C |
| PVA: PVA-PEG (90:10) + 10% PEG 3350 | 54, 80, 195°C | HPMC 6cP: PVA-PEG (90:10) + 20% TEC | 75, 180, 215°C |
| PVA: PVA-PEG (90:10) + 15% PEG 3350 | 56, 84, 197°C | HPC | 79°C |
| PVA: PVA-PEG (90:10) + 20% PEG 3350 | 56, 87, 196°C | PVA: HPC (90:10) | 83, 195°C |
| PVA: PVA-PEG (90:10) + 10% MCT | 79, 197°C | PVA: HPC (90:10) + 10% PEG 400 | 86, 197°C |
| PVA: PVA-PEG (90:10) + 15% MCT | 84, 198°C | PVA: HPC (90:10) + 15% PEG 400 | 83, 195°C |
| PVA: PVA-PEG (90:10) + 20% MCT | 81, 198°C | PVA: HPC (90:10) + 20% PEG 400 | 86, 199°C |
| PVA: PVA-PEG (90:10) + 10% TEC | 80, 194°C | PVA: HPC (90:10) + 10% PEG 3350 | 57, 82, 195°C |
| PVA: PVA-PEG (90:10) + 15% TEC | 78, 194°C | PVA: HPC (90:10) + 15% PEG 3350 | 57, 82, 195°C |
| PVA: PVA-PEG (90:10) + 20% TEC | 80, 193°C | PVA: HPC (90:10) + 20% PEG 3350 | 56, 82, 195°C |
| HPMC 6cP | 178°C | PVA: HPC (90:10) + 10% MCT | 81, 195°C |
| HPMC 6cP: PVA-PEG (90:10) | 81, 178, 210°C | PVA: HPC (90:10) + 15% MCT | 78, 195°C |
| HPMC 6cP: PVA-PEG (90:10) + 10% PEG 400 | 82, 165, 215°C | PVA: HPC (90:10) + 20% MCT | 80, 198°C |
| HPMC 6cP: PVA-PEG (90:10) + 15% PEG 400 | 76, 170, 207°C | PVA: HPC (90:10) + 10% TEC | 83, 197°C |
| HPMC 6cP: PVA-PEG (90:10) + 20% PEG 400 | 76, 205°C | PVA: HPC (90:10) + 15% TEC | 81, 195°C |
| HPMC 6cP: PVA-PEG (90:10) + 10% PEG 3350 | 80, 180, 210°C | PVA: HPC (90:10) + 20% TEC | 78, 195°C |
| HPMC 6cP: PVA-PEG (90:10) + 15% PEG 3350 | 79, 180, 215°C | PEG 3350 | 60°C |

**Table 5.22: $T_g$ of polymer blends (casted film) with plasticizer.**

| **Polymer blends** | $T_g$ |
|---|---|
| PVA: PVA-PEG (90:10) + 20% TEC | 85, 198°C |
| HPMC 6cP: PVA-PEG (90:10) + 20% TEC | 86, 130, 198°C |

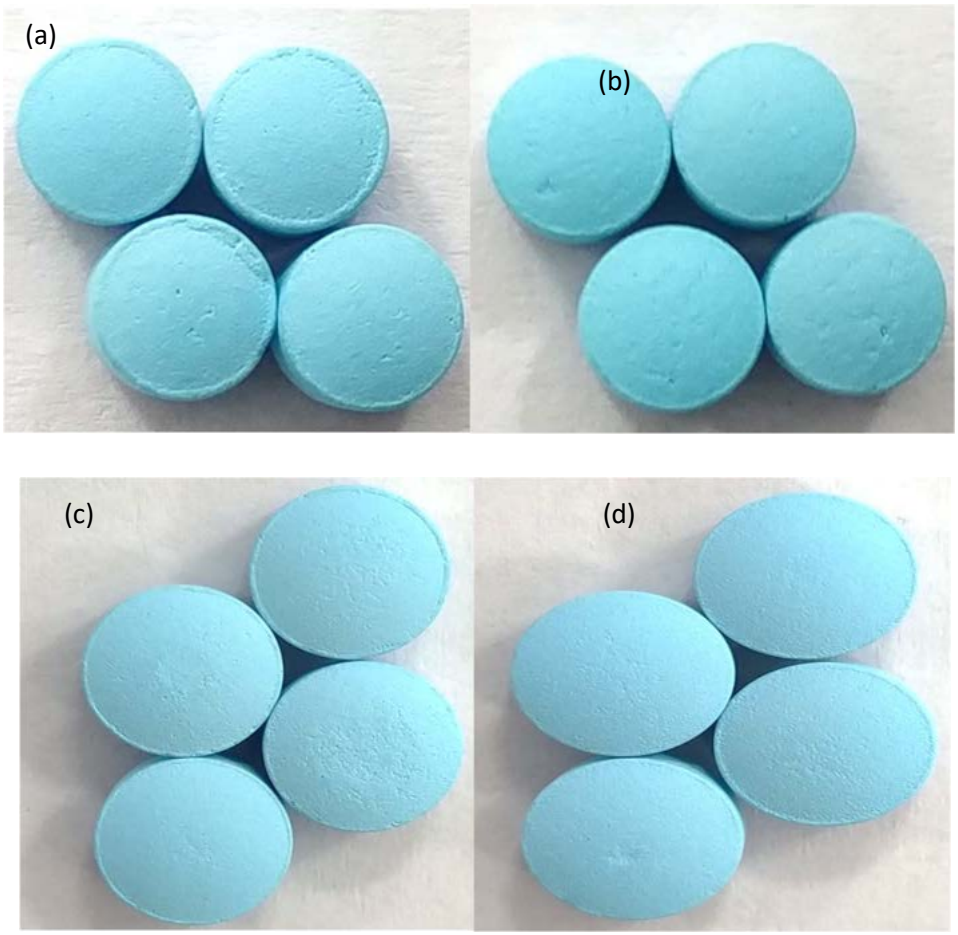
Above findings indicate that, both "PVA and PVA-PEG Copolymer" and "PVA and HPC" have good miscibility in their blends at 90:10 ratios behaves like a homopolymer and support for single-phase behavior as observed through DSC thermograms. Although PVA and PVA-PEG Copolymer have a similarity in their chemical structure (-[-$CH_2$-CHOH-]$_n$-) which favors formation of single-phase DSC thermograms. However, in case of polymer blend "PVA and HPC" may have morphological and micro-structural changes occurred in the polymer matrix indicating hydroxyl ions of HPC are coordinated through hydrogen bonds with the hydroxyl groups in PVA[165].

In case of casted films of PVA: PVA-PEG Copolymer (90:10) with 20% TEC, DSC thermograms showed there is no significant reduction in both the phases of transition (glass transition phase and melting transition phase) of PVA, this may be due to both polymer and plasticizer have close $T_g$ value 85°C and 74.4°C which makes analysis a little challenging. Whereas, in case of polymer blend HPMC 6cP: PVA-PEG Copolymer (90:10) + 20% TEC, there is significant reduction in $T_g$ of HPMC polymer, however, other polymer presents in this blend i.e. PVA-PEG Copolymer have no reduction in $T_g$, which also having $T_g$ close to plasticizer (TEC). Above finding indicates that, in casted film, TEC have an ability to penetrate the HPMC polymeric chain as a result, the polymer chain can move around at lower temperatures resulting in decrease in $T_g$ of HPMC. HPMC 6 cP and PVA-PEG Copolymer polymers do not have complete miscibility in casted films which may be due to difference in their molecular weights (21kDa for HPMC 6 cP and 45kDa for PVA-PEG Copolymer[165-166]), they exhibit phase separation at micro level and their aggregation into small domains dispersed in the polymer matrix. This phase separated domains will have a specific effect on the mechanical properties of the casted films so prepared but will have little effect on their glass transition temperature. Literature survey indicates that, blending of high and low molecular weight grades of a polymer can increase its effective strength and lower the incidence of formation of defects in the coated film[132].

### *5.7 Coating of API Formulations (Aspirin tablets and Ranitidine HCl tablets)*

Aspirin and ranitidine tablets separately coated using Formulation T3 and T11 with aqueous dispersion at 20% solids. Both the coated tablets had smooth uniform surface without formation of defects. Although, different types of polymer blends were used in coating formulation T3 and T11 (PVA: PVA-PEG Copolymer and HPMC 6cp: PVA-PEG Copolymer respectively), still coated tablets have similar kind of physical appearance (refer to Fig. 5.17).

**Fig. 5.17**: **Photographs of coated Aspirin tablets and Ranitidine tablets.**




(a) and (b): Aspirin tablets coated with T3 and T11 respectively

(c) and (d): ranitidine tablets coated with T3 and T11 respectively

The coating process parameters used in all coatings was similar, coating dispersion was prepared at 20% solids having enough viscosity to produce

relatively small droplets during coating process which resulted in smooth surface on coated tablets and no color variability in tablet to tablet. In all coatings, coating process parameters involves use of higher bed temperature (more than 42°C), higher atomization air pressure (~ 1.5 bar) which have positive impact to get smaller droplets as well as to avoid sticking tablets during coating process.

For pharmaceutical application point of view, good adhesion between a polymer and the surface of a core is desirable to produce defects free tablet coating. Two important forces that influence adhesion are the strength of interfacial bonds and the internal stress within the film[70]. Excipients used in the substrate can influence the extent of interfacial bonding between the polymeric film and the solid. Type of polymer, additives used in the coating formulation, including solvent system, plasticizer, pigments and coating process parameters, influence internal stress and thus alter polymer adhesion. Considering all these factors, said coating formulation system (T3 and T11) prepared using polymer blends were successfully applied on aspirin tablets and ranitidine tablets with good adhesion to the surface of core, which resulted in tablets with elegant appearance and excellent surface smoothness.

Coated tablets were tested for disintegration test (DT), Assay and dissolution. In case of Aspirin tablets additional test of Free Salicylic acid (FSA) was conducted to confirm impurities generated during coating process. Result of tablets testing are depicted in below Tablet 5.23 to Table 5.27.

**Table 5.23: Disintegration test result of Aspirin tablets (n=6), Ranitidine tablets (n=6).**

| Aspirin Tablets | DT [a] | Ranitidine tablets | DT [a] |
|---|---|---|---|
| Core tablets | 1-2 minutes | Core tablets | 39-44 seconds |
| Tablets coated with T3 | 1-3 minutes | Tablets coated with T3 | 1-3 minutes |
| Tablets coated with T11 | 2-3 minutes | Tablets coated with T11 | 2-3 minutes |

***[a] DT limit: Not more than 30 minutes[167]***

**Table 5.24: Assay result of Aspirin tablets (n=20), Ranitidine tablets (n=10).**

| Aspirin Tablets | Assay [b] (%) | Ranitidine tablets | Assay [b] (%) |
|---|---|---|---|
| Core tablets | 102.2 ± 0.68 | Core tablets | 103.2 ± 0.26 |
| Tablets coated with T3 | 102.8 ± 0.83 | Tablets coated with T3 | 102.9 ± 0.33 |
| Tablets coated with T11 | 105.1 ± 0.48 | Tablets coated with T11 | 101.4 ± 1.25 |

***[b] Assay limit: 90 to 110 % of labelled amount of aspirin[168], ranitidine[169].***

**Table 5.25**: **Dissolution result of Aspirin tablets (n=6).**

| Time (min.) | % Drug Release (Core tablets) | Drug Release [c] % (Tablets coated with T3) | Drug Release [c] % (Tablets coated with T11) |
|---|---|---|---|
| **10** | 70.2(54.0-85.9) ±12.9 | 44.3 (31.4 - 53.2) ± 8.09 | 40.5 (19.4 - 53.3) ± 11.82 |
| **20** | 92.3 (84.4-104.1) ±6.6 | 85.6 (77.6 - 93.5) ± 5.7 | 79.3 (54.1 - 87.7) ± 12.6 |
| **30** | 101.9 (96.4-108.7) ±4.5 | 103.9 (100.6 - 105.4) ± 1.9 | 101.6 (90.0 - 106.9) ± 6.5 |

***[c] Dissolution limit: NLT 70% of the labelled amount of aspirin dissolved in 30 min[170].***

**Table 5.26**: **Dissolution result of Ranitidine tablets (n=6)**.

| Time (min.) | % Drug Release (Core tablets) | Drug Release [d] % (Tablets coated with T3) | Drug Release [d] % (Tablets coated with T11) |
|---|---|---|---|
| **10** | 77.0 (56.7 - 87.3) ± 12.3 | 81.9 (78.8 - 83.8) ± 1.9 | 81.9 (77.7 - 87.6) ± 3.5 |
| **20** | 88.1 (79.5 - 97.4) ± 7.3 | 90.6 (87.1 - 93.7) ± 2.6 | 90.1 (87.6 - 92.0) ± 1.7 |
| **30** | 92.3 (83.9 - 97.4) ± 5.0 | 93.0 (91.2 - 96.3) ± 2.0 | 92.2 (90.3 - 95.3) ± 1.8 |
| **45** | 94.0 (88.1 - 98.1) ± 3.8 | 95.0 (93.2 - 97.5) ± 1.6 | 93.4 (91.5 - 95.2) ±1.4 |

***[d] Dissolution limit: NLT 80% of the labelled amount of ranitidine dissolved in 45min[169].***

**Table 5.27**: **Free Salicylic Acid (FSA) result of Aspirin tablets (n=20).**

| **Aspirin Tablets** | **Core Tablets** | Coated with T3 | Coated with T11 |
|---|---|---|---|
| **FSA[e] (%)** | 0.11 ± 0.01 | 0.18 ± 0.06 | 0.16 ± 0.02 |

***[e] Free salicylic acid limit: NMT 0.3% for core tablets and NMT 3.0% for coated tablets[168].***

Analytical testing results showed that there is no significant difference in DT, assay, dissolution profile for core and coated tablets of aspirin and ranitidine. The selected coating formulations (T3 and T11) prepared with polymer blends have an ability to produce a film which readily get solubilized in aqueous media. Therefore, it can be used as immediate release coating formulation for tablets products with addition benefit such as protection of the active ingredients from air, moisture, or light, masking of unpleasant tastes and odors, or improvement of appearance, with maintaining analytical testing result of tablets within respective monographs.

## 5.8 Stability Evaluation

### 5.8.1 Stability of Placebo tablets Coated using formulations T3 and T11

- Placebo tablets coated using formulation T3 & T11 at 3% WG using 20**%** W/W solids in water was tested for disintegration and color difference test.
- Disintegration testing: 6-month stability study of coated tablets showed no significant difference in disintegration time. Coated tablets were disintegrated in less than 120 seconds throughout the stability study till 6 months results are depicted in Table 5.28. The above finding indicates that, coating formulation prepared with polymer blend have no significant impact on disintegration of tablets throughout the 6-month stability study.

**Table 5.28**: **Disintegration time (in seconds) results of coated placebo tablets.**

| Sample details | Initial | 1 month | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|---|
| | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formulation T3 | 28-50 | 29-55 | 26-58 | 24-40 | 33-49 | 25-39 | 43-59 |
| Formulation T11 | 39-59 | 51-66 | 43-90 | 43-67 | 50-90 | 52-60 | 70-102 |

- Color Difference: 6-month stability study of coated tablets showed slightly increase (~ 1.49) in DE at 30/65 and 40/75 condition (Limit: NMT 2.0; as a general understanding for light blue colored tablets). Results are depicted in Table 5.29. The above finding indicates that, coating formulation prepared with polymer blend providing good color stability.

**Table 5.29**: **Color Difference results of coated placebo tablets**.

| Sample details | Test Parameter | | Initial | 1 month | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formula T3 | CIE | DE | 0.98 | 0.67 | 0.33 | 0.47 | 0.67 | 1.29 | 1.49 |
| | | DL | 0 | 0.1 | -0.04 | -0.38 | -0.51 | -0.59 | 0.06 |
| | | Da | 0.87 | -0.63 | 0 | 0.21 | -0.15 | 1.13 | 0.32 |
| | | Db | -0.46 | -0.19 | 0.33 | -0.18 | 0.42 | 0.24 | 1.46 |
| | | Dc | -0.35 | 0.61 | 0.21 | -0.04 | -0.16 | -1.01 | -1.18 |
| | | DH | 0.91 | -0.26 | 0.25 | 0.28 | -0.42 | 0.56 | -0.92 |
| | CMC | DE | 0.66 | 0.36 | 0.2 | 0.24 | 0.35 | 0.68 | 0.88 |
| | | DL | 0.00 | 0.04 | -0.01 | -0.14 | -0.18 | -0.21 | 0.02 |
| | | DC | -0.18 | 0.31 | -0.11 | -0.02 | -0.08 | -0.51 | -0.6 |
| | | DH | 0.63 | -0.18 | -0.17 | 0.19 | -0.29 | 0.39 | -0.64 |
| Formula T11 | CIE | DE | 0.12 | 1.16 | 0.57 | 1.29 | 0.91 | 0.64 | 1.37 |
| | | DL | 0.04 | -0.12 | -0.29 | 0.29 | -0.69 | 0.16 | -0.55 |
| | | Da | -0.02 | 1.12 | -0.48 | 0.78 | -0.43 | 0.31 | -0.94 |
| | | Db | -0.11 | 0.27 | 0.13 | 0.99 | 0.4 | 0.54 | 0.83 |
| | | Dc | 0.08 | -1.03 | 0.28 | -1.23 | 0.08 | -0.58 | 0.21 |
| | | DH | 0.07 | 0.53 | -0.41 | -0.26 | -0.58 | -0.22 | -1.24 |
| | CMC | DE | 0.07 | 0.66 | 0.34 | 0.68 | 0.48 | 0.35 | 0.91 |
| | | DL | 0.01 | -0.04 | -0.11 | 0.1 | -0.25 | 0.06 | -0.2 |
| | | DC | 0.04 | -0.54 | 0.15 | -0.65 | 0.04 | -0.31 | 0.11 |
| | | DH | 0.05 | 0.37 | -0.29 | -0.19 | -0.41 | -0.15 | -0.88 |

**5.8.2 Stability study results of Ranitidine Hcl tablets 150 mg (Coated using formulation T3 & T11 at 3% WG using 20% W/W solids in water)** tested for dissolution testing, assay and disintegration test. Results are mentioned in Table 5.30, Table 5.31 and Table 5.32 respectively.

- Dissolution testing: Dissolution testing results obtained from stability study of Ranitidine Hcl tablets 150 mg coated with formulation T3 and T11 at 3% WG using 20% W/ W solids in water showed no significant change in drug release of coated tablets when tested as per USP monograph.

**Table 5.30**: **Dissolution results of Ranitidine Hcl tablets 150 mg**.

| Sample details | Time (min) | Initial | 3 months | | 6 months | |
|---|---|---|---|---|---|---|
| | | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formulation T3 | 10 | 81.9 ± 1.9 | 84 ± 8.2 | 78.3 ± 5.4 | 76.7 ± 9.0 | 72.0 ± 9.1 |
| | 20 | 90.6 ± 2.6 | 86.6 ± 5.7 | 84.9 ± 4.5 | 87.2 ± 4.6 | 78.1 ± 6.9 |
| | 30 | 93.0 ± 2.0 | 90.7 ± 2.7 | 87.0 ± 3.7 | 90.0 ± 3.0 | 79.0 ± 6.7 |
| | 45 | 95.0 ± 1.6 | 93.5 ± 1.9 | 90.3 ± 2.7 | 92.5 ± 2.4 | 86.5 ± 6.3 |
| Formulation T11 | 10 | 81.9 ± 3.5 | 89.6 ± 3.3 | 74.1 ± 9.2 | 71.9 ± 12.2 | 42.3 ± 7.1 |
| | 20 | 90.1 ± 1.7 | 93.1 ± 2.6 | 87.3 ± 4.7 | 85.2 ± 6.0 | 78.8 ± 9.0 |
| | 30 | 92.2 ± 1.8 | 93.8 ± 2.0 | 89.5 ± 4.1 | 87.7 ± 4.3 | 83.7 ± 6.5 |
| | 45 | 93.4 ± 1.4 | 94.4 ± 1.5 | 91.3 ± 3.4 | 89.5 ± 3.1 | 86.5 ± 4.4 |

- Assay testing: Assay results obtained from stability study of Ranitidine Hcl tablets 150 mg coated with formulation T3 and T11 at 3% WG using 20% W/ W solids in water showed no significant change in assay of coated tablets when tested as per procedure mentioned in USP monograph all tablets complied for assay test limits. Results are depicted in Table 5.31

**Table 5.31: Assay results of Ranitidine Hcl tablets 150 mg**.

| Sample details | Initial (%) | 1 month | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|---|
| | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formulation T3 | 102.9 | 98.5 | 98.4 | 96.6 | 94.2 | 91.6 | 90.5 |
| Formulation T11 | 101.4 | 99.6 | 99.2 | 95.9 | 95.5 | 93.2 | 91.5 |

- Disintegration testing: Results obtained from stability study of coated Ranitidine Hcl tablets 150 mg showed no significant change in disintegration time of coated tablets. All tablets were disintegrated within 5 minutes. Results are depicted in Table 5.32.

**Table 5.32**: **Disintegration time (in minutes) results of Ranitidine Hcl tablets 150 mg**.

| **Sample details** | **Initial (min)** | **1 month** | | **3 months** | | **6 months** | |
|---|---|---|---|---|---|---|---|
| | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formulation T3 | 1 – 3 | 1 – 3 | 1 – 3 | 1 – 3 | 1 – 2 | 1 – 3 | 1 – 4 |
| Formulation T11 | 2 – 3 | 1 – 4 | 1 – 4 | 1 – 2 | 1 – 3 | 1 – 3 | 1 – 2 |

- Appearance testing: Results obtained from stability study of coated Ranitidine Hcl tablets 150 mg showed no significant change in appearance, results are depicted in Fig. 5.18 and 5.19.

**Fig. 5.18: Appearance of coated Ranitidine Hcl tablets 150 mg after cutting into two halves.**

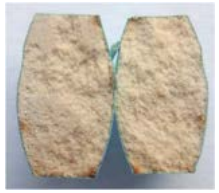
| Sample details | Initial | 1 month | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|---|
| | | 30°C/65% RH | 40°C/75% RH | 30°C/65% RH | 40°C/75% RH | 30°C/65% RH | 40°C/75% RH |
| Formula T3 |  |  |  |  |  |  |  |
| Formula T11 |  |  |  |  |  |  |  |

**Fig. 5.19: Appearance of coated Ranitidine Hcl tablets 150 mg (uncut).**

| **Sample details** | **Initial** | **1 month** | | **3 months** | | **6 months** | |
|---|---|---|---|---|---|---|---|
| | | 30°C/65% RH | 40°C/75% RH | 30°C/65% RH | 40°C/75% RH | 30°C/65% RH | 40°C/75% RH |
| Formulation T3 |  |  |  |  |  |  |  |
| Formulation T11 |  |  |  |  |  |  |  |

**5.8.3 Stability study results of Aspirin tablets (Coated using formulation T3 & T11 at 3% WG using 20% W/W solids in water)** tested for dissolution, assay, free salicylic acid and disintegration test.

- Dissolution testing: Dissolution testing results obtained from stability study of Aspirin tablets 75 mg coated with formulation T3 and T11 at 3% WG using 20% W/ W solids in water showed no significant change in drug release of coated tablets when tested as per IP monograph. Results are depicted in Table 5.33.

**Table 5.33: Dissolution results of coated Aspirin tablets 75 mg (Testing performed as per IP monograph).**

| Sample details | Time (Min) | 3 months | | 6 months | |
|---|---|---|---|---|---|
| | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formulation T3 | 10 | 38.4 ± 14.36 | 19.9 ± 7.12 | 31.2 ± 15.49 | 16.8 ± 6.0 |
| | 20 | 74.2 ± 20.6 | 45.4 ± 14.0 | 63.3 ± 25.3 | 29.0 ± 12.4 |
| | 30 | 94.1 ± 16.4 | 67.5 ± 16.5 | 80.3 ± 26.7 | 40.7 ± 16.3 |
| | 45 | 106.7 ± 5.3 | 90.1 ± 14.7 | 94.6 ± 20.1 | 70.8 ± 18.1 |
| Formulation T11 | 10 | 33.3 ± 18.93 | 39.9 ± 9.24 | 41.0 ± 7.88 | 18.9 ± 12.9 |
| | 20 | 68.7 ± 21.0 | 74.1 ± 18.0 | 80.1 ± 10.7 | 39.8 ± 21.6 |
| | 30 | 89.9 ± 12.0 | 96.2 ± 5.9 | 100.2 ± 9.3 | 56.6 ± 24.5 |
| | 45 | 103.7 ± 3.9 | 104.1 ± 2.4 | 110.8 ± 5.8 | 73.9 ± 24.8 |

- Assay : Assay results obtained from stability study of Aspirin tablets 75 mg coated with formulation T3 and T11 at 3% WG using 20% W/ W solids in water showed

no significant change in assay results of coated tablets when tested as per procedure mentioned in USP monograph, results are depicted in Table 5.34.

**Table 5.34: Assay results of coated Aspirin tablets 75 mg.**

| Sample details | Initial (%) | 1 month | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|---|
| | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formulation T3 | 102.8 | 105.4 | 107.2 | 107.8 | 105.8 | 98.7 | 101.5 |
| Formulation T11 | 106.9 | 107.8 | 107.0 | 107.0 | 108.8 | 99.5 | 96.8 |

- Test for Free Salicylic Acid: Free salicylic acid results obtained from stability study of Aspirin tablets 75 mg coated with formulation T3 and T11 at 3% WG using 20% W/ W solids in water showed no significant change in free salicylic acid results of coated tablets when tested as per procedure mentioned in USP monograph, results are depicted in Table 5.35.

**Table 5.35: Free Salicylic acid results of coated Aspirin tablets 75 mg.**

| Sample details | Initial (%) | 1 month | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|---|
| | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formulation T3 | 0.18 | 0.23 | 0.17 | 0.22 | 0.28 | 0.37 | 0.78 |
| Formulation T11 | 0.16 | 0.32 | 0.23 | 0.32 | 0.86 | 0.52 | 0.90 |

- Disintegration testing: Results obtained from stability study of coated Aspirin tablets 75 mg showed no significant change in disintegration time coated tablets were disintegrated within 5 minutes, results are depicted in Table 5.36.

**Table 5.36: Disintegration time (in minutes) results of Ranitidine Hcl tablets 150 mg.**

| **Sample details** | **Initial (min)** | **1 month** | | **3 months** | | **6 months** | |
|---|---|---|---|---|---|---|---|
| | | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH | 30°C/ 65% RH | 40°C/ 75% RH |
| Formulation T3 | 1 – 3 | 1 – 2 | 1 – 2 | 1 – 3 | 1 – 3 | 1 – 4 | 1 – 3 |
| Formulation T11 | 2 – 3 | 1 – 2 | 1 – 2 | 1 – 2 | 1 – 3 | 1 – 2 | 1 – 3 |

- Appearance testing: Results obtained from stability study of coated Aspirin tablets 75 mg showed no significant change in appearance, results are depicted in Fig. 5.20 and Fig. 5.21.

**Fig. 5.20: Appearance of coated Aspirin tablets after cutting into two halves:**

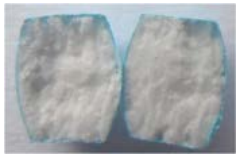
| **Sample details** | **Initial** | **1 month** | | **3 months** | | **6 months** | |
|---|---|---|---|---|---|---|---|
| | | 30°C/65% RH | 40°C/75% RH | 30°C/65% RH | 40°C/75% RH | 30°C/65% RH | 40°C/75% RH |
| Formula T3 |  |  |  |  |  |  |  |
| Formula T11 |  |  |  |  |  |  |  |

**Fig. 5.21: Appearance of coated Aspirin tablets (uncut tablets):**

| **Sample details** | **Initial** | **1 month** | | **3 months** | | **6 months** | |
|---|---|---|---|---|---|---|---|
| | | 30°C/65% RH | 40°C/75% RH | 30°C/65% RH | 40°C/75% RH | 30°C/65% RH | 40°C/75% RH |
| Formula T3 |  |  |  |  |  |  |  |
| Formula T11 |  |  |  |  |  |  |  |

## *5.9 Quality by design (QbD) approach*

### 5.9.1 Defects

Coating trials that exhibited defects are shown in Table 5.37. In both the coating formulations (T3 and T11), 6 trials out of 15 showed more than 80% defects on coated tablets and of those 5 trials (using T3 formulation) and 7 trials (using T11 formulation) had mean defects value not more than 5%. These trials indicate that even when a wide range of coating parameters were employed, the number of defects observed with the coating formulation (T3, T11) was low. Coating trials 2, 5, 8, 10 and 14 exhibited almost 100% defects in both the coating formulates T3 and T11. These trials had high spray rates coating conditions where significant over wetting of the tablet bed occurred, leading to sticking of tablets and rough surface. Tablets coated with the inlet temperature of more than 50°C and spray rates less than 5 g/min had no defects and having visual good color uniformity and smooth appearance. This indicates the robust nature of the product performance (T3 and T11) across a broad range of coating temperatures. The occurrence of defects with T3 formulation was on higher side as compared to that observed with T11 formulation. This may be due to presence of high proportion of PVA in T3 formulation attributed to its inherent tackiness[152].

**Table 5.37: Coating defects (%) observed per trial (mean coating defect %)**

| Trial No. | T3 formulation | T11 formulation | Trial No. | T3 formulation | T11 formulation |
|---|---|---|---|---|---|
| **1** | 4 | 4 | **9** | 10 | 0 |
| **2** | 100 | 96 | **10** | 82 | 81 |
| **3** | 88 | 92 | **11** | 2 | 2 |
| **4** | 8 | 2 | **12** | 0 | 0 |
| **5** | 100 | 98 | **13** | 5 | 0 |
| **6** | 12 | 6 | **14** | 100 | 94 |
| **7** | 34 | 16 | **15** | 4 | 2 |
| **8** | 96 | 100 | | | |

### 5.9.2 Disintegration Time

Tablet disintegration was consistent across all coating trials. All coated tablets disintegrated in less than 90 seconds, irrespective of coating formulation applied (T3, T11). This indicating that CQA (Disintegration test) is largely independent of coating process parameters for T3 and T11 coating formulation. Average disintegration time depicted in below Table 5.38.

**Table 5.38: Average Coated Tablet Disintegration time for each trial**

| Trial No. | T3 formulation | T11 formulation | Trial No. | T3 formulation | T11 formulation |
|---|---|---|---|---|---|
| | DT (Seconds) | | | DT (Seconds) | |
| **1** | 45-59 | 35-49 | | | |
| **2** | 31-57 | 20-31 | **9** | 20-31 | 37-69 |
| **3** | 32-45 | 22-41 | **10** | 26-44 | 29-40 |
| **4** | 40-60 | 38-49 | **11** | 45-58 | 42-63 |
| **5** | 24-32 | 35-55 | **12** | 47-59 | 42-65 |
| **6** | 46-69 | 35-43 | **13** | 32-43 | 50-69 |
| **7** | 29-48 | 35-70 | **14** | 35-50 | 24-46 |
| **8** | 22-38 | 36-43 | **15** | 32-45 | 44-89 |

### 5.9.3 Gloss

The gloss results indicated that all coating trials of T3 and T11 (except runs 5, 3, 14, 2, 8 and 10) produced tablets with gloss values greater than 50 gloss units. Gloss can be correlated to surface smoothness, so conditions which prolong or increase frictional forces tend to favour gloss development. This can be seen in Fig. 5.22 and Fig. 5.23, where contour plots show that gloss increases under the influence of reduced spray rate, higher inlet temperature and lower % solids. Based on the trial results, a multivariant model was developed for T3 and T11 coating formulation to determine the optimized process parameters and operating space based on CQA goals. Selection of CQA goals and their relative importance plays a significant role in determining the optimized process parameters necessary to deliver enhanced appearance and productivity and minimize defects formation using T3 and T11 coating formulation.

**Fig. 5.22: Graphical representation of tablets gloss V/s coating trial number for T3 formulation**

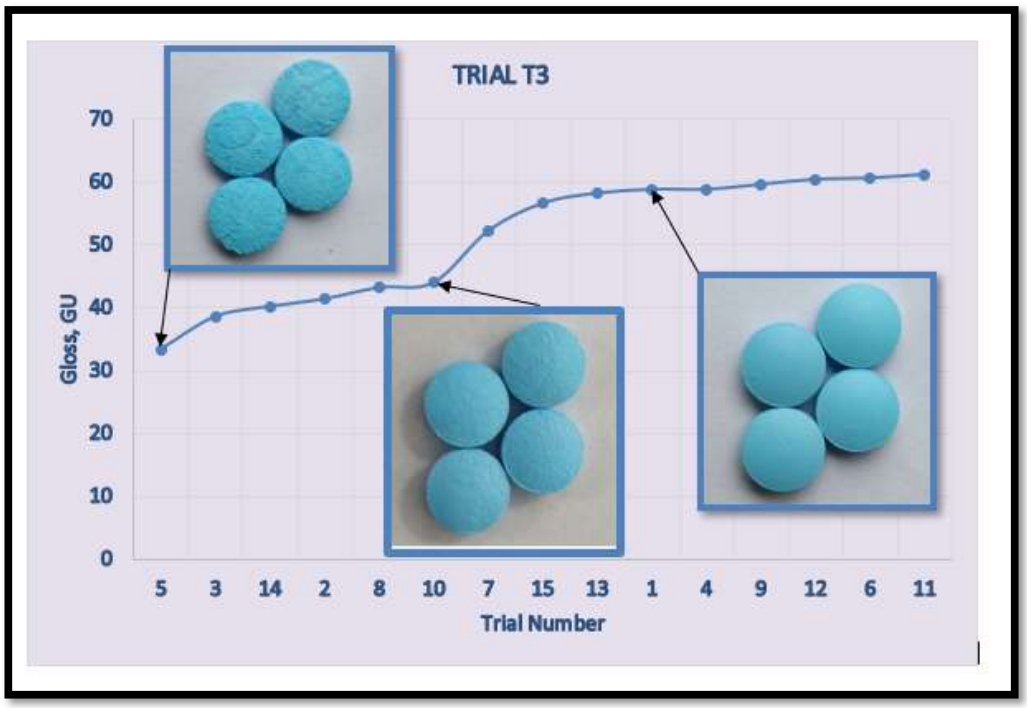
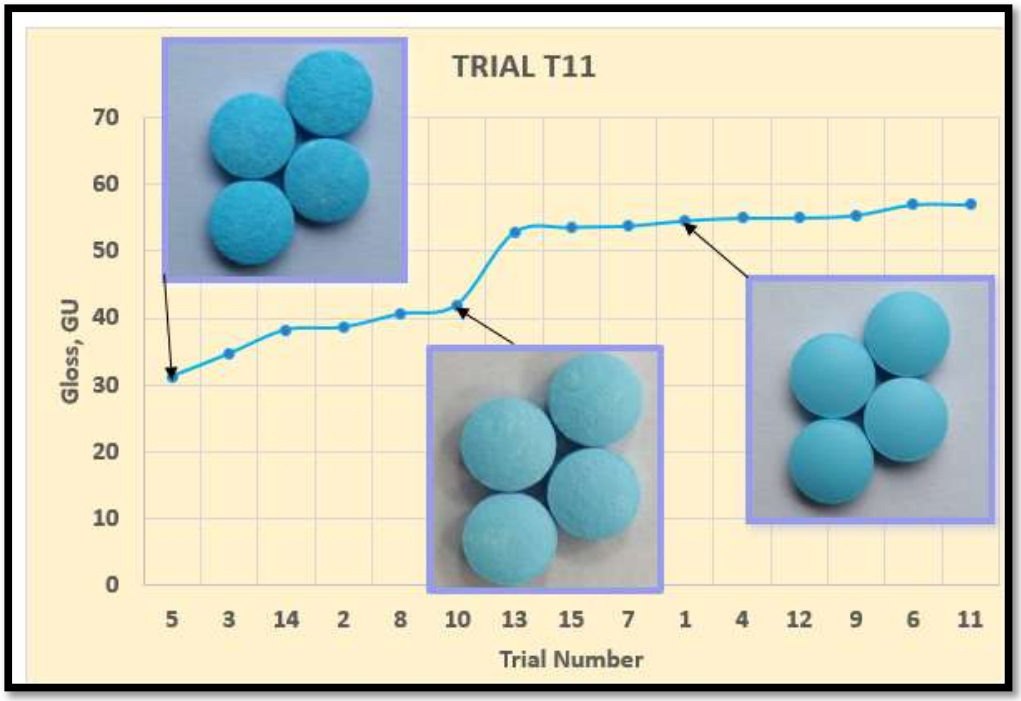


**Fig. 5.23: Graphical representation of tablets gloss V/s coating trial number for T11 formulation**



## 5.10 Surface Profilometry

Gloss can be defined as that attribute of a surface that causes it to have a shiny or lustrous appearance and it is used for the description of coated tablet. In physical terms gloss can be ascribed to the specular reflection of light by the surface and it is this property that is measured to assess gloss[172]. It has been observed that for film coated tablets, the measured gloss can be corelated to its inherent surface roughness measurement[172]. Therefore, in present work it was decided to use surface roughness measurement as a direct measure of gloss. Surface measurement was monitored visually as well as using analytical tool.

Various analytical tools have been reported for surface characterization of core and coated tablets such as laser profilometer[173], near-infrared spectroscopy[174-176], optical scanning profilometer[177], scanning electron microscopy (SEM) and energy dispersive X-ray (EDX)[178-180]. Raman spectroscopy, near infrared spectroscopy reported to use in detection of active pharmaceutical ingredients in tablet formulation[172,181]. Ideally these and other spectroscopic methods give information about the material properties of tablet but not about the surface roughness. When a probe wave with optical wavelengths are used, one can consider surface roughness as a source of noise, which is usually manifested in cases where coherent laser radiation is utilized.

In present work optical profilometry or surface microscopy of film-coated tablets was performed with a Raman microscopy equipped with Atomic Force Microscopy and laser light to guide the microscope through an optical fiber (WITec alpha 300RA+). The objective of present work is to

unravel the impact of variables and understand the interplay between coating formulation and type of polymer blend. This study focuses on measuring the surface roughness of coated tablets in which coating formulation were prepared from varying the concentration of polymer blend with different proportions of additives.

### *5.10.1 Surface Roughness Measurement:*

Surface roughness measurement was performed for tablets coated with T1 to T16 (pigmented and non-pigmented formulation) with optical profilometer to compare the tablet coating components and subsequent its impact on roughness value. Fig. 5.24 showed microscopic images at different micron levels under optical profilometer for tablets coated with T1 and T9. In order to compare the impact of various formulation variables on the surface roughness properties the plot of polymer concentration versus surface roughness was carried. Fig. 5.25 showed comparison of surface roughness amplitude values, Sa (arithmetic mean height) for HPMC versus PVA polymer blends. Bivariate analysis was found to showed significant differences between samples that contained opacifier as well as pigment versus samples that did not contain $TiO_2$ and colorant. This is in-line with visual observation of coated tablets, PVA based polymer blend showed comparatively higher surface roughness values and these values increases with increase in concentration of PVA and decrease in concentration of talc in coating formulation (T4, T5, T6, T7, T8 and T8). However, for HPMC based polymer blend showed lower value in surface roughness irrespective of concentration of polymer and talc present in coating formulation. Slightly higher roughness value was

observed with T15 and T16 containing higher concentration of HPMC (72% and 81% respectively). Further, in order to ascertain the surface roughness values and their impact on the processing conditions, statistical analytical tool was used such as boxplot, multi-plot analysis, correlogram analysis, multivariant analysis and one-way anova test.

**Fig. 5.24: Microscopic images of tablets (T1 and T9) under optical profilometer**

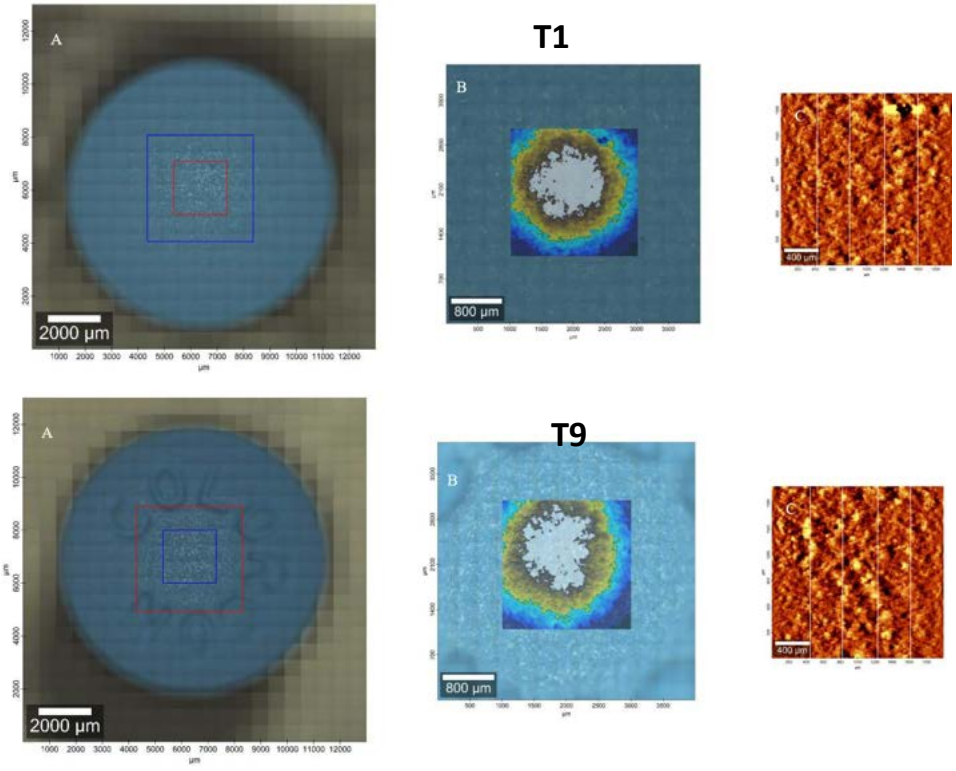
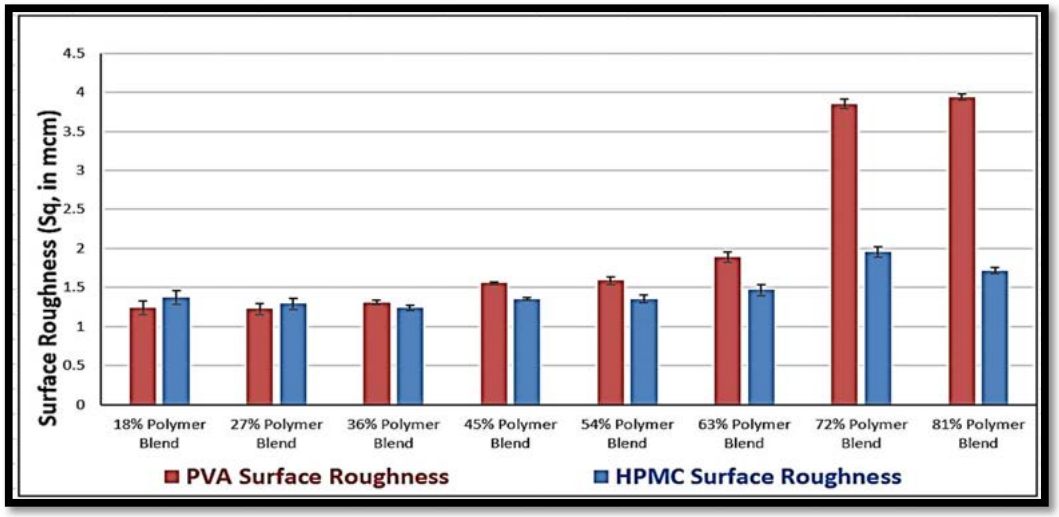


**Fig. 5.25: Comparison of Sa values for HPMC versus PVA polymer blends**




### *5.10.2. Statistical analysis:*

From the boxplot (Fig. 5.26), it is inferred that the spread of the PVA based polymer coating has a wide range of surface value results. Presence or absence of additives in coating formulation was found to immensely influence the PVA polymer than the HPMC based polymer blend.

**Fig. 5.26: Boxplot for comparison of PVA versus HPMC**

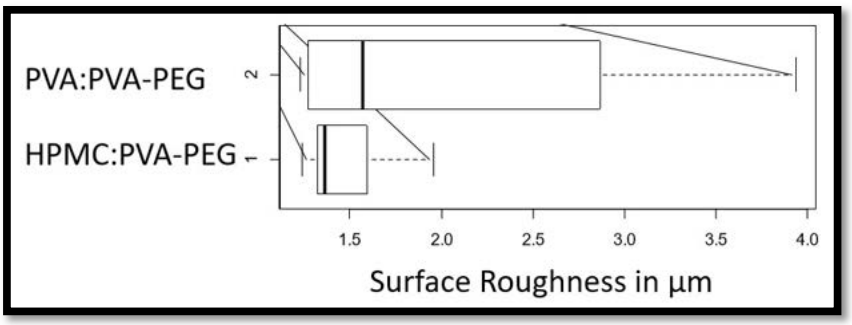


**Fig. 5.27: Multi-plot analysis, formulation variables versus Sa**

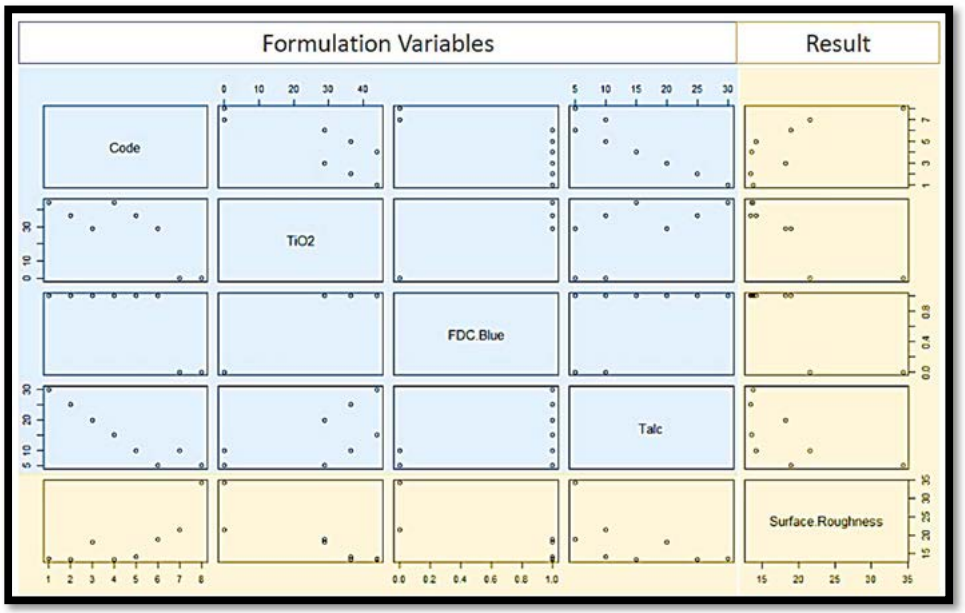
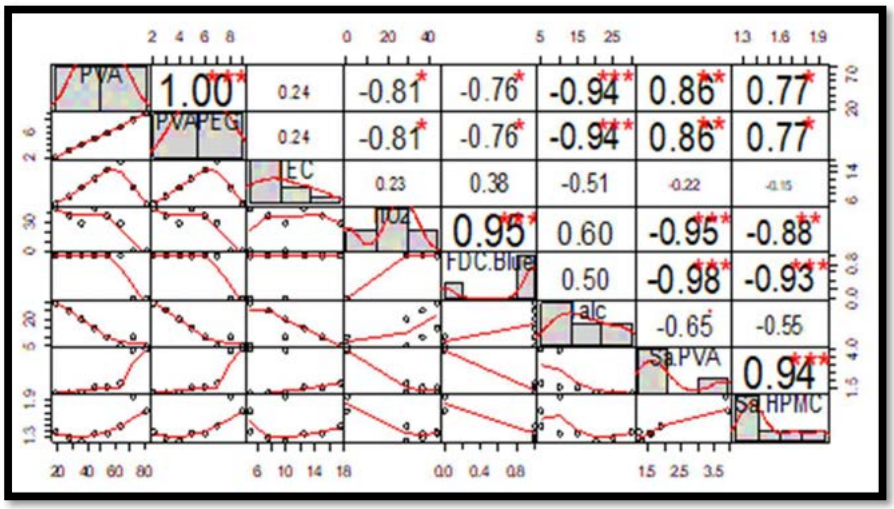



Fig. 5.27, multi-plot analysis of formulation variables (type and concentration of polymer blends, pigment versus non-pigmented formulation and influence of other additives talc, TEC) versus Sa values indicated that, indicates that there are more than one factor contributing to the surface roughness. Correlogram analysis (Fig. 5.28) was performed to highlight the most correlated variables. Correlation matrix was reordered according to the degree of association between the variables. Correlation coefficient values range from "-1" to "0" to "+1". The values close to "-1" is highly correlated negatively whereas values close to "+1" is correlated positively. On the other hand, values close to "0" are not correlated or does not influence the variables. The distribution of each variable is shown on the diagonal. On the bottom of the diagonal: the bivariate scatter plots with a fitted line are displayed. On the top of

the diagonal: the value of the correlation plus the significance level as stars (*). Each significance level is associated to a symbol: p values (0, 0.001,0.01, 0.05, 0.1) <=> symbols (“***”, “**”, “*”, “.”).

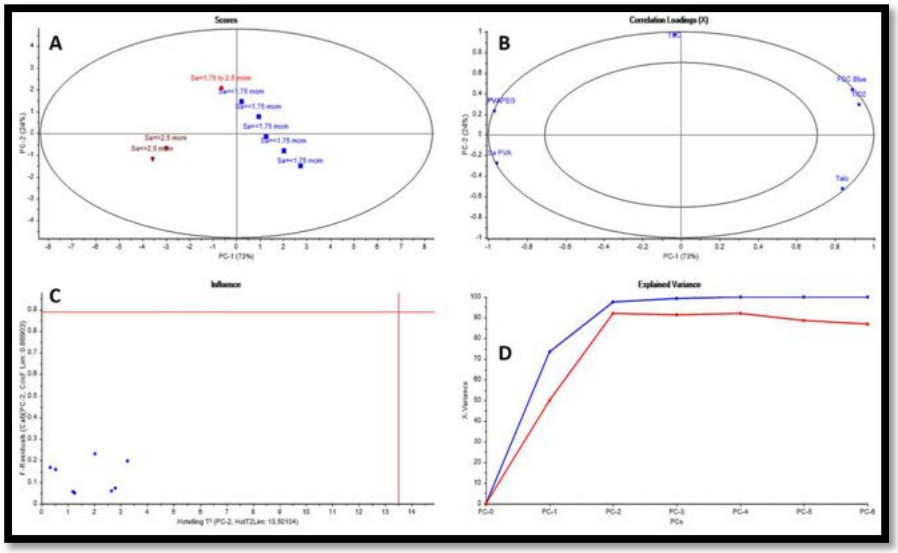
**Fig. 5.28: Correlation between variables and measurements (Sa)**




Correlogram analysis demonstrated that, surface roughness is positively correlated to polymer to additive ratio whereas it is negatively correlated to titanium dioxide, colorant, as well as talc concentration. Both polymers (PVA and HPMC) and surface roughness are less influenced by the presence TEC. PVA:PVA-PEG polymer blend formulation are more positively correlated to surface roughness as compared to that observed with HPMC:PVA-PEG polymer blend. From this analysis, multicollinearity between the variables exist, therefore, multivariate data analysis was performed like Principal Component Analysis (PCA).

PCA was carried out which reduces the dimensionality of a set of variables (y data structure) while retaining the maximum variability in terms of the variance covariance structure where the x, y dataset transformed to a new set of coordinate systems which is lesser in dimension than the number of original variables.

**Fig. 5.29: PCA for PVA:PVA-PEG Copolymer blend samples**



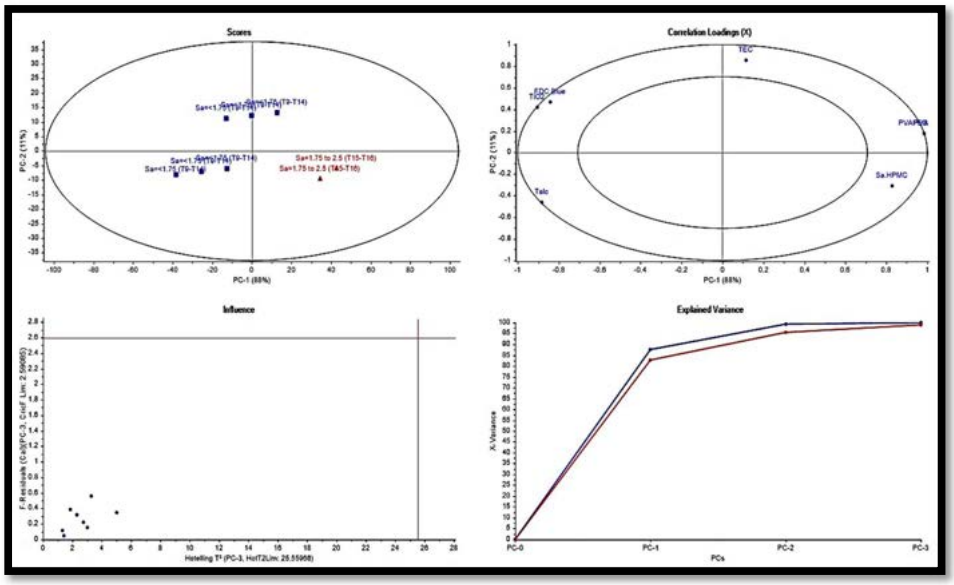

Multivariate data analysis of PVA:PVA-PEG Copolymer blend using PCA provides majorly 4 plots as shown in Fig. 5.29 A-D. Plot of scores (Fig. 5.29 A) for the first two principal components with 95 confidence indicating, no data point lies outside this ellipse. There is clear pattern in the data, i.e., the roughness increases as the polymer to additive concentration as well as polymer to additive composition changes. Three groups based on surface roughness is obtained i.e. 1 75 µm, 1 75 2 5 µm and 2 5 µm. Fig. 5.29 B shows the correlation loadings plot for; group 1 (independent variables) for

FDC Blue and $TiO_2$, group 2 (independent variables) for talc and group 3 (dependent variable) for surface roughness or measurement response, group 4 (independent variable) for polymer (PVA : PVA-PEG Copolymer blend) and group 5 (independent variable) for TEC. Summary described with respect to the group 3 i.e. dependent variable which is surface roughness. This is indicating that, polymer and roughness parameters are positively correlated such that increase in polymer composition will increase Sa and vice versa. Polymer, colorant, $TiO_2$ and talc are negatively correlated, that is there presence reduces the roughness as well higher the concentration lowers the roughness. TEC is close to mid-point line indicating its presence or absence will not influence roughness value. Fig. 5.29 C, since data points are within the red point region, it means there are no noise or outliers similar to results from Fig. 5.29 A. The Fig. 5.29 D is used to ascertain how many components are required to interpret the influence of formulation variables on the surface roughness and the results indicate two PC's are enough as plateau reached and any more inclusion leads to over fitting the model, in summary, two to three PC's explain 98 variability in the data.

Similar PCA was performed for HPMC:PVA-PEG Copolymer blend samples (Fig. 5.30 A-D). Plot of scores (Fig. 5.30 A) for the first two principal components with 95 confidence indicating, no data point lies outside this ellipse. Fig. 5.30 B shows the correlation loadings plot for the first two principal components which is similar to observed with 30B plot. Fig. 5.30 C, since data points are within the red point region, it means there are no noise or outliers similar

to results from Fig. 5.29 A. The Fig. 5.30 D is used to ascertain how many components are required to interpret the influence of formulation variables on the surface roughness and the results indicate three PC's are enough as plateau reached and any more inclusion leads to over fitting the model, in summary, two to three PC's explain 98 variability in the data. In comparison to the PVA polymer blend plot, only the directions have changed otherwise the patterns both in scores and loading are the same.

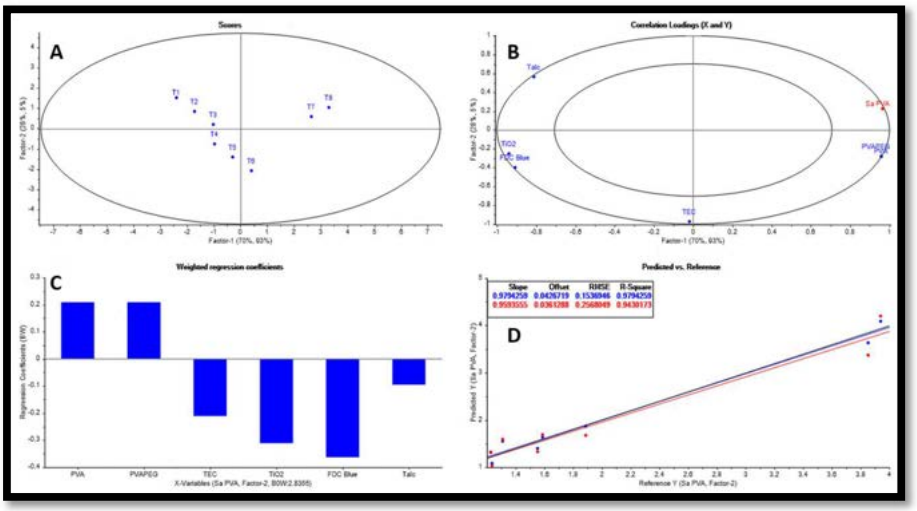
**Fig. 5.30: PCA for HPMC:PVA-PEG polymer blend samples**




Multivariate regression analysis i.e. Partial Least Squares Regression (PLSR) was performed for both PVA:PVA-PEG polymer band and HPMC :PVA-PEG polymer blend, refer to Fig. 5.31 (A-D) and Fig. 5.32 (A-D) respectively. This plot helps to

understand the influence of formulation factors on the surface roughness. In case of PVA, plots of PLSR scores (Fig. 5.31 A) and PLSR loadings (Fig. 5.31 B) are interpreted similar to PCA scores and loadings (refer Fig. 5.29 A and Fig. 5.29 B, respectively). Fig. 5.31 C is similar to the correlogram and/or loading lots of PCA/PLSR, that is, graphical points above 0 indicate a positive correlation with the surface roughness or 'Y variable' or 'dependent variable' while values below zero demonstrate a negative correlation. Fig. 5.31 D is the prediction vs reference plot and is used to measure the validity of the PLS model. There is a linear correlation with R-Square of >0.95 and a very low root mean square error (RMSE) indicates the model is valid in >95 instances.

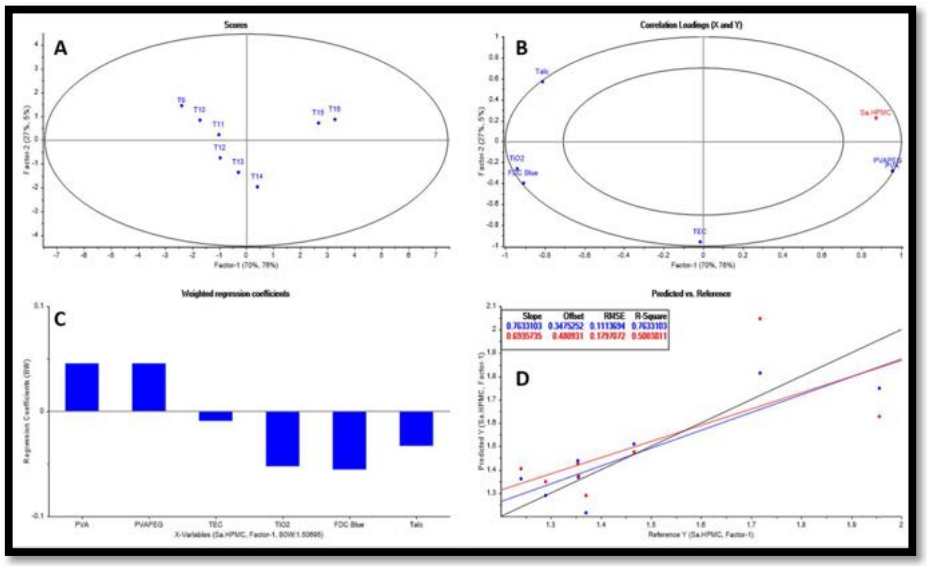
**Fig. 5.31: PLSR for PVA:PVA-PEG Copolymer blend samples**




Similarly, PLSR plot described for HPMC:PVA-PEG polymer bend (Fig. 5.32 A-D). PLSR scores (Fig. 5.32 A) and PLSR loadings (Fig. 5.32 B) are interpreted similar to PCA scores and loadings (refer Fig. 5.30 A and 5.30

B, respectively). Fig. 5.32 C is similar to the correlogram and/or loading lots of PCA/PLSR, that is, graphical points above 0 indicate a positive correlation with the surface roughness or 'Y variable' or 'dependent variable' while values below zero demonstrate a negative correlation. Fig. 5.32 D is the prediction vs reference plot and is used to measure the validity of the PLS model. There is slightly weaker linear correlation with R-Square of >0.76. However, the root mean square error (RMSE) of <1 indicates the model is valid in >75 instances.

**Fig. 5.32: PLSR for HPMC:PVA-PEG polymer blend samples**




From boxplot, correlogram analysis, PCA, PLS it is established that the HPMC:PVA-PEG Copolymer blend performed better than the PVA:PVA-PEG polymer blend. In order to determine if there are any significant differences between the surface roughness values (Sa) of HPMC:PVA-PEG and PVA:PVA-PEG polymer blend in the

various formulation conditions, one way ANOVA test was carried out. ANOVA test was carried out in Rstudio using generic R function aov () and summary.aov () which is used to summarize the model. The model predicted that, p value is less than the 5% significance level (p value < 0.05), therefore, it can be concluded that there are significant differences in the surface roughness values between the two polymers within the studied formulation ranges.

### *5.10.3. Interpretation of statistical analysis:*

Boxplot analysis indicated that the spread of surface roughness (Sa) values for PVA: PVA-PEG Copolymer polymer blend was broader than the HPMC: PVA-PEG Copolymer polymer blend. Univariate data analysis was able to only extract the impact of surface roughness (Sa) on placebo coded tablets due to pigmentation, i.e., the pigmented tablets displayed less surface roughness than the non-pigmented tablets. Univariate data analysis was seriously limited to understand the interaction between different formulation variables. Multivariate data analysis like PCA was employed and there was a trend in the data observed which extracted the influence as well as the interaction of various formulation parameters on the surface roughness. Multivariate regression models were developed to extract the influence of various parameters on the regression and a significant correlation for PVA:PVA-PEG polymer blend was obtained whereas slightly weaker correlation was obtained for HPMC polymer blend. In summary, within the studied protocol of various composition the polymer PVA was found to be influenced and a better multivariate linear model was obtained whereas the HPMC polymer was found to resist the changes to the surface

roughness. Statistical significance was carried out using One way ANOVA test, p value was found to be less than the 5% significance level (p value < 0.05), hence concluded that there are significant differences in the surface roughness values between the two polymers within the studied formulation ranges. In summary, based on the chemometric data analysis as well as the ANOVA results provided evidence that HPMC: PVA-PEG polymer blend performed better with respect to surface roughness values. These results are to be correlated with the formulation performance tests.

# *CHAPTER - 6*

# *SUMMARY & CONCLUSION*

## SUMMARY AND CONCLUSIONS

From all the experimental work and investigation carried out the following conclusions can be drawn that have helped in achieving our objective of understanding polymer and applying that to advancement of preparing optimized polymer blends to offer advance coating chemistry.

- Polymer blends PVA: PVA-PEG (ratio 90:10) and HPMC 6Cp: PVA-PEG (ratio 90:10) can be successfully used in the aqueous coating formulation. For PVA: PVA-PEG (ratio 90:10), polymer blend concentration 20% to 40% showed smooth-coated tablet surface without any visible defects, whereas, for HPMC 6Cp: PVA-PEG (ratio 90:10) 20% to 90% concentration showed smooth-coated tablet surface without any visible defects. This blend had wider usable range that is based on more coherent film formation and this is reflected in their higher Youngs Modulus values compared to PVA: PVA-PEG blend.
- Additives in the coating formulation including plasticizer, pigments and anti-tacking agent, influence internal stresses and thus alter film quality on the tablet surface. Higher concentration of additives (>70%) resulted in more brittle films due to lowering of tensile strength, reduction in extension at break and toughness of film.
- Polymer blends PVA and PVA-PEG and PVA and HPC have good miscibility in their blends at 90:10 ratios behave like a homopolymer and support for single-phase behavior as observed through Differential Scanning Calorimetry thermograms.
- Polymer blend HPMC 6cP: PVA-PEG (90:10) with 20% TEC, there is a significant reduction in glass transition temperature ($T_g$) of HPMC

polymer with the additional benefit of an increase in effective strength and lowering incidence of defect formation on the coated surface.

- PVA: PVA-PEG (ratio 90:10) and HPMC 6Cp: PVA-PEG (ratio 90:10) based coating formulations (T3 and T11) were successfully applied on model Active pharmaceutical ingredient (API) formulations (Aspirin tablets and Ranitidine Hcl tablets) which resulted in coated tablets having elegant appearance and excellent surface smoothness. These coated tablets containing active ingredients complied with their respective Indian Pharmacopoeial monographs. These formulations when subjected to accelerated stability conditions as per ICH guidelines showed good results over the total study period of six months.
- A Quality by Design (QbD) approach was used successfully to identify and characterize the impact of varying critical coating process parameters on critical quality attributes of T3 and T11 coated placebo tablets. Very low defect levels were obtained with T3 and T11 coating formulation prepared with polymer blends [PVA: PVA-PEG (ratio 90:10) and HPMC 6Cp: PVA-PEG (ratio 90:10) respectively] even when using a broad range of coating process conditions.
- Surface Profilometry studies confirmed that more than one additive contributes to surface characteristics of films. The HPMC Blends formulations showed better performance V/s PVA based blends when the concentration of pigments is varied in these formulations
- Statistical analysis of surface roughness data proved our hypothesis that the presence of additives that influence surface tension (e.g. talc) helps in reducing roughness. Also when compared, the two blends system of HPMC and PVA there is sufficient evidence to say that HPMC bases system had slightly better performance compared to PVA with respect to surface roughness values.

**Scope of Future Work**:

Based on all details reported in this study, this data may be used for further evaluation using different additives whose selection will be driven by specific active core properties.

Researched may wish to dwell further on this subject in areas on Film Coating to be used as sub coat or as topcoat on enteric coating etc.

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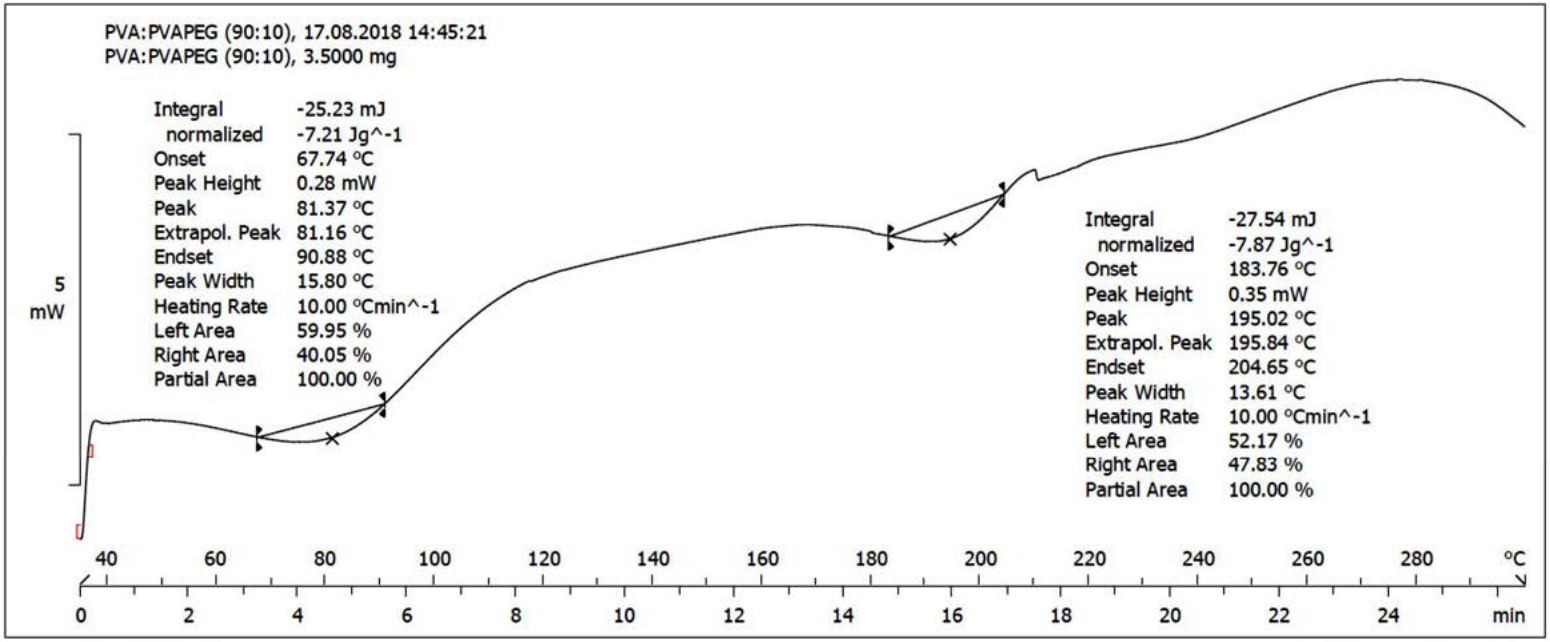
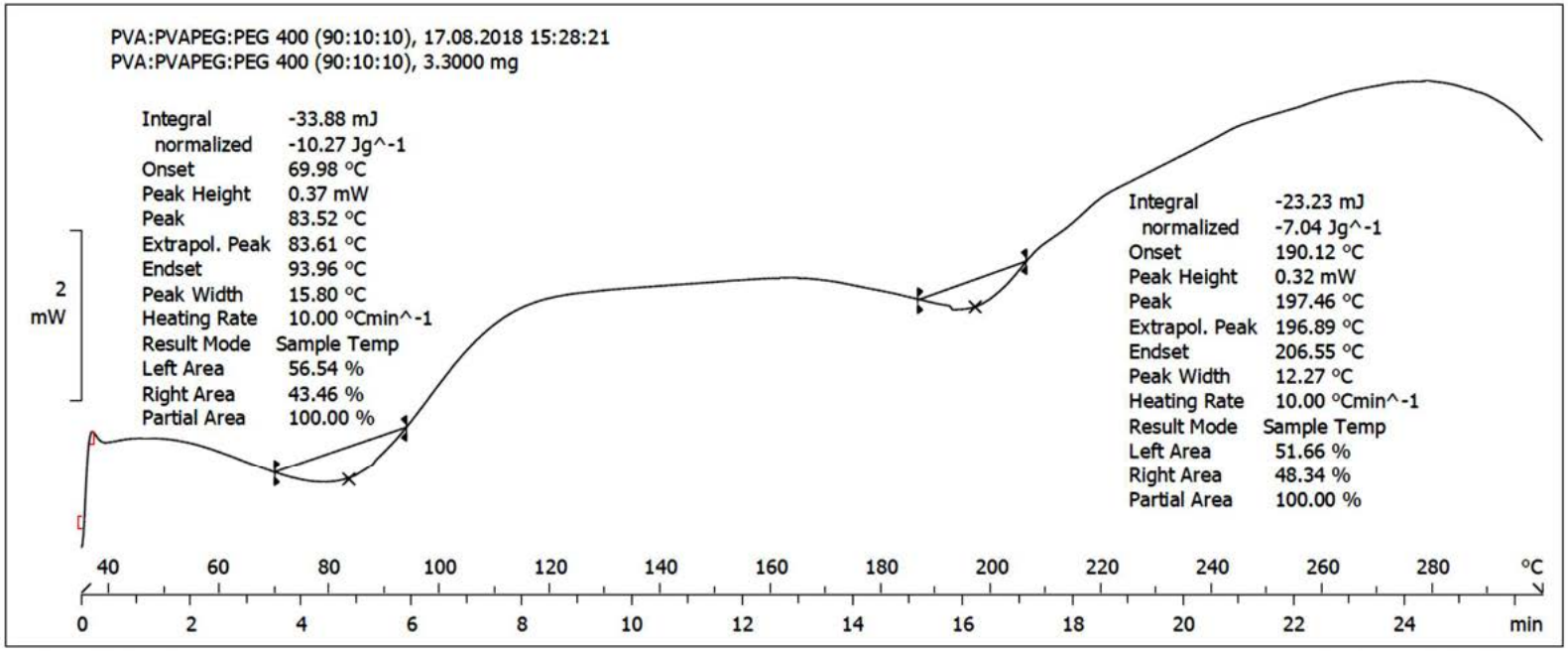
# *ANNEXTURE – I*

# *Differential Scanning Calorimetry Scans*

**BATCH 1 - PVA: PVA-PEG (90:10)**

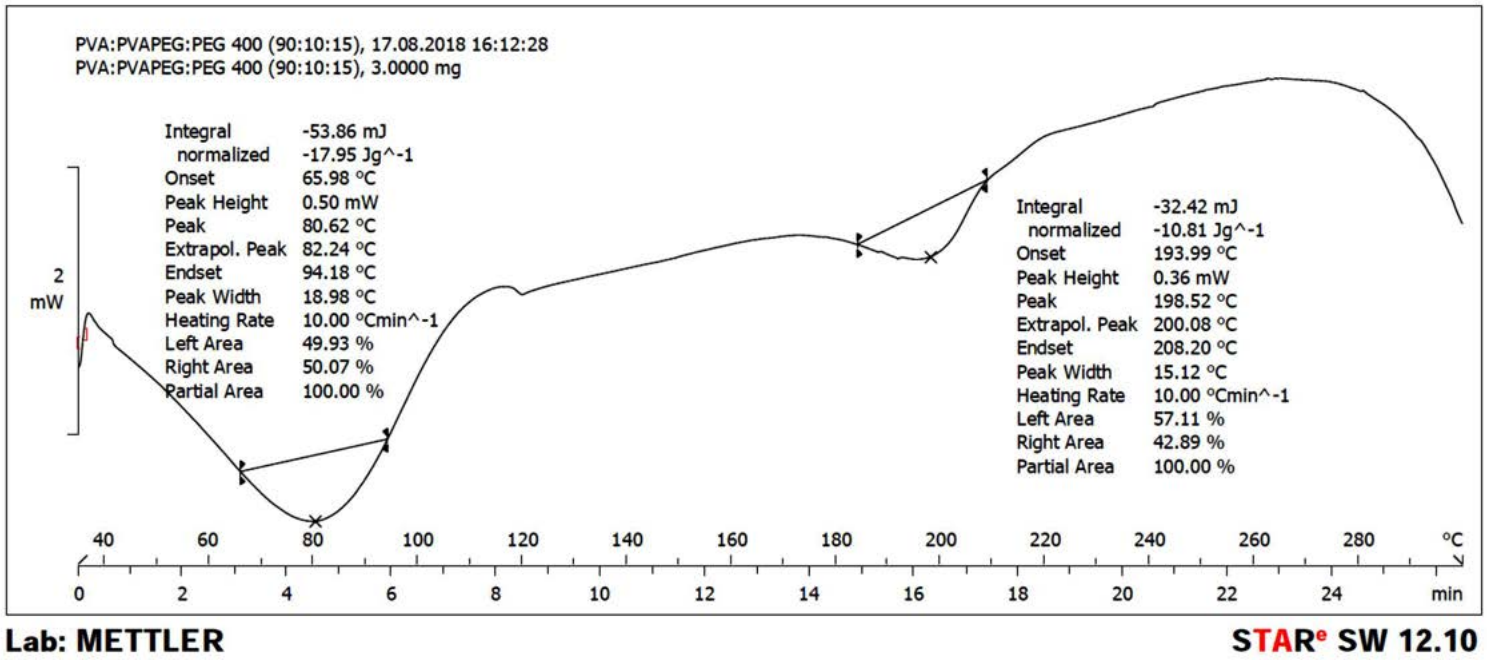


**BATCH 2 - PVA:PVA-PEG:PEG 400 (90:10:10)**

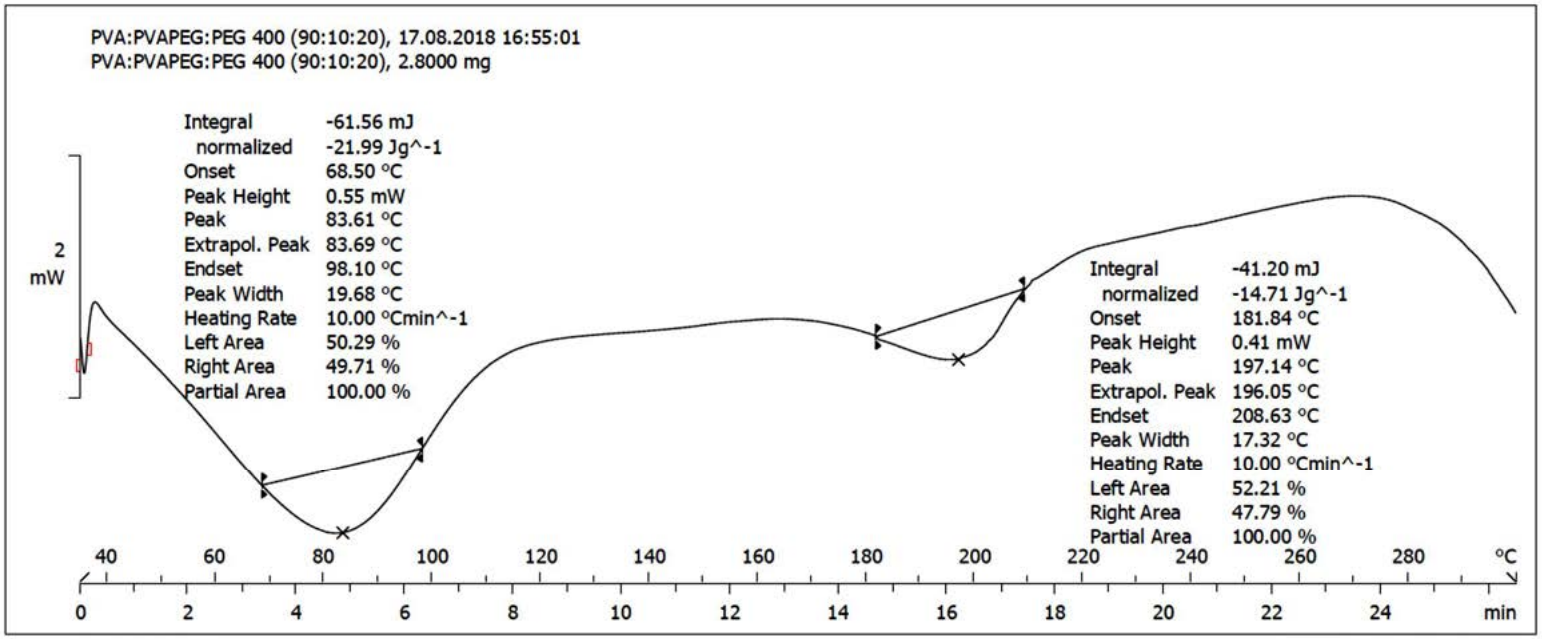



**Lab: METTLER** **STARe SW 12.10**

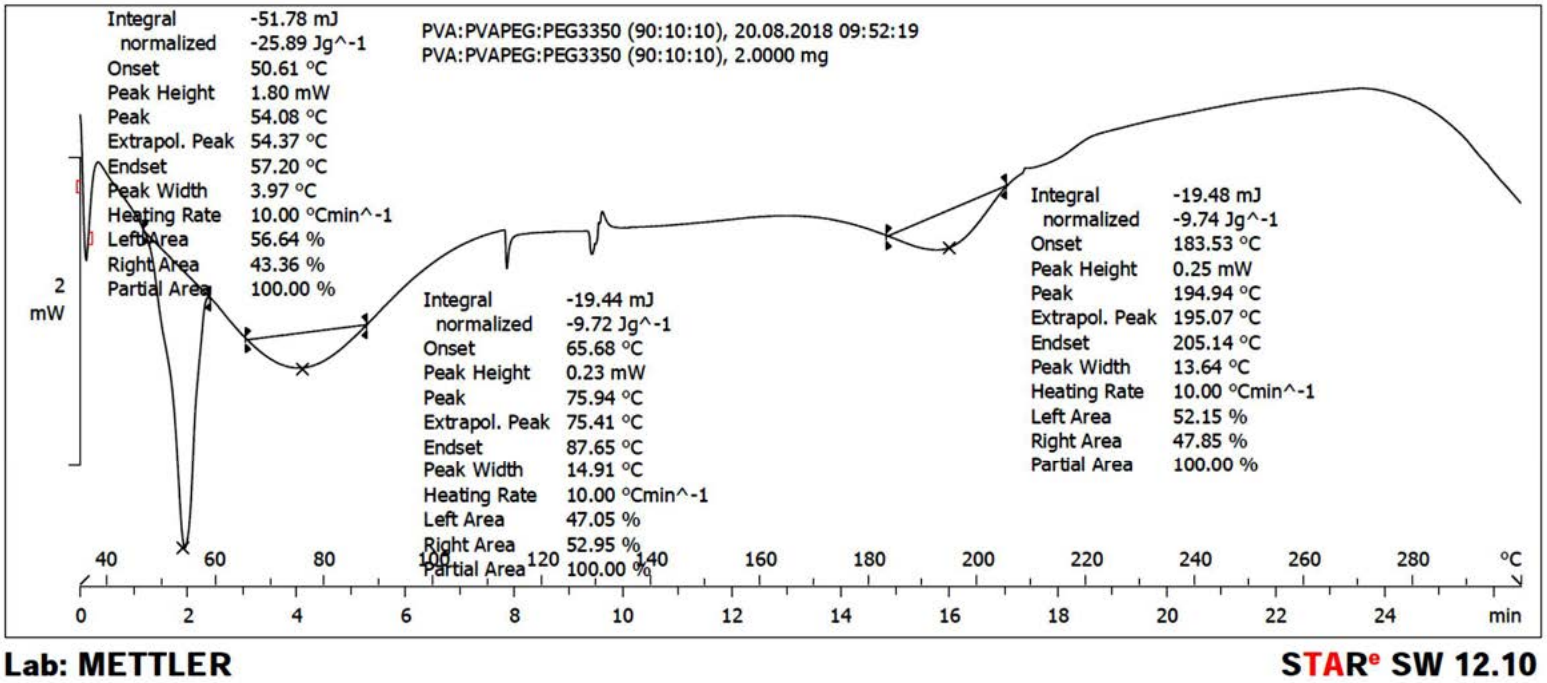
**BATCH 3 - PVA:PVA-PEG:PEG 400 (90:10:15)**



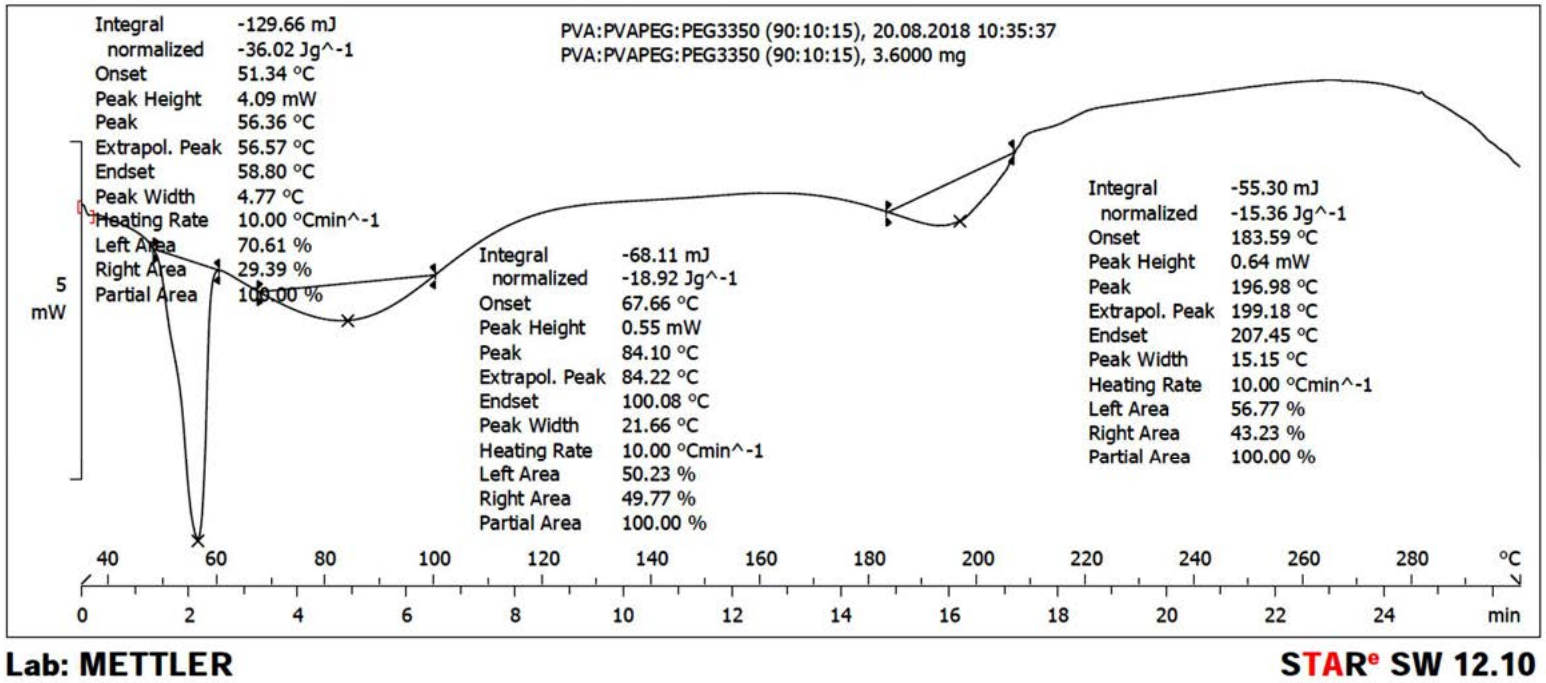
**BATCH 4 - PVA:PVA-PEG:PEG 400 (90:10:20)**



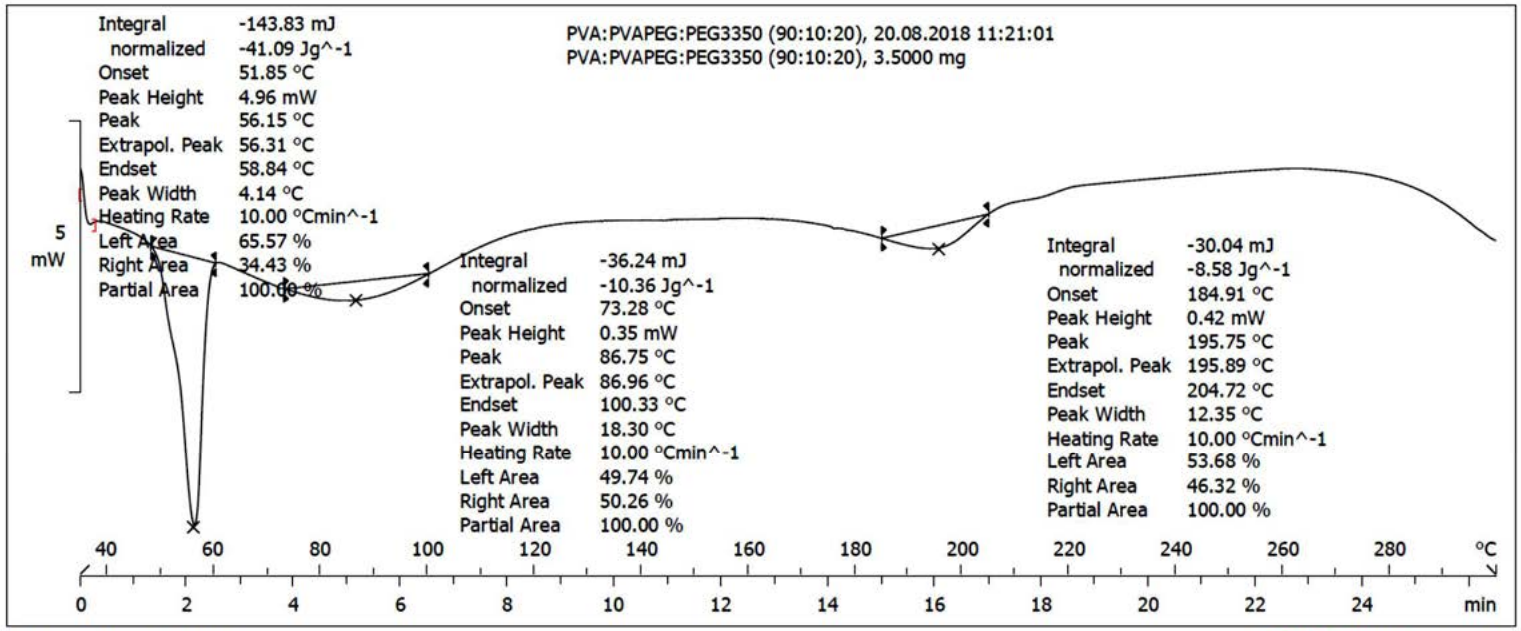
**BATCH 5 - PVA:PVA-PEG:PEG 3350 (90:10:10)**



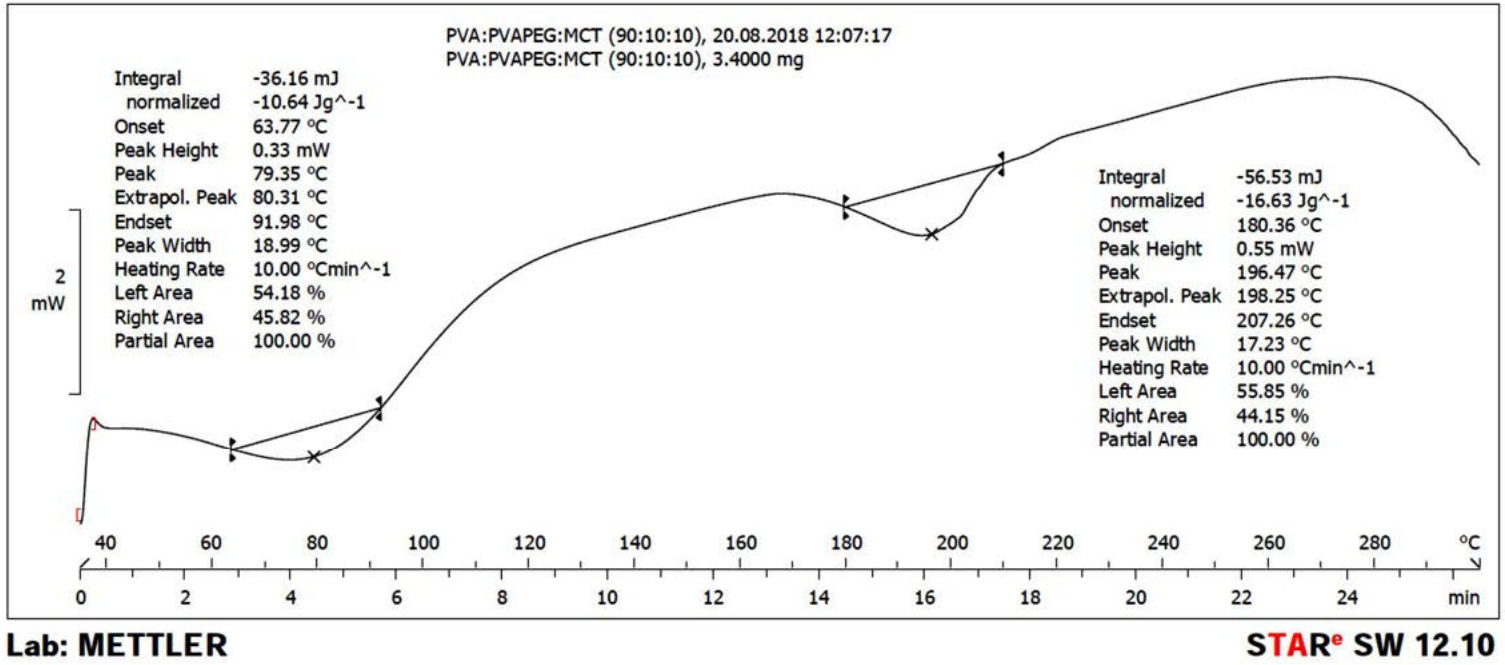
**BATCH 6 - PVA:PVA-PEG:PEG 3350 (90:10:15)**



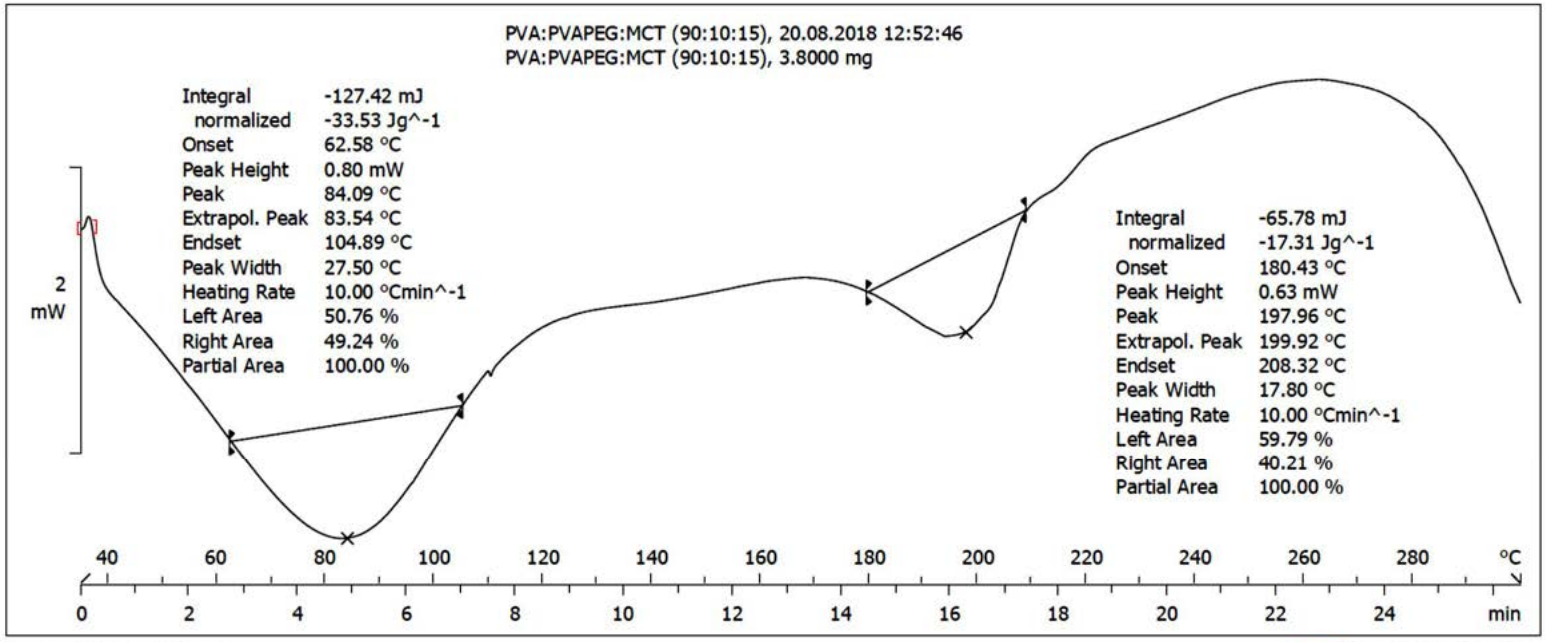
**BATCH 7 - PVA:PVA-PEG:PEG 3350 (90:10:20)**



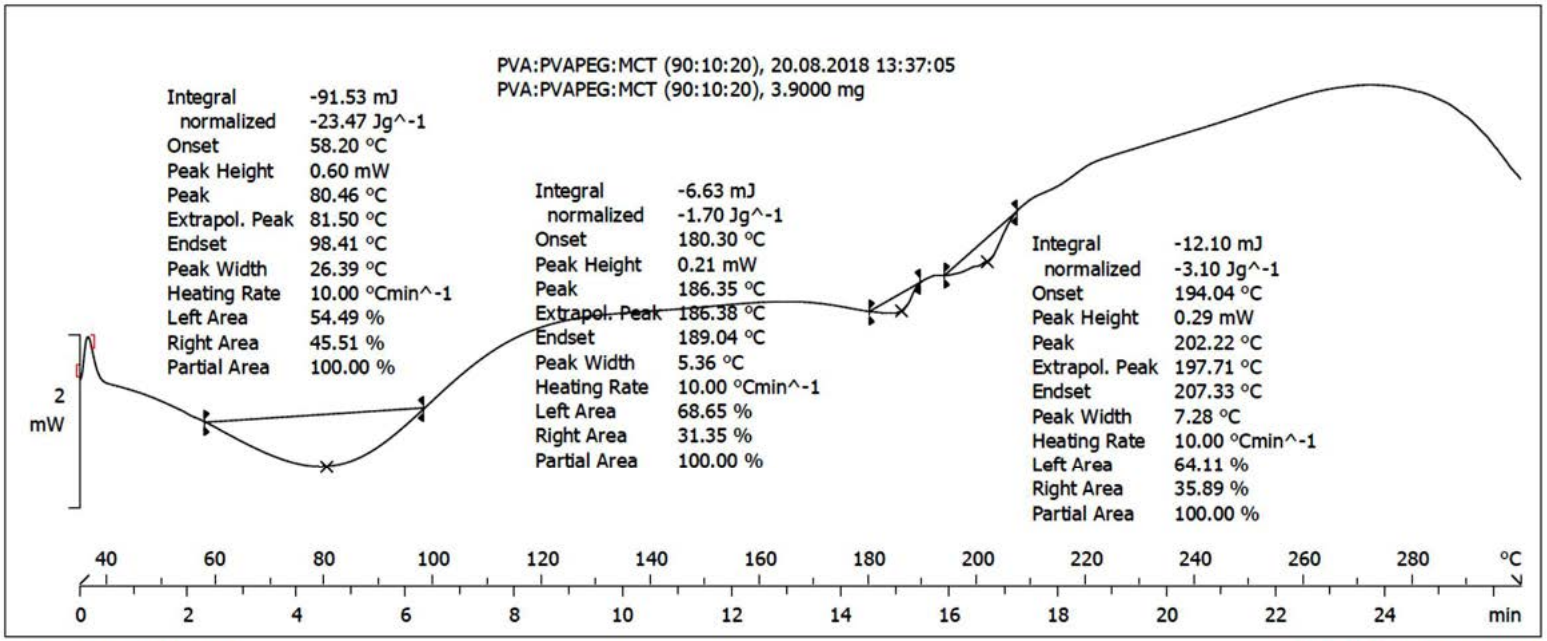
**BATCH 8 - PVA:PVA-PEG:MCT (90:10:10)**



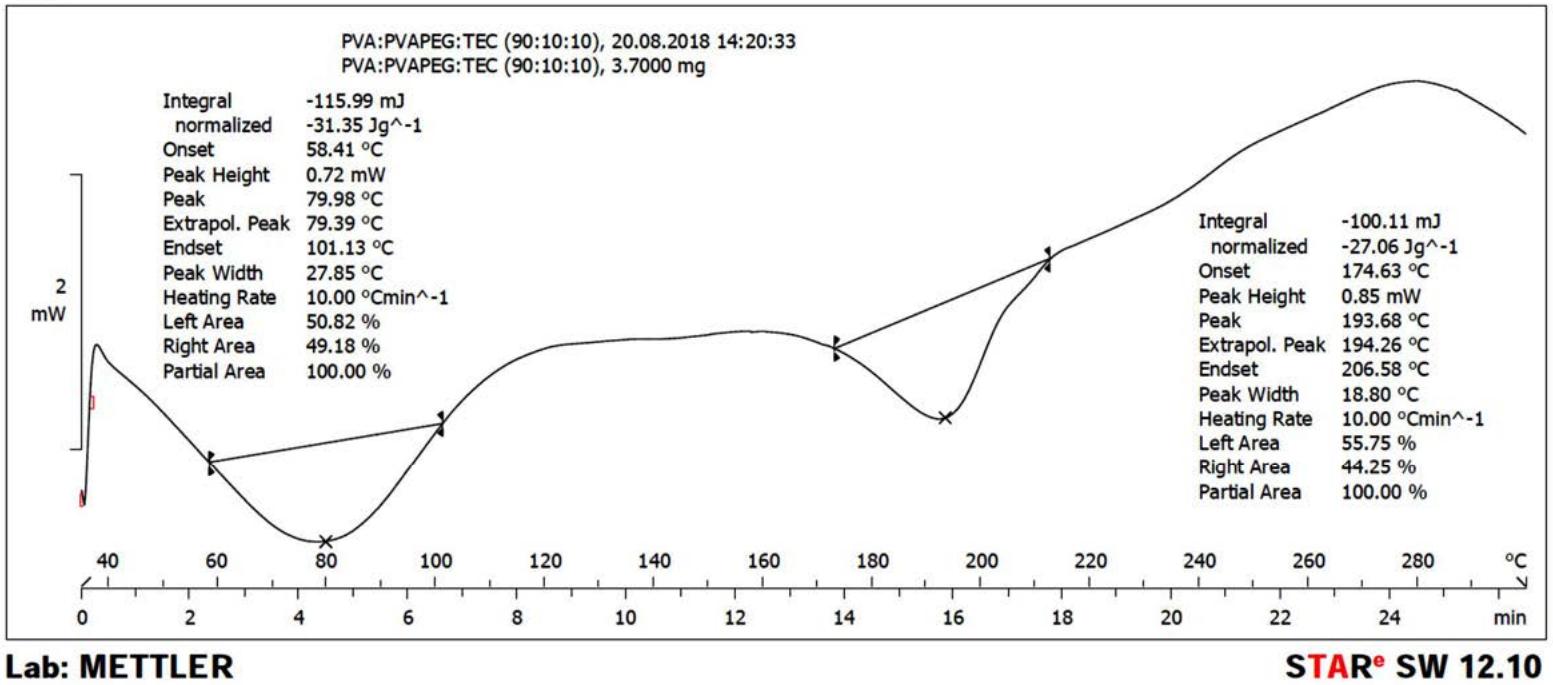
**BATCH 9 - PVA:PVA-PEG:MCT (90:10:15)**



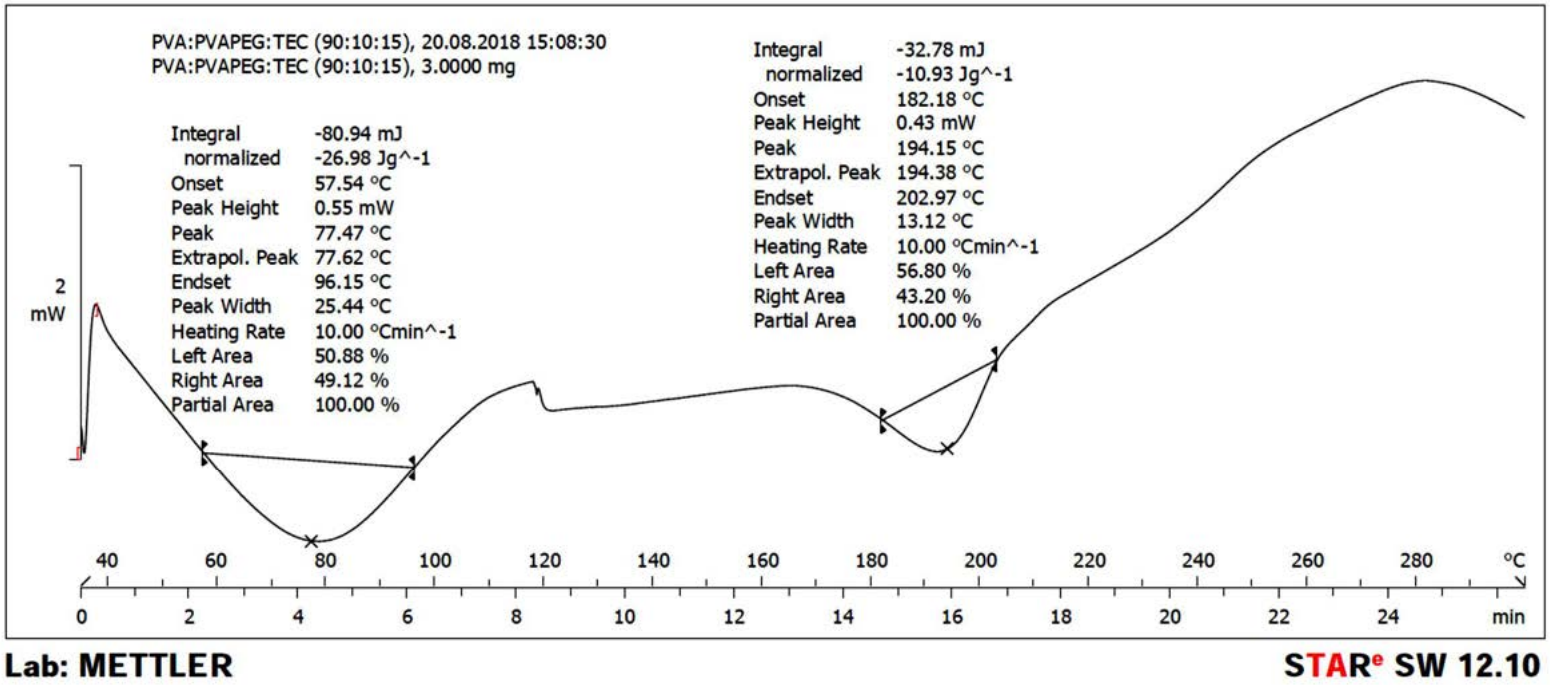
**BATCH 10 - PVA:PVA-PEG:MCT (90:10:20)**



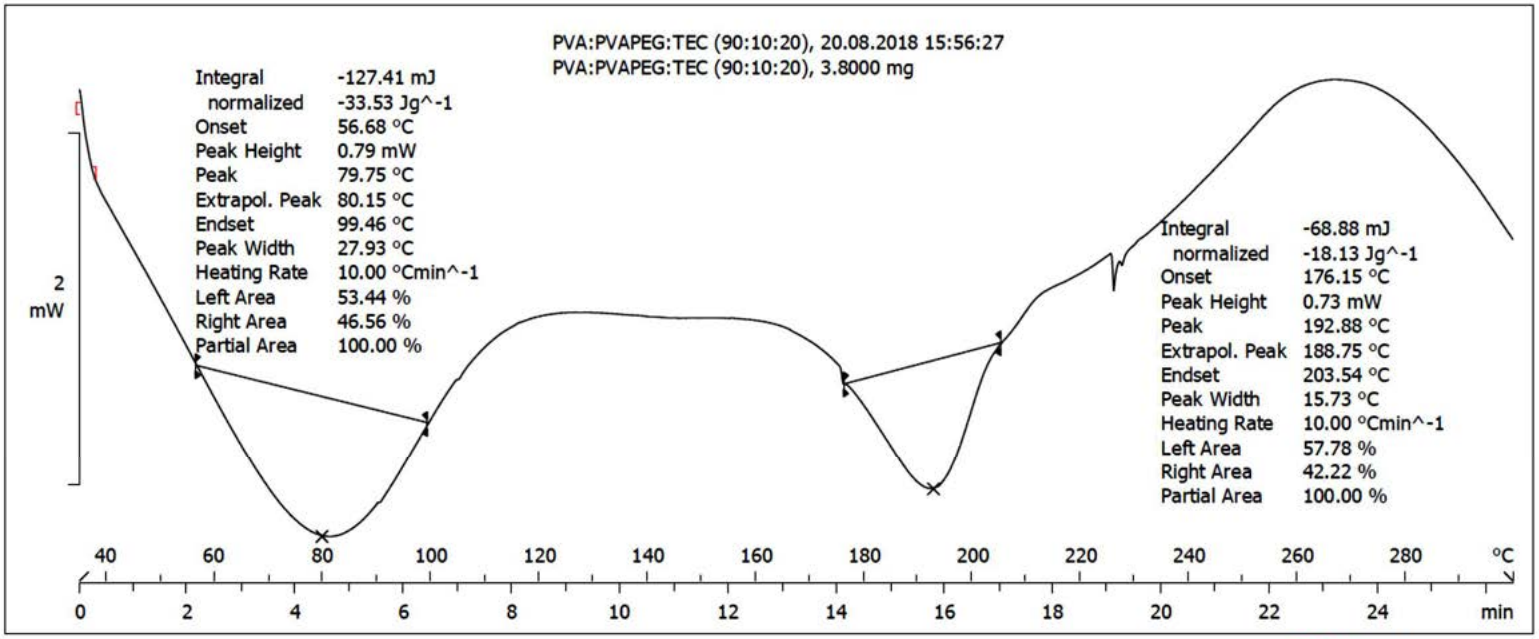
**BATCH 11 - PVA:PVA-PEG:TEC (90:10:10)**



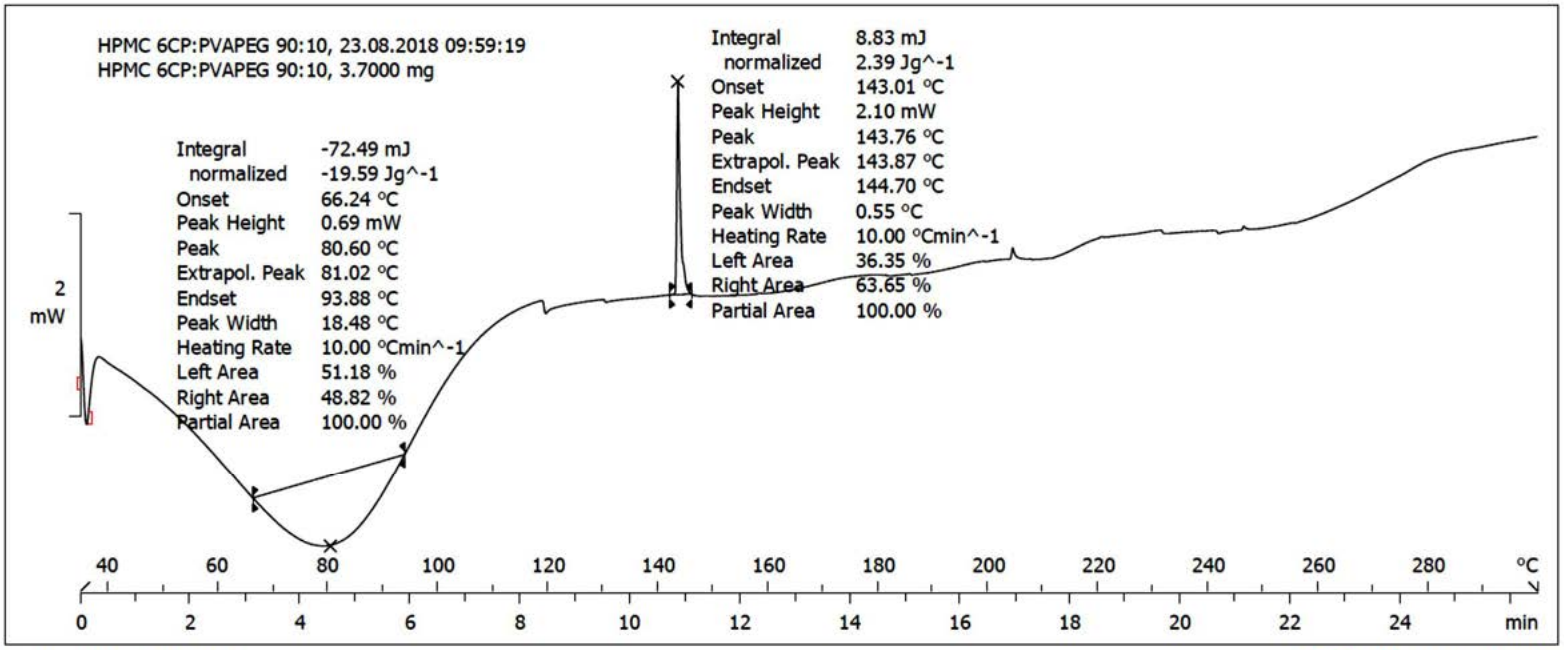
**BATCH 12 - PVA:PVA-PEG:TEC (90:10:15)**



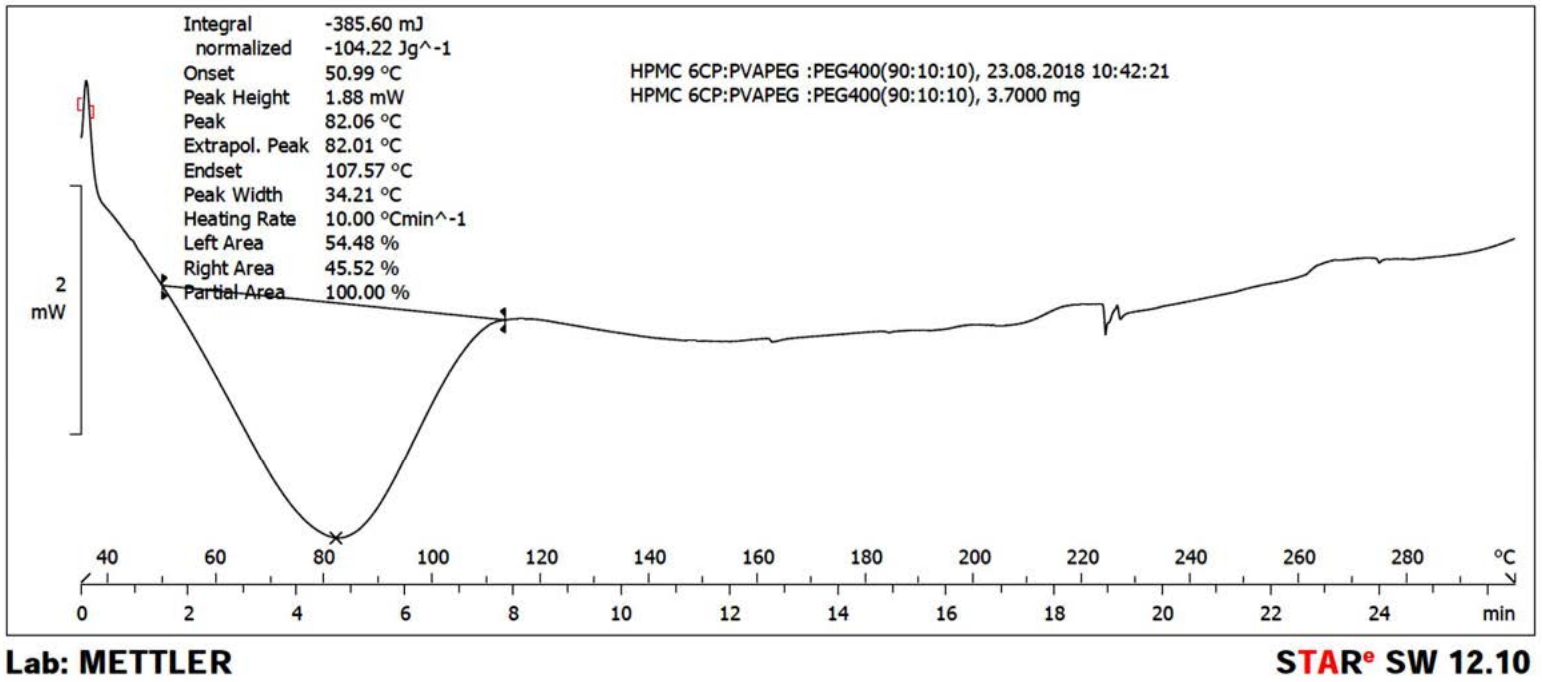
**BATCH 13 - PVA:PVA-PEG:TEC (90:10:20)**



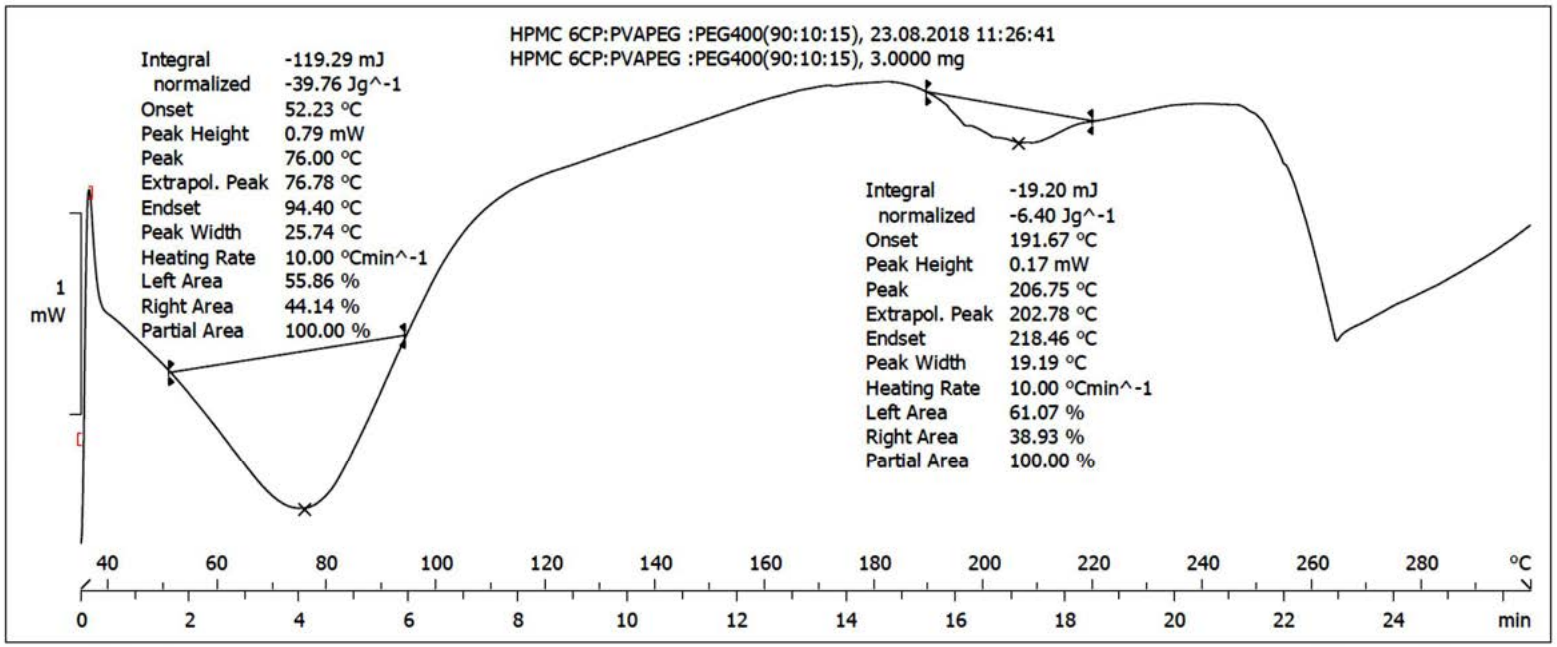
**BATCH 14 - HPMC 6CP:PVA-PEG (90:10)**



**BATCH 15 - HPMC 6CP:PVA-PEG:PEG 400 (90:10:10)**



**BATCH 16 - HPMC 6CP:PVA-PEG:PEG 400 (90:10:15)**



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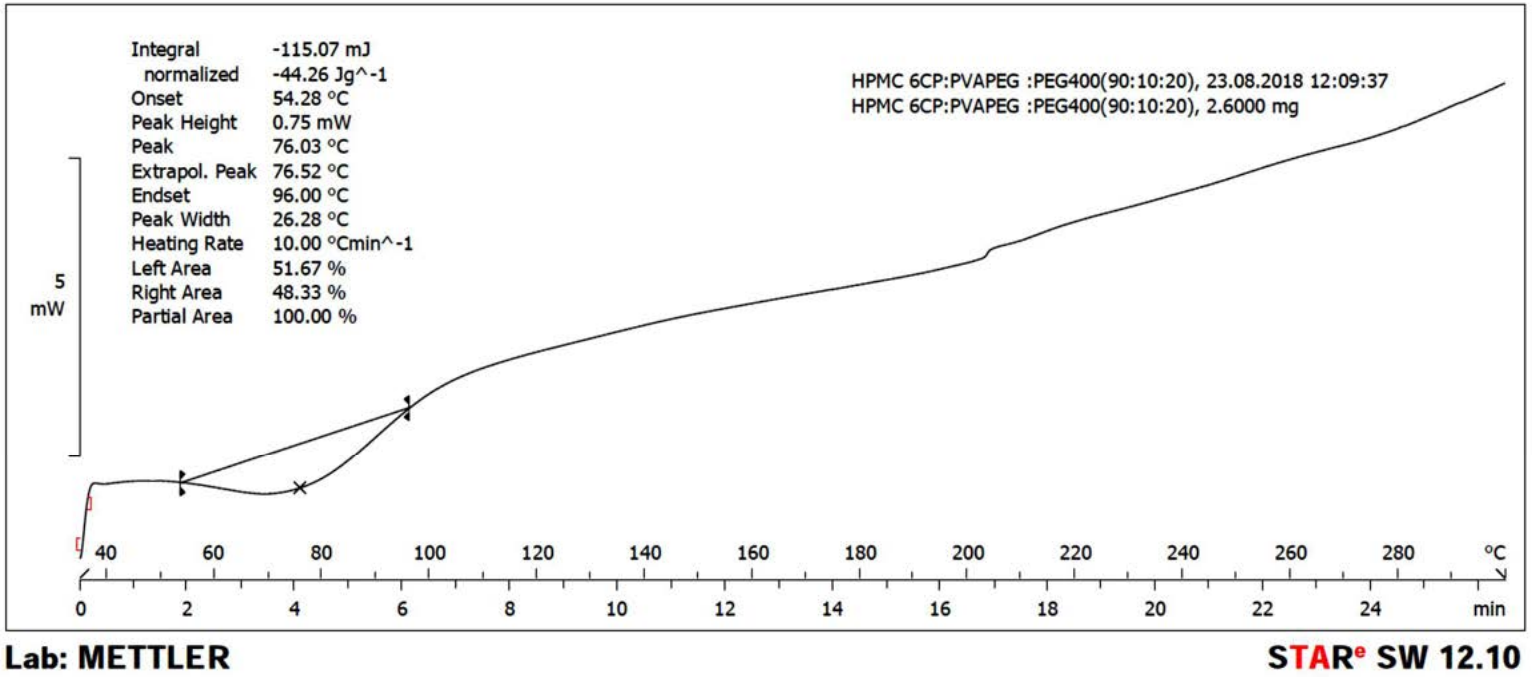
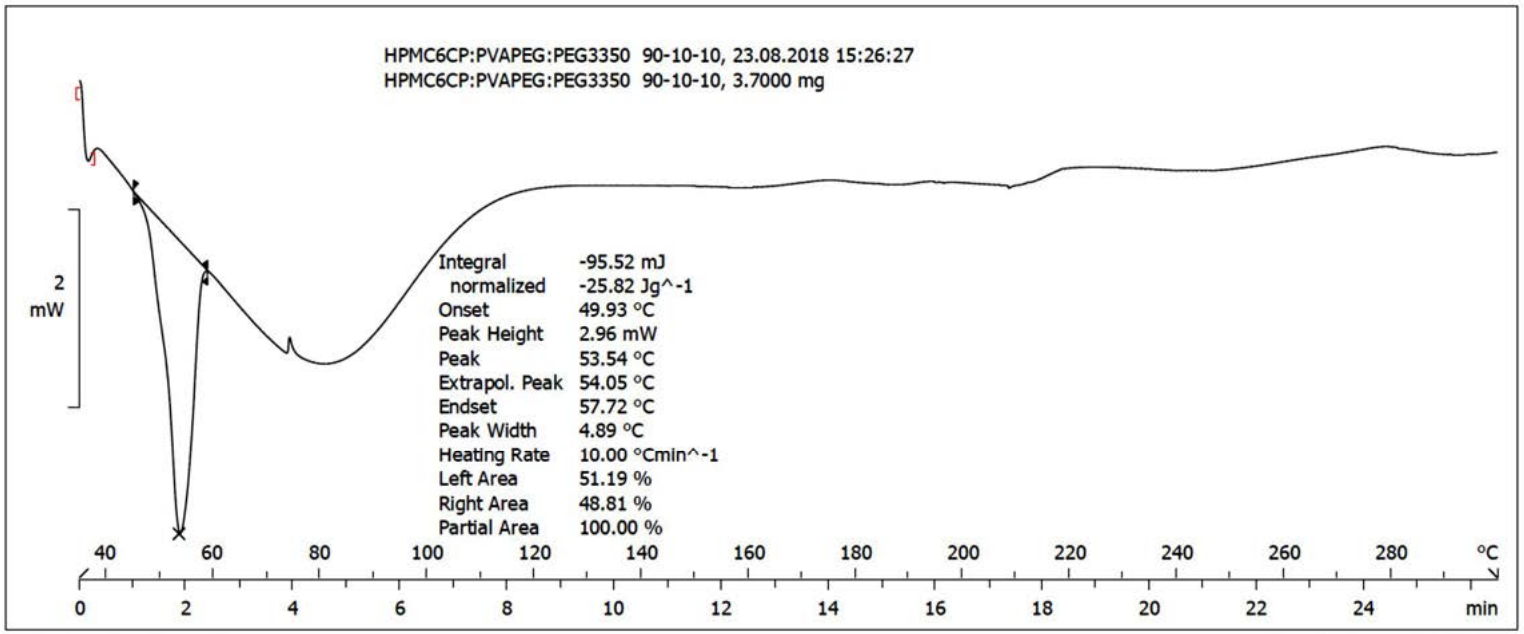
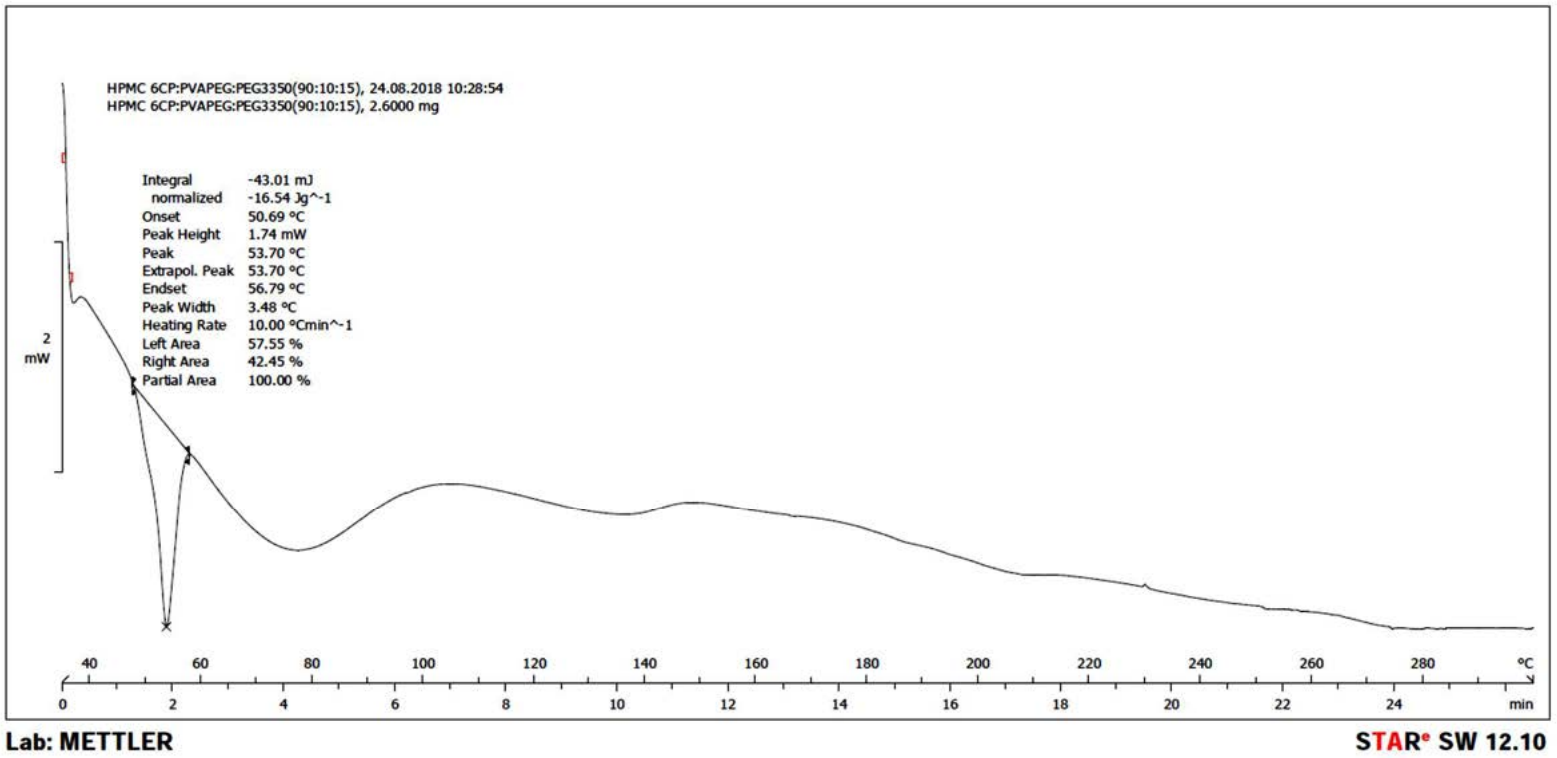


**BATCH 18 - HPMC 6CP:PVA-PEG:PEG 3350 (90:10:10)**

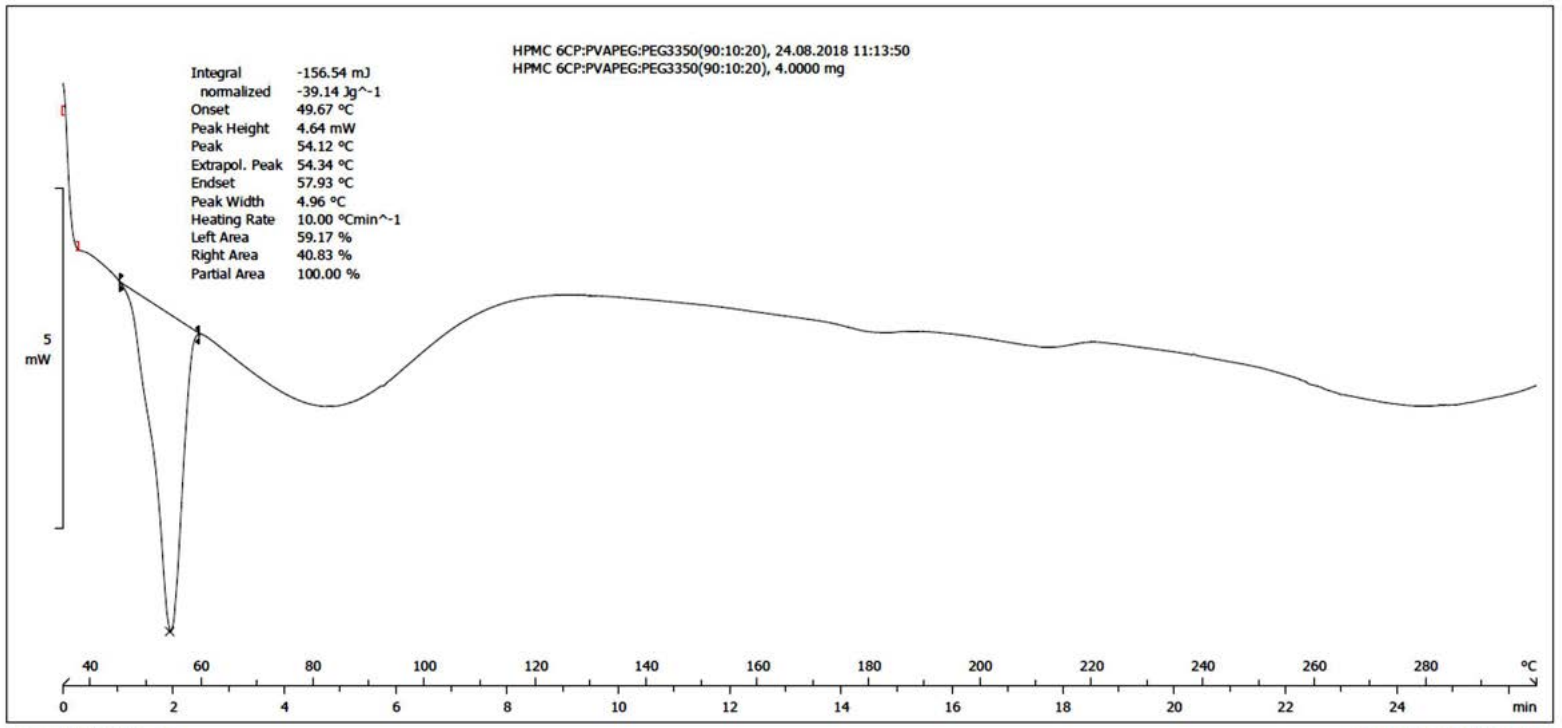



**Lab: METTLER** **STARe SW 12.10**

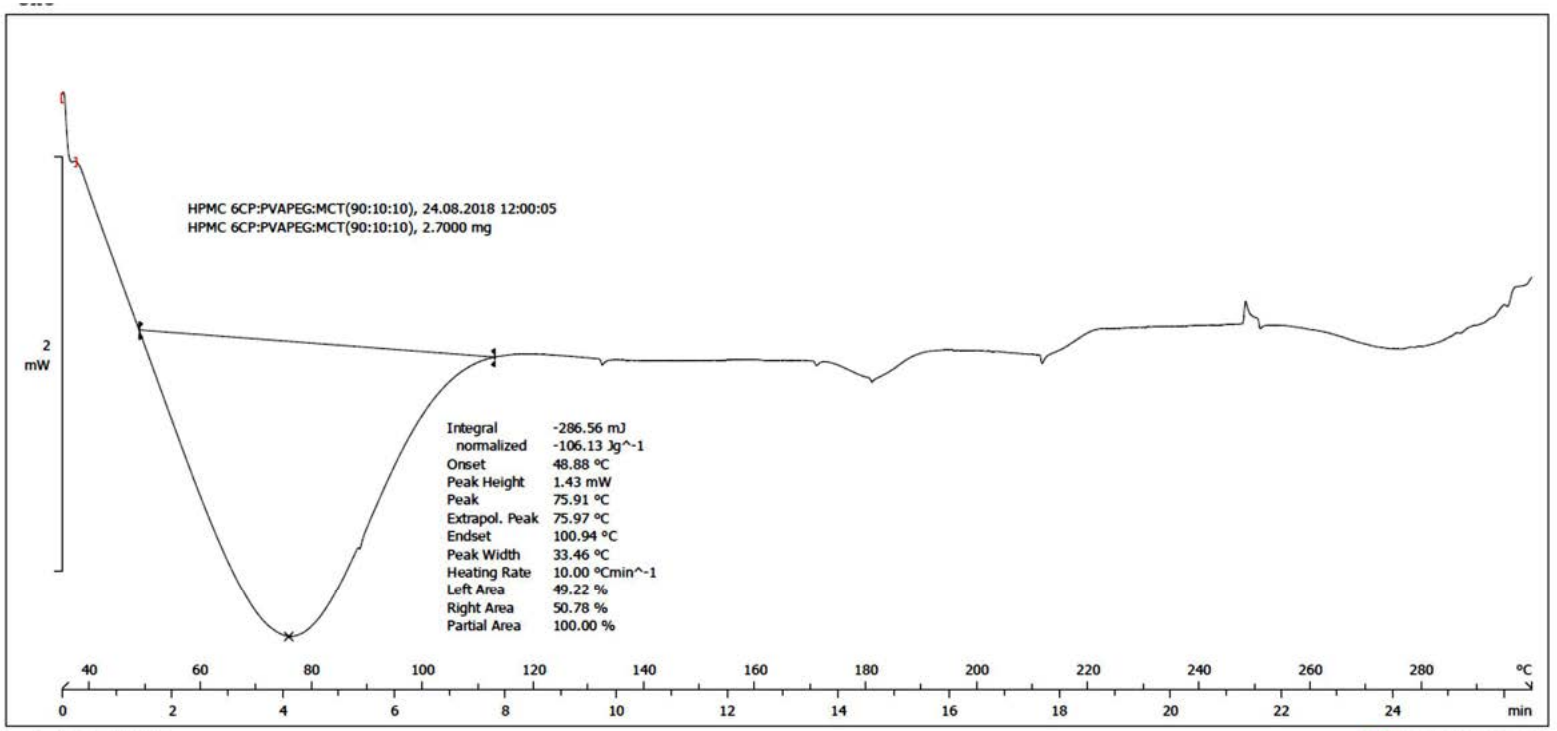
**BATCH 19 - HPMC 6CP:PVA-PEG:PEG 3350 (90:10:15)**



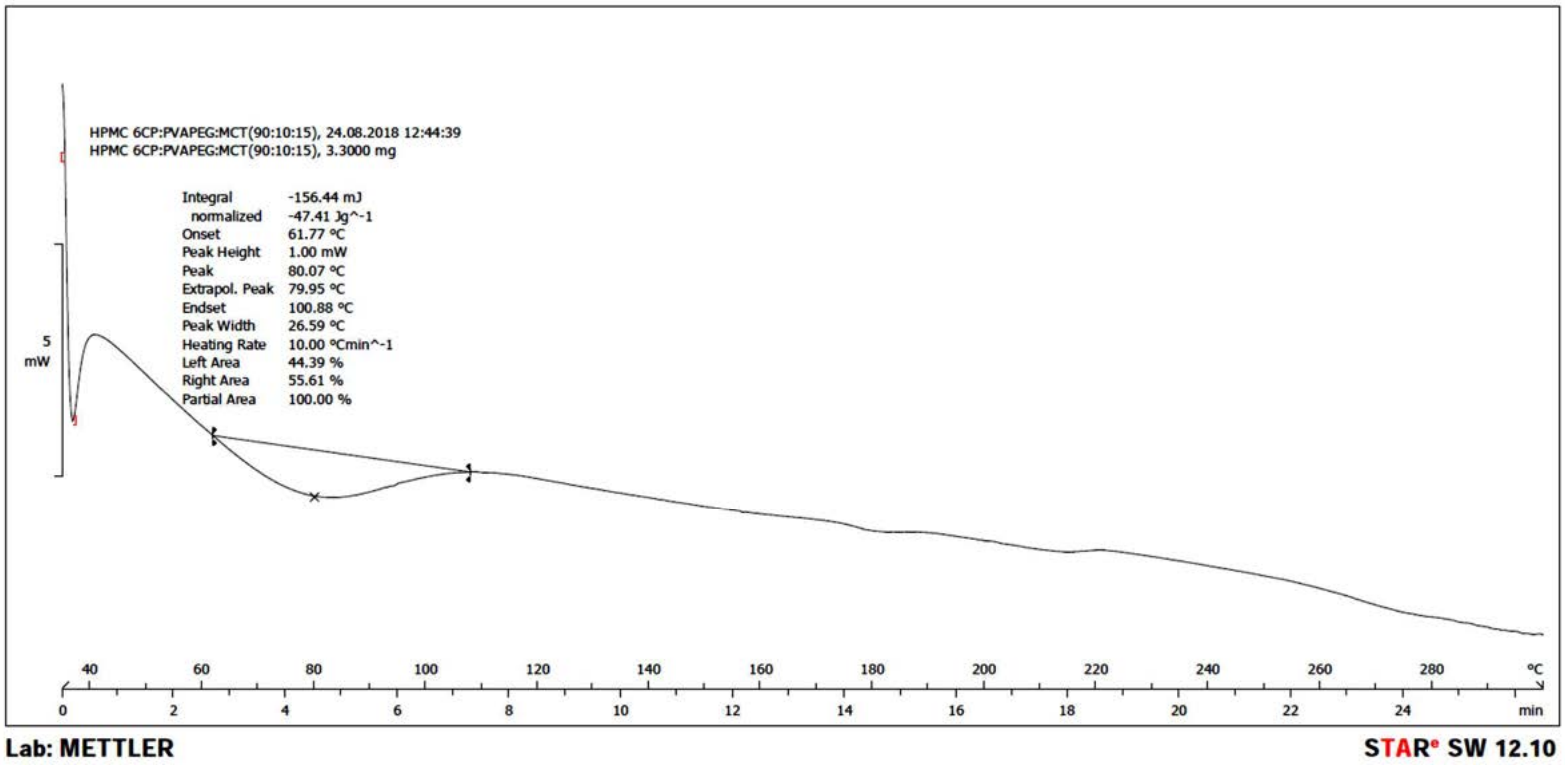
**BATCH 20 - HPMC 6CP:PVA-PEG:PEG 3350 (90:10:20)**



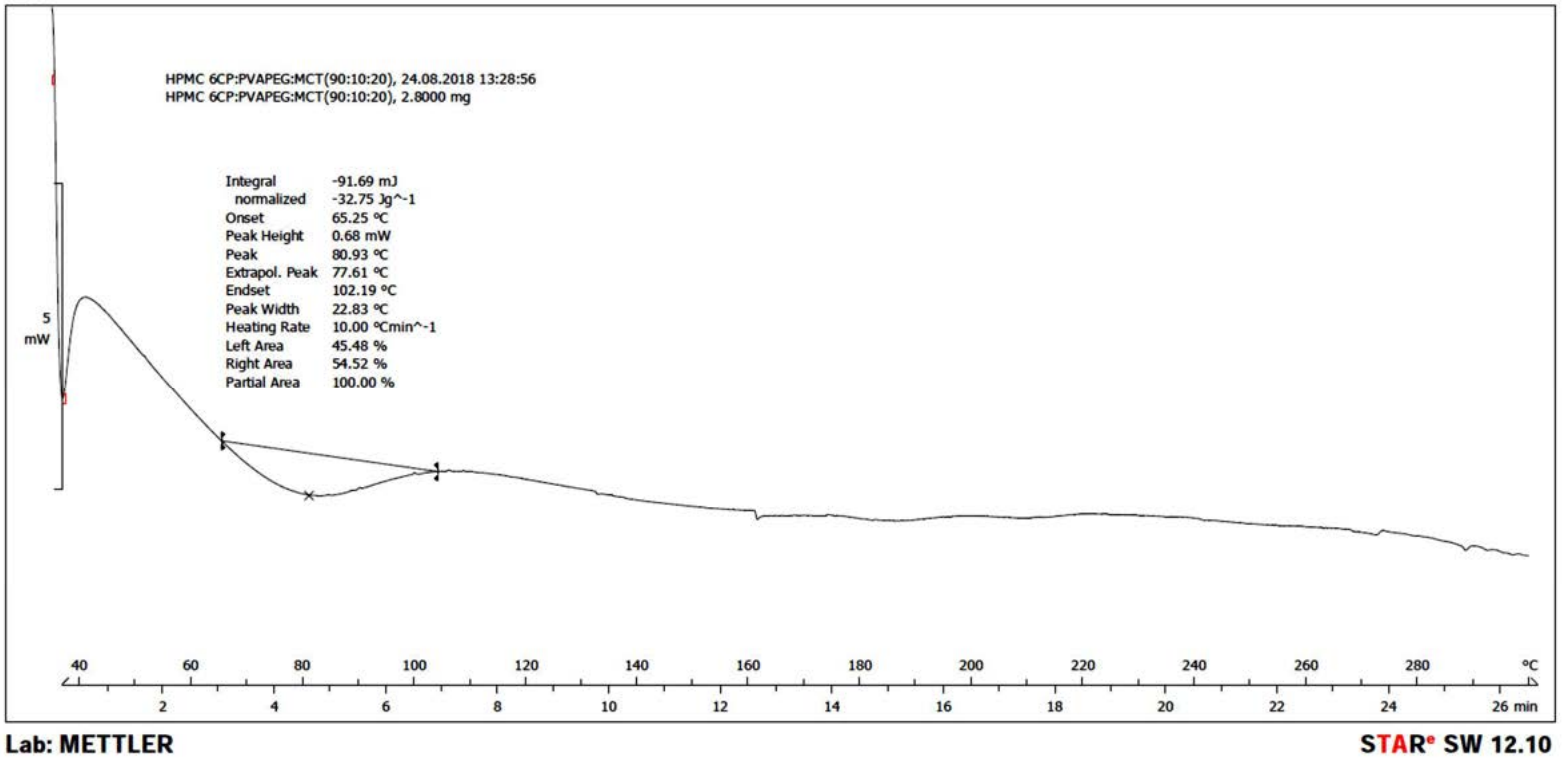
**BATCH 21 - HPMC 6CP:PVA-PEG:MCT (90:10:10)**



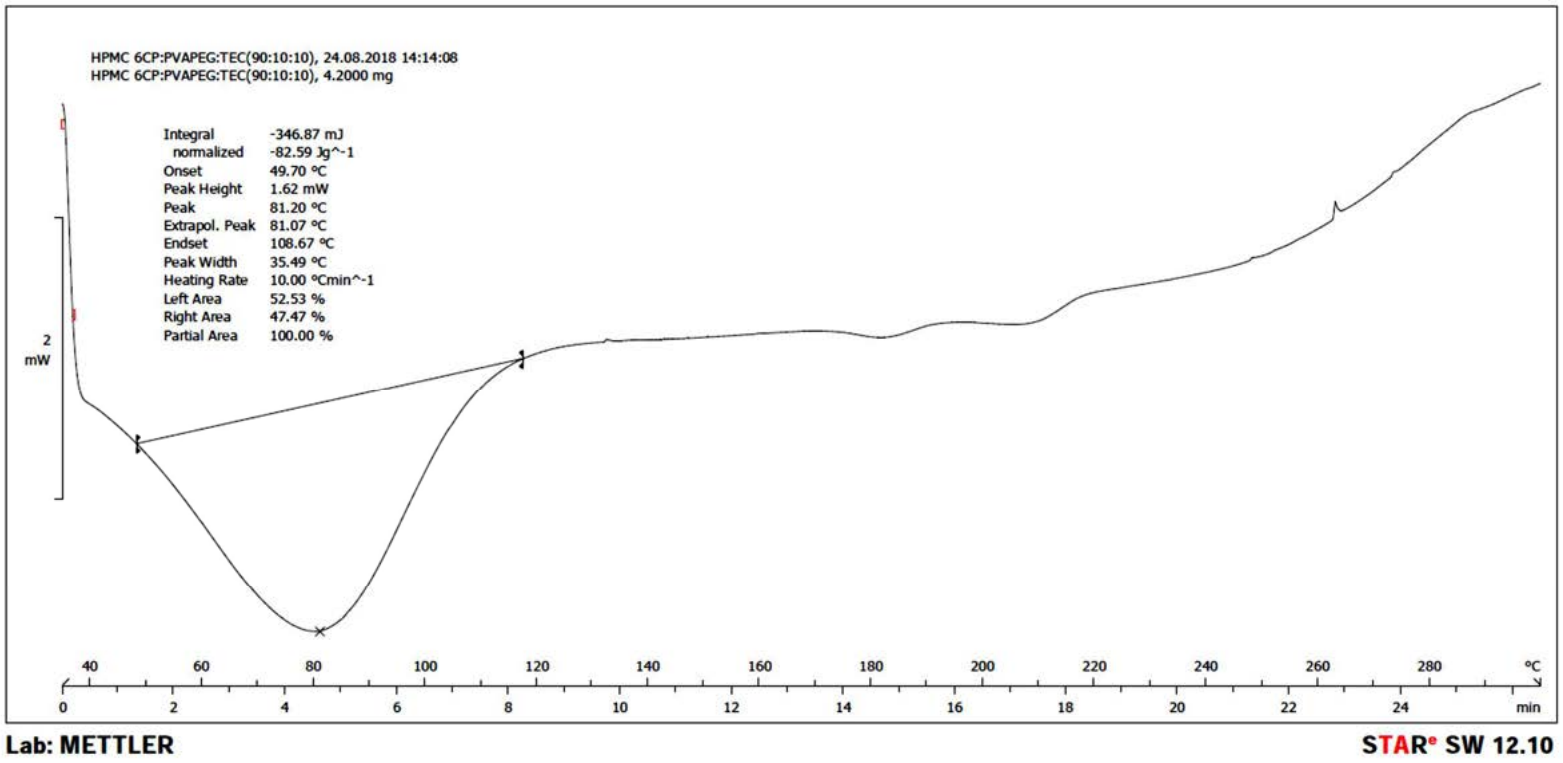
**BATCH 22 - HPMC 6CP:PVA-PEG:MCT (90:10:15)**



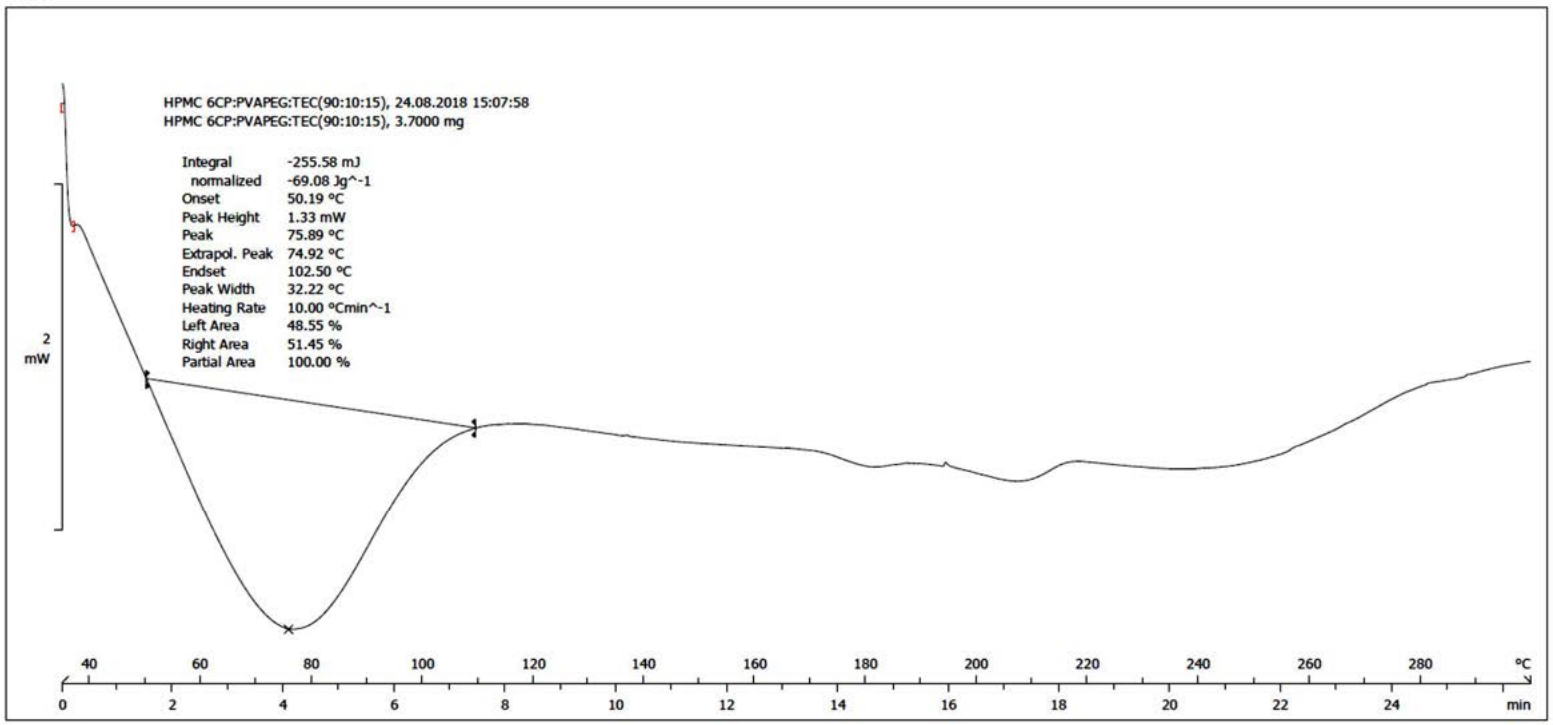
**BATCH 23 - HPMC 6CP:PVA-PEG:MCT (90:10:20)**



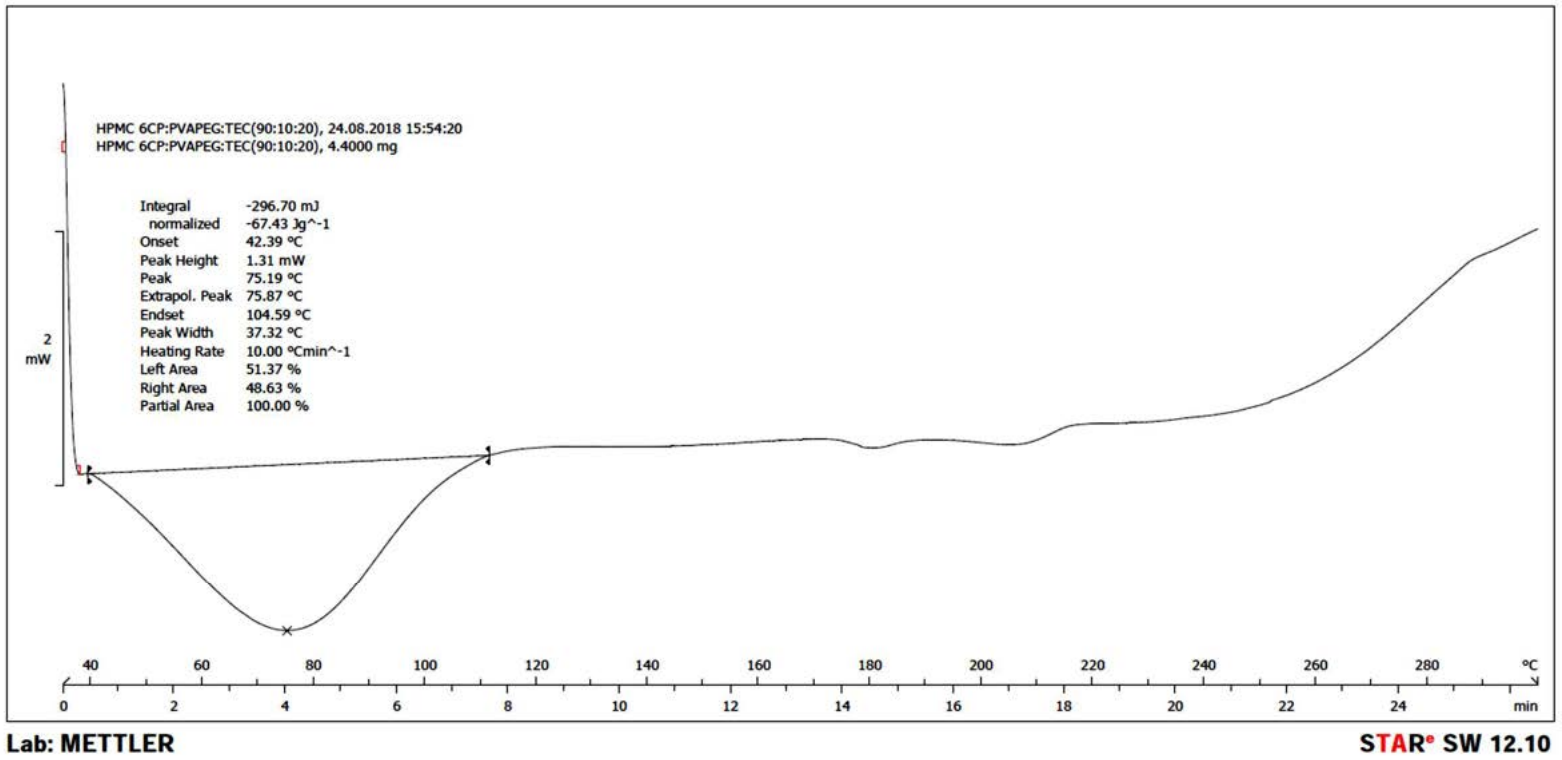
**BATCH 24 - HPMC 6CP:PVA-PEG:TEC (90:10:10)**



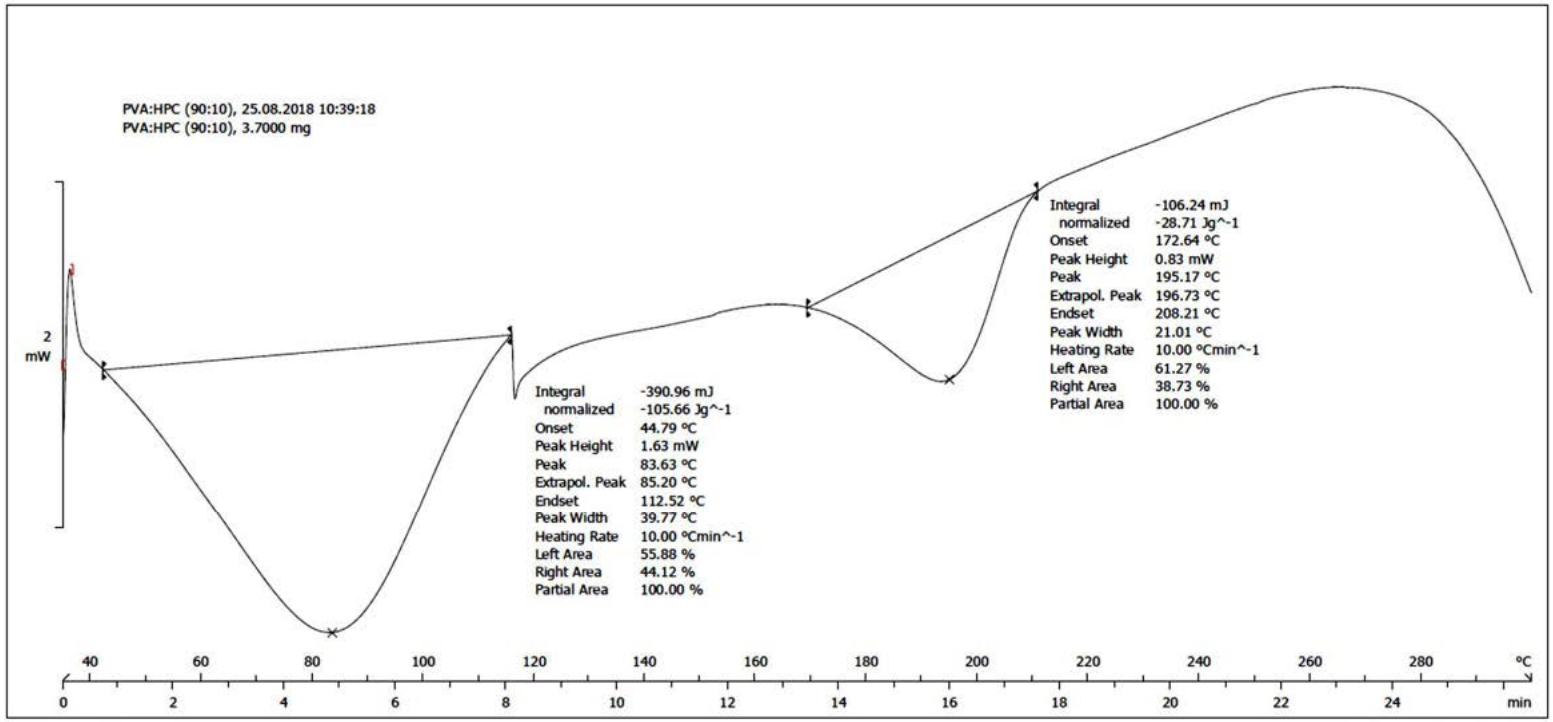
**BATCH 25 - HPMC 6CP:PVA-PEG:TEC (90:10:15)**



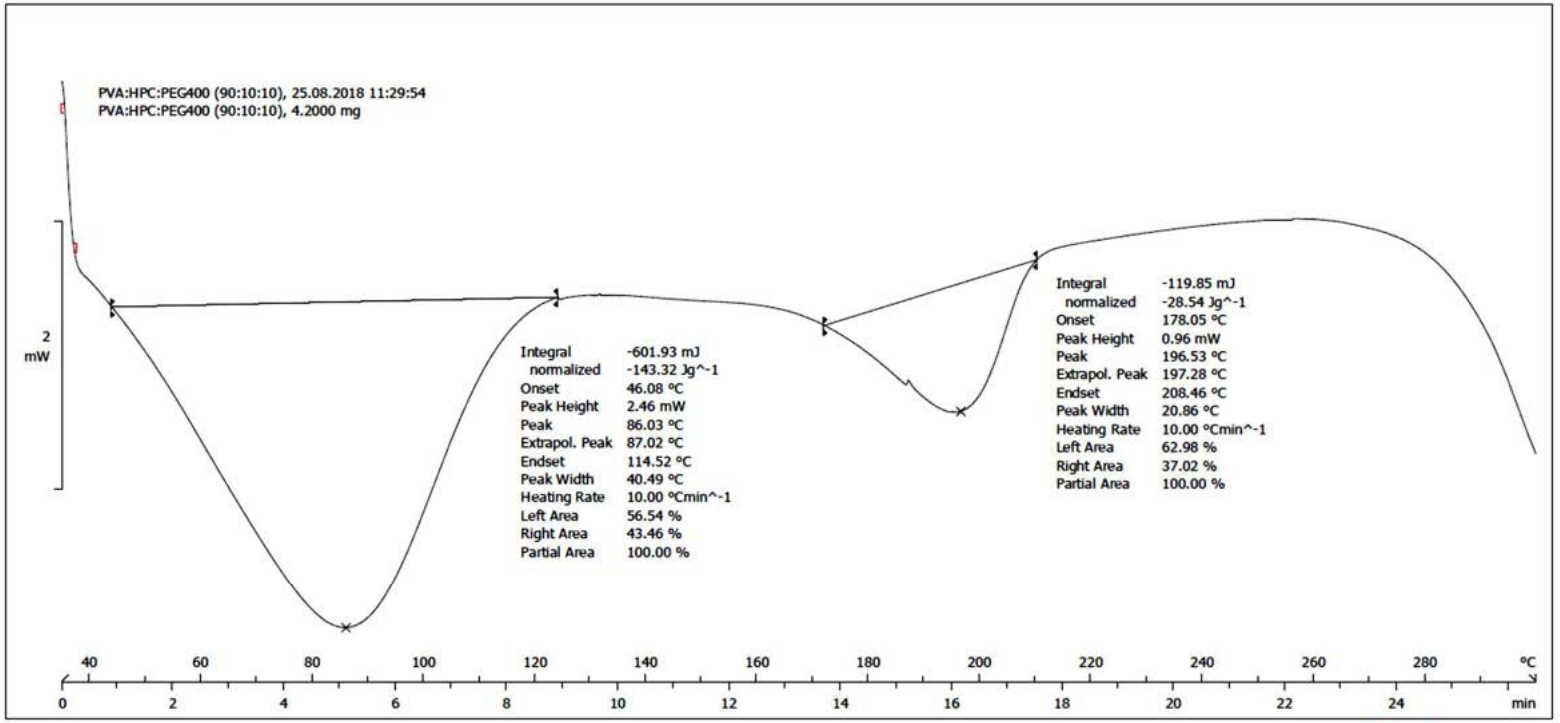
**BATCH 26 - HPMC 6CP:PVA-PEG:TEC (90:10:20)**



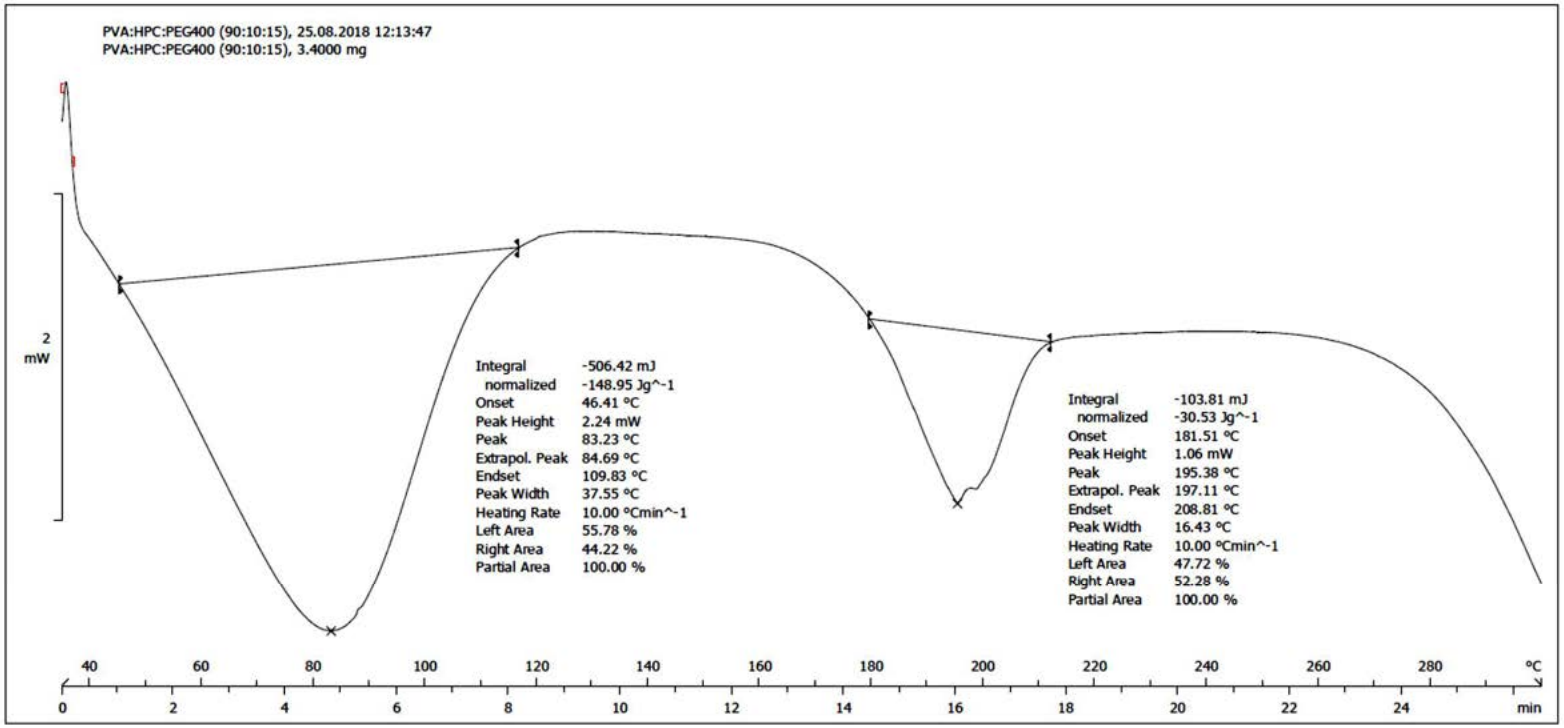
**BATCH 27 - PVA:HPC (90:10)**



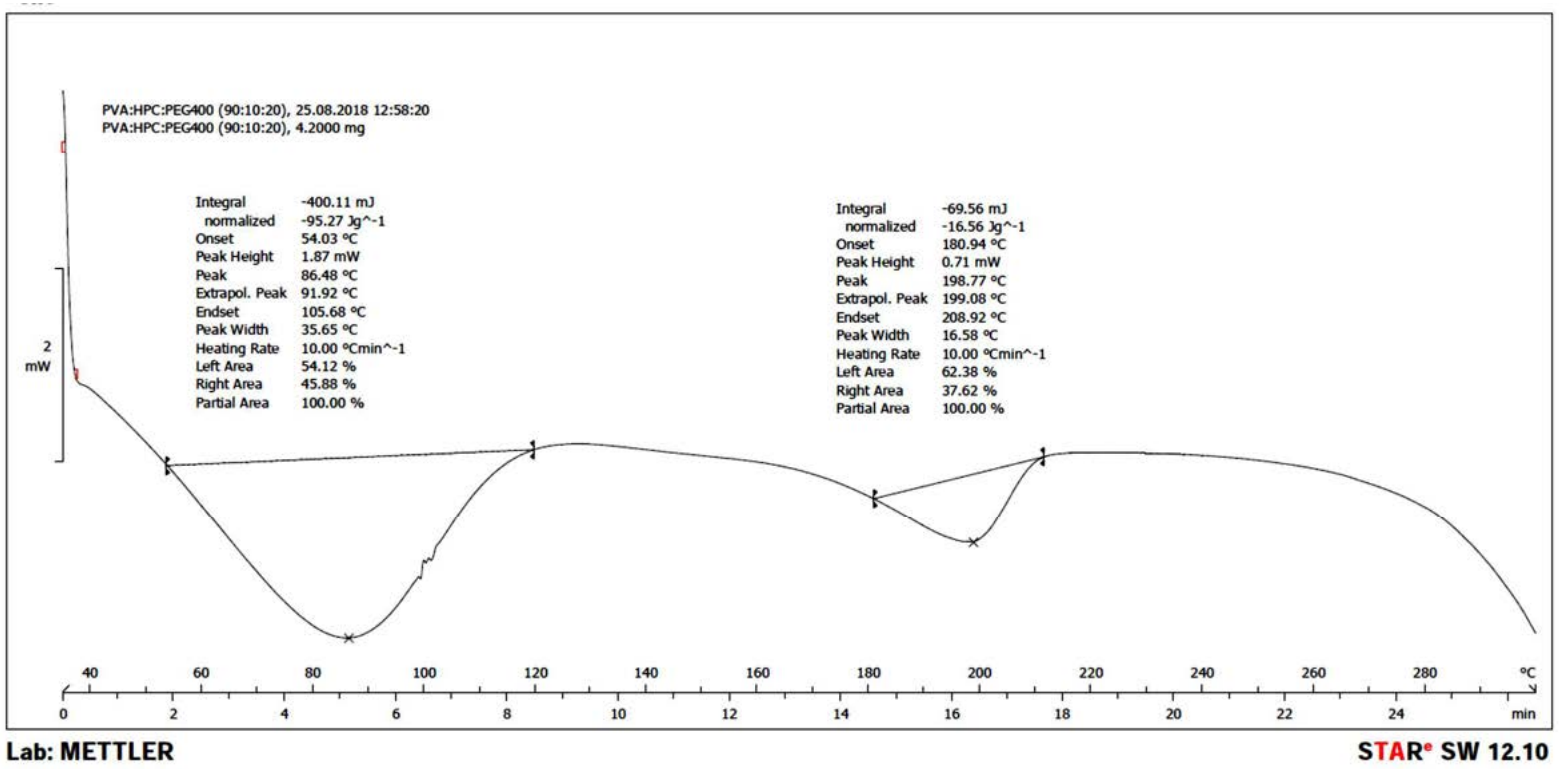
**BATCH 28 - PVA:HPC:PEG 400 (90:10:10)**



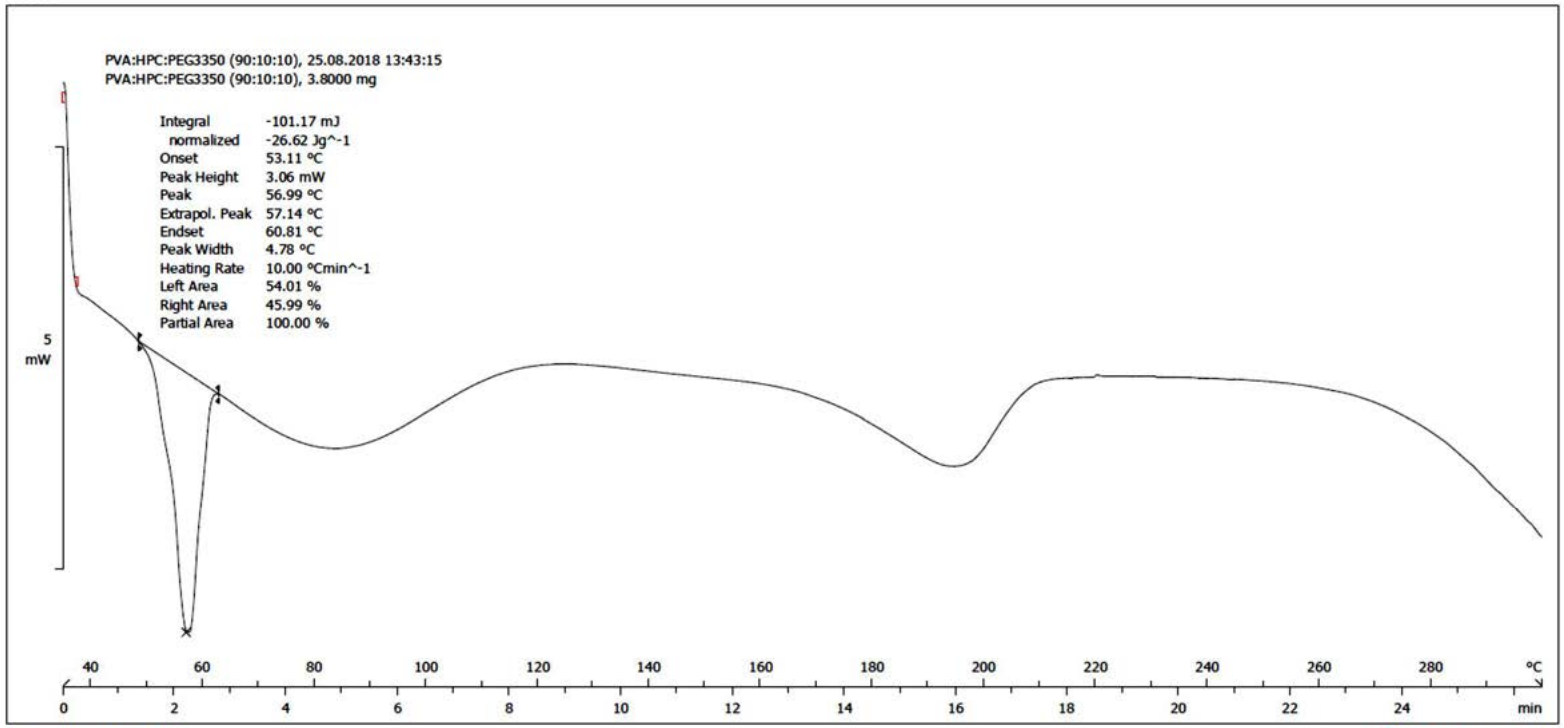
**BATCH 29 - PVA:HPC:PEG 400 (90:10:15)**



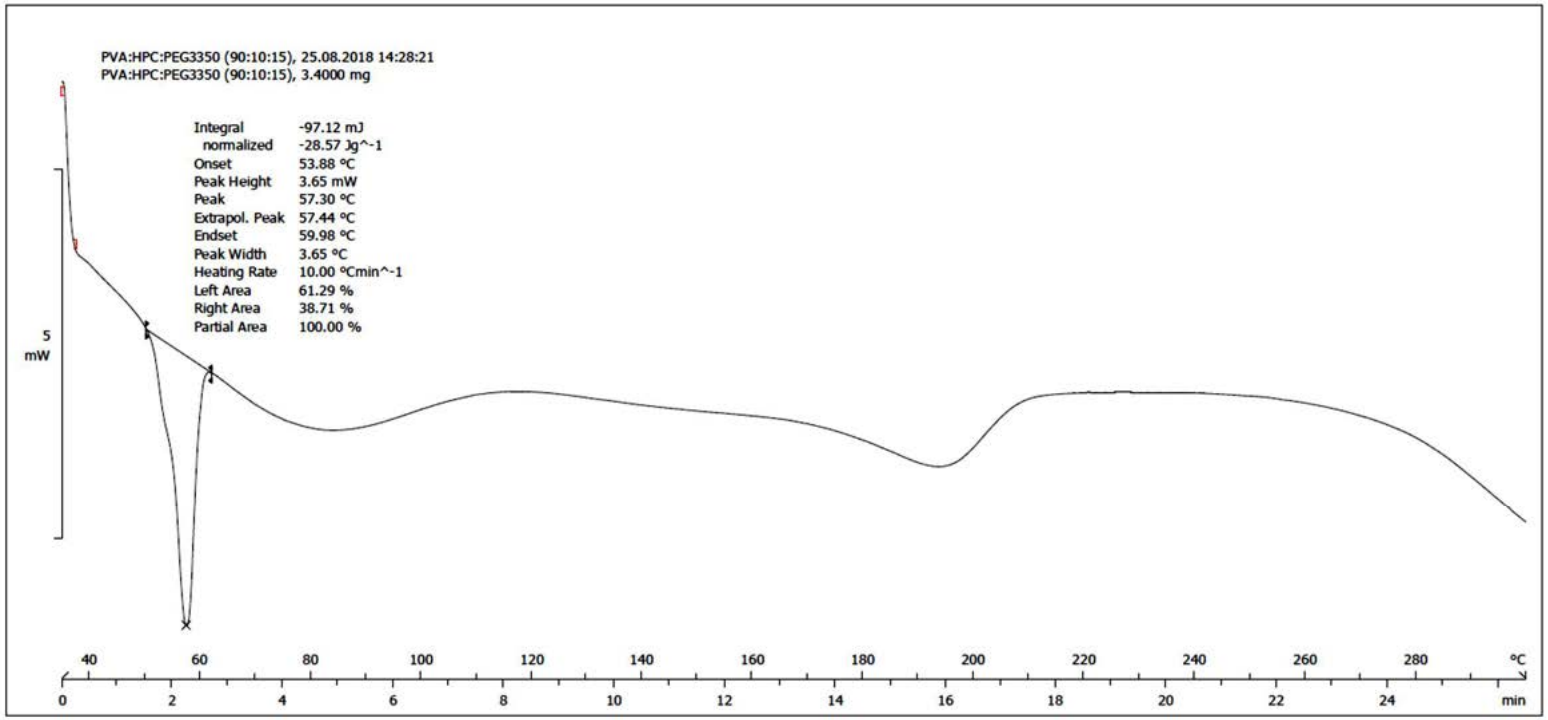
**BATCH 30 - PVA:HPC:PEG 400 (90:10:20)**



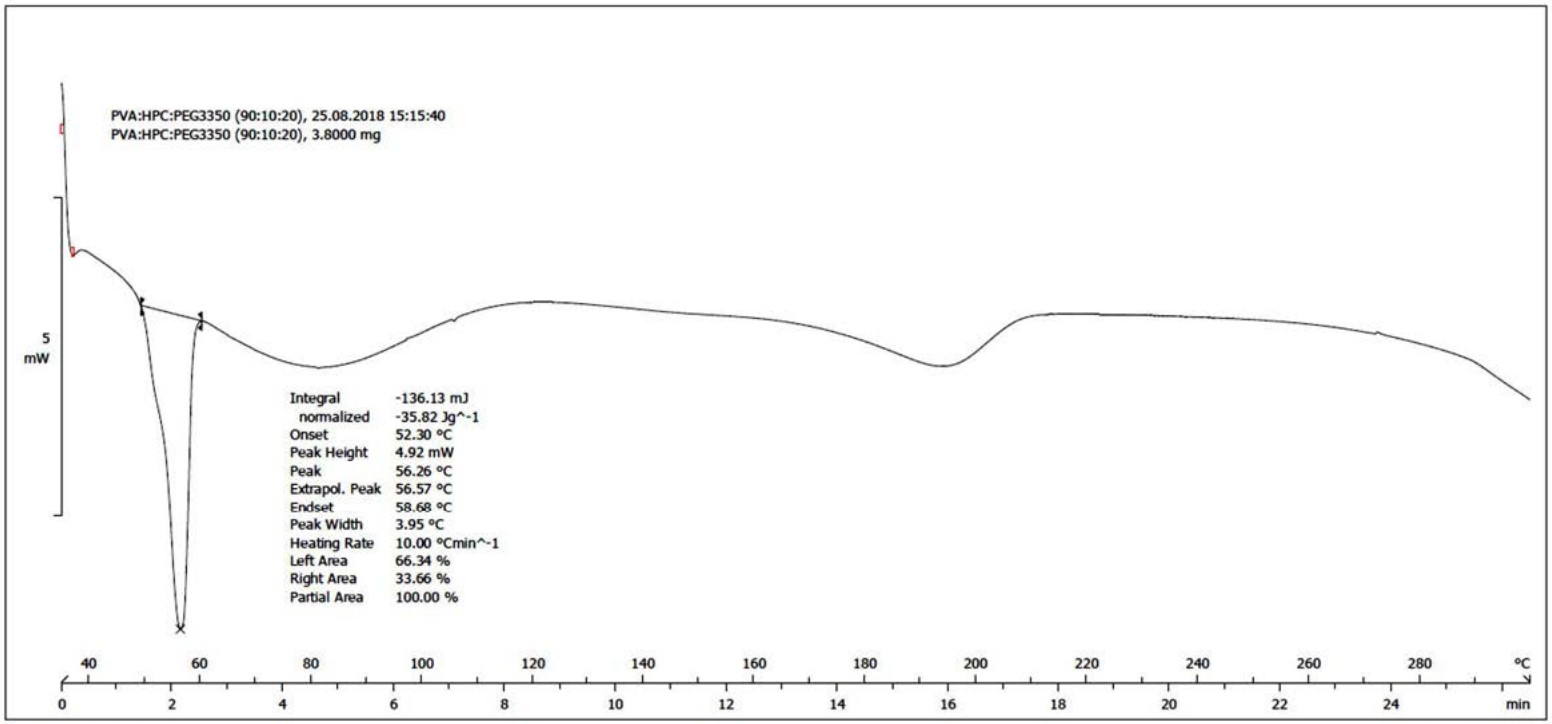
**BATCH 31 - PVA:HPC:PEG 3350 (90:10:10)**



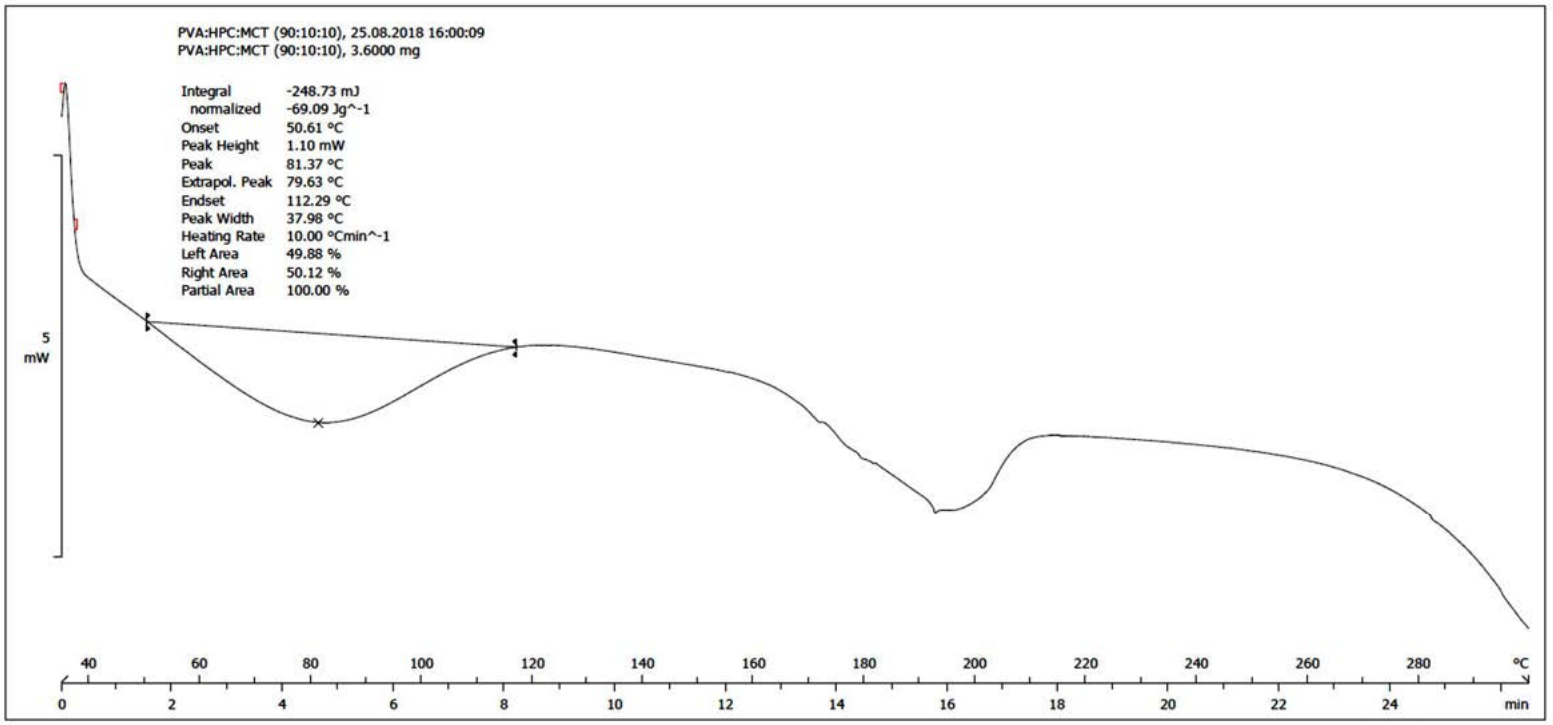
**BATCH 32 - PVA:HPC:PEG 3350 (90:10:15)**



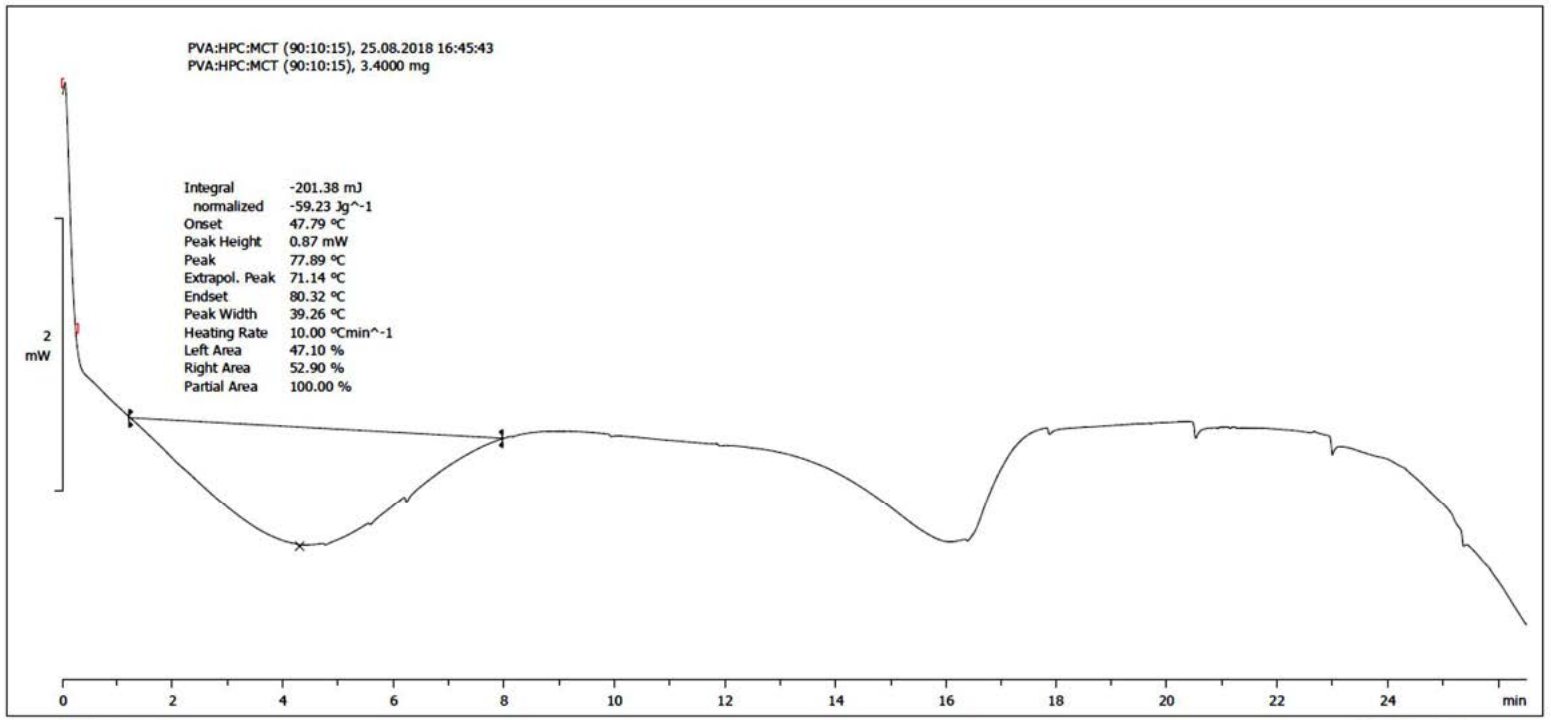
**BATCH 33 - PVA:HPC:PEG 3350 (90:10:20)**



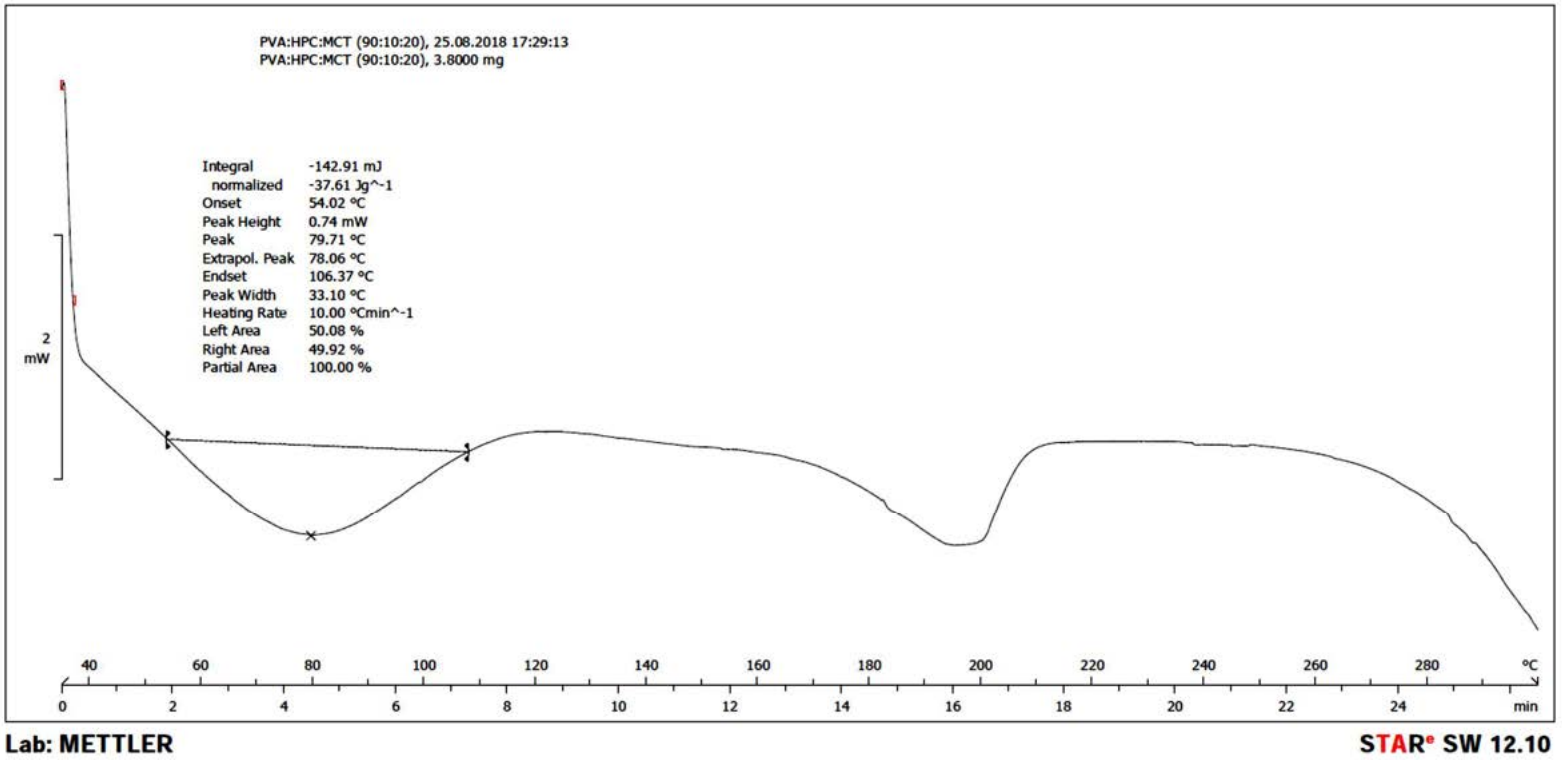
**BATCH 34 - PVA:HPC:MCT (90:10:10)**



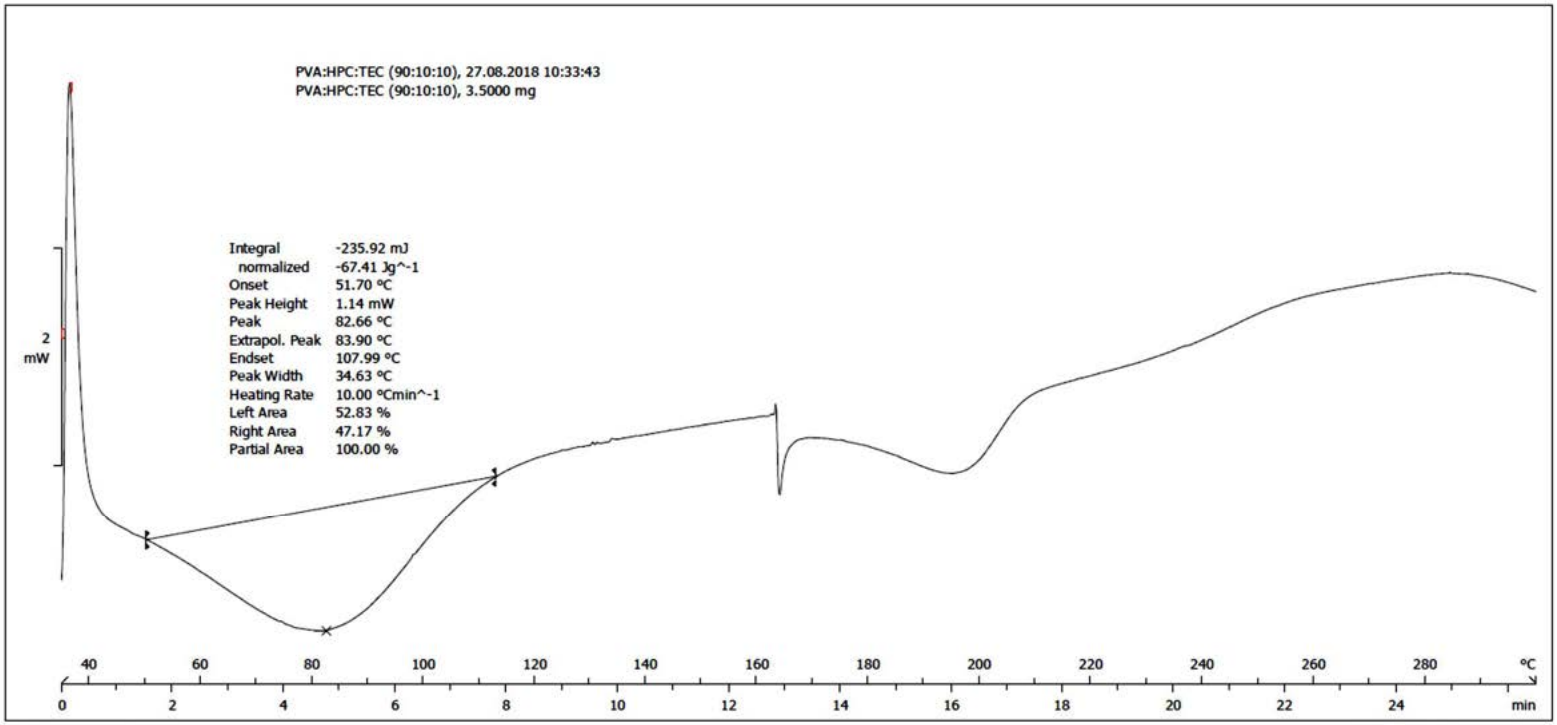
**BATCH 35 - PVA:HPC:MCT (90:10:15)**



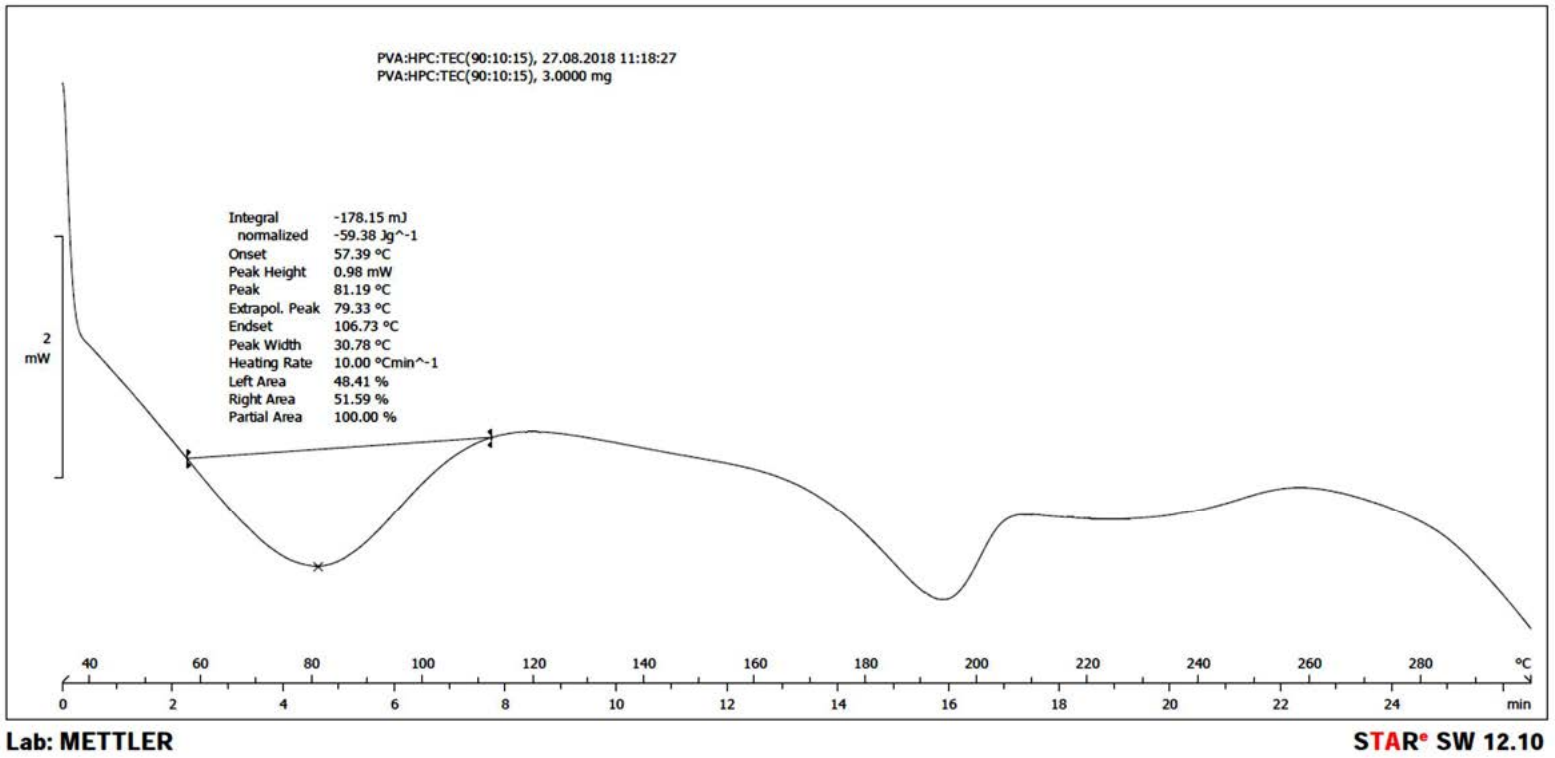
**BATCH 36 - PVA:HPC:MCT (90:10:20)**



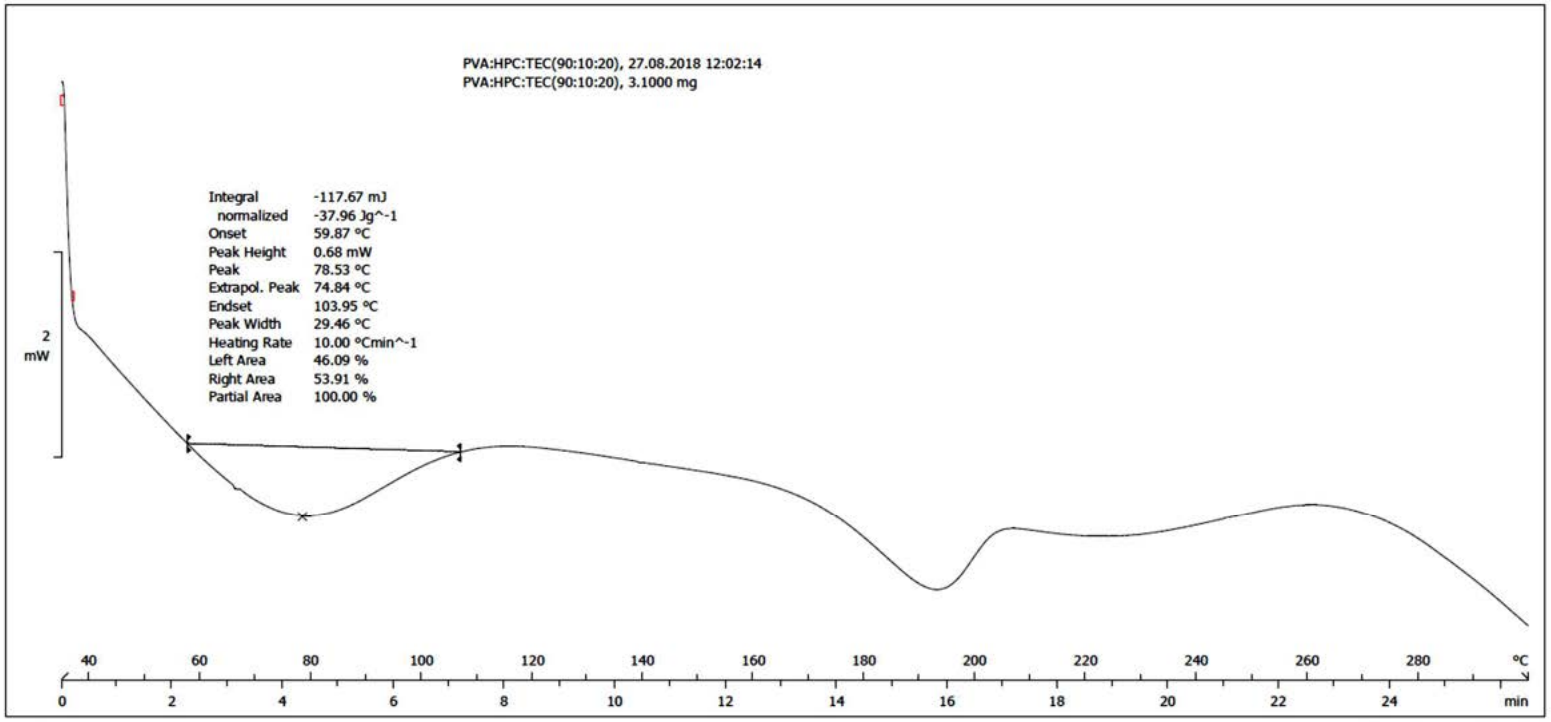
**BATCH 37 - PVA:HPC:TEC (90:10:10)**



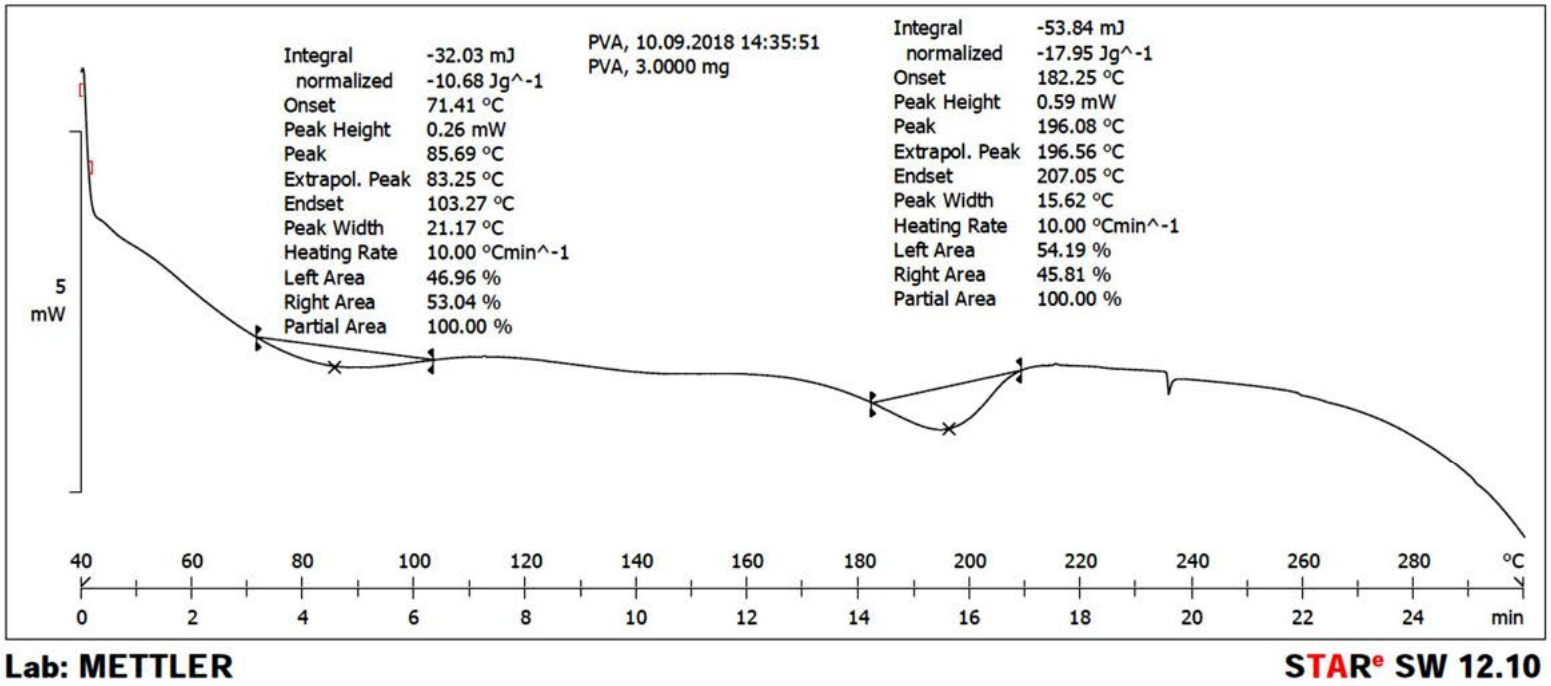
**BATCH 38 - PVA:HPC:TEC (90:10:15)**



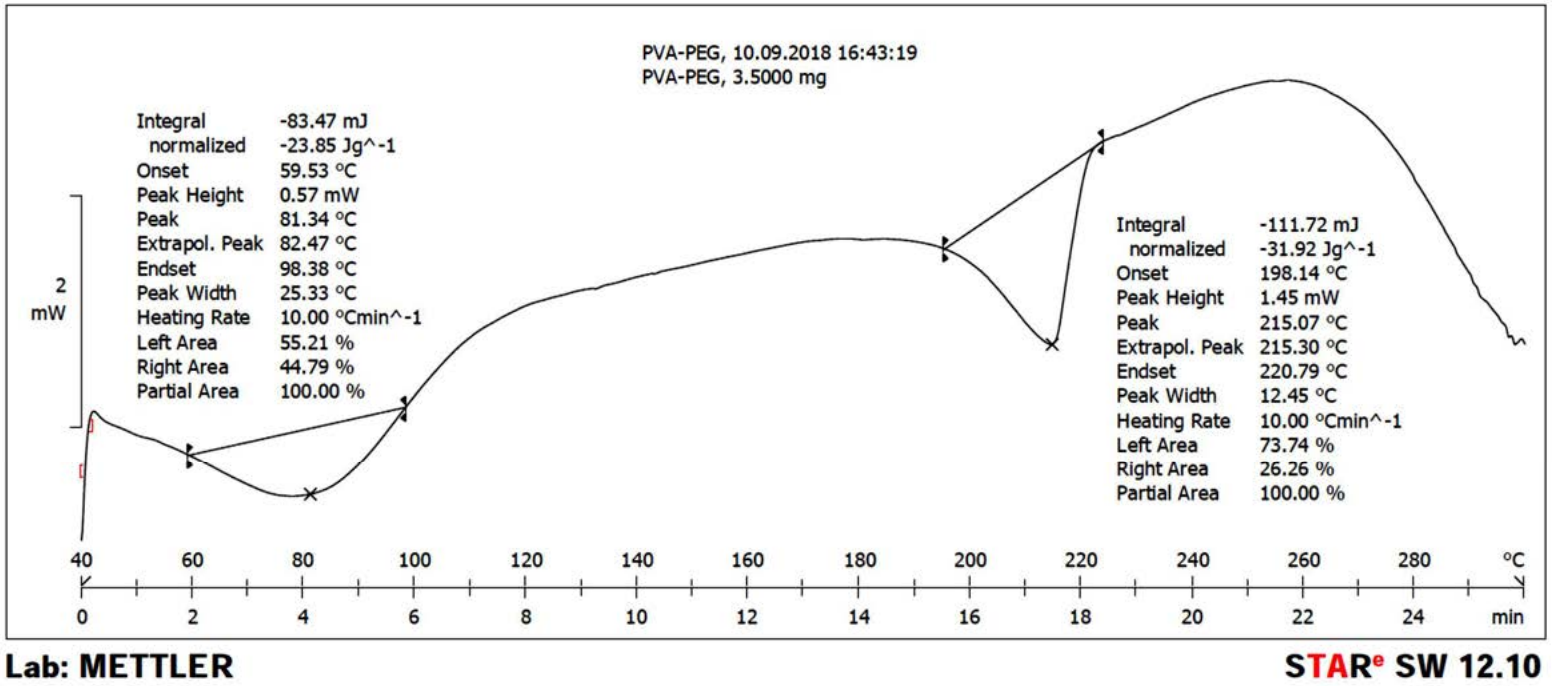
**BATCH 39 - PVA:HPC:TEC (90:10:20)**



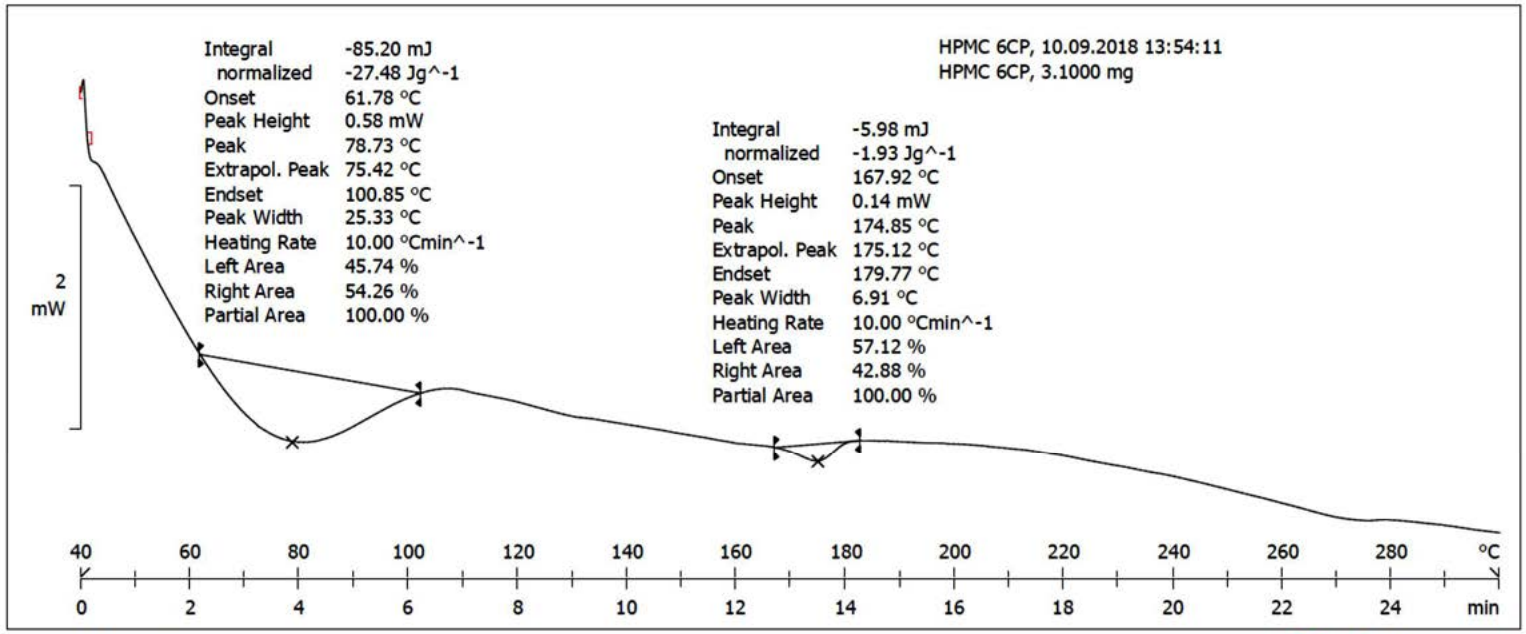
**Poly vinyl alcohol (PVA)**



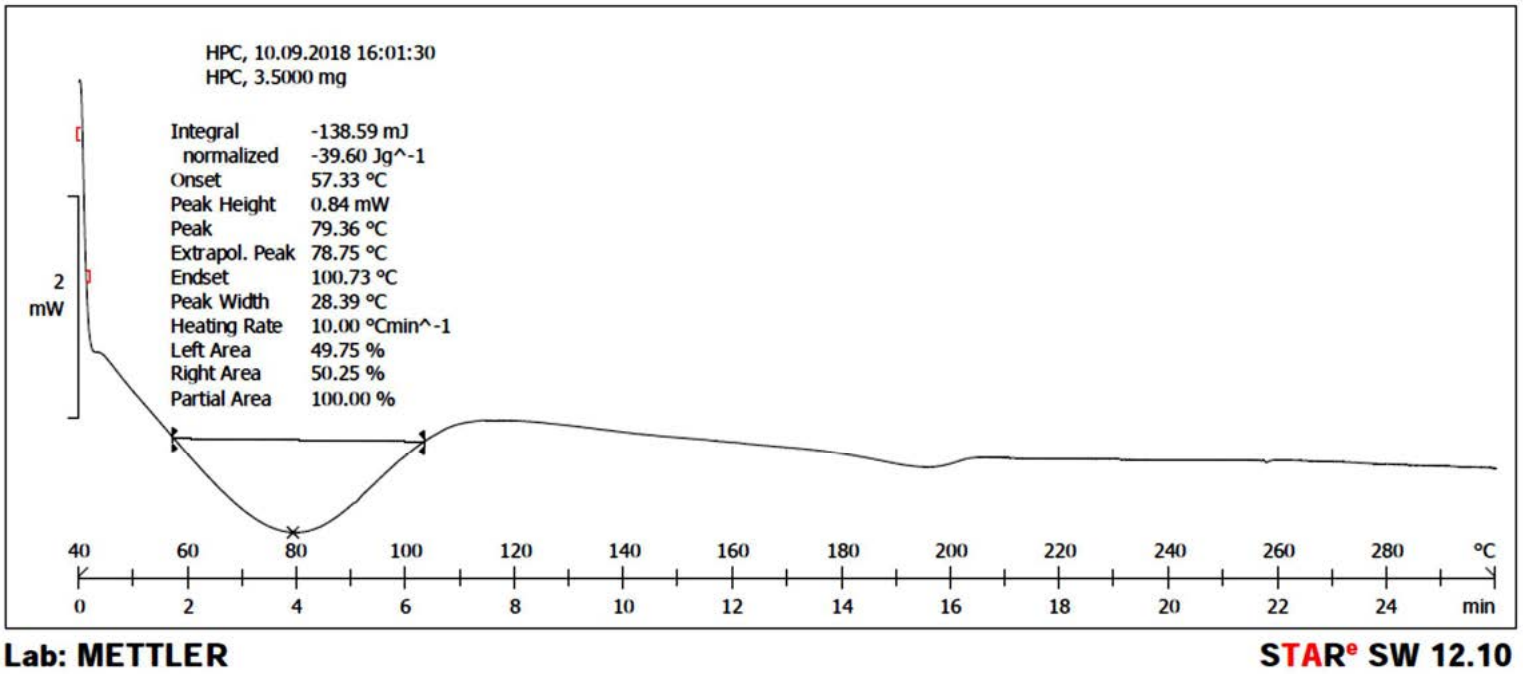
**Polyvinyl alcohol + PEG graft co-polymer (PVA-PEG)**



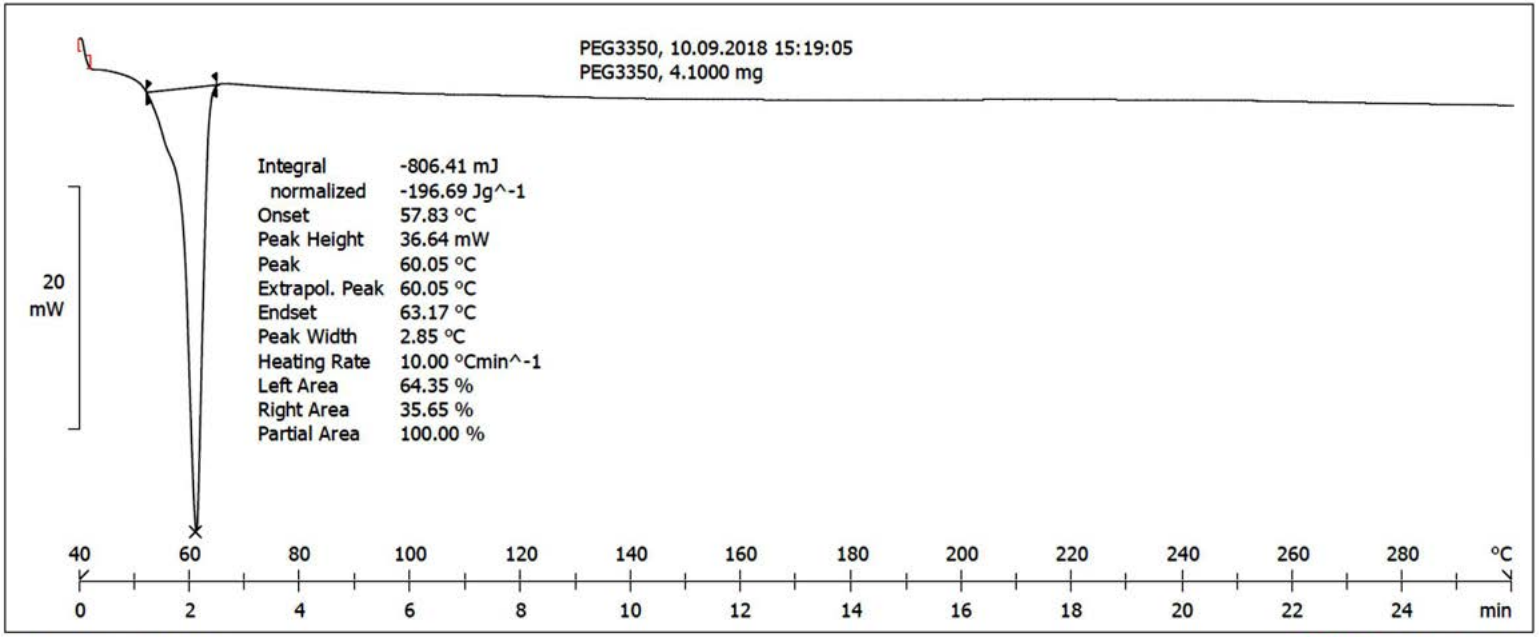
**Hypromellose 6cp (HPMC)**



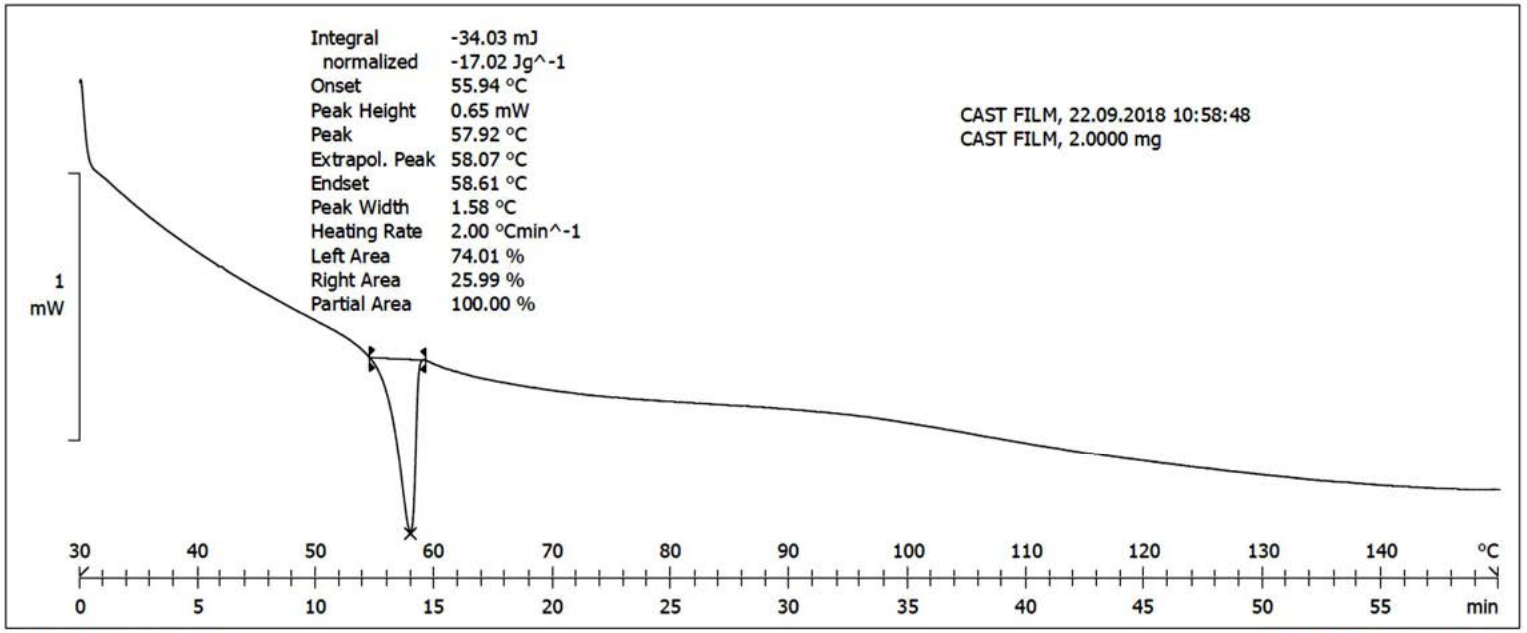
**Hydroxypropyl Cellulose (HPC)**



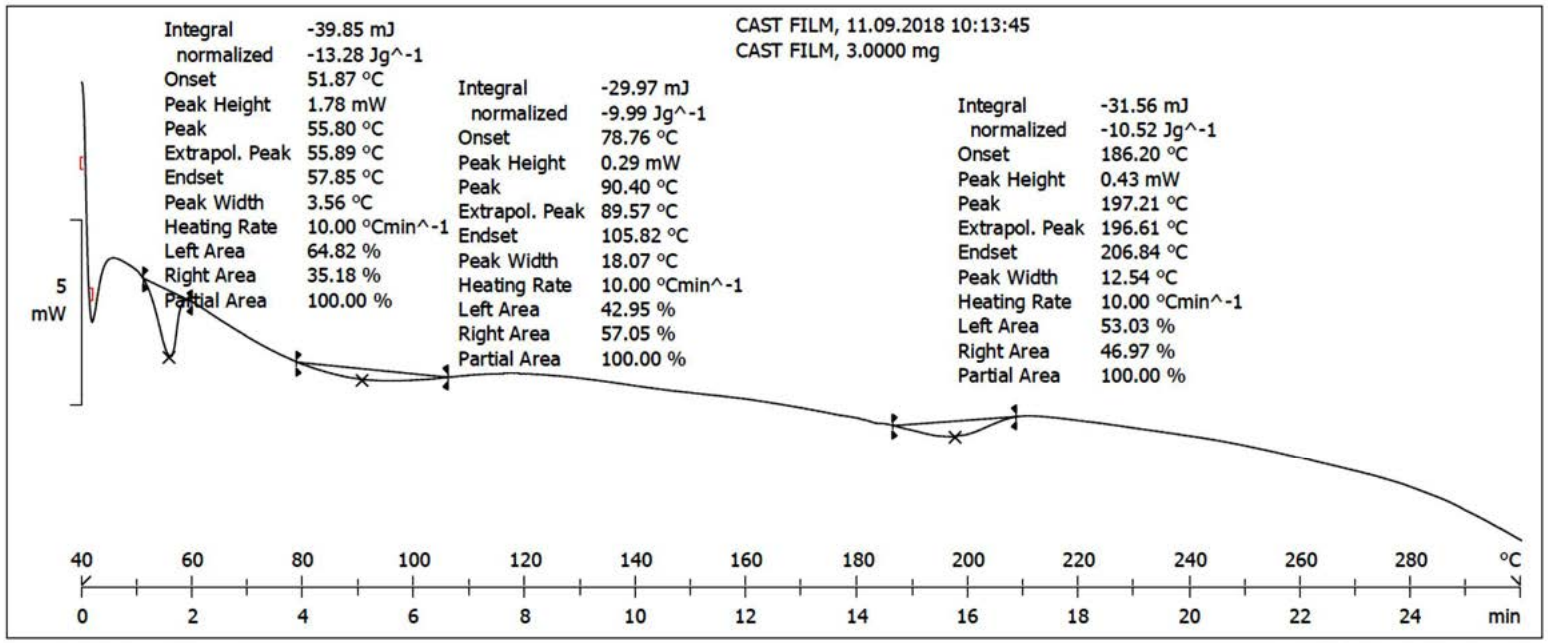
**Polyethylene Glycol 3350 (PEG 3350)**



**Casted Films of Polymer Blend – PVA:PVA-PEG (90:10) + 10% PEG 3350**



**Casted Film of Polymer Blend – PVA:PVA-PEG (90:10) + 20% PEG 3350**



# *ANNEXURE – II*

# *LIST OF PUBLICATIONS*

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*Journal of Global Trends in Pharmaceutical Sciences*

# FILM COATING POLYMERS–UNDERSTANDING SYNERGY OF BLENDS ON MECHANICAL PROPERTIES OF FILMS IN AQUEOUS SYSTEM

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PVA-PEG Graft Copolymer,
HPMC, HPC,
Mechanical Property,
Tensile Strength,
Young's Modulus.

**ABSTRACT**

Mechanical strength (of casted film) and viscosity (in aqueous media) parameters have been accessed using polymer blend of PVA: Sodium CMC; PVA: PVA-PEG; PVA: HPC and HPMC 6cP: PVA-PEG at concentration ratio's of 90:10, 80: 20, 70:30, 60:40 and 50:50 respectively. The presence of PVA and PVA-PEG polymers in a different ratios resulted in lowering the viscosity of polymer blends in aqueous solution. Similarly, the presence of PVA and PVA-PEG in polymer blend exhibited great impact on Young's Modulus and extension at break of casted film. PVA has high tensile strength and flexibility [23]. Tensile strength properties of the casted films are discussed with particular reference to Young's Modulus and Extension at break for the polymer blends.

## INTRODUCTION:

Polymer is a large molecule, or macromolecule, composed of many repeated subunits. The term "polymer" derives from the ancient Greek word *polus*, meaning "many, much" and *meros*, meaning "parts", and refers to a molecule whose structure is composed of multiple repeating units, from which originates a characteristic of high relative molecular mass and attendant properties [1]. Herman Staudinger, who received the Noble Price in Chemistry in 1953, coined the term "macromolecule" in 1922 and used it about polymers [2]. The only difference between the two terms is that polymers are made of repeating units called monomers, whereas macromolecules are generally used to refer to any large molecule not just those made of repeating units. Thus polymers can be considered as subset of macromolecules. Polymers are widely used in pharmaceutical industry from centuries due to wide range of application and advantages offered by them in modern medicine [3]. Most predominantly used group of polymers are the cellulose ethers, which includes hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) methylcellulose (MC) and acrylates. One of the main applications of these polymers is used in the manufacturing of film coating system. The film coating systems provides a physical protection to the dosage form which is depending on its mechanical characteristics and this is important to predict the stability and release property of film-coated dosage form. The selection of a polymer for coating application depends on many factors, such as polymer solubility, viscosity, film permeability and mechanical properties of film coat. In the development of a film coating system, evaluation of the mechanical properties of free films can readily characterize the fundamental properties of the coating.

The mechanical properties of polymers may range between an almost perfect elastic state (original strain recovers after removal of an applied stress) to an almost Newtonian viscous state (the deformation is permanent and the original strain is not recovered). Lever & Rhys classify the properties of film coat on the basis of their characteristic stress-strain curves (soft and weak, soft and tough, hard and brittle, hard and strong, hard and tough)[4]. Tobolsky observed in deformational behaviour (viscoelasticity behaviour), polymers may undergo different regions such as glassy, transition, rubbery, rubbery liquid and liquid [5]. The mechanical properties of such film coat are often determined on polymeric films prepared by casting or spraying techniques [6] and elucidated in terms of glass transition temperature ($T_g$), tensile strength, toughness, elastic or Young's modulus, minimum film forming temperature (MFT), moisture effect and plasticiser performance [7-11]. Ideally increasing the tensile strength of the coating reduces the risk of cracking and reducing the elastic modulus decreases the potential of occurrence of bridging and cracking. These properties will be influenced by environmental factors (temperature, humidity, time, and rate of stressing the polymer, pressure, stress and strain amplitude), the chemical composition of the polymer (molecular weight, crosslinking and branching, crystallinity) and the presence of diluent (plasticiser, residual solvent, additives or fillers) [12, 13].The tensile properties of HPMC films depends on the concentration of pigments (e.g., titanium dioxide); the films became more brittle as the concentration of pigments increased, as evidenced by the decrease in elongation and increase in Young's modulus [14]. Hsu et al, showed the addition of titanium dioxide to polyvinyl alcohol also resulted in a decrease in tensile strength [15]. The presence of a plasticizer in the film coating is essential to reduce the brittle properties and to achieve effective coatings of the pellets or tablets without the formation of cracks or defects. Plasticizers lower the $T_g$ and enhance the coalescence of the colloidal polymeric particles to form a uniform homogenous film over the substrate. Rowe noted that, the average molecular weight and molecular weight distribution of polymers are important factors in the coating process since it will influence not only solution viscosity but also the mechanical properties of the final film coat [16]. For a given polymer-solvent system, the viscosity varies with the molecular weight of the polymer. During the film coating process, the film coating formulations are encountered a wide range of share rates. These range from the low values in the tubing delivering solutions to the spray gun, to values of around 300 to 20,000 $s^{-1}$ as it passes through the spray nozzle to highly variable shear rates produced by the high-velocity atomizing air [17]. Newtonian solutions are likely to exhibit the same rheological behaviour at all stages of the coating process irrespective of the share rate encountered, whereas non-Newtonian behaviour may vary in viscosity at various stages during the coating process and different coating conditions. Most of present scientific work on mechanical properties, rheological profile of film coating system is based on the utilisation of different types of polymers either alone or in combination with other additives (plasticizer, pigments and solvent system); also commercially formulated coating system are available with either single polymer or combination of polymers at different ratios along with other additives to enhance the effectiveness of films coat for providing better protection to the pharmaceutical dosage form, however, limited data is available on mechanical properties of film coat formulated using blends of polymer in aqueous system. Therefore, present work of determination of mechanical properties (of casted film) and viscosity (of aqueous solution) is emphasized on blends of polymers to find the best ratio of polymer blends that can be used in coating system. The main objective of this work was to investigate the mechanical properties of polymer blends at different ratios in aqueous system. Two most useful assessments of polymer blends are described in this article; viscosity and tensile testing.

## METHODS AND PROCEDURES

### Materials:

Following polymers were used for preparation of polymer blend:

- Poly (vinyl alcohol) (PVA), Manufacturer: Nippon Gohsei

(Gohsenol GL-05FS), Lot No.: 64M52T, Viscosity: 5.3 cP.

- Polyvinyl alcohol - Polyethylene glycol graft copolymer (PVA-PEG), Manufacturer: BASF (Kollicoat IR), Lot No.: 38230468E0, Viscosity: 120cP.
- Sodium Carboxymethyl Cellulose (Sodium CMC), Manufacturer: Montello (Cellogen HP-8A), Lot No.: 2543B1, Viscosity: 43cP for 2% aqueous solution.
- Hydroxypropyl cellulose (HPC), Manufacturer: Ashland (Klucel LF), Lot No.: 4673, Viscosity: 80 cP for 5% aqueous solution.
- Hydroxypropyl methylcellulose (HPMC 6cP), Manufacturer: DOW (Methocel E6 Premium LV), Lot No.: D011G4CL02, Viscosity: 5.9 cP for 2% aqueous solution.

**Preparation of Polymer Blends:**

The following polymers were selected for preparation of polymer blends (PVA: Sodium CMC, PVA: PVA-PEG, PVA: HPC and HPMC 6cP: PVA-PEG) at a concentration ratio of 90:10, 80: 20, 70:30, 60:40 and 50:50 respectively. Selected polymers were blended by first weighing the polymer having higher ratio and then followed by another polymer having lower ratio. The two are blended using domestic blender for 10 min duration. The complete system is in dry form with no liquids in the formula.

**Determination of Viscosity of polymer blends in aqueous solution:**

The solution of polymer blends was prepared in purified water at 20% solids (for PVA: PVA-PEG O) and 15% solids (for PVA: Sodium CMC, PVA: HPC and HPMC 6cP: PVA-PEG). Accurately weighed purified water in the mixing vessel, stir vigorously to form a vortex and polymer blend powder was then slowly added under stirring into the vortex. After all the powder was added, the mixer speed was reduced to nearly eliminate the vortex and mixed for 30 minutes and kept aside the solution for overnight to remove the air bubbles from the solution. Viscosity testing was performed using Brookfield Pro DV II + pro viscometer equipped with Spindle S01 (except for PVA: Sodium CMC at 50: 50 ratios, viscosity was measured using Spindle S05) and temperature of the solution was maintained at 25ºC (±0.5). The rpm of spindle was maintained at a different speed level during determination of viscosity (Table 1). Viscosity of individual polymers (Sodium CMC, HPMC 6 cP, PVA-PEG, PVA and HPC) was also determined at different % solids as a control. Procedure used for preparation of solution and viscosity as mentioned above. Refer to Table 2 for details of viscosity parameters.

**Determination of tensile strength**

The solution of polymer blends was prepared in purified water at 20% solids (PVA: PVA-PEG for all ratios) and 15% solids (PVA: Sodium CMC, PVA: HPC and HPMC 6cP: PVA-PEG for all ratios). Films of these solutions were casted at an approximate thickness of 100 µ on glass plates with the help of a film casting knife. These casted films were allowed to dry overnight at room conditions (~ 25°C ±2°C, 65% RH ± 2% RH). The films were cut into pieces of uniform shape (75 mm x 10 mm) with the help of Dogbone cutter (RR/HCP, Ray-Ran Test Equipment, UK). Tensile strength of these casted film pieces was determined using Tensile strength tester (5942, Instron, UK). Ten samples of each type of film was tested using Instron 5942 equipment and the tensile strength properties were determined through Bluehill 3 software. In the similar way tensile testing of individual polymers (Sodium CMC, HPMC 6 cP, PVA-PEG and PVA) was also determined as a control. Tensile testing of HPC polymer alone was not determined as casting the film using this polymer did not result in satisfactory film.

**RESULT AND DISCUSSION**

**Determination of Viscosity of polymer blends in aqueous solution**

Among all polymer blends, PVA: PVA-PEG blend showed lowest viscosity as compared to that of other polymer blend. Although 20% solids solution was prepared for PVA: PVA-PEG blend as this blend showing very low viscosity at 15 % solids, whereas other polymer blends solution was prepared at 15% solids.

Also there is gradual decrease in viscosity for the polymer blend PVA: PVA-PEG from the ratio of 90:10 (viscosity: 1360 cP) to 50:50 (Viscosity: 483 cP).In case of PVA: Sodium CMC polymer blend, lowest viscosity (763 cP) was observed at (90:10 ratio). Other polymer blends HPMC 6cP: PVA-PEG and PVA: HPC showed lowest viscosity at 50: 50 ratios (725 cP) and 90:10 ratios (485 cP) respectively. Individual polymer viscosity showed lowest viscosity for PVA-PEG (155 cP at 20% solids) followed by PVA (1960 cP at 20% solids), HPMC 6cP (2220 cP at 15% solids), HPC (2060 cP at 10% solids) and Sodium CMC (8933 cP at 8% solids). These finding indicates that, the contribution of PVA and PVA-PEG resulted in lowering the viscosity of polymer blends in aqueous solution. Additionally, PVA and PVA-PEG are co-polymers which have lower chain mobility when interacting with water molecule and also act as surface active agent to reduces the surface tension of aqueous solutions and thus cumulative impact is lowering the viscosity of polymer blend [18-21]. Results of viscosity for polymer blends and individual polymers are depicted in Table 1 & 2 respectively.

**Determination of tensile strength**

Tensile strength measurement alone is not useful in predicting the mechanical performance of films; however, higher values of tensile strength are indicative of abrasion resistance [22].

Polymer blend PVA: PVA-PEG showed gradual decrease in Young's Modulus from the ratio of 90:10 (1304 MPa) to 50:50 (532 MPa), whereas changes in the extension at break value (40 to 60 mm) in all ratios. In case of PVA: Sodium CMC polymer blend, lowest Young's Modulus (858.32 MPa), highest extension at break (23.30 mm)was observed at 90:10 ratios. For HPMC 6cP: PVA-PEG polymer blend showed lowest Young's Modulus (1146.64 MPa) with extension at break 1.98 mmat 50: 50 ratios. Highest extension at break (16.22 mm) was observed at 90:10 ratios for PVA: HPC polymer blend with Young's Modulus 1905.15 mPa. Individual polymer showed lowest Young's Modulus for PVA (24.22 MPa) followed by PVA-PEG (87.15 MPa), Sodium CMC (2752.88 MPa) and HPMC 6cP (2877.43 MPa).

The above findings indicate that the presence of PVA and PVA-PEG in polymer blend has great impact on Young's Modulus and extension at break of casted film. PVA has high tensile strength and flexibility [23]. The presence of PVA in polymer blend at higher ratio showed higher Young's Modulus and extension at break (PVA: PVA-PEG at 90:10 ratios: 1304.02 MPa Young's Modulus and 59.20 mm Extension at break), (PVA: HPC at 90:10 ratios: 1905.15 MPa Young's Modulus and 16.22 mm Extension at break). However, in case of PVA: Sodium CMC polymer blend, the Young's Modulus increases and Extension at break decreases as the concentration of PVA is decreases in the polymer blend (at 90:10 ratios858.32 MPa Young's Modulus and 23.30 mm extension at break and at 50:50 ratios Young's modulus increases to 2402.57 MPa and Extension at break decreases to 1.37 mm. Figure 1 and 2 represent the relationship between the ratio of polymer blends verses Young's Modulus and Extension at break respectively.

Also, the presence of PVA-PEG in HPMC 6cP, showed marginal decrease in Young's Modulus and extension at break as the concentration of PVA increases in the polymer blend. Other tensile testing properties such as Tensile stress at maximum load, Tensile strain at break, Toughness and Energy at Break was also monitored for all polymer blends and respective data represented in Table 3 to 7.

Table 1: Result of viscosity for polymer blends solution in aqueous media

| Sr. No. | Blend Details | | | Viscosity (cP) | Spindle Number | Spindle Speed (rpm) | Torque (%) |
|---|---|---|---|---|---|---|---|
| | Polymer blend | % w/w solids | Polymer ratio | | | | |
| 1. | PVA:PVA-PEG | 20 % | 90: 10 | 1360 | S01 | 3.0 | 40.8 |
| 2. | | | 80: 20 | 1147 | S01 | 3.0 | 34.4 |
| 3. | | | 70: 30 | 1090 | S01 | 3.0 | 32.7 |
| 4. | | | 60: 40 | 628 | S01 | 6.0 | 37.2 |
| 5. | | | 50: 50 | 483 | S01 | 12.0 | 58.0 |
| 6. | PVA: Sodium CMC | 15 % | 90: 10 | 763.3 | S01 | 6.0 | 45.7 |
| 7. | | | 80: 20 | 2647 | S01 | 1.5 | 39.7 |
| 8. | | | 70: 30 | 12383 | S01 | 0.6 | 74.4 |
| 9 | | | 60: 40 | 17640 | S01 | 0.5 | 88.2 |
| 10. | | | 50: 50 | 32800 | S05 | 5.0 | 41.0 |
| 11. | HPMC 6cP:PVA-PEG | 15 % | 90: 10 | 2447 | S01 | 3.0 | 73.4 |
| 12. | | | 80: 20 | 1550 | S01 | 3.0 | 46.5 |
| 13. | | | 70: 30 | 1470 | S01 | 3.0 | 44.1 |
| 14. | | | 60: 40 | 1060 | S01 | 3.0 | 31.8 |
| 15. | | | 50: 50 | 725.3 | S01 | 6.0 | 43.3 |
| 16. | PVA: HPC | 15 % | 90: 10 | 485 | S01 | 10.0 | 48.3 |
| 17. | | | 80: 20 | 660 | S01 | 10.0 | 66.0 |
| 18. | | | 70: 30 | 720 | S01 | 3.0 | 21.6 |
| 19. | | | 60: 40 | 1387 | S01 | 1.5 | 20.8 |
| 20. | | | 50: 50 | 1607 | S01 | 3.0 | 48.2 |

Table 2: Result of viscosity for individual polymersolution in aqueous media

| Sr. No. | Blend Details | | Viscosity (cP) | Spindle Number | Spindle Speed (rpm) | Torque (%) |
|---|---|---|---|---|---|---|
| | Polymer | % w/w solids | | | | |
| 1. | PVA-PEG | 20 % | 154.6 | S01 | 30.0 | 45.3 |
| 2. | | 25 % | 1930 | S01 | 3.0 | 57.9 |
| 3. | | 40 % | 32960 | S05 | 5.0 | 41.2 |
| 4. | HPMC 6 cP | 15 % | 2220 | S01 | 3.0. | 65.4 |
| 5. | HPC | 10 % | 2060 | S01 | 3.0 | 61.8 |
| 6. | | 15 % | 6400 | S02 | 3.0 | 48.1 |
| 7. | PVA | 20 % | 1960 | S01 | 3.0 | 58.8 |
| 8. | Sodium CMC | 08 % | 8933 | S01 | 0.6 | 53.6 |
| 9. | | 15 % | 137000 | S07 | 6.0 | 20.7 |

Figure 1: Graphical presentation of Young's Modulus for the polymer blends of different ratios

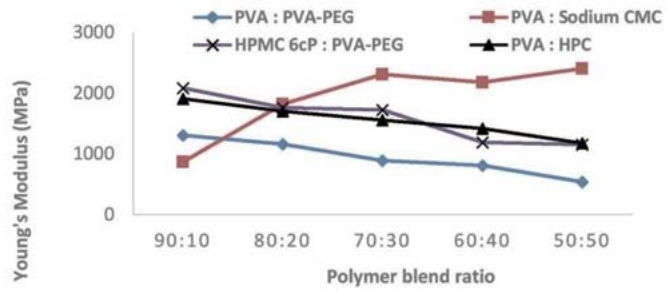


Figure 2: Graphical presentation of Extension at break for the polymer blends of different ratios

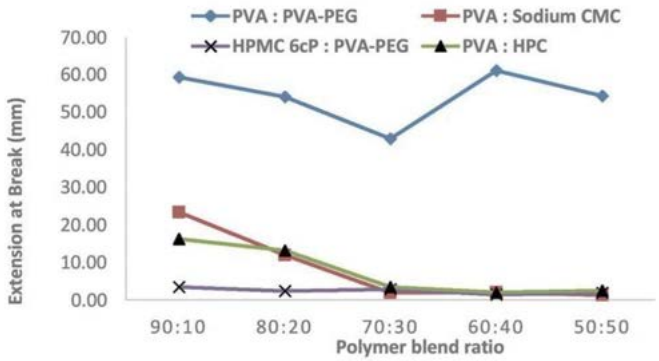


**Table 3: Tensile strength properties of polymer blend (PVA: PVA-PEG)**

| PVA: PVA-PEG combination | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| 90: 10 | 20 % | 1304.02 ± 144.52 | 25.79 ± 1.85 | 107.47 ± 16.79 | 0.02002 ± 0.00 | 0.54207 ± 0.15 | 59.20 ± 9.23 |
| 80: 20 | | 1152.87 ± 122.81 | 23.49 ± 1.77 | 97.93 ± 23.21 | 0.02053 ± 0.00 | 0.39712 ± 0.11 | 53.97 ± 12.76 |
| 70: 30 | | 880.53 ± 253.52 | 19.64 ± 3.94 | 77.41 ± 28.27 | 0.02332 ± 0.01 | 0.27854 ± 0.15 | 42.84 ± 15.60 |
| 60: 40 | | 802.56 ± 185.07 | 21.75 ± 2.62 | 110.48 ± 22.22 | 0.02828 ± 0.01 | 0.42261 ± 0.17 | 61.00 ± 12.24 |
| 50: 50 | | 532.65 ± 190.97 | 16.76 ± 2.98 | 98.15 ± 32.06 | 0.03690 ± 0.02 | 0.24669 ± 0.08 | 54.29 ± 17.71 |

**Table 4: Tensile strength properties of polymer blend (PVA: Sodium CMC)**

| PVA: Sodium CMC combination | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| 90: 10 | 15 % | 858.32 ± 228.61 | 7.37 ± 2.03 | 41.84 ± 3.49 | 0.00857 ± 0.00 | 0.04005 ± 0.02 | 23.30 ± 1.87 |
| 80: 20 | | 1814.14 ± 473.87 | 21.87 ± 2.81 | 21.56 ± 9.79 | 0.01290 ± 0.00 | 0.09525 ± 0.05 | 11.97 ± 5.45 |
| 70: 30 | | 2302.46 ± 167.51 | 23.86 ± 4.41 | 3.51 ± 1.91 | 0.01043 ± 0.00 | 0.01759 ± 0.01 | 1.94 ± 1.06 |
| 60: 40 | | 2171.68 ± 210.67 | 27.30 ± 1.06 | 3.80 ± 0.79 | 0.01270 ± 0.00 | 0.02007 ± 0.01 | 2.11 ± 0.44 |
| 50: 50 | 10 % | 2402.57 ± 109.53 | 30.61 ± 1.58 | 2.48 ± 0.51 | 0.01276 ± 0.00 | 0.01345 ± 0.00 | 1.37 ± 0.28 |

**Table 5: Tensile strength properties of polymer blend (HPMC 6cP: PVA-PEG)**

| HPMC 6cP: PVA – PG combination | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness Tensile/modulus | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| 90: 10 | 15 % | 2079.99 ± 319.05 | 27.18 ± 4.40 | 6.32 ± 1.46 | 0.01308 ± 0.00 | 0.02105 ± 0.01 | 3.48 ± 0.81 |
| 80: 20 | | 1753.74 ± 109.54 | 32.28 ± 2.59 | 4.31 ± 0.91 | 0.01848 ± 0.00 | 0.01779 ± 0.01 | 2.38 ± 0.50 |
| 70: 30 | | 1719.87 ± 111.40 | 35.48 ± 1.59 | 5.33 ± 1.04 | 0.02068 ± 0.00 | 0.02704 ± 0.01 | 2.93 ± 0.57 |
| 60: 40 | | 1185.02 ± 77.51 | 19.00 ± 1.96 | 2.76 ± 0.59 | 0.01605 ± 0.00 | 0.00722 ± 0.00 | 1.52 ± 0.32 |
| 50: 50 | | 1146.64 ± 224.61 | 21.33 ± 5.18 | 3.59 ± 1.17 | 0.01847 ± 0.00 | 0.01221 ± 0.01 | 1.98 ± 0.64 |

**Table 6: Tensile strength properties of polymer blend (PVA: HPC)**

| PVA: HPC combination | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| 90: 10 | 15 % | 1905.15 ± 313.40 | 23.77 ± 1.44 | 29.38 ± 13.89 | 0.01271 ± 0.00 | 0.16288 ± 0.11 | 16.22 ± 7.67 |
| 80: 20 | | 1696.42 ± 315.29 | 21.19 ± 4.15 | 23.71 ± 22.53 | 0.01266 ± 0.00 | 0.06266 ± 0.04 | 13.15 ± 12.53 |
| 70: 30 | | 1550.31 ± 370.62 | 19.80 ± 5.05 | 6.33 ± 3.25 | 0.01294 ± 0.00 | 0.02760 ± 0.02 | 3.49 ± 1.80 |
| 60: 40 | | 1412.63 ± 277.94 | 15.01 ± 2.52 | 3.72 ± 2.50 | 0.01087 ± 0.00 | 0.00983 ± 0.01 | 2.05 ± 1.37 |
| 50: 50 | | 1168.26 ± 148.45 | 15.40 ± 0.95 | 4.49 ± 1.80 | 0.01335 ± 0.00 | 0.01097 ± 0.01 | 2.48 ± 0.99 |

**Table 7: Tensile strength properties of individual polymers**

| Polymers | % w/w solids | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/modulus) | Energy at break (J) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| HPMC 6 cP* | 15 % | 2877.43 ± 350.99 | 57.47 ± 9.48 | 8.30 ± 2.45 | 0.01882 ± 0.00 | 0.04586 ± 0.02 | 4.59 ± 1.35 |
| Sodium CMC+ | 8 % | 2752.88 ± 793.24 | 50.74 ± 13.68 | 12.96 ± 2.05 | 0.01851 ± 0.00 | 0.09622 ± 0.02 | 7.16 ± 1.13 |
| PVA* | 20 % | 24.22 ± 9.19 | 16.67 ± 3.06 | 221.77 ± 31.1 | 0.76414 ± 0.24 | 0.94581 ± 0.30 | 125.44 ± 17.7 |
| PVA – PG^ | 25 % | 87.15 ± 25.46 | 4.23 ± 1.53 | 25.18 ± 16.52 | 0.04832 ± 0.01 | 0.00646 ± 0.00 | 14.64 ± 9.64 |

**CONCLUSION:**

This work describes the fundamental mechanical properties of polymer blends. The viscosity of the polymer HPC, Sodium CMC and HPMC 6cP is greatly reduced when it is blended with PVA and PVA-PEG. Young's Modulus, Extension at break of the casted film is influenced by varying the ratio of PVA and PVA-PEG in polymer blends. While using polymer blends, the ultimate tensile properties of the films depend on the mechanical properties of individual polymer.

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Research Article

# Understanding the Mechanical Properties of Polymer Blends in the Presence of Plasticizers and Other Additives

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**ABSTRACT**

This work describes the evaluation of the fundamental mechanical properties of casted films of polymer blends containing plasticizer and other additives. The ultimate tensile properties of the films are depending on both type and concentration of plasticizer and other additives. The mechanical property data can be used to explain physicochemical interaction between polymer blends with plasticizer and additives.

**Keywords:** Polyvinyl Alcohol, PVA-PEG Graft Copolymer, HPMC, HPC, Mechanical Property, Tensile Strength, Young's Modulus.

## INTRODUCTION

Polymers have been used in pharmaceutical formulations for several reasons including protection of the dosage form against environmental conditions and for hiding a bad taste, odor or appearance. The evaluation of mechanical properties of polymeric films for the development of film coating system, provides an essential information to verbalizing their performance in pharmaceutical dosage forms and it helps the pharmaceutical scientist to predict the stability and drug-release properties of film coated solid dosage forms.[1]

The mechanical properties of the polymers determine its response to stresses and hence its resistance to rupture. The most commonly measured mechanical properties are elucidated in terms of glass transition temperature (Tg), tensile strength, toughness, Young's modulus, minimum film forming temperature (MFT), moisture effect and plasticizer performance. Ideally, increasing the tensile strength of the coating reduces the risk of cracking and reducing the elastic modulus decreases the potential of occurrence of bridging and cracking.[2-6]

Commercial film coating system does not consist of polymer alone but also contains other ingredients such as plasticizers, pigments and anti-adherents for a specific reason, either to assist processing or to improve performance and appearance. Addition of such other ingredients can affect the mechanical properties of the film coatings causing a decrease in their tensile strength and an increase in their modulus of elasticity thus affecting their performance in suit on the tablet surface.[7] Plasticizers are added to reduce the brittleness, improve flow, and improve flexibility of polymeric chains.[8-9] In addition, they will also increase toughness and strength of polymeric films, lower the glass transition temperature, decreasing internal stress and enhance the coalescence of the colloidal polymeric particles to form a uniform homogenous film over the substrate.[10] The mechanism of action for a plasticizer is for the plasticizer molecules to interpose themselves between the individual polymer strands thus breaking down polymer-polymer interactions. This action is facilitated as the polymer-plasticizer interaction which is stronger than the polymer-polymer interaction.[11-12] Plasticizer must be able to diffuse into and interact with the polymer and have minimal tendency for migration or exudation from the polymer to be effective. Generally, the addition of plasticizer increases the ductility of the film, but this is often accompanied by a reduction in its tensile strength and modulus of elasticity. The addition of plasticizer, therefore, results in soft, tough film. Excessive addition of plasticizers may cause tablet tacking, plasticizer bleeding, color depletion or interaction with active ingredients and may significantly affect drug release.[13-14]

The addition of pigments into a coating formulation may improve the esthetic appearance of the final product.[15] Pigments fall into three main categories; synthetic water-soluble organic dyes, insoluble aluminum and inorganic pigments. The influence of aluminum lakes and inorganic pigments on the properties of films is generally very different to that of plasticizers and significantly affecting the physical, mechanical, adhesive, and drug-release properties of the films.[16-18] At a specific concentration, known as the critical pigment volume concentration (CPVC), the polymer present is insufficient to surround all the insoluble particles, and marked changes in the mechanical properties of the film will occur.[19] The amount of insoluble filler incorporated in aqueous dispersion must be optimized without exceeding CPVC. Evidently, increase in concentration of pigment has shown the cellulosic films to become more brittle.[20]

Water insoluble anti-adherents such as talc and glyceryl monostearate (GMS) are most commonly used in film coating formulations and they have been shown to

influence the mechanical and drug-release properties.[21-25] However, when water soluble additives such as lactose, sodium lauryl sulfate are also added in aqueous coating formulations, their inclusion resulted in a reduction of the tensile strength of all the films tested; indeed, some films became too brittle to test.[26] The effects of additives in coating formulations were dependent on the balance between their influence on the internal stress of film coating and the strength of the film-tablet interface.[27] Titanium dioxide, may be used in coatings to protect photosensitive drugs from exposure to light, thus improving product stability.[28] But, addition of titanium dioxide to polyvinyl alcohol also resulted in a decrease in tensile strength.[29]

In this paper an attempt has been made to correlate the mechanical properties of casted films. The mechanical properties were observed for:

(i) Polymer blends with plasticizer

(ii) Polymer blends with plasticizer and additives

The results of these studies have generally been interpreted in terms of the physicochemical interaction between polymer blends with plasticizer and additives.

## MATERIALS AND METHODS

The polymers and plasticizers were used in this study are Poly (vinyl alcohol) (PVA; Manufacturer: Nippon Gohsei (Gohsenol GL-05FS), Lot No.: 64M52T, Viscosity: 5.3 cP), Polyvinyl alcohol - Polyethylene glycol graft copolymer (PVA-PEG; Manufacturer: BASF (Kollicoat IR), Lot No.: 38230468E0, Viscosity: 120 cP), Hydroxypropyl cellulose (HPC; Manufacturer: Ashland Lot No.: 4673, Viscosity: 80 cP for 5% aqueous solution), Hydroxypropyl methylcellulose (HPMC 6cP; Manufacturer: DOW [Methocel E6 Premium LV], Lot No.: D011G4CL02, Viscosity: 5.9 cP for 2% aqueous solution), PEG 400 (Manufacturer: Clariant International, Lot No: DEG4401829), PEG 3350 (Manufacturer: Clariant International, Lot No: DEA4006020), Medium chain triglycerides (MCT; Manufacturer: IOI Oleochemical, Lot No: 141129-6), Triethyl citrate (TEC; Manufacturer: Vertellus, Lot No: 0000157958). Additives used in this study are titanium dioxide (TiO2; Manufacturer: Brentag Specialties, Lot No: 0001161) and talc (Manufacturer: Luzenac, Lot No: S.180/18).

Plasticizers were selected in this study based on their solubility in water; PEG is soluble in water, TEC is slightly soluble in water whereas MCT is practically insoluble in water. The polymers selected in this study are water soluble, having different chemistry, hence, its interaction (physical) with plasticizers must be different in the presence of water insoluble additives (TiO2 and Talc).

### Preparation of polymer blends

i) Polymer blends with plasticizer

Polymer blends were prepared by mixing in domestic blender (Robot coupe; R4 V.V; UK) at 90:10 ratio (PVA: PVA-PEG; HPMC 6cP: PVA-PEG and PVA: HPC) followed by addition plasticizer (PEG 400, PEG 3350, TEC and MCT) at 10%, 15% and 20% (concentration with respect to total quantity of polymer). Separate polymer blends were prepared for each plasticizer and concentration level, therefore there are total 36 polymer blends.

ii) Polymer blends with plasticizer and additives

Polymer blends were prepared by mixing in domestic blender (Robot coupe; R4 V.V; UK) at 90:10 ratio followed by addition of additives at different ratios (Polymer: diluent ratio; 20:80, 30:70, 40:60, 50:50, 60:40 ratio respectively) and plasticizer. PEG 3350 was used as a plasticizer at different concentration level with respect to polymer blends to additives ratio as given in below Table 1. All polymer blends have similar quantity of PEG 3350 with respect to total quantity of polymers.

### Film casting and evaluation of mechanical properties

For "polymer blends with plasticizer", the solution of polymer blends was prepared in purified water at 20% solids (PVA: PVA-PEG) and 15% solids (HPMC 6cP: PVA-PEG and PVA: HPC). In case of "polymer blends with plasticizer and additives" the solution of all polymer blends was prepared in purified water at 20% solids. Films of these solutions were casted at an approximate thickness of 100 µ on glass plates with the help of a film casting knife. Casted films were allowed to dry overnight at room conditions (~ 22°C ±2°C, 50% RH ± 2% RH). The films were cut into pieces of uniform shape (75 mm x 10 mm) with the help of Dogbone cutter (RR/HCP, Ray-Ran Test Equipment, UK). Tensile strength of these casted film pieces was determined using Tensile strength tester (5942, Instron, UK) equipped with Bluehill 3 software. A total of 10 films under each combination were evaluated for its mechanical properties.

## RESULTS AND DISCUSSION

i) Polymer blends with plasticizer

It has been reported that the selection of plasticizers in coating formulation has distinct effect on the mechanical properties of the polymeric films in aqueous dispersion.[30] In present study showed that, both type of plasticizer and its concentration have an impact on result of mechanical properties (modulus of elasticity, tensile strength) of casted films. The modulus of elasticity is a measure of the stiffness and rigidity of the film. The tensile strength data of different polymer blends with respective concentration of plasticizers are presented in below Table 2, 3 and 4. In case of PEG 400 as a plasticizer, all polymer blend PVA: PVA-PEG, HPMC 6cP: PVAPEG and PVA: HPC at 90:10 ratio showed gradual decrease in Young's Modulus, tensile stress at max load as the concentration of plasticizer increases in the blend, whereas extension at break increases as the concentration of plasticizer increases in polymer blend. In the similar line, there was significant difference in Young's modulus value and extension at break in PEG 400 plasticized polymers blends as

compared to that of polymer blends formulated without plasticizer. This increased extension at break caused by addition of plasticizer was explained by the increase in chain mobility in the presence of plasticizer. Increasing plasticizer content led to an increase in percent elongation and a reduction in strength.[31-33] The above finding indicates that, the introduction of PEG 400 as a plasticizer to the polymer blends promoted increase in viscoelastic behavior of the polymers which resulted in films were more soft and tough. A soft and tough film will possess a low tensile strength but much greater elongation and a higher area under the curve (toughness).[34]

However, opposite scenario was observed with PEG 3350 plasticized films. The polymers blends showed gradual increase in Young's modulus and decrease in extension at break. There was increase in extension at break when the plasticizer was included in the film at the 10% and 15% level. No further increase was found in the extension as the plasticizer increased from 15% to 20%. Similarly, Young's modulus decreases at 10% plasticizer level and further there was slight increase in Young's modulus at 15% plasticizer level. Although, there was significant difference in Young's modulus value and extension at break for the PEG 3350 plasticized polymers bends as compared to that non-plasticized polymer blend. This is mainly due to the plasticizing efficiency of polyethylene glycols decreases with increasing molecular weight. The high-molecular-weight solid PEG additives exhibited phase separation.[11] Similar effects were reported by Aulton with the inclusion of PEGs. Plasticization efficiency increased with decreasing PEG molecular weight and possibly due to the greater number of plasticizer molecule available to interact with the polymer.[35] Rowe reported decrease in elasticity of polymeric film with increasing molecular weight grade of PEG, this was mainly attributed to decrease in mole fraction of the hydroxyl groups.[36]

In case of MCT and TEC as a plasticizer polymer blend PVA: PVA-PEG, HPMC 6cP: PVAPEG showed decrease in Young's modulus and increase in extension at break as compared to that of polymer blends formulated without plasticizer. However, in case of polymer blends PVA: HPC showed leaching of plasticizers (for both MCT and TEC) from the polymeric films as well as some kind of phase separation of polymers were also observed. The leaching was quite rapid from the casted films and increased with increasing level plasticizers. Although casted films of polymer blends (PVA: HPC; 90:10) with inclusion of plasticizers (MCT and TEC) at 10%, 15% and 20% concentration were successfully formulated, however, stain of liquid plasticizer (MCT and TEC) as well as separation of polymers were visually observed on the surface of casted films indicating that, these plasticizers are not compatible for this polymer blends. Bodmeier and Paeratakul reported the leaching of water soluble plasticizers (TEC) from polymeric films prepared by casting and drying of plasticized Aquacoat dispersion.[37]

**Table 1**: The selection of polymer blend and respective ingredients.

| Polymer blend | Name of Ingredients | Polymer blend to Additives ratio | | | | |
|---|---|---|---|---|---|---|
| | | 20:80 | 30:70 | 40:60 | 50:50 | 60:40 |
| | | T1 | T2 | T3 | T4 | T5 |
| | | Quantities (%) | | | | |
| PVA: PVA-PEG (ratio 90:10) | PVA | 18 | 27 | 36 | 45 | 54 |
| | PVAPG | 2 | 3 | 4 | 5 | 6 |
| | PEG 3350 | 5 | 7.5 | 10 | 12.5 | 15 |
| | TiO2 | 45 | 37.5 | 30 | 22.5 | 15 |
| | Talc | 30 | 25 | 20 | 15 | 10 |
| | Total (%) | 100 | 100 | 100 | 100 | 100 |
| HPMC 6Cp: PVA-PEG (ratio 90:10) | HPMC 6cP | T6 | T7 | T8 | T9 | T10 |
| | | 18 | 27 | 36 | 45 | 54 |
| | PVAPG | 2 | 3 | 4 | 5 | 6 |
| | PEG 3350 | 5 | 7.5 | 10 | 12.5 | 15 |
| | TiO2 | 45 | 37.5 | 30 | 22.5 | 15 |
| | Talc | 30 | 25 | 20 | 15 | 10 |
| | Total (%) | 100 | 100 | 100 | 100 | 100 |
| PVA: HPC (ratio 90:10) | PVA | T11 | T12 | T13 | T14 | T15 |
| | | 18 | 27 | 36 | 45 | 54 |
| | HPC | 2 | 3 | 4 | 5 | 6 |
| | PEG 3350 | 5 | 7.5 | 10 | 12.5 | 15 |
| | TiO2 | 45 | 37.5 | 30 | 22.5 | 15 |
| | Talc | 30 | 25 | 20 | 15 | 10 |
| | Total (%) | 100 | 100 | 100 | 100 | 100 |

**Table 2:** Tensile strength properties of PVA: PVA-PEG blends with inclusion of different plasticizers.

| Blend Details | | | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| Polymer blend | Plasticizer concentration | | | | | | |
| PVA: PVA-PEG (90:10); 20% w/w Solids | *0% | | 1304.02 ± 144.52 | 25.79 ± 1.85 | 107.47 ± 16.79 | 0.02002 ± 0.00 | 59.20 ± 9.23 |
| | PEG 400 | 10% | 116.99 ± 32.48 | 20.65 ± 6.31 | 1.21 ± 0.28 | 0.18 ± 0.05 | 93.19 ± 21.32 |
| | | 15% | 88.84 ± 16.91 | 16.57 ± 3.41 | 1.61 ± 0.39 | 0.19 ± 0.04 | 123.493 ± 30.26 |
| | | 20% | 85.31 ± 10.68 | 18.02 ± 2.68 | 1.99 ± 0.37 | 0.21 ± 0.04 | 152.18 ± 28.09 |
| | PEG 3350 | 10% | 113.66 ± 25.91 | 13.55 ± 1.69 | 0.92 ± 0.10 | 0.12 ± 0.02 | 69.54 ± 7.86 |
| | | 15% | 203.39 ± 68.86 | 18.89 ± 6.97 | 1.25 ± 0.38 | 0.10 ± 0.04 | 94.68 ± 28.84 |
| | | 20% | 156.56 ± 41.40 | 10.12 ± 0.74 | 0.84 ± 0.16 | 0.07 ± 0.02 | 63.53 ± 12.30 |
| | MCT | 10% | 89.79 ± 28.48 | 14.29 ± 4.92 | 1.20 ± 0.26 | 0.16 ± 0.05 | 91.60 ± 19.59 |
| | | 15% | 152.82 ± 93.05 | 15.78 ± 5.28 | 1.38 ± 0.55 | 0.14 ± 0.09 | 104.93 ± 41.95 |
| | | 20% | 149.17 ± 83.95 | 15.10 ± 2.50 | 1.27 ± 0.37 | 0.14 ± 0.08 | 96.91 ± 28.50 |
| | TEC | 10% | 399.98 ± 153.69 | 13.34 ± 4.05 | 0.61 ± 0.56 | 0.04 ± 0.03 | 46.44 ± 11.79 |
| | | 15% | 168.83 ± 70.80 | 12.67 ± 5.58 | 0.97 ± 0.31 | 0.10 ± 0.07 | 74.27 ± 23.30 |
| | | 20% | 219.19 ± 93.55 | 16.38 ± 2.86 | 1.21 ± 0.28 | 0.09 ± 0.05 | 92.25 ± 21.38 |

**Table 3:** Tensile strength properties of HPMC 6cP: PVA-PEG blends with inclusion of different plasticizers.

| Blend Details | | | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| Polymer blend | Plasticizer concentration | | | | | | |
| HPMC 6cP: PVA-PEG (90:10); 15% w/w Solids | 0% | | 2079.99 ± 319.05 | 27.18 ± 4.40 | 6.32 ± 1.46 | 0.01308 ± 0.00 | 3.48 ± 0.81 |
| | PEG 400 | 10% | 1118.27 ± 174.35 | 14.79 ± 2.33 | 0.027 ± 0.01 | 0.013 ± 0.00 | 2.03 ± 0.39 |
| | | 15% | 1260.53 ± 157.22 | 14.16 ± 2.17 | 0.024 ± 0.00 | 0.011 ± 0.00 | 1.782 ± 0.34 |
| | | 20% | 1072.34 ± 157.77 | 14.19 ± 2.27 | 0.045 ± 0.02 | 0.013 ± 0.00 | 3.371 ± 1.17 |
| | PEG 3350 | 10% | 1681.18 ± 51.32 | 20.83 ± 0.87 | 0.04 ± 0.01 | 0.01 ± 0.00 | 2.93 ± 0.72 |
| | | 15% | 1546.04 ± 123.84 | 18.20 ± 1.36 | 0.03 ± 0.01 | 0.01 ± 0.00 | 2.34 ± 0.56 |
| | | 20% | 1547.67 ± 126.06 | 19.78 ± 2.25 | 0.04 ± 0.01 | 0.01 ± 0.00 | 2.73 ± 0.66 |
| | MCT | 10% | 1334.16 ± 107.78 | 15.61 ± 1.96 | 0.03 ± 0.01 | 0.01 ± 0.00 | 1.90 ± 0.52 |
| | | 15% | 1128.88 ± 180.04 | 14.68 ± 2.97 | 0.02 ± 0.01 | 0.01 ± 0.00 | 1.88 ± 0.58 |
| | | 20% | 964.36 ± 62.54 | 10.75 ± 1.34 | 0.02 ± 0.00 | 0.01 ± 0.00 | 1.22 ± 0.21 |
| | TEC | 10% | 939.67 ± 178.41 | 11.14 ± 2.84 | 0.02 ± 0.01 | 0.01 ± 0.00 | 1.68 ± 0.44 |
| | | 15% | 1028.54 ± 207.33 | 11.97 ± 3.94 | 0.03 ± 0.01 | 0.01 ± 0.00 | 2.061 ± 0.49 |
| | | 20% | 695.13 ± 72.19 | 8.43 ± 1.00 | 0.04 ± 0.01 | 0.01 ± 0.00 | 2.75 ± 0.53 |

**Table 4:** Tensile strength properties of PVA: HPC blends with inclusion of different plasticizers.

| Blend Details | | | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| Polymer blend | Plasticizer concentration | | | | | | |
| PVA: HPC (90:10); 15% w/w Solids | *0% | | 1905.15 ± 313.40 | 23.77 ± 1.44 | 29.38 ± 13.89 | 0.01271 ± 0.00 | 16.22 ± 7.67 |
| | PEG 400 | 10% | 164.05 ± 29.87 | 18.01 ± 3.23 | 0.70 ± 0.18 | 0.11 ± 0.02 | 53.48 ± 13.63 |
| | | 15% | 101.73 ± 20.89 | 13.23 ± 4.20 | 0.76 ± 0.24 | 0.13 ± 0.02 | 58.43 ± 18.17 |
| | | 20% | 127.67 ± 48.15 | 11.85 ± 4.09 | 0.44 ± 0.20 | 0.09 ± 0.02 | 34.04 ± 15.61 |
| | PEG 3350 | 10% | 169.85 ± 47.74 | 12.74 ± 3.40 | 0.69 ± 0.19 | 0.08 ± 0.02 | 52.25 ± 14.24 |
| | | 15% | 233.90 ± 46.96 | 9.66 ± 1.46 | 0.44 ± 0.10 | 0.04 ± 0.01 | 33.59 ± 7.56 |
| | | 20% | 433.65 ± 37.87 | 7.62 ± 2.11 | 0.26 ± 0.09 | 0.02 ± 0.01 | 19.61 ± 6.83 |
| | MCT | 10% | Film properties unable to determine due to visual leaching of added plasticizer (MCT and TEC) at all concentration level from the casted films | | | | |
| | | 15% | | | | | |
| | | 20% | | | | | |
| | TEC | 10% | | | | | |
| | | 15% | | | | | |
| | | 20% | | | | | |

*Reproduced from Ref 38.

ii) Polymer blends with plasticizer and additives

The modulus of elasticity in general practice was found to increase when pigments were added to the polymer systems.[27,39-40] Present study showed that, additives at all concentration levels have an impact on result of mechanical properties (modulus of elasticity, tensile strength) of casted films of polymer blends. Although all polymer blends contain similar concentration of plasticizer (PEG 3350) with respect to total concentration of polymer). Tensile strength data presented in Table 5. All polymer blends showed gradual increase in Young's modulus and decrease in extension at break as the concentration of additives in the casted film increases. The tensile strength properties data of different polymer blends with respective concentration of additives are represented in below Table 2. Among all polymers blend, PVA: PVA-PEG (90:10) and PVA: HPC (90:10) showed comparatively higher extension at break as compared to that observed with HPMC: PVA-PEG (90:10) at all concentration level of additives. Also, literature survey indicates that, PVA crystallinity was depressed in the presence of the additives[41] which may have further impact on mechanical properties of polymer blends. Casted film of polymer blend HPMC 6CP: PVA-PEG (90:10) and PVA: HPC (90:10) showed harder and brittle at 20:80 ratio of polymers: additives, hence, mechanical properties of this ratio was not determined, however, in case of PVA: PVA-PEG (90:10) ratio showed comparatively less brittleness at 20:80 ratio of polymers: additives. Hard and brittle films exhibit a high tensile strength and Young's modulus with little elongation. The presence of brittleness in casted film at high concentration of additives may be due to these insoluble additives (titanium dioxide and talc) acting as stress concentrations, thereby promoting the initiation of cracks in the film and/or the presence of interactions between the additives and the polymer.[42] Ideally these water insoluble additives are defects in the film[43], which enhances film failure and therefore decrease in elongation. Further this brittleness as well as Young's Modulus of casted film decreases in all polymer blends as the concentration of additives decreases.

**Table 5:** Tensile strength properties of different polymer blends with varying concentration of additives.

| Blend Details | | | Young's Modulus (MPa) | Tensile stress at maximum load (MPa) | Tensile strain at break (%) | Toughness (Tensile/ modulus) | Extension at break (mm) |
|---|---|---|---|---|---|---|---|
| Polymer ratio | Polymers: additives ratio | | | | | | |
| PVA: PVA-PEG (90:10) | 20:80 | T1 | 7067.6 ± 1780.66 | 15.697 ± 2.66 | 0.005 ± 0.001 | 0.002 ± 0.0 | 0.355 ± 0.080 |
| | 30:70 | T2 | 3914.7 ± 677.7 | 15.375 ± 2.27 | 0.008 ± 0.003 | 0.003 ± 0.0 | 0.707 ± 0.133 |
| | 40:60 | T3 | 3352.9 ± 946.9 | 10.697 ± 2.90 | 0.011 ± 0.002 | 0.003 ± 0.00 | 0.847 ± 0.140 |
| | 50:50 | T4 | 1316.5 ± 212.7 | 10.962 ± 0.011 | 0.011 ± 0.005 | 0.006 ± 0.00 | 2.402 ± 2.370 |
| | 60:40 | T5 | 1030.8 ± 112.1 | 5.777 ± 0.85 | 0.056 ± 0.016 | 0.005 ± 0.00 | 4.228 ± 1.220 |
| | 100:0 | * | 156.6 ± 41.40 | 10.120 ± 0.74 | 0.840 ± 0.16 | 0.070 ± 0.02 | 63.530 ± 12.30 |
| HPMC 6CP: PVA-PEG (90:10) | 20:80 | T6 | Film is brittle, unable to determine film properties | | | | |
| | 30:70 | T7 | 6051.3 ± 366.58 | 10.872 ± 1.83 | 0.002 ± 0.001 | 0.002 ± 0.00 | 0.212 ± 0.04 |
| | 40:60 | T8 | 5053.9 ± 440.6 | 14.801 ± 3.33 | 0.005 ± 0.002 | 0.002 ± 0.00 | 0.445 ± 0.17 |
| | 50:50 | T9 | 3018.9 ± 282.7 | 19.134 ± 1.83 | 0.009 ± 0.001 | 0.006 ± 0.00 | 0.719 ± 0.09 |
| | 60:40 | T10 | 2070.8 ± 458.60 | 10.131 ± 1.02 | 0.024 ± 0.006 | 0.005 ± 0.00 | 1.805 ± 0.50 |
| | 100:0 | * | 1547.7 ± 126.06 | 19.780 ± 2.25 | 0.040 ± 0.01 | 0.010 ± 0.00 | 2.730 ± 0.66 |
| PVA: HPC (90:10) | 20:80 | T11 | Film is brittle, unable to determine film properties | | | | |
| | 30:70 | T12 | 8618.3 ± 735.8 | 14.601 ± 1.78 | 0.003 ± 0.001 | 0.001 ± 0.00 | 0.287 ± 0.07 |
| | 40:60 | T13 | 4402.5 ± 442.7 | 12.141 ± 0.91 | 0.008 ± 0.001 | 0.004 ± 0.00 | 0.618 ± 0.15 |
| | 50:50 | T14 | 2079.6 ± 396.9 | 8.503 ± 1.21 | 0.020 ± 0.006 | 0.004 ± 0.00 | 1.551 ± 0.51 |
| | 60:40 | T15 | 1166.1 ± 94.94 | 6.599 ± 0.67 | 0.054 ± 0.014 | 0.005 ± 0.00 | 4.064 ± 1.09 |
| | 100:0 | * | 433.7 ± 37.87 | 7.620 ± 2.11 | 0.260 ± 0.09 | 0.020 ± 0.01 | 19.610 ± 6.83 |

*data from polymer blends with plasticizer

The increased Young's modulus may be related to the increased stiffness and brittleness of hybrid composite films by the addition additives in polymer blend. This may be brought about in two ways; first, the mobility of polymer phase may be physically hindered by the presence of the additives particles (this is a hydrodynamic effect). Second, additives-polymer interaction (a reinforcing effect) could stiffen the molecular chains of portions of the polymer matrix at the additives -polymer interface thus reducing segmental mobility. Thus, decrease in extension at break caused by addition of additives can be further explained by the decrease in chain mobility of polymers in the presence of high concentration of additives. Additives therefore, reduce

intermolecular bonding between polymer molecules and affect the properties of the film (decreasing polymer mobility as well as its elongation). Here elongation has been considered as a measure of the deformation capacity, i.e. the ability to deform under stress, of a film.

From the tensile strength data (from Table 5), minimum concentration of additives (less than 70%) in polymer blend is recommended, in order to produce continuous film (reduces the brittleness of casted film). Ideally increasing the tensile strength of the coating reduces the risk of cracking and reducing the elastic modulus decreases the potential of occurrence of bridging.

Polymers with high additive capacity can be defined as those that can incorporate very high levels of insoluble additives while still retaining their functional characteristics. A more well-defined concept, in this regard, is the CPVC (critical pigment volume concentration) [19, 44-45]. According to this theory, below the CPVC, the polymer is able to completely bind and surround the additives particles, forming a dense and continuous film, however, above the CPVC, there is incomplete binding of pigment particles by the polymer, resulting in the formation of voids within the film.[46-47] In present study, continuous film formed with polymer blends having less than 70% of additives. Figure 1 showed graphical presentation of polymers: additives concentration (%) vs Young's Modulus (mPa) vs Extension at break (mm).

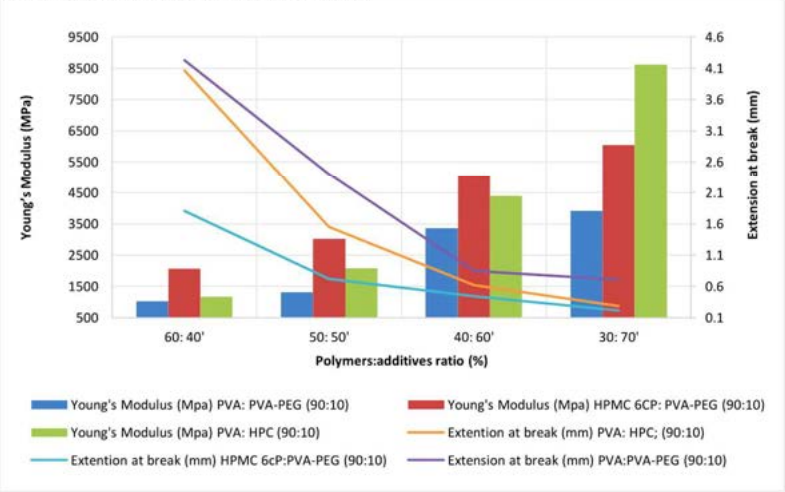


**Figure 1:** Graph of Polymers: additives concentration (%) vs Young's Modulus (mPa) vs Extension at break (mm)

## CONCLUSION

The mechanical properties of films prepared from aqueous dispersion of polymer blends with inclusion of different types of plasticizers and water insoluble additives (different concentration levels) provide valuable information to predict the best ratio of polymer blends with plasticizers and additives that can be used in the development of coating formulation.

The presences of plasticizers in polymer blends have a significant impact on reduction of modulus of elasticity of polymer. This is required to reduce the brittle properties and to achieve effective coatings on different formulations (pellets, tablets) without the formation of cracks and defects. Thus, plasticizers are essential ingredients for most polymers of pharmaceutical interest. Choice of plasticizer and its concentration play an important role in changing the physical properties of polymer to render it more useful in performing its function as a film-coating material.

In contrast, addition of additives (titanium dioxide and talc) in polymer blend resulted in reduction in tensile strain, extension at break and toughness while the Young's modulus increased. High concentration of additives will provide hard and brittle film indicating high tensile strength and Young's modulus with little elongation. Low concentration (below critical level) of additives, polymeric films become soft and tough which possess lower tensile strength and higher elongation.

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# *ANNEXURE – II*

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