"EVALUATION OF PROCESS PARAMETER OF HOT MELT EXTRUSION PROCESS FOR FIXED DOSE COMBINATION OF ANTIRETROVIRAL DRUG"

A Thesis Submitted to

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In Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACEUTICS

BY

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MAY 2012

CERTIFICATE

This is to certify that **Mr. RAKESH MISHRA** *have prepared the thesis entitled* ***"Evaluation of process parameter of hot melt extrusion process for fixed dose combination of antiretroviral drug"****, in partial fulfillment for the award of M. Pharm. degree of the Nirma University, under our guidance. He has carried out the work at the Department of Formulation & Development (NDDS), Torrent Research Centre, Bhat, Gandhinagar.*

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DECLARATION

I hereby declare that the dissertation entitled "Evaluation of process parameter of hot melt extrusion process for fixed dose combination of antiretroviral drug", is based on the original work carried out by me under the guidance of Mrs. Jaya Abraham Assistant General Manager, Torrent Research Centre and Prof. Tejal Mehta, Professor & Head, Department of Pharmaceutics and pharmaceutical Technology, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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C. AIM OF PRESENT INVESTIGATION

The oral route of drug administration is the most common and preferred method of drug delivery due to convenience and ease of administration. Although the oral route of administration is preferred, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route. Drug absorption from the gastrointestinal (GI) tract can be limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.

The aim of the present study was to prepare solid dispersion through the hot melt extrusion process for fixed dose combination of antiretroviral drug DCPT 139 and DCPT 140. DCPT 139 and DCPT 140 a fixed dose combination in the ratio of 4:1 respectively used for antiretroviral therapy, exhibits poor water solubility and hence shows dissolution rate limited absorption. In recent years research work is concentrated on various methods to improve the solubility characteristics of poorly soluble drugs and preparation of solid

dispersion through hot melt extrusion process is one among them. The solubility problem can be solved by incorporating drug in a hydrophilic polymer matrix under elevated temperature so that the drug get dispersed molecularly in the matrix and get converted into amorphous form due to higher temperature processing, which improves the solubility and dissolution rate of the drug.

1 INTRODUCTION TO HOT MELT EXTRUSION TECHNOLOGY

1.1 HISTORY

Hot-melt extrusion is a widely applied processing technique within the plastics industry. Hot-melt extrusion is the process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. Currently, more than half of all plastic products, including plastic bags, sheets, and pipes, are manufactured by this process [1]. Hot melt extrusion was first introduced in the plastics industry in the mid-nineteenth century to prepare polymeric insulation coatings to wires. The number of hot-melt extrusion patents issued for pharmaceutical systems has steadily increased since the early 1980's (Figure 1.1) with international scope (Figure 1.2).

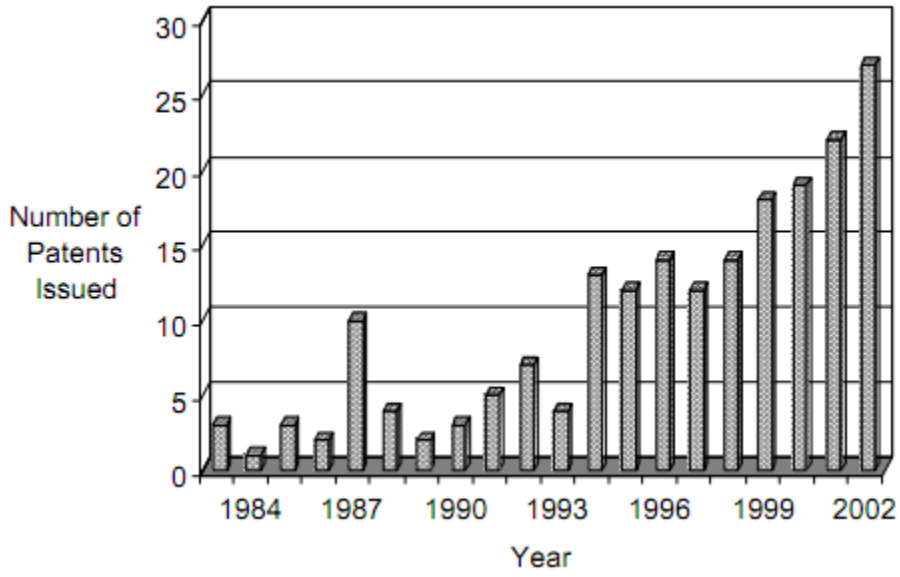


Figure 1.1: The number of hot-melt extrusion patents issued for pharmaceutical applications from 1983 to 2002.

(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:910, 2007)

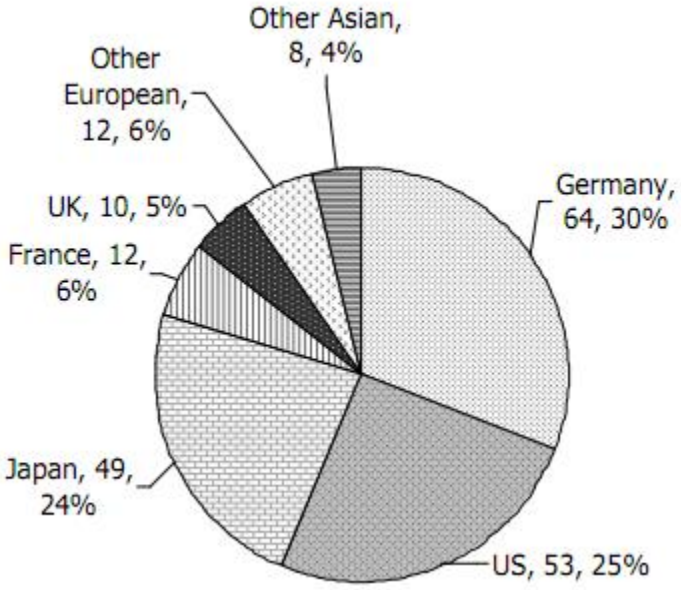


Figure 1.2: The number and percentage of hot-melt extrusion patents issued since 1983 for pharmaceutical applications by country.

(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:910, 2007)

Several research groups have demonstrated hot-melt extrusion processes as a viable method to prepare pharmaceutical drug delivery systems, including granules [2], pellets [3, 4], sustained release tablets [5-9], transdermal and transmucosal drug delivery systems [10-17] and implants [18-21].

1.2 ADVANTAGES

Hot-melt extrusion offers many advantages over traditional pharmaceutical processing techniques including:

- Hot-melt extrusion has been used to improve the bioavailability of drug substances by formation of molecular dispersions.
- Solvents and water are not necessary reducing the number of processing steps and eliminating time-consuming drying steps.
- The active ingredients do not need to be compressible and the entire procedure is continuous and efficient.

- The intense mixing and agitation imposed by the rotating screw cause de-aggregation of suspended particles in the molten polymer resulting in a more uniform dispersion.

1.3 DISADVANTAGES

- Thermal process (drug/polymer stability).
- Flow properties of the polymer are essential to processing.
- Limited number of available polymers.
- Requires high energy input.
- The melt technique process cannot be applied to heat sensitive material owing to the elevated temperature involved.

1.4 EQUIPMENT, PRINCIPLES OF EXTRUSION AND PROCESS TECHNOLOGY

1.4.1 Hot-Melt Extrusion Equipment

Extrusion processes can be categorized as ram extrusion or screw extrusion. Screw extrusion consists of a rotating screw inside a heated barrel, while ram extrusion operates with a positive displacement ram capable of generating high pressures to push materials through the die. During ram extrusion, materials are introduced into a heated cylinder. After an induction period to soften the materials, a ram (or a piston) pressurizes the soft materials through the die and transforms them into the desired shape. High-pressure is the operating principle of the ram extrusion. The major drawback of ram extrusion is limited melting capacity which causes poor temperature uniformity in the extrudate. Whereas, materials are subjected to higher shear stress and more intense mixing in a screw extruder. Extrudates prepared by screw extrusion are more homogeneous, in comparison with extrudates that are processed by ram extrusion. Screw extruders include single screw and twin screw extruders.

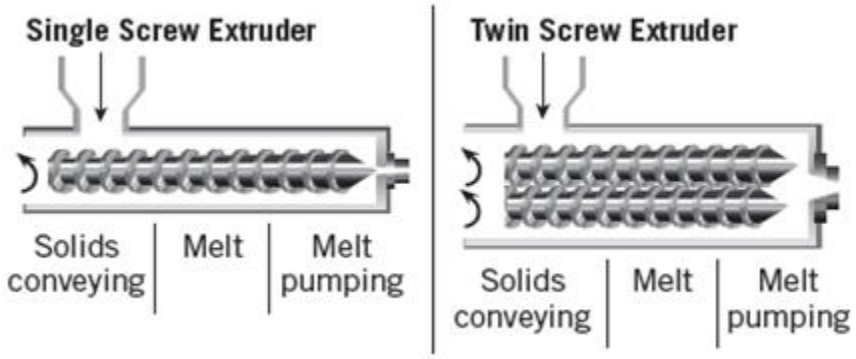


Figure 1.3: Cross section of single and twin screw extruder barrel

(Ref. Particle Sciences drug development services technical Brief 2011 volume 3)

In a twin screw extruder, two screws can either rotate in the same (co-rotating extruder) or the opposite (counter-rotating extruder) direction.

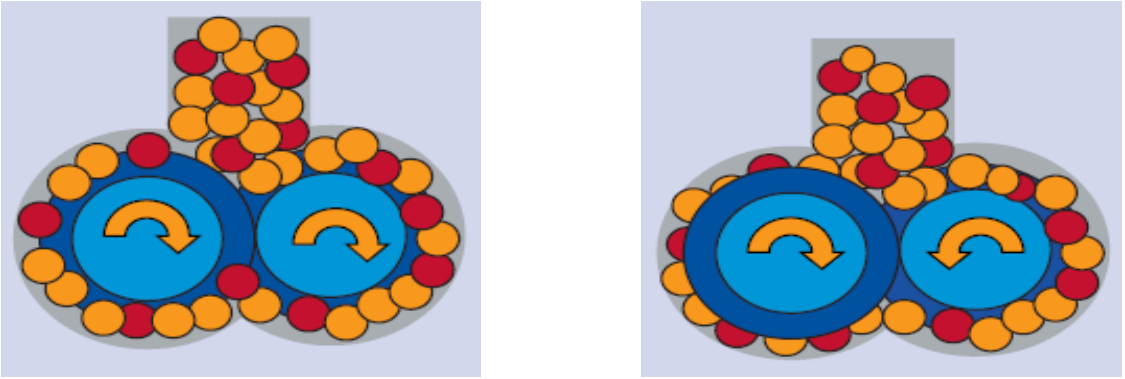


Figure 1.4: Co rotating and counter-rotating extruder direction respectively.

(Ref. K.kolter, M.Karl, S.Nalawade, N.Rottmann "Hot-melt Extrusion with BASF Pharma polymer" pg no.11 oct-2010)

Twin screw extruders have several advantages over single screw extruders, such as easier material feeding, high kneading and dispersing capacities, less tendency to over heat and shorter transit time. In an extrusion process dimensions of the screws are given in terms of L/D ratio, which is length of the screw divided by the diameter. Typical extrusion process lengths are in the 20 to 40:1L/D range or longer. Diameter of the screws used is 18-27 mm extruder for pilot scale and 60mm extruder for production scale.

Most commercial extruders have a modular design to facilitate changing screws. The design of the screw has a significant impact on the process and can be selected to meet particular requirements such as high or low shear. Whelan and Dunning have reviewed the various screw designs available [23]. Specific screw features are displayed in Figure 1.5. Screws are designed with several sections, with the function of each section ranging from feeding, mixing, compression, and metering. Most screws are made from surface coated stainless steel to reduce friction and the possibility of chemical reactions.

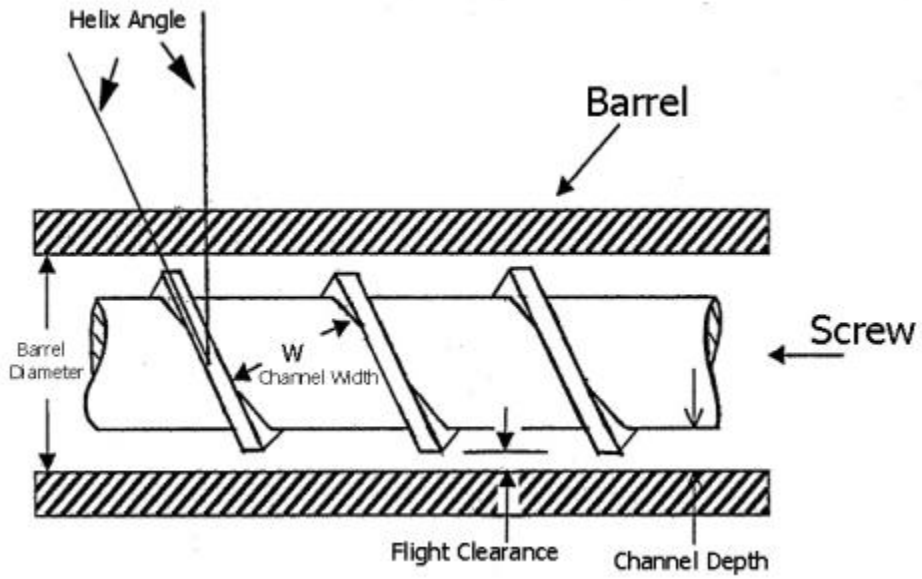


Figure 1.5: Diagram of an extruder screw.

(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:913, 2007)

The channel depth is the distance from the screw roots to the inner barrel surface, the flight clearance is the distance between the screw flight and the inner barrel surface, the channel width is the distance between two neighboring flights and the helix angle is the angle between the flight and the direction perpendicular to the screw axis. The screw is typically divided into three sections along the length of the barrel: feeding, melting or compression, and metering as shown in Figure 1.6.

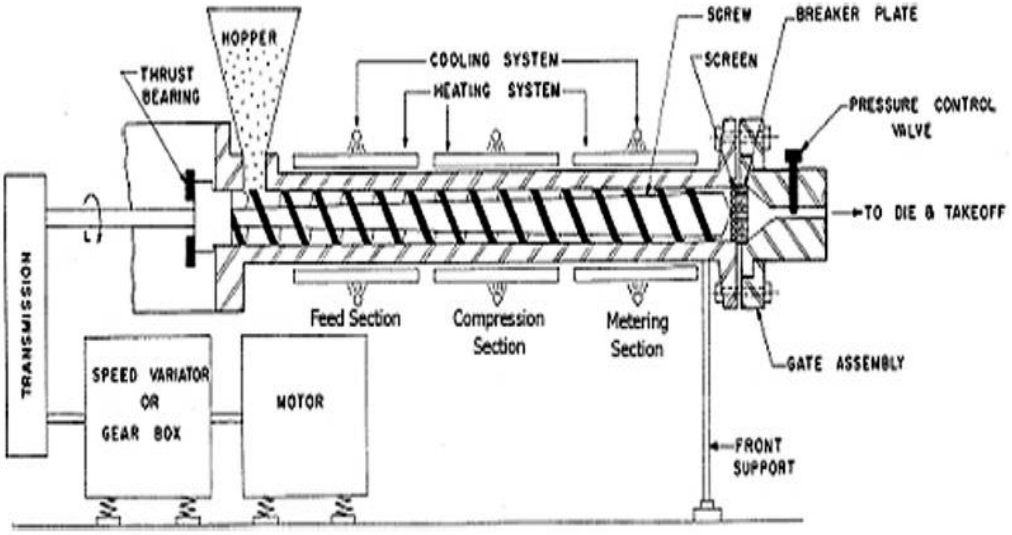


Figure 1.6: Schematic diagram of a single screw extruder.

(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:913, 2007)

The purpose of the feeding section is to transfer the materials from the hopper to the barrel. The channel depth is usually widest in this section to facilitate mass flow. A decrease in channel depth in the compression zone increases the pressure which removes entrapped air. The polymer typically begins to soften and melt in the compression zone. Thermoplastic polymers primarily exist in a molten state when entering the metering section. The mass flow rate of the extrudate is highly dependent upon the channel depth and the length of the metering section. For the purpose of compression and metering of material different elements are employed over screw such as conveyers or kneaders.

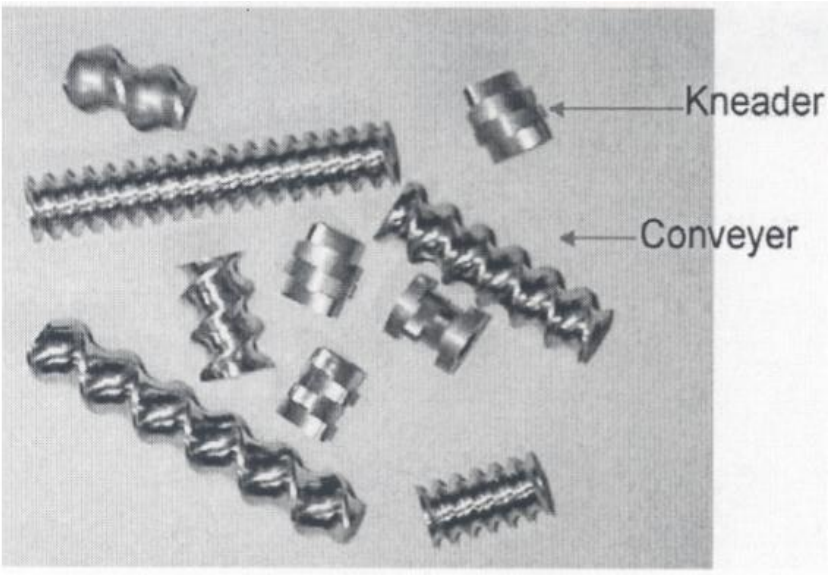


Figure 1.7: Screw Parts Conveying and Kneading Elements

(Ref. K.kolter, M.Karl, S.Nalawade, N.Rottmann "Hot-melt Extrusion with BASF Pharma polymer" pg no.13 oct 2010)

The die is attached at the end of the barrel. The shape of the die controls the form of the extrudate (Figure 1.8). Generally, the cross section of the extrudate will increase upon leaving the die, a phenomenon known as "die swell" due to the viscoelastic properties of polymers. This entropy driven event occurs as the individual polymer chains recover from the deformation imposed by the rotating screw by "relaxing" and increasing their radius of gyration.

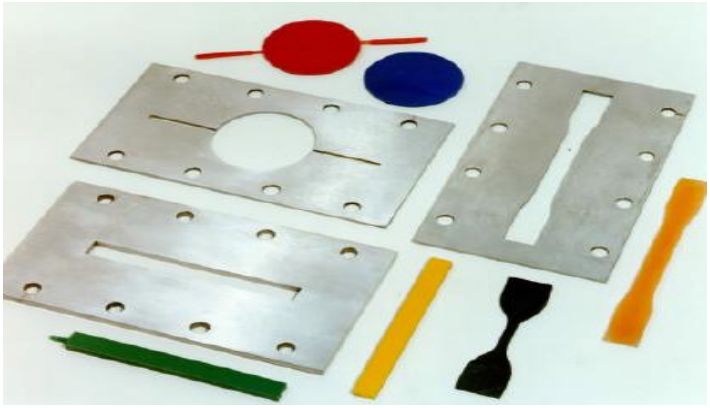


Figure 1.8: Dies and resultant extrudate shapes.

(Ref. M Crowley, Dissertation on physiochemical and mechanical characterization of Hot-melt extruded dosage form pg no.12, 2003)

Several types of downstream equipment are necessary to further process the extrudate into its desired form. Pelletizers are used to chop small diameter rods into pellets or granules (Figure 1.9). For film applications, chill rolls and torque winders are used to rapidly cool and collect the extrudate (Figure 1.10). Film thickness can be adjusted by changing the rotation speed of the chill rolls or the torque winder.

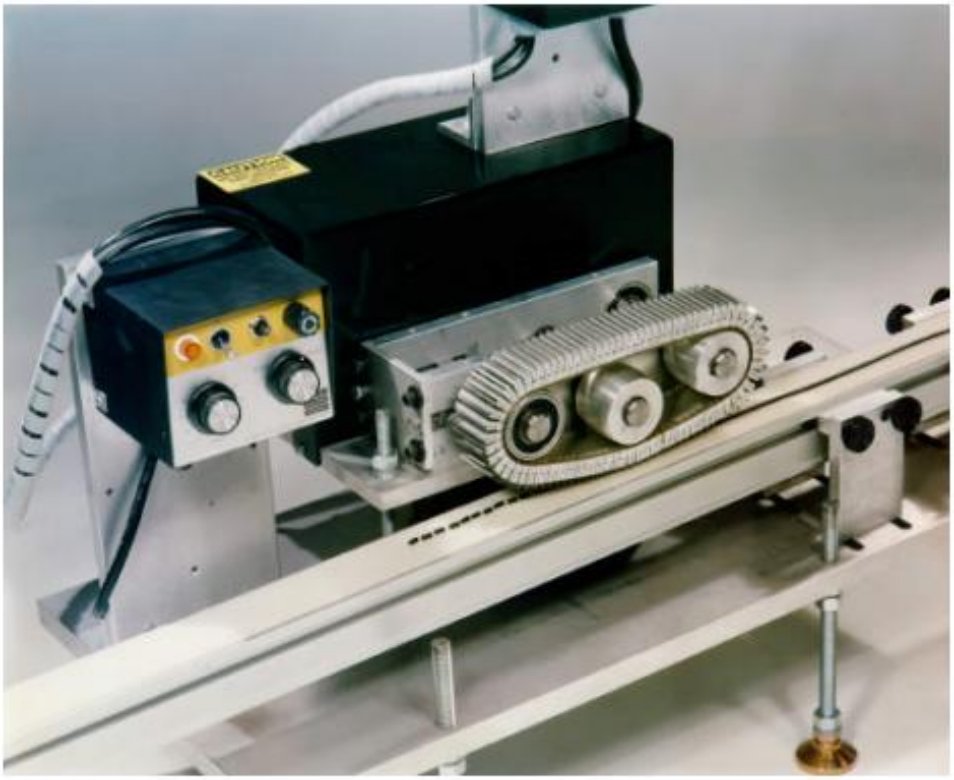


Figure 1.9: Pelletizers used to chop rod shaped extrudates into pellets or granules.
(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:911, 2007)

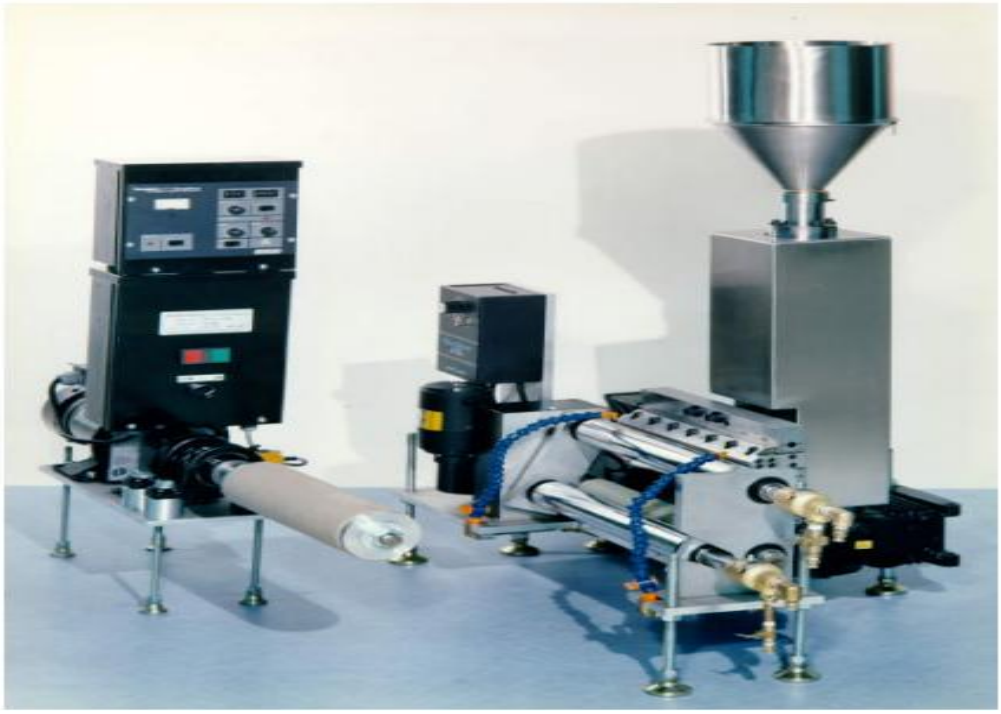


Figure 1.10: Hot-melt extrusion film assembly with chill rolls and torque winder.

(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:915, 2007)

1.4.2 The Hot-Melt Extrusion Process

The different zones of the barrel are pre-set to specific temperatures before the extrusion process. The feed stock is placed in the hopper and transferred into the heated barrel by the rotating screw. The feed stock must have good flow properties. This requirement is usually met by insuring that the angle of the feed hopper exceeds the angle of repose of the feed materials. When this prerequisite is not met, the feed stock tends to form a solid bridge at the throat of the hopper resulting in erratic flow. In these situations, a force feeding device can be used. As the feed stock is moved along the length of the barrel, heat is generated by shearing imposed by the rotating screw in addition to conduction from the electrical heating bands. The efficiency of the feeding section is dependent upon the friction coefficient between the feed materials and the surface of the barrel and screw. High friction along the barrel and low friction at the screw interface contribute to efficient mass flow in the feed section. Obviously, the bulk density, particle shape, and compression properties of the raw materials impact the feeding efficiency. The transfer of

the material should be efficient in order to maintain an increase in pressure in the compression zone and the metering zone. The pressure rise in these zones insures efficient output of the extrudate. It is also possible to fine-tune the barrel temperature at the feeding section in order to optimize the friction at the surface of the barrel. Inconsistent material feed may result in a "surge" phenomenon that will cause cyclical variations in the output rate, head pressure and product quality. The temperature of the melting zone is normally set 15 - 60ºC above the melting point of semi-crystalline polymers or the glass transition temperature of amorphous polymers [22, 24-26]. The efficiency of the melting process depends on the polymer properties and the extruder design. In general, polymers with low melt viscosities and high thermal conductivities exhibit a more efficient melting process. Changes in the screw design are sometimes warranted to improve the melting process and improve mass flow through the extruder. Solidified polymer components can block the channel if melting is incomplete and result in a surge of material around the blockage. Processing conditions depend on the chemical stability and physical properties of the thermal polymer. Melt viscosity, molecular weight, glass transition temperature, and melting point (in the case of a semi crystalline polymer) should be considered to establish appropriate processing parameters. Polymers are subjected to a mechanical shear stress imposed by the rotating screw, and thermal stress due to the relatively high processing temperatures and pressures. Under these conditions, polymers may undergo chain scission, depolymerization or thermal degradation. Differential scanning calorimetry, thermogravimetric analysis and gel permeation chromatography are often used to monitor polymer stability. Plasticizers, antioxidants, thermal lubricants and other additives are often included in the formulation to address stability concerns.

1.4.3 Wet Extrusion versus Dry Extrusion

Based on the properties of the feed stock, extrusion processes can be classified as wet extrusion or dry extrusion. In wet extrusion, the feed stock is conditioned and softened with the addition of solvents prior to processing. The primary reason for wet extrusion is that extrudates have a superior finish due to the softening, plasticizing and ripening action of the solvents. In some cases, such as cellulose nitrate, wet extrusion under low temperatures and pressures with minimum friction is required because the polymer is

explosive when overheated using dry extrusion processes. Compared with wet extrusion, dry extrusion is a solvent free process. The feed stock is generally in solid form and heat is required to soften or melt the materials. In the dry extrusion process, materials are softened by the heated barrel, the shearing effect of a rotating screw and friction during transit. The extrudate solidifies after exiting the extruder. For obvious reasons, most of the extrusion processes use the dry technique.

1.5 MATERIALS USED IN HOT-MELT EXTRUSION

For a pharmaceutical material to be processed by hot-melt extrusion, it must be able to deform easily inside the extruder and solidify upon its exit. The materials must meet the same levels of purity and safety as those prepared by traditional techniques. Most of the raw materials used in hot-melt extruded pharmaceuticals have been used in the production of other solid dosage forms such as tablets, pellets, granules and transdermal. Thermal stability of the individual compounds is a prerequisite for the process, although the short processing times encountered in this process may not limit all thermolabile compounds. Hot-melt extruded dosage forms are complex mixtures of active medicaments and functional excipients. Functional excipients may be broadly classified as matrix carriers, release modifying agents, bulking agents, antioxidants, thermal lubricants and miscellaneous additives. The selection and use of various excipients can impart specific properties to hot-melt extruded pharmaceuticals in a manner similar to those in traditional dosage forms. The incorporation of plasticizers may lower the processing temperatures necessary for hot-melt extrusion thus reducing drug and carrier degradation. Drug release from these systems can be modulated by the incorporation of various functional excipients. The dissolution rate of the active compound can be increased or decreased depending on the properties of the rate-modifying agent. For systems that display oxidative or free radical degradation during processing or storage, the addition of antioxidants, acid acceptors, and/or light absorbers may be warranted.

1.5.1 Carriers

In hot-melt extruded drug delivery systems, the active compound is embedded in a carrier formulation comprised of one or more “meltable” substances and other functional

excipients. The meltable substance is generally a polymer or low melting point wax. The selection of an appropriate carrier is important in the formulation and design of a hot-melt extruded dosage form. The properties of the carrier often dictate the processing conditions. The physical and chemical properties of the carrier can control the release of the active compound from the final dosage form. Table 1.1 lists some of the carriers used to prepare hot-melt extruded dosage forms. For systems employing non-polymeric carrier materials, the compatibility between the drug substance and carrier should be addressed. The incorporation of a low melting compound into a low melting point wax may form a eutectic mixture or reduce the melting point of the mixture preventing the formation of a solid dosage form. The production of granules using carnauba wax has been reported [27-29]. The granules contained diclofenac sodium and could be produced at temperatures less than the reported melting point of the wax material. The use of waxes and other wax-based materials have the potential advantage of being relatively inert.

Table 1.1 Carriers used to prepare hot-melt extruded dosage forms

Chemical name	**Trade name**	**Tg* (°C)**	**Tm** (°C)**	**References**
Ammonio methacrylate copolymer	Eudragit RS/RL	64	-	[3, 30, 31]
Poly(dimethylaminoethylmathacrylate-co-methacrylic acid	Eudragit E	50	-	[10, 14, 16]
Poly(methacrylic acid-co-methyl methacrylate)1:2	Eudragit S	160	-	[2]
Hydroxypropyl cellulose	Klucel	130	-	[11-16, 29]
Ethyl cellulose	Ethocel	133	-	[2, 3, 8, 32]
Cellulose actetate butyrate	CAB 381-0.5	125	157	[2, 3, 33]
Cellulose acetate phthalate	-	165	192	[2, 34]
Polyethylene oxide	Polyox WSR	-67	65-80	[5, 7, 9, 11-13]

Polyethylene glycol	Carbowax	-20	37-63	[16, 35-39]
Polyvinyl acetate	Sentry plus	35-40	-	[6, 33]
Polyvinyl pyrrolidone	Kollidon	168	-	[2, 38, 39, 41-43]
Hydroxypropyl methylcellulose phthalate	-	137	150	[2, 44]
Hydroxypropyl methylcellulose	Methocel	175	-	[46]
Polyvinyl alcohol	Elvanol	-	-	[2]
Poly(lactide-co-glycolide)	PLGA	-	-	[19, 20]
Poly(ethylene-co-vinyl acetate)	Elvax 40W	-36	45	[3, 48, 49]
Polyvinylpyrrolidone-co-vinyl acetate	Kollidon® VA64	106	-	[36, 38, 45]
Polyethylene	-	-125	140	[10] [33]
Citric acid	-	-	153	[62-64]
Glyceryl Palmitosterate	Precirol ATO 5	-	52-55	[46]
Carnuba wax	-	-	82-85	[27-29]
Isomalt	Palatinit	-	145-150	[57-59]
Pregelatinized starch	-	-	-	[53]

*Glass transition Temperature

** Melting Temperature

(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:918, 2007)

Drug release kinetics from hot-melt extruded dosage forms is highly dependent upon the choice of the carrier material. Carriers used in hot-melt extruded dosage forms have included water insoluble polymers and waxes such as ethyl cellulose or carnauba wax in which the rate of drug release is diffusion controlled. Water soluble polymers have included hydroxypropyl cellulose, polyethylene oxide, poly (vinyl pyrrolidone) in which the drug is released by a diffusion and erosion mechanism. Functional excipients have

also been used to modify drug release rates in these systems. Depending upon the physical and chemical properties of these additional excipients, various release profiles may be achieved. Functional excipients have been formulated into hot-melt extruded dosage forms to modify the drug release rate by altering the porosity or tortuosity of the dosage form. Viscosity increasing agents have been incorporated into polymeric matrices to limit and reduce the initial burst often observed with these systems. The use of ionic and / or pH dependent polymers as the carrier matrix may achieve zero-order drug release or site specific drug delivery along the gastrointestinal tract. Swelling agents and super disintegrants such as AcDiSol and Explotab have been investigated as a method to modulate drug release. It has been reported that Explotab could be used as a "super-absorbent" in hydroxypropylcellulose hot-melt extruded transdermal films to facilitate moisture uptake in wound care applications [14]. A similar approach of drug release modification was applied to wax-containing systems [27-29]. Hydroxypropylcellulose, Eudragit L, and sodium chloride were incorporated into diclofenac sodium/carnauba wax matrices. Increasing the cellulose derivative or methacrylic acid copolymer concentration in the system resulted in a substantial increase in the release of diclofenac sodium. The release of diclofenac sodium from hydroxypropylcellulose/wax matrices was less pH dependent than the system containing wax/Eudragit L since the methacrylic acid copolymer is insoluble in water or in solutions with pH<6. The effect of sodium chloride was less pronounced and was attributed to the negligible swelling effect of this material.

1.5.2 Plasticizers

Plasticizers are typically low molecular weight compounds capable of softening polymers to make them more flexible. The use of polymeric carriers in hot-melt extrusion often requires the incorporation of a plasticizer into the formulation to improve the processing conditions during the manufacturing of the extruded dosage form or to improve the physical and mechanical properties of the final product. Plasticization of the polymer is generally attributed to the inter-molecular secondary valence forces between the plasticizer and the polymer. Plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains. In so doing, the ease of movement of polymer chains with respect to

each other is dramatically reduced. Plasticizers were also found to facilitate the fusion process of semi-crystalline polymers [65, 66]. Less energy is usually required to melt semi-crystalline polymers following the addition of one or more plasticizers. With the addition of a plasticizer, a hot-melt extrusion process can be conducted at lower temperatures and with less torque. Both the active ingredient and the polymer will be more stable during the extrusion process due to these improved processing conditions. Materials that are commonly used as plasticizers which are approved by the Food and Drug Administration for use in pharmaceutical dosage forms are listed in Table 1.2. Plasticizers used for the preparation of pharmaceutical dosage forms must have good efficiency, stability, polymer – plasticizer compatibility and permanence. Triacetin [3], citrate esters [10, 12], and low molecular weight polyethylene glycols [3, 5, 12] have been investigated as plasticizers in hot-melt extruded systems. Additionally, several drug substances have been reported to function as plasticizers in hot-melt extruded dosage forms [5, 7, 8, 10, and 12]. The physical and mechanical properties and drug release rate of pharmaceutical dosage forms is dependent on the permanence of the plasticizers. Permanence of a plasticizer during processing and storage is very important and the evaporation of highly volatile plasticizers from the dosage form during storage has been reported. Arwidsson and coworkers [67] reported a dramatic change in drug release properties of coated tablets due to volatilization of the plasticizer during curing and storage. Repka and McGinity [12] demonstrated that the amount of plasticizer remaining in hot-melt extruded films over time was a function of the plasticizer type and storage conditions. Plasticizers may also improve the physical-mechanical properties of hot-melt extruded dosage forms. In transdermal films, the addition of a plasticizer to the polymer matrix can improve the film's flexibility [10, 12]. Plasticizers often influence the product's tensile strength and elastic modulus.

Table 1.2 Common plasticizers used in pharmaceutical dosage forms

Type	Examples
Citrate esters	Triethyl citrate, Acetyl triethylcitrate
Fatty acid esters	Butyl sterate, glycerol monosterate, stearyl alcohol
Sebacate esters	Dibutyl sebacate
Pthalate esters	Diethyl phthalate, Dibutyl phthalate, Dioctyl phthalate
Glycol derivatives	PEG,PG
Others	Triacetin, Mineral oil, Castor oil
Vitamin E TPGS	D-α- tochopheryl PEG 1000 succinate

1.5.3 Other Processing Aids

The excessive temperatures needed to process unplasticized or under plasticized polymers may lead to polymer degradation. The stability of polymers that are susceptible to degradation can be improved with the addition of antioxidants, acid receptors and or light absorbers during hot-melt extrusion. One manufacturer of these materials recommends the incorporation of an antioxidant into formulations containing low molecular weight hydroxypropylcellulose [68]. Similarly, polyethylene oxide has been reported to be protected from free radical and oxidative degradation by the incorporation of an antioxidant [7]. Antioxidants are classified as preventive antioxidants or chain-breaking antioxidants based upon their mechanism. Preventive antioxidants include materials that act to prevent initiation of free radical chain reactions. Reducing agents, such as ascorbic acid, are able to interfere with auto-oxidation in a preventive manner since they preferentially undergo oxidation. The preferential oxidation of reducing agents protects drugs, polymers and other excipients from attack by oxygen molecules. These antioxidants are sometimes called oxygen scavengers. They are most effective when used in a closed system where oxygen can not be replaced once it is consumed. Chelating agents such as edetate disodium (EDTA) and citric acid are another type of preventive antioxidant that decrease the rate of free radical formation by forming a stable complex with metal ions that catalyze these reduction reactions. Hindered phenols and aromatic

amines are the two major groups of chain breaking antioxidants that inhibit free radical chain reactions. Commonly used antioxidants such as butylated hydroxyanisole, butylated hydroxytoluene and vitamin E are hindered phenols. Because the O -H bonds of phenols and the N-H bonds of aromatic amines are very weak, the rate of oxidation is generally higher with the antioxidant than with the polymer. Other materials have been used to facilitate hot-melt extrusion processing. Waxy materials like glyceryl monostearate have been reported to function as a thermal lubricant during hot-melt processing. Vitamin E TPGS has been reported to plasticize polymers and enhance drug absorption (Table 1.3).

Table 1.3 Common processing aids used in hot-melt extruded dosage forms

Chemical Name	Trade Name	References
Saccharose monopalmitate	Sucroester	[36, 43]
Glycerolester and PEG ester	Gelucire 44/14	[36]
Glyceryl monosterate	Imwitor	[54-56]
Vitamin E	-	[7]
Vitamin E Succinate	-	[7]
Vitamin E TPGS	-	[7, 13, 16]
Butylated Hydroxy Anisole	-	[7]

(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:921, 2007)

1.5.4 Drugs

The properties of the active drug substance often limit the formulation and processing choices available to the pharmaceutical scientist in the development of dosage forms. Hot-melt extrusion offers many benefits over traditional processing techniques. The process is anhydrous which avoids potential hydrolytic degradation pathways. In addition, poorly compactable materials can be prepared as tablets without the compression process. Hot-melt extruded tablets can be produced by cutting an extruded rod to the desired dimensions. As an initial assessment, the thermal, chemical, and physical properties of the drug substance must be characterized. Depending on the unique properties of the drug substance and the other materials in the formulation, the drug may

be present as undissolved particles, a solid solution, or a combination in the final dosage form. The state of the drug in the dosage form may have a profound impact on the processability and stability of the product. Solid dispersion systems may be more stable and more easily processed than solid solution systems, but solid solution systems may be produced that are transparent and may have increased bioavailability of poorly soluble compounds. Table 1.4 gives a partial listing of some of the drug substances that have been formulated and processed by hot-melt extrusion. The active compound may help or hinder the functionality of the other components in the formulation. Oxprenolol hydrochloride was shown to melt under the hot-melt extrusion processing conditions thus decreasing the viscosity of the extrudate to yield a material with poor handling properties [3]. In similar work preparing dosage forms by injection molding, Cuff and Raouf reported that fenoprofen calcium inhibited the hardening of a PEG-MCC matrix, resulting in an unusable product [37]. In contrast, Lidocaine was shown to lower the glass transition temperature of Eudragit E/HDPE films [10], and hydrocortisone demonstrated a time dependent lowering of the glass transition temperature of HPC films [12]. Thus, the drug substance can be both beneficial and detrimental to properties of hot-melt extruded dosage forms.

Table 1.4 Drug Substances processed by hot-melt extrusion techniques.

Drug	Tm(°C)	References
Nifedipine	175	[42, 44, 45]
Indomethacin	162.7	[38, 42, 45]
Piroxicam	204.9	[42]
Tolbutamide	128.4	[42, 45]
Lacidipine	184.8	[38, 42, 45]
Chlorpheniramine maleate	135	[5, 7, 12, 15, 30]
Theophylline	235	[4, 6, 33, 54-56]
Oxprenolol Hydrochloride	108	[3]
Lidocaine	68.5	[10]
Hydrocortisone	220	[12]
Phenylpropanolamine HCl	192	[46]

Ethinyl estradiol	144	[48]
Acetylsalicyclic acid	135	[60, 61]
Dilteazem HCl	210	[3]
Diclofenac Sodium	284	[29]
Acetaminophen	170	[57]
Nicardipine HCl	180	[47]
Etonogestrel	200	[48, 49]

(Ref. Michael M. Crowley and Feng Zhang "Pharmaceutical Applications of Hot -Melt Extrusion: Part I" Drug Development and industrial pharmacy, 33:922, 2007)

1.6 PROPERTIES OF HOT-MELT EXTRUDED DOSAGE FORMS

1.6.1 Chemical Stability of Drug Substances during Hot-Melt Extrusion

The stability of the active ingredients during hot-melt extrusion should be closely monitored since it is conducted at elevated temperatures. Hydrolysis, solvolysis and oxidation are three primary mechanisms of drug degradation. Drugs containing carboxylic acids, phosphoric acids or carbonyl functional groups are vulnerable to hydrolysis [71]. Water or a solvent must be present for hydrolysis or solvolysis to occur. Since hot-melt extrusion is a solvent free process, hydrolysis and solvolysis are often not a concern. Oxidation is also a free-radical chain reaction with three distinctive stages: initiation, propagation and termination. Oxidative drug degradation during hot-melt extrusion has been reported by Aitken-Nicol [10] and Repka [12]. Peroxides formed due to the oxidation of polymeric carrier were shown to induce the oxidation of the active ingredient [72]. High-pressure liquid chromatography is the most commonly used technique to investigate the stability of drug substances. Stability indicating methods should be developed so that the active ingredient is separated from the degradants. The purity of drug peak can be studied using a photo diode-array detector to confirm the reliability of the assay.

1.6.2 Thermal and Crystalline Properties of Hot-Melt Extruded Dosage Forms

Drug and polymers are subjected to elevated temperatures, high pressure and intense mixing during the hot-melt extrusion process. At these elevated temperatures, the solubility of the drug in the polymer carrier is increased. Depending upon the processing

conditions, some crystalline drugs either melt or become solubilized in the polymer matrix during the process. Recrystallization and nucleation of drug molecules from the polymer melt is retarded during the cooling of the extrudate due to reduced solute migration and the difficulty in nucleation in a highly viscous polymer medium. Furthermore, polymer viscosity increases dramatically with the decrease in the temperature. Following hot-melt extrusion, the active ingredient can be present in one of two forms: as a crystal embedded in the hardened polymer phase, or as individual molecules dissolved in the polymer matrix. Formation of a drug-polymer solid dispersion in hot-melt extruded dosage forms has been reported [6, 10]. Complexation between drug and polymer may also contribute to the formation of a solid solution.

Solid solutions containing the drug and an amorphous polymer are generally regarded as interstitial solid solutions where drug molecules occupy the interstitial space between the polymer chains. For a semi-crystalline polymer, some drugs were reported to be concentrated in the amorphous regions of the polymer, and some drugs were reported to be solubilized in the crystalline matrix of the polymer. Because the drug is dispersed at a molecular level, a solid dispersion is a metastable form. It is susceptible to aging effect and the drug may recrystallize from the matrix during the storage under elevated temperature and high humidity. Crystallization of chloramphenicol palmitate from the solid dispersion in PVP was reported. The methods that have been used to characterize hot-melt extrudates are summarized in Table 1.5.

Table 1.5: Common Methods used for the characterization of hot- melt extrudates.

Thermo analytical Methods	Differential Scanning Calorimetry Thermo Gravimetric Analysis Hot stage Microscopy
X-ray Diffraction & Dissolution Testing	-
Microscopic methods	Polarized Light microscopy Scanning electron microscopy Transmission electron microscopy
Nuclear Magnetic Resonance	-
Mechanical Analysis	Tensile strength Elongation

In addition to characterizing the hot-melt extrudate, these methods can be used to differentiate between solid solutions (molecularly dispersed drug), solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug and carrier. It is challenging to precisely characterize systems which are molecularly dispersed from those that are not due to the complexity of the systems, and different analytical methods may yield contrasting results. In general, dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions. Thermoanalytical methods include those that examine the system melt extrusion. DSC can be used for the quantitative detection of transitions (melting point, glass transition) in which energy is required or liberated (i.e. endothermic and exothermic phase transformations). Generally, the hot-melt extrudate is scanned and compared to a physical mixture of the drug, polymeric carrier and other excipients. The lack of a melting transition in the DSC scan of the hot-melt extrudate indicates that the drug is present in an amorphous rather than crystalline form. Thermogravimetric analysis (TGA) is a measure of thermally induced weight loss of a material as a function of applied temperature. TGA is limited to studies involving either a weight gain or loss, and is commonly used to study desolvation and decomposition. TGA can be used as a screening tool for the thermal stability of materials used in hot-melt extrusion. Microthermal analysis has been used to identify phase separation in hot-melt extrudates containing itraconazole and Eudragit E100. In this approach, differences in the thermal topography of hot-melt extrudates can be discerned. X-ray diffraction (XRD) is also used to characterize the crystalline properties of hot-melt extruded dosage forms. The principle of XRD is based on Bragg's law, in which parallel incident X-rays strike the crystal planes and are then diffracted at angles related to the spacing between the planes of molecules in the lattice. Crystallinity is reflected by a characteristic fingerprint region in the diffraction pattern. If the fingerprints of the drug and carrier do not overlay one another, the crystallinity of the drug and polymer following hot-melt extrusion can be determined. Thus, X-ray diffraction can be used to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However,

the sensitivity of the XRD technique is limited and cannot generally detect crystallinity of less than 10%. Infrared spectroscopy can be used to detect changes in bonding between functional groups due to structural changes or a lack of crystal structure. IR can be used to differentiate between peaks that are sensitive to changes in crystallinity from those that are not. Solid state nuclear magnetic resonance (NMR) has been used to probe the crystallinity of materials. Although any NMR-active nucleus can be studied, most efforts have focused on 13C investigations. Microscopy is one of the best methods to study the crystalline properties of hot-melt extrudates. Both optical and electron methods are suitable to examine the surface morphology of samples to probe for the presence of crystalline particles or amorphous domains. It is also possible to obtain reliable particle size information using these techniques.

1.7 APPLICATIONS IN THE PHARMACEUTICAL INDUSTRY

- For masking the bitter taste of an active drug.
- Formulation of polymer-drug solutions/dispersions.
  -Increased drug solubility
  -Increased drug dissolution rate
- Formulation of controlled release dosage forms (including implants).
- Formulation of targeted release dosage forms.
- Formulation of orodispersible tablets.
- Formulation of parenteral depots and topical drug delivery system.

1.8 MARKETED PRODUCTS

Oral Formulations:

Gris-PEG – Griseofulvin in PEG matrix (Novartis Consumer Health)

Adalat SL – Nifedipine in PEG matrix (Abbott Laboratories)

Rezulin – Troglitazone in PVP matrix (Parke-Davis)

Cesamet – Nabilone in PVP matrix (Eli Lilly)

Implants:

Zoladex – Goserelinacetate in polylactide-co-glycolide matrix (Astrazeneca)

Depot – Profact – Buserelin in polylactide-co-glycolide matrix (Aventis)

1.9 INTRODUCTION TO SOLID DISPERSION

1.9.1 Definition of solid dispersions:

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

Based on their molecular arrangement, five different types of solid dispersions can be distinguished

A. Simple eutectic mixtures
B. Solid solutions
    - According to their miscibility
        a) Continuous
        b) Discontinuous solid solutions
    - According to the way in which the solvate molecules are distributed in the solvendum
        a) Substitutional crystalline solid solutions
        b) Interstitial crystalline solid solutions
C. Glass suspension
D. Glass solutions
E. Amorphous precipitation in a crystalline carrier

1. Simple eutectic mixtures:

Solid eutectic mixtures are usually prepared by rapid cooling of a co melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with certain composition, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

2. Solid solutions:

2.1 Continuous solid solutions

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

2.2 Discontinuous solid solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. The term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component.

2.3 Substitutional crystalline and Interstitial crystalline solid solutions

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter.

3. Glass solutions and Glass suspensions

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The familiar term glass however, can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature Tg. On heating, it softens progressively and continuously without a sharp melting point. A glass solution requires miscibility or solid solubility, complex formation or upon fast cooling or evaporation during preparation. In case of glass suspension particle size of dispersed phase dependent on cooling/evaporation rate and obtained after crystallization of drug in amorphous matrix.

4. Amorphous Precipitation in Crystalline Carrier: It is postulated that drug with propensity to super cooling has more tendency to solidify as an amorphous form in presence of carrier. This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form (while in simple eutectic mixtures drug is precipitated in crystalline form). Ex. Precipitation of sulfathiazole in crystalline urea.

1.10 INTRODUCTION TO DCPT 139

1. **Name of the Drug** **:** DCPT139
2. **Molecular Structure** **:** Confidential
3. **Molecular Formula** **:** Confidential
4. **Category** **:** Antiretroviral
5. **Physicochemical properties:**

a) Appearance	**:**	A white or almost white powder
b) Solubility	**:**	Practically insoluble in water, freely soluble in methanol, sparingly soluble in acetone and very slightly soluble in acetonitrile.
c) Melting point range	**:**	124 – 127 °C
d) Partition Coefficient (log P)	**:**	3.91
e) Dissociation constant (pKa)	**:**	14.98

1.11 INTRODUCTION TO DCPT 140

1. **Name of the Drug** **:** DCPT140
2. **Molecular Structure** **:** Confidential
3. **Molecular Formula** **:** Confidential
4. **Category** **:** Antiretroviral
5. **Physicochemical properties:**

   a) **Appearance** **:** A white or almost white powder

   b) **Solubility** **:** Practically insoluble in water, freely soluble in methanol, sparingly soluble in acetone and very slightly soluble in acetonitrile.

   c) **Melting point range** **:** 120 – 123 °C

   d) **Partition Coefficient (log P)** **:** 4.24

   e) **Dissociation constant (pKa)** **:** 14.23

1.12 INTRODUCTION TO POLYMERS:

1.12.1 SOLUPLUS

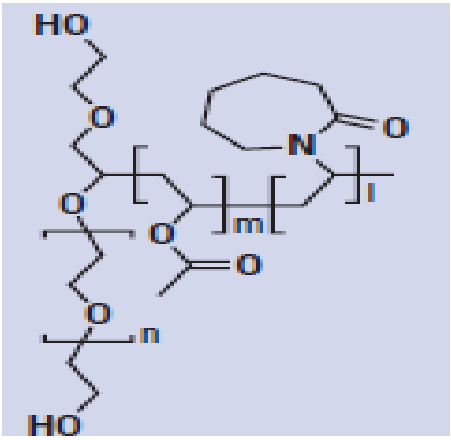
General information: Soluplus is a polymeric solubilizer with an amphiphilic chemical structure. Due to its bifunctional character it is able to act as a matrix polymer for solid solutions on the one hand, on the other hand it is capable of solubilizing poorly soluble drugs in aqueous media.

Description: Soluplus is a polyvinyl caprolactam-polyvinylacetate-polyethylene glycol graft copolymer. Contains PEG6000, Vinyl caprolactam and Vinylacetate in the ratio of (13: 57: 30) respectively.

Appearance: White to yellowish free flowing granules.

Molecular weight: 118000g/mol

Molecular structure:



Solubility: Soluble in water and many organic solvents.

K-value (1% in ethanol): 31-41

Glass Transition Temperature (Tg): ~70°C

1.12.2 KOLLIDON VA64

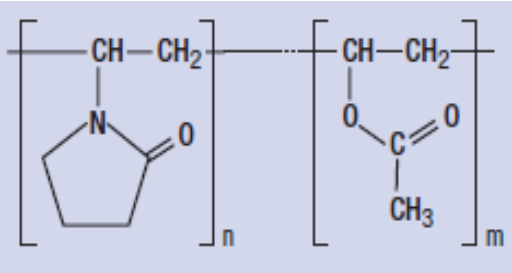
General information: Kollidon VA64 manufactured by free radical polymerization of 6 parts of N-vinyl pyrrolidone and 4 parts of vinyl acetate. Vinylpyrrolidone is a hydrophilic, water soluble monomer whereas vinyl acetate is lipophilic and water insoluble. The ratio of both the monomers is balanced in such a way that the polymer is still freely water soluble.

Description: It contains Vinyl pyrrolidone and Vinyl acetate in the ratio of 60:40 respectively.

Appearance: White to yellowish free flowing granules.

Molecular weight: 55000g/mol

Molecular structure:



Solubility: Solutions of upto 50% can be prepared in water, ethanol, isopropanol and methanol. Less soluble in ether and cyclic hydrocarbons.

K-value (1% in water): 25-31

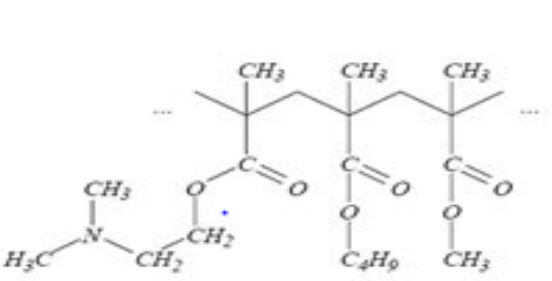
Glass Transition Temperature (Tg): ~106°C

1.12.3 EUDRAGIT EPO

Description: Eudragit EPO is a cationic copolymer containing Poly (butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) in the ratio of 1:2:1 respectively.

Appearance: It is a white powder with a characteristic amine-like odour.

Molecular structure:



Solubility: Soluble in gastric fluid up to pH 5.0.

Swellable and permeable above pH 5.0

Glass Transition Temperature (Tg): ~48°C

2.1 LITERATURE REVIEW OF HOT MELT EXTRUSION PROCESS

1. Until recently, hot-melt extrusion had not received much attention in the pharmaceutical literature. Rippie and Johnson [30] prepared pellets containing cellulose acetate phthalate using a rudimentary ram extruder in 1969 to study the dissolution rates based upon pellet geometry.
2. Follonier and coworkers [3] in 1994 investigated the possibility of using hot-melt extrusion technology to produce sustained-release pellets. It was the researchers' goal to prepare a dosage form in a simple and continuous manner. Thermal degradation was recognized as a limitation of this hot-melt process. Diltiazem hydrochloride, a relatively stable and freely soluble drug was incorporated into their polymer–based pellets for sustained release capsules. Polymers and plasticizers were selected prior to extrusion to maximize the possibility of a successful dosage form. In their study, ethyl cellulose, cellulose acetate butyrate, poly (ethyl acrylate/methyl-methacrylate/trimethyl ammonio ethyl methacrylatechloride) (Eudragit® RSPM) and poly (ethylene-co-vinyl acetate) (EVAC) were the polymers and the plasticizers were triacetin and diethyl phthalate. The porosity of the pellets was determined by mercury porosimetry. The pellets exhibited a smooth surface and low porosity. The drug release characteristics of diltiazem were biphasic, with the CAB and EVAC pellets giving the slowest release rate. These researchers also reported that the type and amount of plasticizer used, drying time of the polymers, extrusion temperatures, and plasticization times varied with each formulation. They observed that the stability of Eudragit ® RSPM was adequate for extrusion at a temperature of 130°C.
3. Follonier, et al. [2] examined different parameters influencing the release of diltiazem hydrochloride from hot-melt extruded pellets incorporated into hard gelatin capsules. The drug release rate was found to depend upon polymer type, addition of pore-forming additives or hydrophilic polymers, and pellet size. The authors obtained in vitro release rates low enough to achieve therapeutic plasma levels for diltiazem hydrochloride with a once or twice daily administration. The addition of hydrophilic polymers helped avoid incomplete drug release due to encapsulated drug clusters in the insoluble matrix. The authors also incorporated various polymeric excipients,

such as croscarmellose sodium (Ac-Di-Sol®) and sodium starch glycolate (Explotab®), into the pellet formulations to vary the drug release rate. The incorporation of swelling agents was able to reduce the initial burst release from the matrix.

4. Miyagawa, Sato, and coworkers [24-25] in 1996 and 1997 prepared controlled release matrices containing diclofenac as a model drug by hot-melt extrusion. The authors used a twin-screw compounding extruder to prepare wax matrix granules composed of carnauba wax, the model drug, and other rate controlling agents. Their study showed that a wax matrix with high mechanical strength could be obtained even when the composition was processed below the melting point of the wax. Dissolution of diclofenac from the wax matrix granules was strongly influenced by the formulation. Hydroxypropylcellulose, methacrylic acid copolymer (Eudragit L-100), and sodium chloride were investigated as dissolution rate controlling materials. The authors emphasized the advantages of using the twin-screw extruder for wax matrix tablets because of the low processing temperatures, high kneading and dispersing ability, and short residence time. The authors observed in their second study that the selection of rate controlling excipients based upon solubility and swelling characteristics had a significant impact on drug release properties from the wax matrix granules.
5. Liu and coworkers [42] compared the properties of wax based granules and tablets prepared by hot-melt extrusion to those prepared by high shear melt granulation. Powder blends containing phenylpropanolamine hydrochloride, Precirol, Sterotex K, and various excipients (microcrystalline cellulose, lactose and Emcompress) were extruded using a single screw extruder with open end discharge. The extrudates were then passed through a 14-mesh screen to form granules. Hot-melt extruded granules were observed to be less spherical than high-shear melt granules and had lower bulk and tap densities. Analysis of the hot-melt extruded granules showed better drug content uniformity among granules of different size ranges compared with high-shear melt granules, resulting in a more reproducible drug release from the corresponding tablets. At the same wax level, drug release from tablets decreased in the order of using microcrystalline cellulose, lactose and Emcompress as the filler excipient. The

observed differences in the dissolution properties of the tablets were due to the differences in the solubility, swellability and density of the filler excipients.

6. Lindberg and coworkers [53-55] prepared effervescent granules using a twin-screw extruder. During extrusion, sodium bicarbonate and anhydrous citric acid were added from separate inlet ports of the extruder, and ethanol was added as a liquid binder and pumped through a nozzle in the extruder barrel to facilitate the formation of the granules.
7. Young and coworkers [4] successfully prepared spherical controlled release theophylline pellets by a hot-melt extrusion (HME) and spheronization process. A powder blend of anhydrous theophylline, Eudragit® Preparation 4135 F, microcrystalline cellulose and polyethylene glycol 8000 powder was sieved, blended and then melt-extruded in a Randcastle Microtruder®. The hot-melt extruded pellets were prepared by first cutting a thin, extruded composite rod into symmetrical pellets. The pellets were then spheronized in a traditional spheronizer at elevated temperatures. The melt-extruded matrix pellets exhibited diffusion-controlled drug release. Drug release from the acrylic matrix system was influenced by the pH of the dissolution medium since the solubility of the matrix polymer, Eudragit® Preparation 4135 F, is pH dependent. The surface morphology of the pellets was found to depend upon the spheronization parameters.
8. Prapaitrakul and coworkers [73] prepared disks using a melt extrusion method in which the molten materials were forced into a mold. The disks contained glyceryl fatty acid esters (Gelucire), polyethylene glycol fatty acid esters, or a combination of the two with chlorpheniramine maleate as a model drug. The release of the drug into distilled water, pH 1.2 buffer, and pH 7.5 buffer exhibited square root of time dependence. An increase in the fatty acid ester hydrophilic-lipophilic balance (HLB) from 1 to 14 resulted in a 10-fold increase in the drug release rate. The maximum release rate was seen from the fatty acid ester with a melting point of 44°C. The pH of the dissolution medium had a minimal impact on the rate of drug release. The release rate was modified by blending Gelucires of different melting points and HLB values.
9. Crowley and coworkers [7] studied the thermal stability of polyethylene oxide (PEO) in sustained release tablets prepared by hot-melt extrusion. The weight average

molecular weight of the polymer was determined using gel permeation chromatography. The chemical stability of PEO was found to be dependent on both the storage and processing temperature, and the molecular weight of the polymer. Storage of the polymer above its melting point significantly increased polymer degradation, and the degradation process was accelerated as the molecular weight of the polymer was reduced. The thermal stability of high molecular weight PEO (1,000,000 or PEO 1M) in sustained release chlorpheniramine maleate (CPM) tablets prepared by hot-melt extrusion was found to depend on the processing temperature and screw speed. Lower molecular weight PEO (100,000 or PEO 100K) was demonstrated to be a suitable processing aid for PEO 1M. Incorporation of PEO 100K reduced degradation of PEO 1M and did not alter the release rate of CPM. Vitamin E, Vitamin E Succinate and Vitamin E TPGS were found to be suitable stabilizers for PEO, however, ascorbic acid was shown to degrade the polymer in solution. Thermal analysis demonstrated that Vitamin E Succinate and Vitamin E TPGS were dispersed at the molecular level in hot-melt extruded tablets. Solubilized Vitamin E Succinate and Vitamin E TPGS suppressed the melting point of the polyethylene oxide. Drug release rates from hot-melt extruded tablets stabilized with antioxidants were found to be dependent on the hydrophilic nature of the antioxidant.

10. Aitken-Nichol and coworkers [10] investigated the viability of hot-melt extrusion technology in 1996 for the production of thin, flexible acrylic films for topical drug delivery. The authors noted that the manufacturing process was not restricted by solvent concerns. The authors compared cast films with hot-melt extruded films. Eudragit® E100 was the primary thermoplastic polymer extruded. The authors reported that hot-melt extrusion was a viable technology for the production of free films of this acrylic resin. Although triethyl citrate was an acceptable plasticizer for this polymer, these researchers found that lidocaine hydrochloride also plasticized for the acrylic films. The authors concluded that the differences in the dissolution rate and ductile properties between cast films and extruded films were due to the amount of drug dissolved in the polymer.
11. Repka and McGinity [13] prepared films containing hydroxypropyl cellulose and polyethylene oxide by hot-melt extrusion with and without Vitamin E TPGS as a

formulation additive. Addition of 1, 3, and 5% Vitamin E TPGS decreased the glass transition temperature of the extruded films containing either a 50:50 or 80:20 ratio of HPC to PEO in an almost linear fashion. The glass transition temperature of the film containing 3% Vitamin E TPGS was lowered by over 11ºC compared to the film without Vitamin E TPGS. The films containing 3% Vitamin E TPGS had similar mechanical properties to films containing 3% PEG 400, but a 3 fold increase in percent elongation was observed compared to films containing 3% triethyl citrate and 3% acetyltributyl citrate. Vitamin E TPGS also facilitated the processing of the HPC/PEO films by decreasing the barrel pressure, drive amps, and torque of the extruder.

12. Rothen-Weinhold and coworkers [18] prepared long-acting poly (lactic acid) implants containing vapreotide, a somatostatin analogue, by hot-melt extrusion. Many peptides are susceptible to degradation and it is difficult to formulate and deliver them without significant loss of biological activity. Furthermore, the authors desired to deliver the peptide for a period of weeks in a controlled manner. However, the authors reported that the peptide degraded during manufacturing. The main degradation product obtained after implant manufacturing was found to be a lactoyl lactyl-vapreotide conjugate.
13. Van Laarhoven et al, [43] a contraceptive vaginal ring containing polyethylene vinylacetate copolymers, etonogestrel and ethinyl estradiol was prepared by melt extrusion. The powders were compounded in a twin-screw extruder, granulated and then spun into fibers. After leaving the extruder, the strands were cooled to room temperature and granulated using a strand granulator. The steroids were completely dissolved in the polymer melt. A co-extrusion procedure was used to prepare the coaxial fibers in which two single screw extruders were connected to a spinning block. The molten polymers were delivered to two gear pumps which were necessary to provide precise flow control of both polymers to the spinneret. Finally, the membrane and core polymers were combined in the spinneret to form the coaxial fiber.
14. Zhang and McGinity [5, 9] describe a novel method to prepare sustained release matrix tablets directly from a single screw hot-melt extruder. These researchers

studied the properties of polyethylene oxide (PEO) as a drug carrier and studied the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets. Large diameter rods (4.5 mm) were extruded and cut into tablets. PEG 3350 was included as a plasticizer to facilitate processing. The stability of the primary polymer, PEO, as a function of processing temperature was determined using gel permeation chromatography. The authors report that polymer type, temperature, and residence time in the extruder impacted the PEO stability. In addition, the researchers showed that additional mixing of the components occurred in the barrel of the extruder, since the content uniformity of the extruded tablets was within 99.0% to 101.0% of the theoretical content. As the PEG 3350 concentration increased, the release of CPM from the extruded matrix tablets was found to increase. The rate of hydration and dissolution rate of the entire matrix system were thus accelerated due to the presence of the plasticizer. The rate of drug release was only slightly affected by changes in drug content until the drug loading reached 20%.

3.1 IDENTIFICATION OF DCPT139 AND DCPT 140

3.1.1 UV ABSORPTION MAXIMA OF DCPT 139

UV Absorption Maxima of DCPT 139 in methanol:

UV scanning was done for 100 µg/ml drug solution from 200-800 nm in methanol. The absorption maximum was found to be at 259 nm.

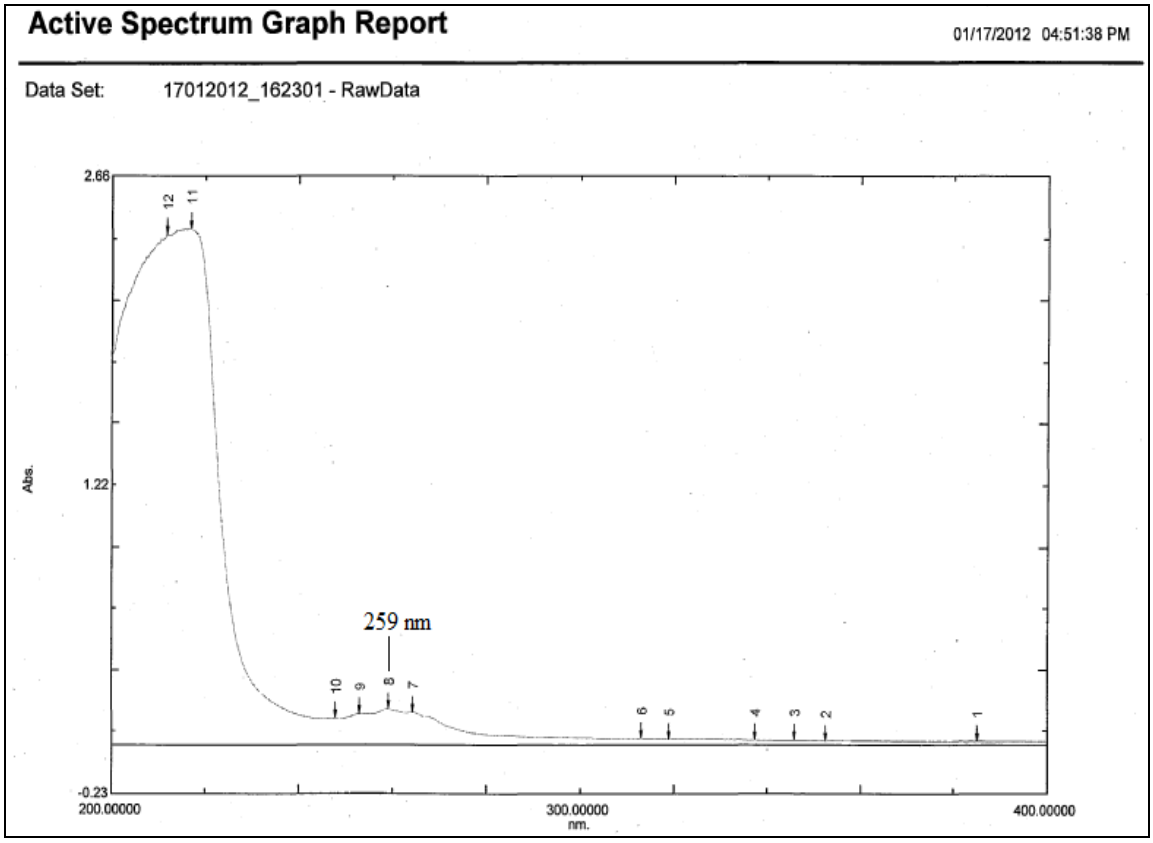


Fig. 3.1: U.V spectrum of DCPT 139 in methanol

CONCLUSION: The above UV spectra of DCPT 139 shows the λmax at 259 nm, which was similar to the reported standard value 259 nm, indicating identity and purity of the drug sample.

3.1.2 ESTIMATION OF DCPT 139

Standard curve of DCPT 139 in methanol:

Preparation of stock solution:

100 mg of DCPT 139 was accurately weighed and transferred in 100 ml volumetric flask. It was dissolved in methanol and volume was made up to the mark with methanol to get 1000µg/ml solution.

Preparation of standard curve in methanol:

From the stock solution 0.5, 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 4.5 ml samples were transferred to 5ml volumetric flask and diluted with the methanol up to the mark to obtain DCPT 139 concentration of 100-900 µg/ml respectively. The wavelength maxima of DCPT 139 in methanol were found to be 259 nm. Absorbance of each solution was measured at 259 nm. The standard curve was performed in triplicate.

Table 3.1: Standard curve of DCPT 139 in methanol at 259 nm

Conc. (µg/ml)	Absorbance			Avg. Absorbance	Standard deviation
	A1	A2	A3		
0	0	0	0	0	0
100	0.119	0.124	0.1154	0.121	0.004
200	0.227	0.216	0.219	0.227	0.006
300	0.295	0.314	0.3167	0.314	0.012
400	0.415	0.4179	0.424	0.423	0.005
500	0.4831	0.5254	0.5221	0.512	0.024
600	0.6114	0.6124	0.6232	0.626	0.007
700	0.7126	0.714	0.719	0.724	0.003
800	0.792	0.7914	0.8123	0.801	0.012
900	0.921	0.9285	0.923	0.928	0.004

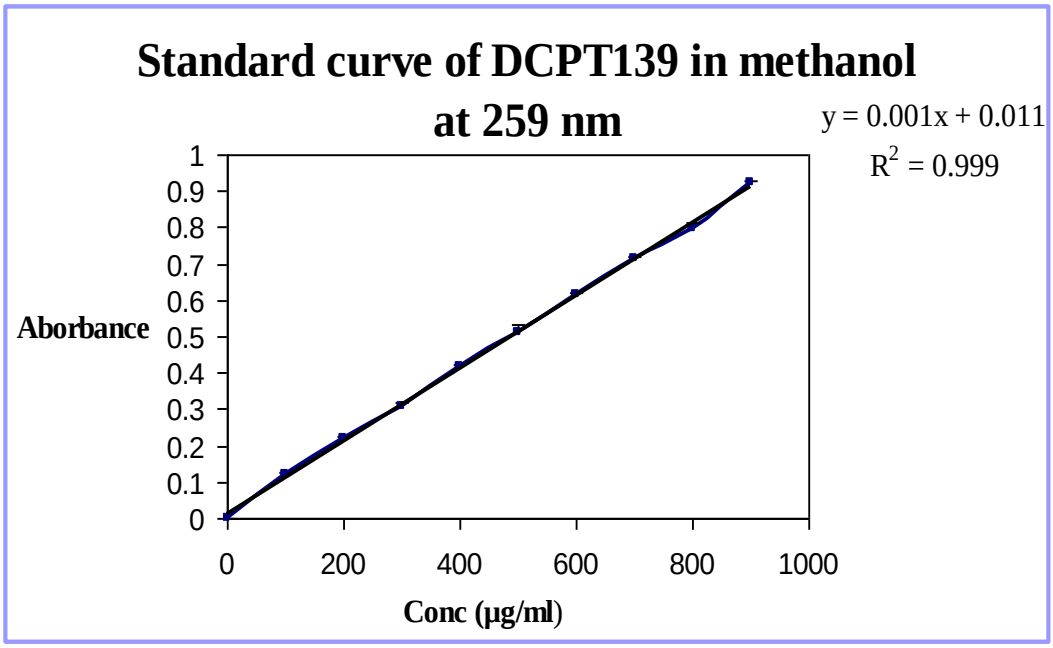


Fig. 3.2: Standard curve of DCPT 139 in methanol

Regression Analysis:

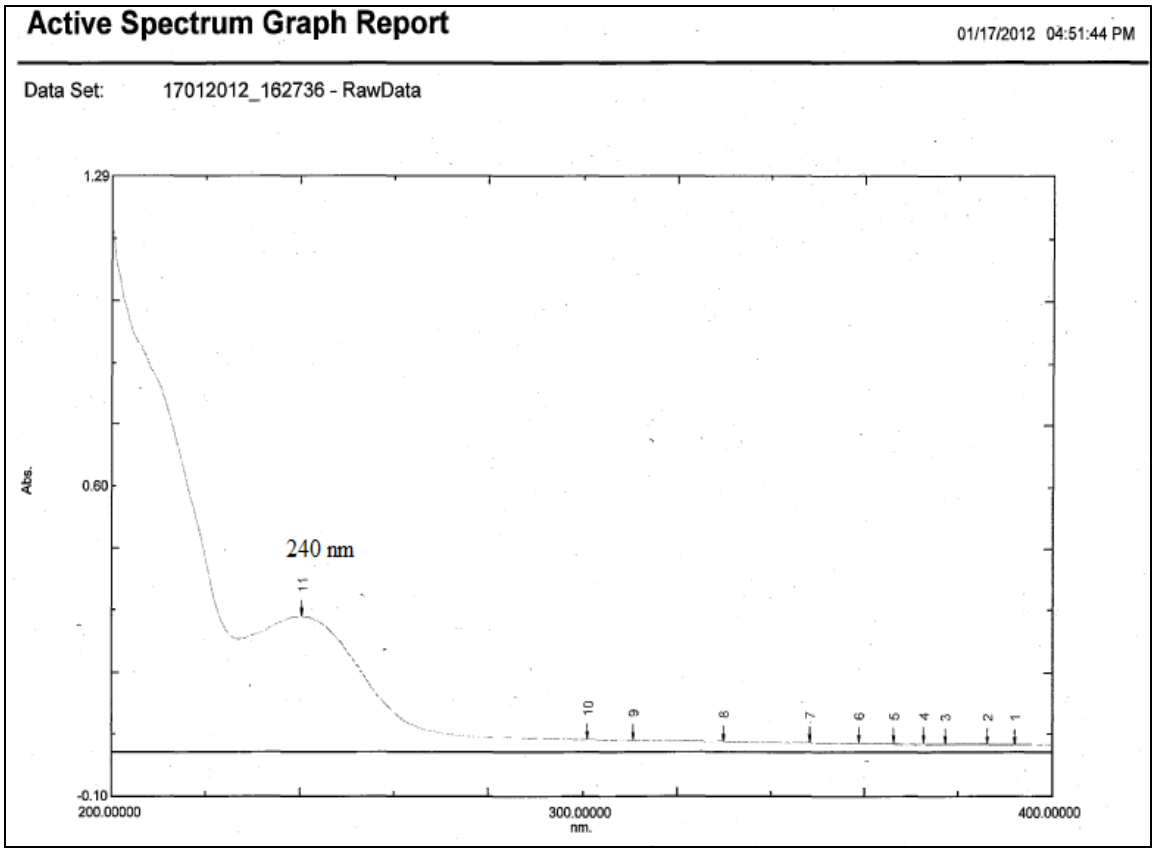
Table 3.2: Regression Analysis for Standard Curve of DCPT 139 in methanol

Regression parameter	**Values**
Correlation coefficient	0.999
Slope	0.001
Intercept	0.011

3.1.3 UV ABSORPTION MAXIMA OF DCPT 140

UV Absorption Maxima of DCPT 140 in methanol:

UV scanning was done for 20 µg/ml drug solution from 200-800 nm in methanol. The absorption maximum was found to be at 240 nm.



. Fig. 3.3: U.V spectrum of DCPT 140 in methanol

CONCLUSION: The above UV spectra of DCPT 140 show the λmax at 240 nm, which was similar to the reported standard value 240 nm, indicating identity and purity of the drug sample.

3.1.4 ESTIMATION OF DCPT 140

Standard curve of DCPT 140 in methanol:

Preparation of stock solution:

10 mg of DCPT140 was accurately weighed and transferred in 100 ml volumetric flask. It was dissolved in methanol and volume was made up to the mark with methanol to get 100µg/ml solution.

Preparation of standard curve in methanol:

From the stock solution 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, and 3.5 ml samples were transferred to 5ml volumetric flask and diluted with the methanol up to the mark to obtain DCPT 140 concentration of 5-70 µg/ml respectively. The wavelength maxima of DCPT 140 in methanol were found to be 240 nm. Absorbance of each solution was measured at 240 nm. The standard curve was performed in triplicate.

Table 3.3: Standard curve of DCPT 140 in methanol at 240 nm

Conc. (µg/ml)	Absorbance			Avg. Absorbance	Standard deviation
	A1	A2	A3		
0	0	0	0	0	0
5	0.0512	0.0423	0.0517	0.050	0.0053
10	0.11	0.112	0.126	0.121	0.0087
15	0.182	0.169	0.184	0.183	0.0081
20	0.234	0.225	0.2216	0.237	0.0064
25	0.331	0.322	0.329	0.331	0.0047
30	0.384	0.3875	0.3716	0.384	0.0084
40	0.523	0.53	0.516	0.521	0.007
50	0.664	0.659	0.673	0.671	0.007
60	0.823	0.841	0.8291	0.830	0.009
70	0.954	0.967	0.963	0.963	0.007

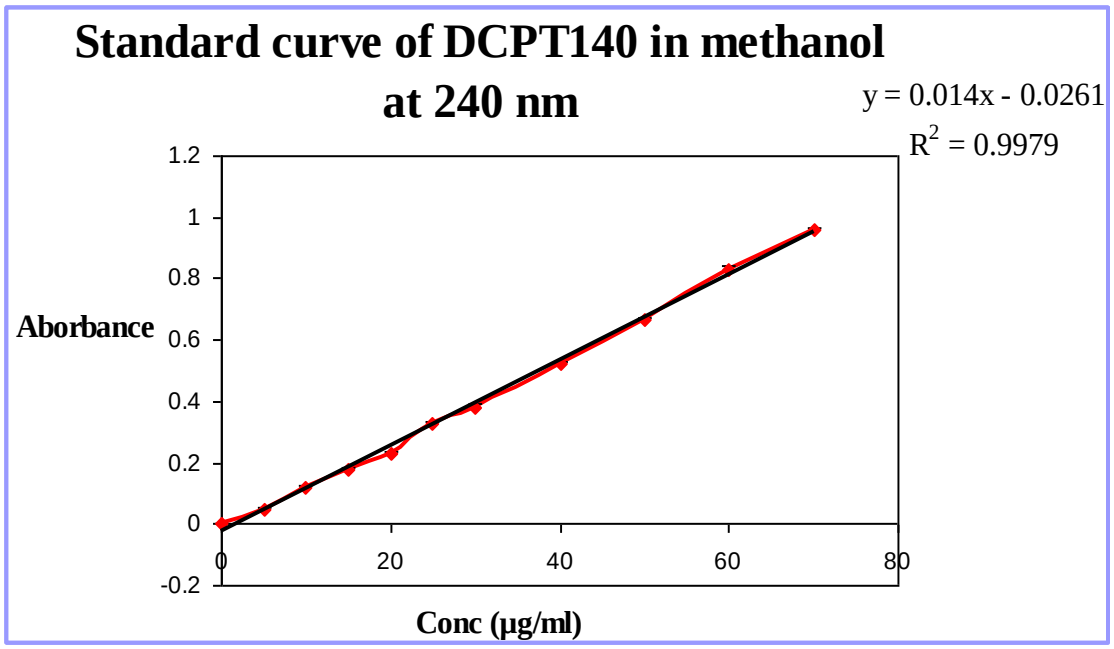


Fig. 3.4: Standard curve of DCPT 140 in methanol

Regression Analysis:

Table 3.4: Regression Analysis for Standard Curve of DCPT 140 in methanol

Regression parameter	**Values**
Correlation coefficient	0.997
Slope	0.014
Intercept	-0.026

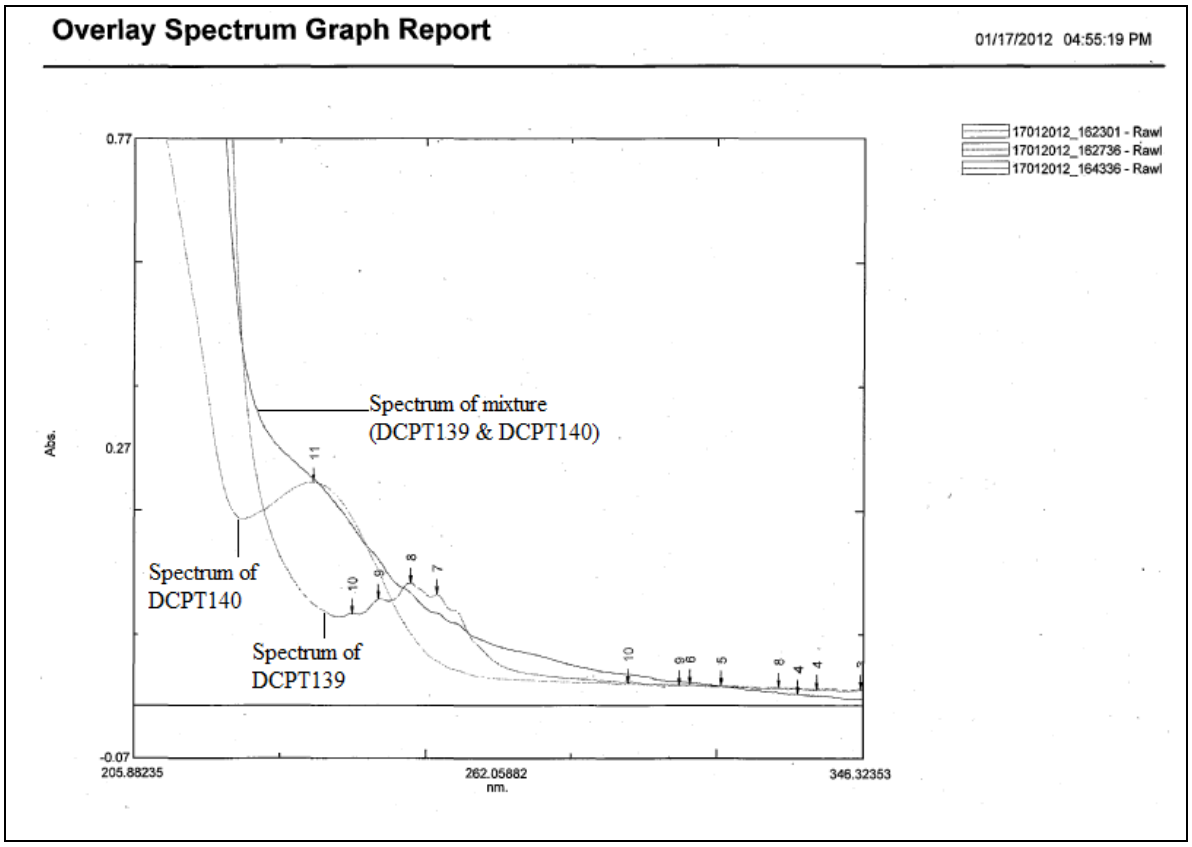


Fig. 3.5: Overlain spectrum of DCPT 139 and DCPT 140 in proportion of 20:80 µg/mL along with spectra of their mixture.

3.2 SIMULTANEOUS ESTIMATION OF DCPT 139 AND DCPT 140 BY VIERODT'S U.V SPECTROPHOTOMETRIC METHOD:-

If a sample contains two absorbing drugs (X and Y) each of which absorbs at the λ_{max} of the other, it may be possible to determine both drugs by the technique of simultaneous equations as:

Cx = (A2 ay1-A1ay2)/ (ax2ay1-ax1ay2),

Cy= (A1ax2-A2ax1)/ (ax2ay1-ax1ay2),

Where:

a) Cx and Cy are the concentration of DCPT140 and DCPT139 respectively.
b) The absorptivity of DCPT140 at λ_1 and λ_2, a_{x1} and a_{x2} respectively.
c) The absorptivity of DCPT139 at λ_1 and λ_2, a_{y1} and a_{y2} respectively.
d) The absorbance's of the diluted sample at λ_1 and λ_2, A_1 and A_2 respectively.

The absorptivity (a) which was calculated using equation:

$$a = A/C$$

Where A and C are the absorbance and concentration (g/100 ml) respectively.

To determine the absorbance's value of DCPT139 at 240 nm and DCPT 140 at 259 nm, calibration curve of both the drug was also taken at the λ_{max} of each other.

3.2.1 Standard Curve of DCPT 139 in Methanol at 240 nm:

100 mg of DCPT 139 was accurately weighed and transferred in 100 ml volumetric flask. It was dissolved in methanol and volume was made up to the mark with methanol to get 1000µg/ml stock solution. From the stock solution 0.5, 1, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 and 4.5 ml samples were transferred to 5ml volumetric flask and diluted with the methanol up to the mark to obtain DCPT 139 concentration of 100-900 µg/ml respectively.

Table 3.5: Standard curve of DCPT 139 in methanol at 240 nm

Conc. (µg/ml)	Absorbance			Avg. Absorbance	Standard deviation
	A1	A2	A3		
0	0	0	0	0	0
100	0.036	0.035	0.0399	0.040	0.003
200	0.0714	0.0723	0.07	0.071	0.001
300	0.094	0.097	0.1	0.102	0.003
400	0.126	0.13	0.129	0.133	0.002
500	0.151	0.172	0.1713	0.161	0.012
600	0.2	0.21	0.16	0.193	0.026
700	0.24	0.232	0.194	0.224	0.025
800	0.273	0.261	0.227	0.257	0.024
900	0.3	0.287	0.2832	0.293	0.009

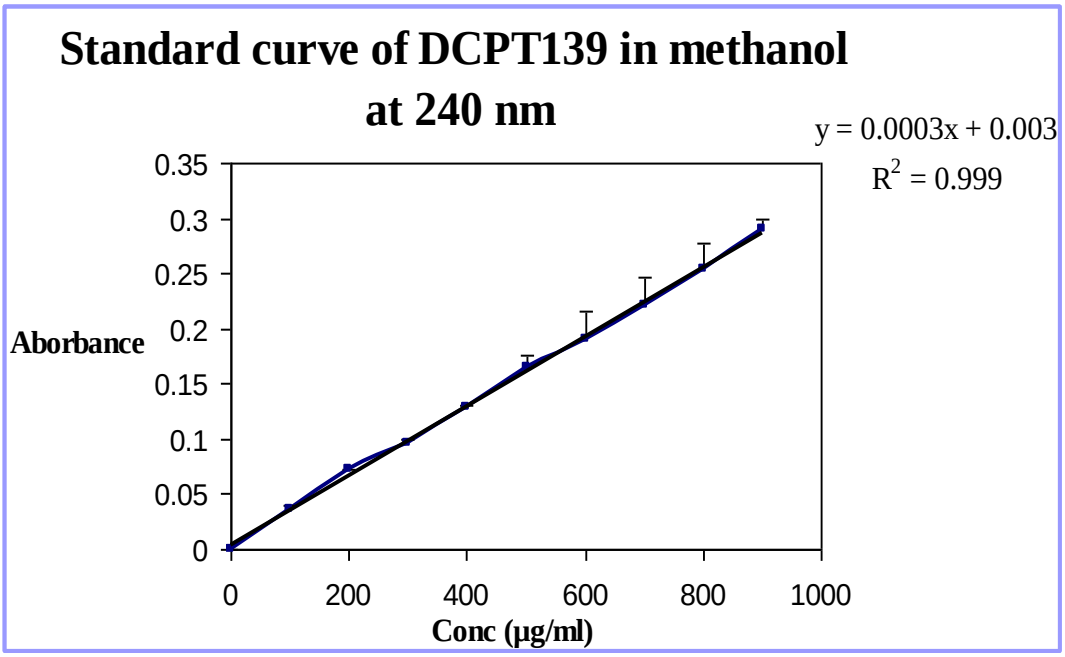


Fig. 3.6: Standard curve of DCPT 139 in methanol

Regression Analysis:

Table 3.6: Regression Analysis for Standard Curve of DCPT 139 in methanol

Regression parameter	**Values**
Correlation coefficient	0.999
Slope	0.0003
Intercept	0.003

3.2.2 Standard curve of DCPT 140 in methanol at 259 nm:

10 mg of DCPT 140 was accurately weighed and transferred in 100 ml volumetric flask. It was dissolved in methanol and volume was made up to the mark with methanol to get 100µg/ml stock solution. From the stock solution 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, and 3.5 ml samples were transferred to 5ml volumetric flask and diluted with the methanol up to the mark to obtain DCPT 140 concentration of 5-70 µg/ml respectively.

Table 3.7: Standard curve of DCPT 140 in methanol at 259 nm

Conc. (µg/ml)	Absorbance			Avg. Absorbance	Standard deviation
	A1	A2	A3		
0	0	0	0	0	0
5	0.014	0.021	0.01	0.020	0.006
10	0.0457	0.03	0.04	0.041	0.008
15	0.0514	0.0671	0.064	0.063	0.008
20	0.09	0.0745	0.1	0.092	0.013
25	0.1	0.117	0.115	0.112	0.009
30	0.125	0.14	0.13	0.133	0.008
40	0.17	0.15	0.19	0.171	0.020
50	0.223	0.211	0.219	0.220	0.006
60	0.261	0.254	0.24	0.251	0.011
70	0.31	0.295	0.319	0.312	0.012

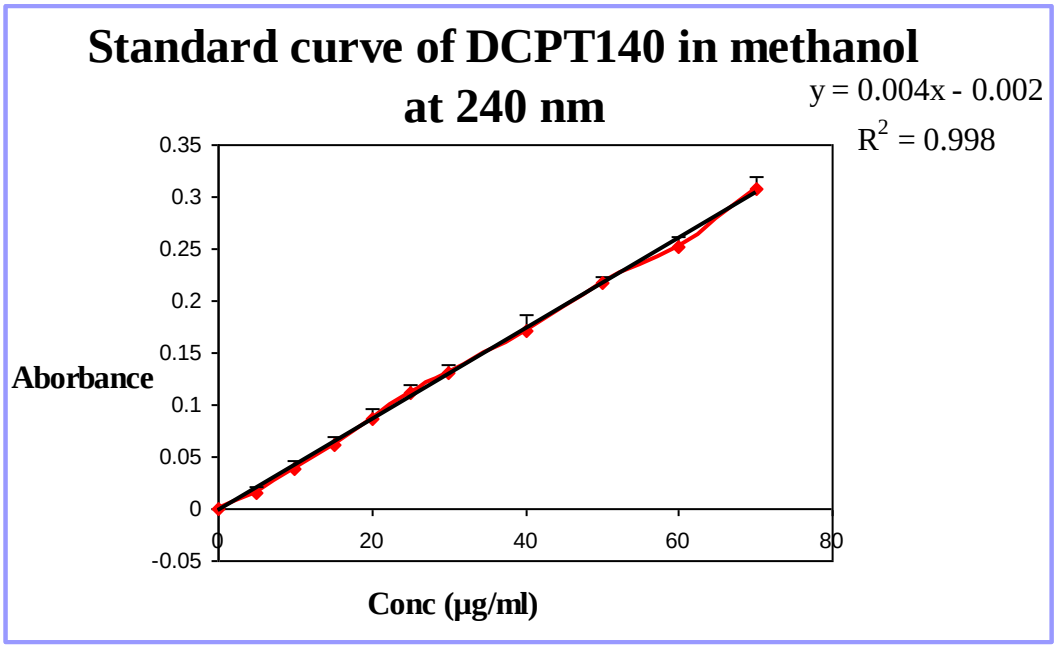


Fig. 3.7: Standard curve of DCPT 140 in methanol

Regression Analysis:

Table 3.8: Regression Analysis for Standard Curve of DCPT 140 in methanol

Regression parameter	**Values**
Correlation coefficient	0.998
Slope	0.004
Intercept	-0.002

Subsequently, the mean absorptivity values were found:

Table 3.9: The mean absorptivity values of DCPT140 and DCPT139 in the proposed method

Absorptivity values	**Wavelengths (nm)**	
	240nm	**259nm**
ax1*	125.31	-
ax2*	-	42.48
ay1**	3.33	-
ay2**	-	10.54

* ax1 and ax2 are the absorptivity values of DCPT140 at 240nm and259nm respectively.
** ay1 and ay2 are the absorptivity values of DCPT139 at 240nm and259nm respectively.

3.3 SOLUBILTY STUDY OF PURE DCPT 139

Procedure-

The solubility of DCPT 139 in water was determined by taking excess quantity of powder, added into 5mL glass vial filled with water. The vial was shaken for 24 hour on lab roller. The solution was filtered through Whatmann filter paper and the drug concentration was determined by taking absorbance at 259nm.

RESULT- The solubility of DCPT 139 in water was found to be 0.09 mg/ml, indicating it is practically insoluble in water.

3.4 SOLUBILTY STUDY OF PURE DCPT 140

Procedure-

The solubility of DCPT 140 in water was determined by taking excess quantity of powder, added into 5mL glass vial filled with water. The vial was shaken for 24 hour on lab roller. The solution was filtered through Whatmann filter paper and the drug concentration was determined by taking absorbance at 240nm.

RESULT- The solubility of DCPT 140 in water was found to be 0.06 mg/ml, indicating it is practically insoluble in water.

3.5 IN VITRO RELEASE PROFILE OF PURE DCPT 139 and DCPT 140

In vitro release study of antiretroviral drug combination i.e. DCPT 139 and DCPT 140 was carried out using USP type I (Basket type) dissolution apparatus at 100 rpm. Accurately weighed 250 mg of drug powder in the ratio of 4:1 containing DCPT 139 (200 mg) and DCPT 140 (50 mg). The release profile was generated in 0.1 N HCL containing 0.5% sodium lauryl sulphate.

Table 3.10: Invitro release profile of pure DCPT 140 and DCPT 139

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
5	0.09	0.07	0.00061	0.00420	0.030	0.210	0	0
15	0.12	0.12	0.00073	0.00843	0.037	0.421	0.030	0.210
20	0.16	0.15	0.00101	0.01018	0.050	0.509	0.067	0.630
30	0.23	0.19	0.00152	0.01190	0.076	0.595	0.117	1.139
40	0.26	0.21	0.00173	0.01295	0.087	0.647	0.193	1.734
50	0.31	0.24	0.00209	0.01434	0.105	0.717	0.279	2.382
60	0.42	0.28	0.00296	0.01462	0.148	0.731	0.384	3.099

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
5.460	37.765	5.46	37.76	10.92	18.88
6.603	75.855	6.63	76.06	13.27	38.03
9.058	91.577	9.12	92.21	18.25	46.10
13.672	107.136	13.79	108.28	27.58	54.14
15.577	116.537	15.77	118.27	31.54	59.14
18.836	129.017	19.12	131.40	38.23	65.70
26.668	131.608	27.052	134.707	54.10	67.35

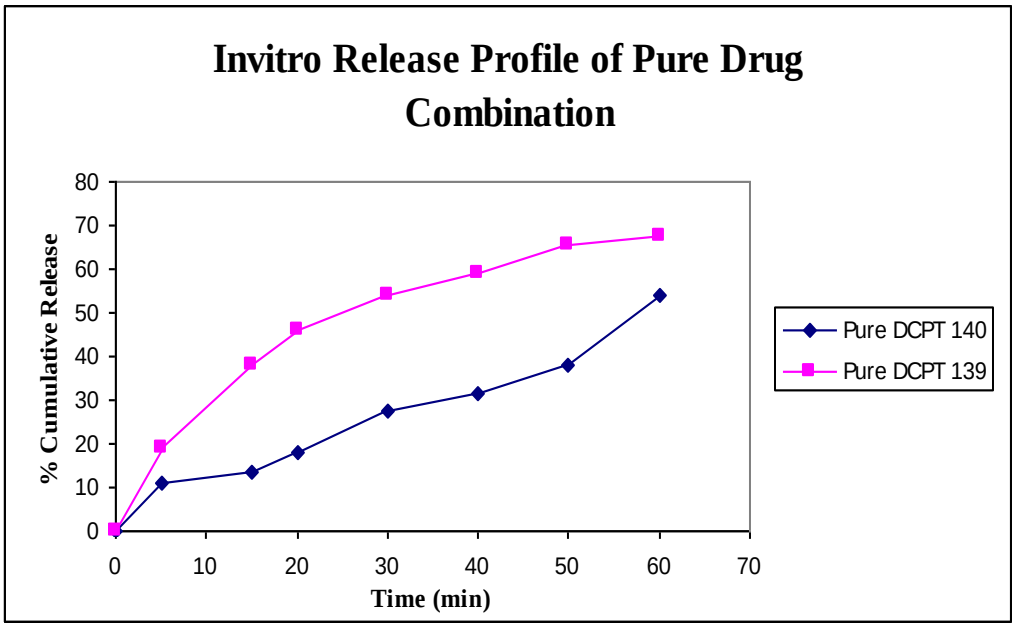


Fig. 3.8: Invitro release profile of pure drug combination

RESULT:

The antiretroviral drug combination i.e. DCPT 139 and DCPT 140 showed only 67.35% and 54.10% drug release respectively within 60 minute. Thus we can conclude that both the drug is poorly soluble in nature and needs dissolution enhancement.

3.6 SCREENING STUDIES FOR SELECTION OF POLYMERS:-

SOLUBILIZATION CAPACITY DETERMINATION:

Film Casting -

Solubilization capacity of active pharmaceutical ingredient in polymer solution was determined by film casting method. An appropriate solvent that dissolves the active pharmaceutical ingredient and the polymer should be selected. When the substances are dissolved after stirring, the solution can be casted on a glass slide, resulting in a thin film. Drying should be performed for 30 minutes under ambient conditions. To analyze the extent of solubilization capacity of polymer for a drug, increasing amount of active pharmaceutical ingredient should be applied for the film casting method (20, 25, 30, 40 and 50% of the polymer). The higher the clearly dissolved drug concentration, the higher the solubilization capacity. A solid solution results in clear and smooth films. Visual inspection of the films was performed 7 days after open storage at room temperature to recognize any type of recrystallization behavior of the drug.

Six hot melt extrusion grade polymers were taken and solubilization capacity was analyzed for the combination drug DCPT139 and DCPT140 present in the ratio 4:1. The total amount of drug taken was 250 mg containing DCPT139 and DCPT140 200 mg and 50mg respectively. The concentration of polymers was varied to prepare different polymer to drug ratio solutions for film casting.

Table 3.11: List of different polymers and solvents taken for film casting

Polymer taken	**Solvent used**
I. Soluplus II. Kollidon VA64 III. Eudragit EPO IV. Klucel ELF	Methanol
V. Polyox WSR N10	Acetonitrile
VI. HPMC 3 cps	Dichloromethane and Methanol (50:50)

Table 3.12: Solubilization capacity of DCPT139 and DCPT140 in Soluplus solution

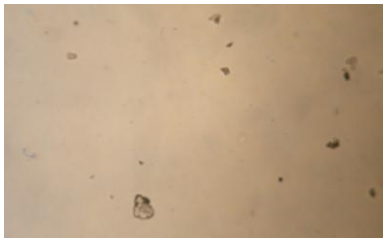
Ratio of polymer to drug	**Soluplus taken (mg)**	**Drug taken (mg)**	**Photographs of film observed under 10X magnification**	**Observation**
80:20	1000	250		Transparent film
75:25	750	250		Transparent film
70:30	583	250		Transparent film
60:40	375	250		Transparent film

50:50	250	250		Crystals observed

RESULT: Transparent films were obtained after film casting, in Soluplus to drug ratio of 80:20 to up to 60:40 indicating high solubilization capacity of DCPT139 and DCPT140 in Soluplus. At 50:50 Soluplus to drug ratio crystallization was observed.

Table 3.13: Solubilization capacity of DCPT139 and DCPT140 in Kollidon VA 64 solution

Ratio of polymer to drug	**Kollidon VA 64 taken (mg)**	**Drug taken (mg)**	**Photographs of film observed under 10X magnification**	**Observation**
80:20	1000	250		Transparent film
75:25	750	250		Transparent film

70:30	583	250		Transparent film
60:40	375	250		Transparent film
50:50	250	250		Crystals observed

RESULT: Transparent films were obtained after film casting, in Kollidon VA 64 to drug ratio of 80:20 to up to 60:40 indicating high solubilization capacity of DCPT139 and DCPT140 in Kollidon VA 64. At 50:50 Kollidon VA 64 to drug ratio crystallization was observed.

Table 3.14: Solubilization capacity of DCPT139 and DCPT140 in Eudragit EPO solution

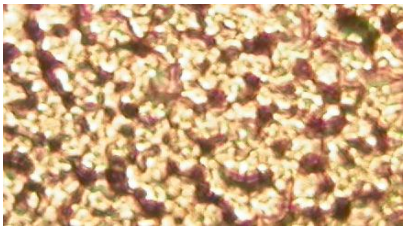
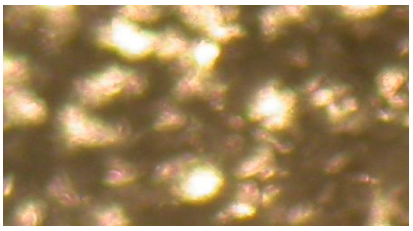
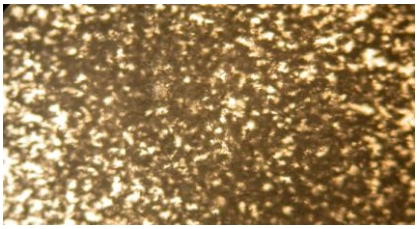
Ratio of polymer to drug	**Eudragit EPO taken (mg)**	**Drug taken (mg)**	**Photographs of film observed under 10X magnification**	**Observation**
80:20	1000	250		Transparent film
75:25	750	250		Transparent film
70:30	583	250		Transparent film
60:40	375	250		Crystals observed

50:50	250	250		Crystals observed

RESULT: Transparent films were obtained after film casting, in Eudragit EPO to drug ratio of 80:20 to up to 70:30 indicating good solubilization capacity of DCPT139 and DCPT140 in Eudragit EPO. At 50:50 and 60:40 Eudragit EPO to drug ratio crystallization was observed.

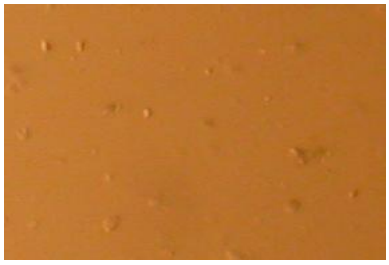
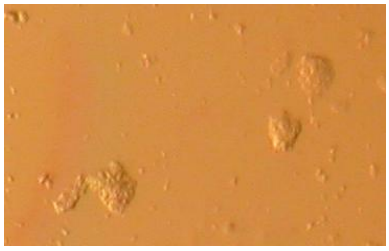
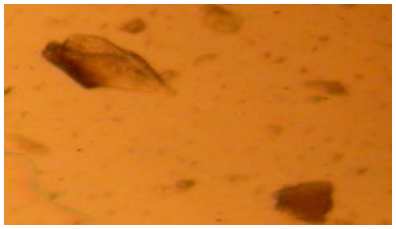
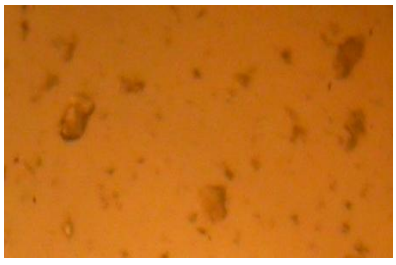
Table 3.15: Solubilization capacity of DCPT139 and DCPT140 in Polyox WSR N 10 solution

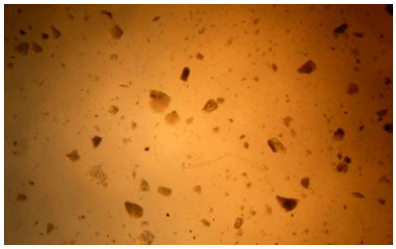
Ratio of polymer to drug	**Polyox WSR N 10 taken (mg)**	**Drug taken (mg)**	**Photographs of film observed under 10X magnification**	**Observation**
80:20	1000	250		Hazy film obtained
75:25	750	250		Hazy film obtained

70:30	583	250		Hazy film obtained
60:40	375	250		Crystals observed
50:50	250	250		Crystals observed

RESULT: Hazy film as well as crystallization of drug was observed after film casting, in Polyox WSR N10 to drug ratio of 80:20 to up to 50:50 indicating lower solubilization capacity of the drug.

Table 3.16: Solubilization capacity of DCPT139 and DCPT140 in Klucel ELF solution

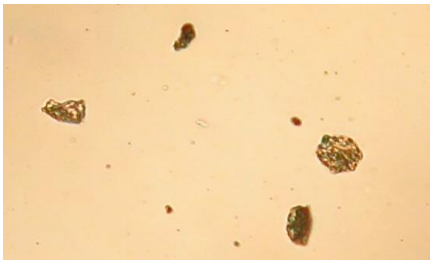
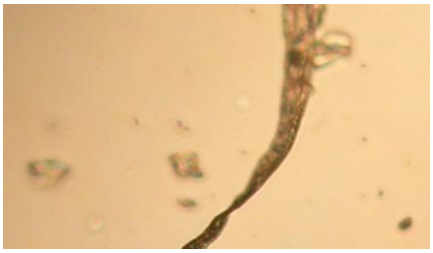
Ratio of polymer to drug	**Klucel ELF taken (mg)**	**Drug taken (mg)**	**Photographs of film observed under 10X magnification**	**Observation**
80:20	1000	250		Crystals observed
75:25	750	250		Crystals observed
70:30	583	250		Crystals observed
60:40	375	250		Crystals observed

50:50	250	250		Crystals observed

RESULT: In case of Klucel ELF crystallization of drug on the film was observed indicating lower solubilization capacity of the drug.

Table 3.17: Solubilization capacity of DCPT139 and DCPT140 in HPMC 3cps solution

Ratio of polymer to drug	**HPMC 3cps taken (mg)**	**Drug taken (mg)**	**Photographs of film observed under 10X magnification**	**Observation**
80:20	1000	250		Transparent film
75:25	750	250		Transparent film

70:30	583	250		Crystals observed
60:40	375	250		Crystals observed
50:50	250	250		Crystals observed

RESULT: DCPT139 and DCPT140 in concentration less than 25% of polymer shows solubility in HPMC 3 cps, but it will result in lower drug loading during extrusion.

CONCLUSION: Soluplus and Kollidon VA 64 in the polymer to drug ratio of 60:40 whereas Eudragit EPO in the polymer to drug ratio of 70:30 could be used for extrusion of DCPT139 and DCPT140.

3.7 PREPARATION OF EXTRUDATES USING SOLUPLUS

3.7.1 POLYMER TO DRUG RATIO 60:40

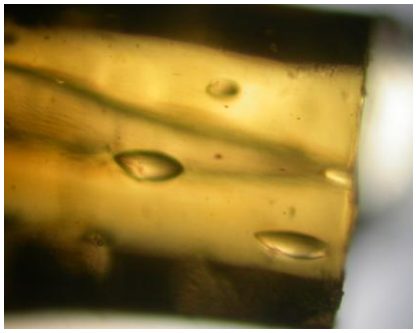
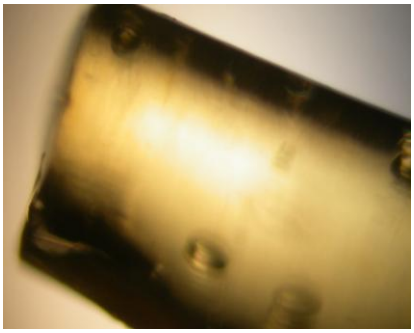
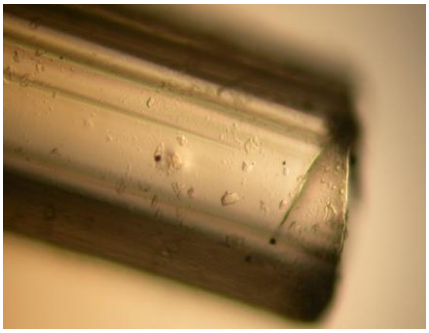
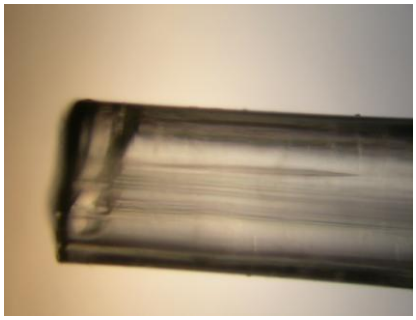
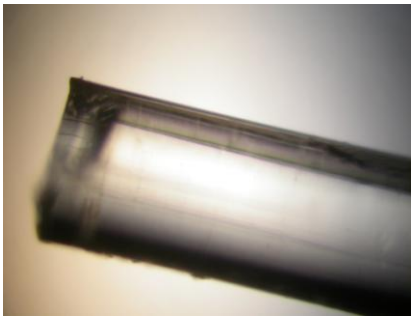
Procedure:-

A batch of 50gm sample containing polymer to drug in the ratio of 60:40 was prepared. The amount of soluplus and drug taken was 30gm and 20gm respectively. DCPT139 and DCPT140 accurately weighed 16gm and 4gm respectively to maintain the drug combination ratio 4:1 (DCPT139 to DCPT140). The weighed polymer and the drug was than pass through 40 mesh sieve alone in order to get the uniform particle size of polymer and the drug. The polymer and drug was than dried in oven to remove any type of moisture present in the sample for 1 to 2 hour at 60°C. The polymer and the drug was finally mixed and subjected to hot melt extrusion process. During the hot melt extrusion process screw speed, barrel temperature and die zone temperature was varied to obtain extrudates.

Table 3.18: Batches prepared with different set parameters of hot melt extrusion process

Parameters	Batches Prepared with Soluplus to drug ratio 60:40					
	S.B 1	**S.B 2**	**S.B 3**	**S.B 4**	**S.B 5**	**S.B 6**
Screw Speed(rpm)	50	80	100	100	100	100
Temperature Barrel 2	140°C	140°C	140°C	150°C	150°C	160°C
Temperature Barrel 3	150°C	150°C	150°C	160°C	165°C	165°C
Temperature Barrel 4	160°C	160°C	160°C	170°C	175°C	175°C
Temperature (Die Zone)	170°C	170°C	170°C	180°C	180°C	190°C

Table 3.19: Photographs of extrudates from batch S.B 1 to S.B 6 observed under 10X magnification

		
S.B 1	S.B 2	S.B 3
		
S.B 4	S.B 5	S.B 6

RESULT: - On 50 rpm and 80 rpm screw speed yellowish extrudates (S.B 1 & S.B 2) were obtained due to increase residence time of the sample, keeping screw speed at 100 rpm slight transparent extrudates (S.B 3) obtain but the drug is not well dispersed. As the temperature of barrel and die zone increased keeping screw speed at 100 rpm the transparency of the extrudates increased (S.B 4 & S.B 5) indicating formation of complete solid solution. As the temperature of die increases to 190°C dark brown extrudates were obtained due to degradation of sample.

CONCLUSION: - Transparent extrudates of batch (containing soluplus to drug ratio 60:40) was obtained keeping screw speed at 100 rpm and temperature range between 150°C to 180°C. Batch S.B 5 was selected for the determination of percentage drug content, solubility studies and dissolution studies.

Batch S.B 5 Evaluation:-

1. **Drug Content Determination:**

Procedure-

Extruded strands of batch S.B 5 were triturated in mortal pastel, the obtained powder was passed through sieve number 40. As per 60:40 ratio accurately weighed 50 mg extrudate powder (i.e. equivalent to 20 mg of combination drug DCPT 139 and DCPT 140), and mixed with 50ml of methanol. Allowed to stand for 10 min with occasional swirling add methanol to produce upto 100 mL. Absorbance of the resulting solution was measured at 240 nm and 259 nm respectively. Drug content was determined from simultaneous equation.

RESULT: The percentage drug content in S.B 5 batch was found to be (DCPT 139) 95.43% w/v and (DCPT 140) 94.19 %w/v.

2. Solubility Studies:

Procedure-

The solubility of DCPT 139 and DCPT140 (batch S.B 5) in water was determined by taking excess quantity of powdered exrudates (passed through 40mesh sieve), added into 5mL glass vials filled with water. The vials were shaken for 24 hour on lab roller. The solution was filtered through Whatmann filter paper and the drug concentration was determined by taking absorbance at 240 nm and 259nm respectively.

RESULT: The solubility of DCPT 139 and DCPT 140 in water was found to be 61.99 mg/ml and 58.77 mg/ml respectively.

3. Dissolution Studies:-

Procedure-

The dissolution studies of Batch S.B 5 were carried out using USP dissolution apparatus Type I (Basket type) at 100 rpm. Dissolution medium (900 mL) consisted of (0.1 N HCL containing 0.5% sodium lauryl sulphate) was used and 5 mL of dissolution medium was withdrawn at (5, 15, 20, 30, 40, 50, 60 min). As per percentage drug content weigh accurately 657.37 mg extrudate powder (i.e. equivalent to 250 mg of combination drug DCPT 139 and DCPT 140). The amount of dissolved drug was determined using UV spectrophotometric method at 240nm and 259nm.

Table 3.20: Invitro release profile of DCPT 140 and DCPT 139 of batch S.B5

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
5	0.2	0.14	0.0014	0.008	0.070	0.384	0	0
15	0.321	0.22	0.0022	0.012	0.112	0.591	0.070	0.384
20	0.38	0.25	0.0027	0.013	0.135	0.644	0.182	0.975
30	0.5	0.33	0.0035	0.017	0.177	0.853	0.317	1.619
40	0.549	0.36	0.0039	0.018	0.195	0.924	0.494	2.471
50	0.625	0.4	0.0045	0.020	0.223	0.999	0.688	3.395
60	0.72	0.441	0.0052	0.021	0.259	1.046	0.911	4.395

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
12.530	69.046	12.530	69.046	25.059	34.523
20.229	106.324	20.299	106.708	40.599	53.354
24.213	115.886	24.395	116.861	48.790	58.431
31.832	153.489	32.149	155.107	64.298	77.554
35.011	166.293	35.505	168.764	71.010	84.382
40.108	179.907	40.796	183.302	81.592	91.651
46.707	188.318	47.618	192.712	95.237	96.356

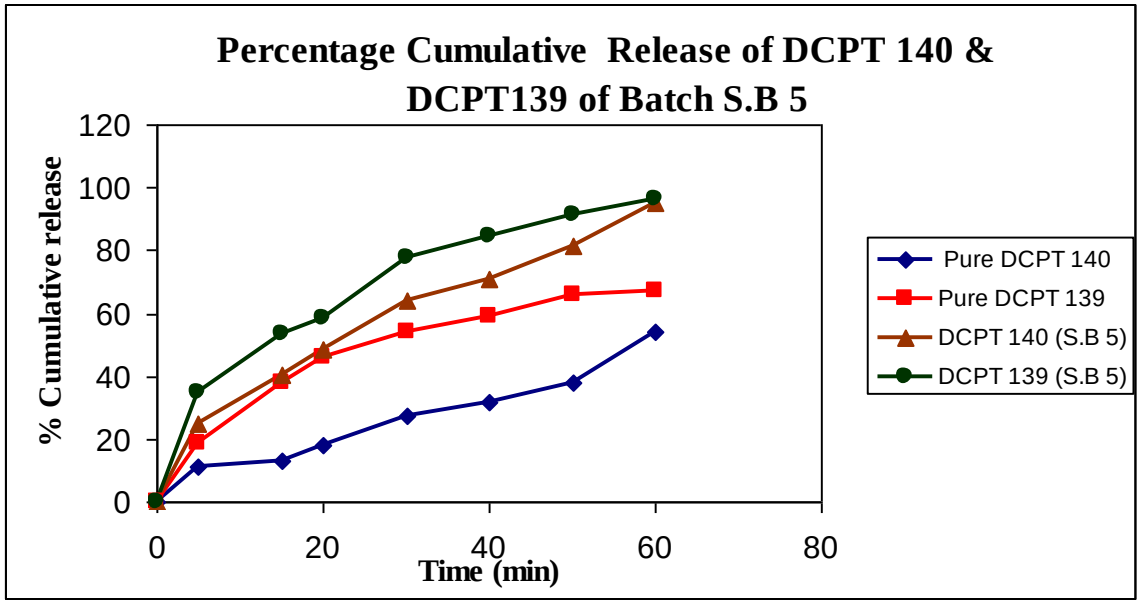


Fig. 3.9: Percentage cumulative release of DCPT 140 & DCPT139 of batch S.B5

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (S.B 5) was found to be 96.6% and 95.23% respectively within 60 minute.

3.7.2 POLYMER TO DRUG RATIO 70:30

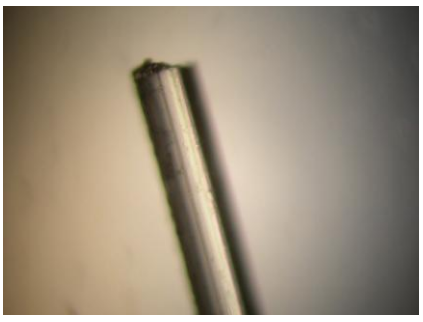
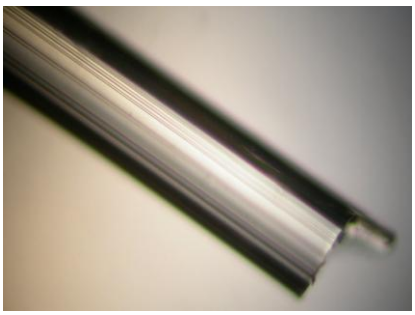
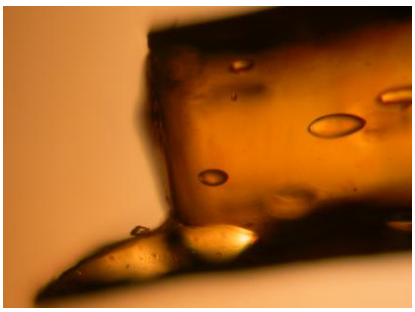
Procedure:-

A batch of 50gm sample containing polymer to drug in the ratio of 70:30 was prepared. The amount of soluplus and drug taken was 35gm and 15gm respectively. DCPT139 and DCPT140 accurately weighed 12gm and 3gm respectively to maintain the drug combination ratio 4:1 (DCPT139 to DCPT140). The weighed polymer and the drug was than pass through 40 mesh sieve alone in order to get the uniform particle size of polymer and the drug. The polymer and drug was than dried in oven to remove any type of moisture present in the sample for 1 to 2 hour at 60°C. The polymer and the drug was finally mixed and subjected to hot melt extrusion process. During the hot melt extrusion process screw speed, barrel temperature and die zone temperature was varied to obtain extrudates.

Table 3.21: Batches prepared with different set parameters of hot melt extrusion process

Parameters	Batches Prepared with Soluplus to drug ratio 70:30		
	S.B 7	**S.B 8**	**S.B 9**
Screw Speed(rpm)	100	80	50
Temperature Barrel 2	140°C	140°C	140°C
Temperature Barrel 3	150°C	150°C	150°C
Temperature Barrel 4	160°C	160°C	160°C
Temperature (Die Zone)	170°C	170°C	170°C

Table 3.22: Photographs of extrudates from batch S.B 7 to S.B 9 observed under 10X magnification

		
S.B 7	S.B 8	S.B 9

RESULT: - At 100 and 80 rpm screw speed transparent extrudates (S.B 7 & S.B 8) obtained at slight lower temperature in sample batch containing polymer to drug ratio 70:30 in comparison to 60:40 batch. But at 50 rpm screw speed with the same

temperature range of 140°C to 170°C burnt extrudates (S.B 9) were obtained due to increase residence time of the sample.

CONCLUSION: - Transparent extrudates of batch (containing soluplus to drug ratio 70:30) was obtained keeping screw speed at 80 rpm and temperature range between 140°C to 170°C. Batch S.B 8 was selected for the determination of percentage drug content, solubility studies and dissolution studies.

Batch S.B 8 Evaluation:-

1. **Drug Content Determination:**

Procedure-

Extruded strands of batch S.B 8 were triturated in mortal pastel, the obtained powder was passed through sieve number 40. As per 70:30 ratio accurately weighed 66.7 mg extrudate powder (i.e. equivalent to 20 mg of combination drug DCPT 139 and DCPT 140), and mixed with 50ml of methanol. Allowed to stand for 10 min with occasional swirling add methanol to produce upto 100 mL. Absorbance of the resulting solution was measured at 240 nm and 259 nm respectively. Drug content was determined from simultaneous equation.

RESULT- The percentage drug content in S.B 8 batch was found to be (DCPT 139) 94.34% w/v and (DCPT 140) 96.05 %w/v.

2. Solubility Studies:

Procedure-

The solubility of DCPT 139 and DCPT140 (batch S.B 8) in water was determined by taking excess quantity of powdered exrudates (passed through 40mesh sieve), added into 5mL glass vials filled with water. The vials were shaken for 24 hour on lab roller. The solution was filtered through Whatmann filter paper and the drug concentration was determined by taking absorbance at 240 nm and 259nm respectively.

RESULT- The solubility of DCPT 139 and DCPT 140 in water was found to be 68.52 mg/ml and 54.67 mg/ml respectively.

3. Dissolution Studies:-

Procedure-

The dissolution studies of Batch S.B 8 were carried out using USP dissolution apparatus Type I (Basket type) at 100 rpm. Dissolution medium (900 mL) consisted of (0.1 N HCL containing 0.5% sodium lauryl sulphate) was used and 5 mL of dissolution medium was withdrawn at (5, 15, 20, 30, 40, 50, 60 min). As per percentage drug content weigh accurately 879.48 mg extrudate powder (i.e. equivalent to 250 mg of combination drug DCPT 139 and DCPT 140. The amount of dissolved drug was determined using UV spectrophotometric method at 240nm and 259nm.

Table 3.23: Invitro release profile of DCPT 140 and DCPT 139 of batch S.B 8

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
5	0.205	0.144	0.0014	0.0079	0.071	0.396	0	0
15	0.325	0.227	0.0023	0.0124	0.113	0.621	0.071	0.396
20	0.387	0.26	0.0027	0.0137	0.136	0.684	0.184	1.017
30	0.509	0.334	0.0036	0.0172	0.180	0.858	0.320	1.701
40	0.549	0.367	0.0039	0.0192	0.194	0.961	0.501	2.559
50	0.619	0.405	0.0044	0.0207	0.219	1.037	0.694	3.520
60	0.71	0.44	0.0051	0.0212	0.255	1.059	0.914	4.557

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
12.830	71.250	12.830	71.250	25.660	35.625
20.373	111.722	20.444	112.118	40.888	56.059
24.522	123.180	24.706	124.197	49.412	62.098
32.454	154.396	32.775	156.097	65.550	78.049
34.833	172.987	35.334	175.546	70.668	87.773
39.498	186.634	40.192	190.154	80.385	95.077
45.928	190.603	46.842	195.160	93.684	97.580

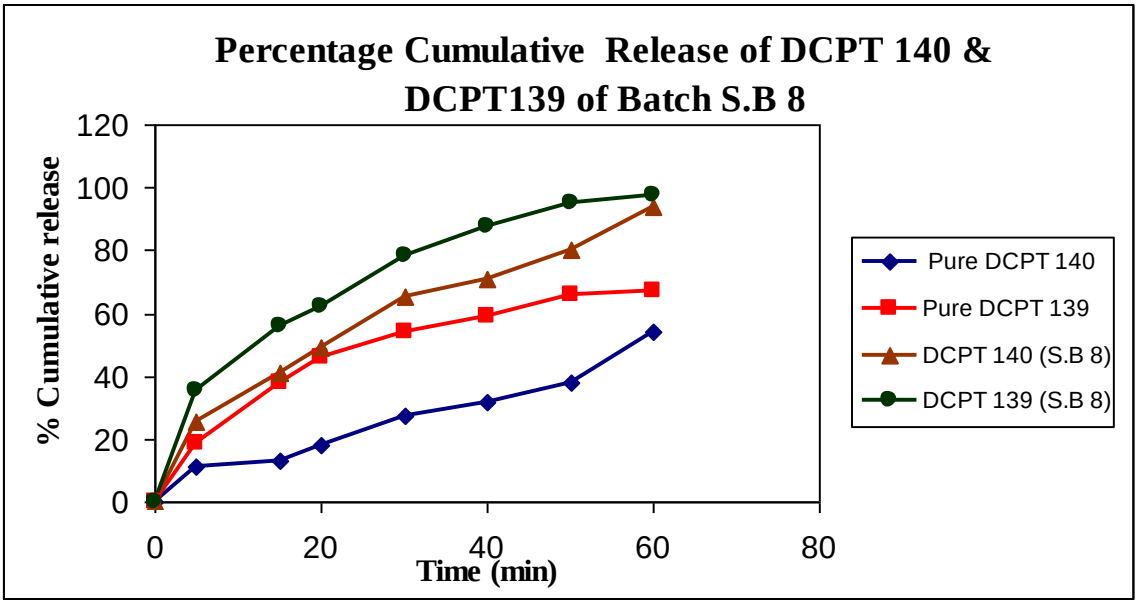


Fig. 3.10: Percentage cumulative release of DCPT 140 & DCPT139 of batch S.B 8

RESULT- The percentage cumulative release of DCPT 139 and DCPT 140 batch (S.B 8) was found to be 97.58% and 93.68% respectively within 60 minute.

3.8 PREPARATION OF EXTRUDATES USING KOLLIDON VA 64

3.8.1 POLYMER TO DRUG RATIO 60:40

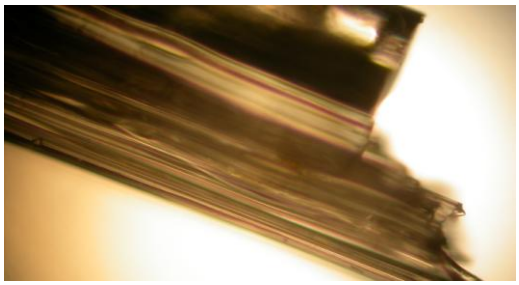
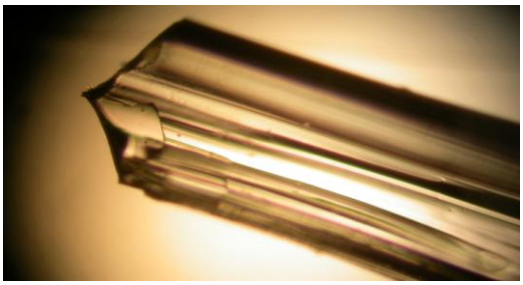
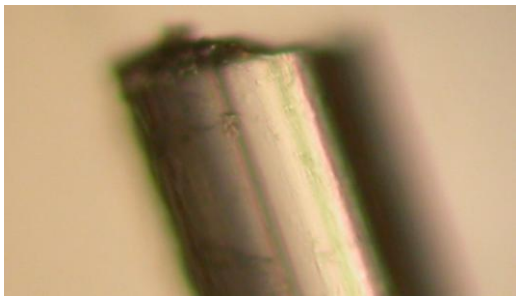
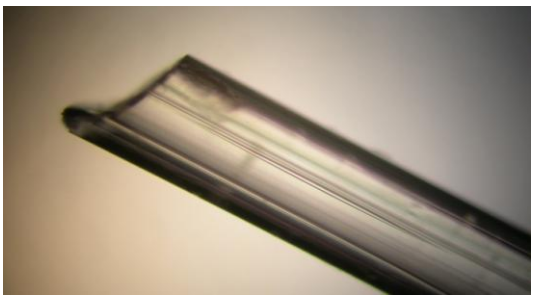
Procedure:-

A batch of 50gm sample containing polymer to drug in the ratio of 60:40 was prepared. The amount of Kollidon VA64 and drug taken was 30gm and 20gm respectively. DCPT139 and DCPT140 accurately weighed 16gm and 4gm respectively to maintain the drug combination ratio 4:1 (DCPT139 to DCPT140). The weighed polymer and the drug was than pass through 40 mesh sieve alone in order to get the uniform particle size of polymer and the drug. The polymer and drug was than dried in oven to remove any type of moisture present in the sample for 1 to 2 hour at 60°C. The polymer and the drug was finally mixed and subjected to hot melt extrusion process. During the hot melt extrusion process screw speed, barrel temperature and die zone temperature was varied to obtain extrudates.

Table 3.24: Batches prepared with different set parameters of hot melt extrusion process

Parameters	**Batches Prepared with Kollidon VA 64 to drug ratio 60:40**			
	K.B 10	**K.B 11**	**K.B 12**	**K.B 13**
Screw Speed(rpm)	80	100	100	100
Temperature Barrel 2	140°C	140°C	150°C	160°C
Temperature Barrel 3	150°C	150°C	160°C	170°C
Temperature Barrel 4	150°C	150°C	160°C	170°C
Temperature (Die Zone)	160°C	160°C	170°C	180°C

Table 3.25: Photographs of extrudates from batch K.B 10 to K.B 13 observed under 10X magnification

 K.B 10	 K.B 11
 K.B 12	 K.B 13

RESULT: - In batch (containing Kollidon VA 64 to drug ratio 60:40) at 80 rpm and 100 rpm screw speed transparent extrudates (K.B 10 & K.B 11) were not obtained. As the temperature of each zone increased by 10°C of the initial set temperature at 100 rpm screw speed clear transparent extrudates (K.B 12 & K.B 13) were obtained.

CONCLUSION: - Transparent extrudates of batch (containing Kollidon VA 64 to drug ratio 60:40) was obtained keeping screw speed at 100 rpm and temperature range between 150°C to 180°C. Batch K.B 13 was selected for the determination of percentage drug content, solubility studies and dissolution studies.

Batch K.B 13 Evaluation:-

1. **Drug Content Determination:**

Procedure-

Extruded strands of batch K.B 13 were triturated in mortal pastel, the obtained powder was passed through sieve number 40. As per 60:40 ratio accurately weighed 50 mg extrudate powder (i.e. equivalent to 20 mg of combination drug DCPT 139 and DCPT 140), and mixed with 50ml of methanol. Allowed to stand for 10 min with occasional swirling add methanol to produce upto 100 mL. Absorbance of the resulting solution was measured at 240 nm and 259 nm respectively. Drug content was determined from simultaneous equation.

RESULT- The percentage drug content in K.B 13 batch was found to be (DCPT 139) 96.49% w/v and (DCPT 140) 93.77% w/v.

2. Solubility Studies:

Procedure-

The solubility of DCPT 139 and DCPT140 (batch K.B 13) in water was determined by taking excess quantity of powdered exrudates (passed through 40mesh sieve), added into 5mL glass vials filled with water. The vials were shaken for 24 hour on lab roller. The solution was filtered through Whatmann filter paper and the drug concentration was determined by taking absorbance at 240 nm and 259nm respectively.

RESULT- The solubility of DCPT 139 and DCPT 140 in water was found to be 55.98 mg/ml and 49.90 mg/ml respectively.

3. Dissolution Studies:-

Procedure-

The dissolution studies of Batch K.B 13 were carried out using USP dissolution apparatus Type I (Basket type) at 100 rpm. Dissolution medium (900 mL) consisted of (0.1 N HCL containing 0.5% sodium lauryl sulphate) was used and 5 mL of dissolution medium was withdrawn at (5, 15, 20, 30, 40, 50, 60 min). As per percentage drug content weigh accurately 653.75 mg extrudate powder (i.e. equivalent to 250 mg of combination drug DCPT 139 and DCPT 140). The amount of dissolved drug was determined using UV spectrophotometric method at 240nm and 259nm.

Table 3.26: Invitro release profile of DCPT 140 and DCPT 139 of batch K.B 13

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
5	0.145	0.105	0.00100	0.00593	0.050	0.297	0	0
15	0.305	0.216	0.00212	0.01197	0.106	0.598	0.050	0.297
20	0.347	0.267	0.00235	0.01587	0.117	0.794	0.156	0.895
30	0.564	0.356	0.00404	0.01751	0.202	0.876	0.273	1.689
40	0.622	0.388	0.00446	0.01882	0.223	0.941	0.475	2.564
50	0.662	0.411	0.00476	0.01983	0.238	0.991	0.698	3.506
60	0.68	0.42	0.00489	0.02013	0.245	1.007	0.936	4.497

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
8.995	53.405	8.995	53.405	17.990	26.7027
19.044	107.686	19.094	107.983	38.188	53.9915
21.126	142.842	21.282	143.737	42.564	71.8686
36.319	157.605	36.593	159.294	73.185	79.6468
40.171	169.404	40.646	171.968	81.293	85.9841
42.804	178.431	43.503	181.937	87.005	90.9685
44.024	181.203	44.959	185.700	89.919	92.8499

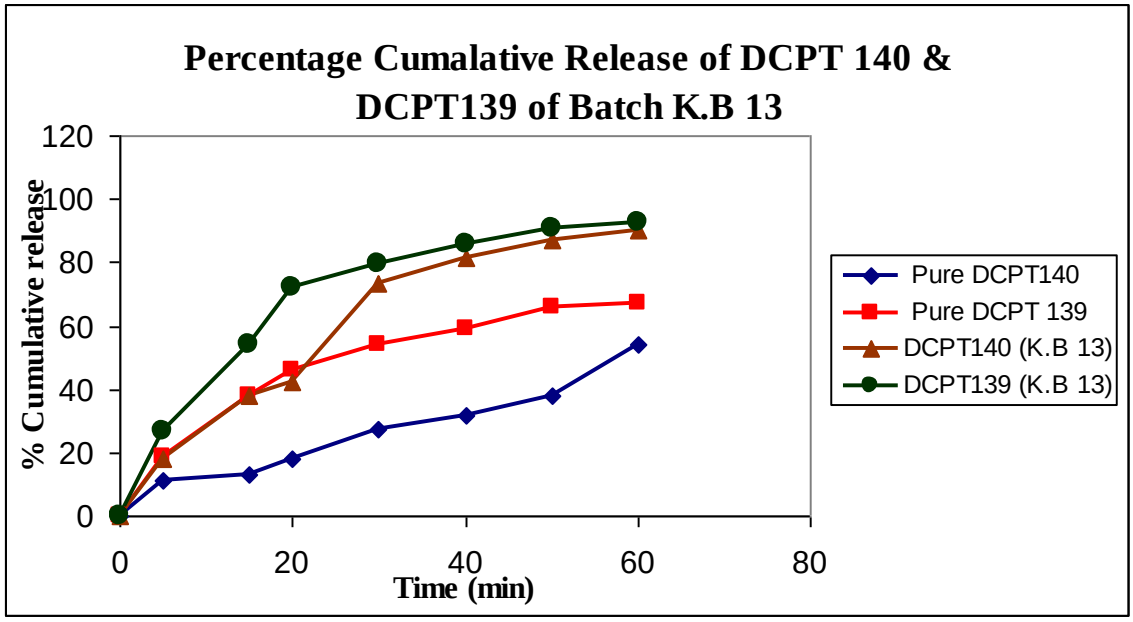


Fig. 3.11: Percentage cumulative release of DCPT 140 & DCPT139 of batch K.B 13

RESULT- The percentage cumulative release of DCPT 139 and DCPT 140 batch (K.B 13) was found to be 92.84% and 89.91% respectively within 60 minute.

3.8.2 Polymer to drug ratio 70:30

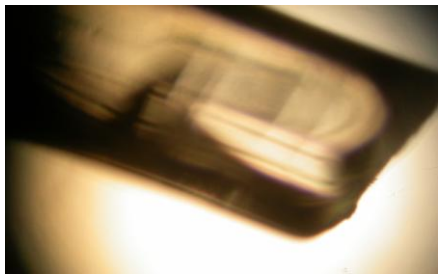
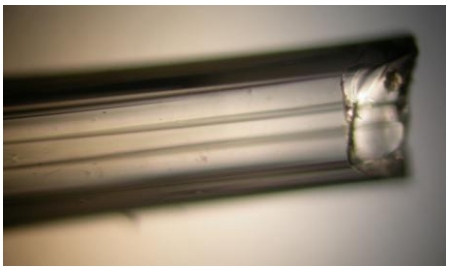
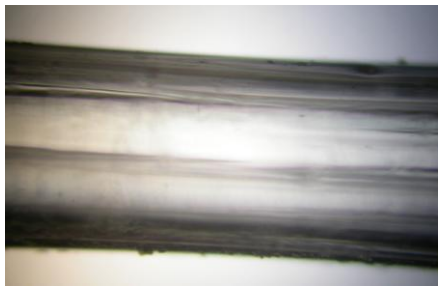
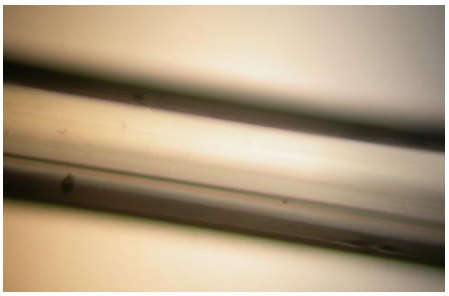
Procedure:-

A batch of 50gm sample containing polymer to drug in the ratio of 70:30 was prepared. The amount of kollidonVA64 and drug taken was 35gm and 15gm respectively. DCPT139 and DCPT140 accurately weighed 12gm and 3gm respectively to maintain the drug combination ratio 4:1 (DCPT139 to DCPT140). The weighed polymer and the drug was than pass through 40 mesh sieve alone in order to get the uniform particle size of polymer and the drug. The polymer and drug was than dried in oven to remove any type of moisture present in the sample for 1 to 2 hour at 60°C. The polymer and the drug was finally mixed and subjected to hot melt extrusion process. During the hot melt extrusion process screw speed, barrel temperature and die zone temperature was varied to obtain extrudates.

Table 3.27: Batches prepared with different set parameters of hot melt extrusion process

Parameters	Batches Prepared with Kollidon VA 64 to drug ratio 70:30			
	K.B 14	**K.B 15**	**K.B 16**	**K.B 17**
Screw Speed(rpm)	80	100	100	100
Temperature Barrel 2	140°C	140°C	150°C	160°C
Temperature Barrel 3	150°C	150°C	160°C	170°C
Temperature Barrel 4	150°C	150°C	160°C	170°C
Temperature (Die Zone)	160°C	160°C	170°C	180°C

Table 3.28: Photographs of extrudates from batch K.B 14 to K.B 17 observed under 10X magnification

 K.B 14	 K.B 15
 K.B 16	 K.B 17

RESULT: - In batch (containing Kollidon VA 64 to drug ratio 70:30) at 80 rpm screw speed slight transparent extrudates (K.B 14) obtained as the screw speed increased to 100 rpm and temperature of each barrel by 10°C of the initial set temperature clear transparent extrudates (K.B 15 - K.B 17) are obtained in all the cases.

CONCLUSION: - In batch (containing Kollidon VA 64 to drug ratio 70:30) temperature has not much effect on the transparency of extrudates, it can be prepared in the temperature range of 140°C to 180°C keeping screw speed at 100 rpm. Batch K.B 15 was selected for the determination of percentage drug content, solubility studies and dissolution studies.

Batch K.B 15 Evaluation:-

1. **Drug Content Determination:**

Procedure-

Extruded strands of batch K.B 15 were triturated in mortal pastel, the obtained powder was passed through sieve number 40. As per 70:30 ratio accurately weighed 66.7 mg extrudate powder (i.e. equivalent to 20 mg of combination drug DCPT 139 and DCPT 140), and mixed with 50ml of methanol. Allowed to stand for 10 min with occasional swirling add methanol to produce upto 100 mL. Absorbance of the resulting solution was measured at 240 nm and 259 nm respectively. Drug content was determined from simultaneous equation.

RESULT- The percentage drug content in K.B 15 batch was found to be (DCPT 139) 94.98% w/v and (DCPT 140) 94.57 %w/v.

2. Solubility Studies:

Procedure-

The solubility of DCPT 139 and DCPT140 (batch K.B 15) in water was determined by taking excess quantity of powdered exrudates (passed through 40mesh sieve), added into 5mL glass vials filled with water. The vials were shaken for 24 hour on lab roller. The solution was filtered through Whatmann filter paper and the drug concentration was determined by taking absorbance at 240 nm and 259nm respectively.

RESULT- The solubility of DCPT 139 and DCPT 140 in water was found to be 52.46 mg/ml and 50.63 mg/ml respectively.

3. Dissolution Studies:-

Procedure-

The dissolution studies of Batch K.B 15 were carried out using USP dissolution apparatus Type I (Basket type) at 100 rpm. Dissolution medium (900 mL) consisted of (0.1 N HCL containing 0.5% sodium lauryl sulphate) was used and 5 mL of dissolution medium was withdrawn at (5, 15, 20, 30, 40, 50, 60 min As per percentage drug content weigh accurately 872.06 mg extrudate powder (i.e. equivalent to 250 mg of combination drug DCPT 139 and DCPT 140). The amount of dissolved drug was determined using UV spectrophotometric method at 240nm and 259nm.

Table 3.29: Invitro release profile of DCPT 140 and DCPT 139 of batch K.B 15

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
5	0.16	0.108	0.00113	0.00571	0.0563	0.2856	0	0
15	0.274	0.2	0.00188	0.01138	0.0942	0.5691	0.056	0.285
20	0.389	0.258	0.00275	0.01340	0.1374	0.6701	0.150	0.854
30	0.572	0.361	0.00409	0.01775	0.2046	0.8877	0.288	1.524
40	0.61	0.384	0.00437	0.01883	0.2184	0.9415	0.492	2.412
50	0.666	0.416	0.00478	0.02021	0.2389	1.0106	0.711	3.353
60	0.694	0.427	0.00500	0.02037	0.2498	1.0187	0.950	4.364

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
10.125	51.412	10.125	51.412	20.251	25.706
16.957	102.435	17.013	102.720	34.026	51.360
24.733	120.619	24.884	121.473	49.767	60.737
36.836	159.793	37.123	161.317	74.247	80.659
39.308	169.469	39.800	171.881	79.600	85.940
42.999	181.916	43.710	185.270	87.419	92.635
44.972	183.358	45.921	187.722	91.843	93.861

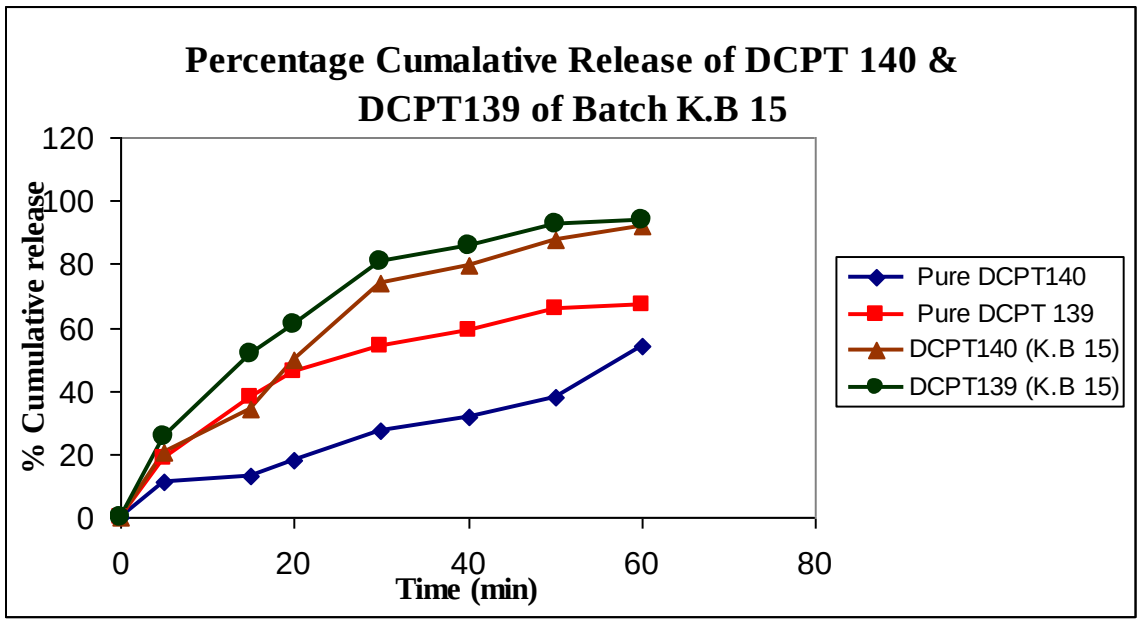


Fig. 3.12: Percentage cumulative release of DCPT 140 & DCPT139 of batch K.B 15

RESULT- The percentage cumulative release of DCPT 139 and DCPT 140 batch (K.B 15) was found to be 93.86% and 91.84% respectively within 60 minute.

3.9 PREPARATION OF EXTRUDATES USING EUDRAGIT EPO

3.9.1 POLYMER TO DRUG RATIO 70:30

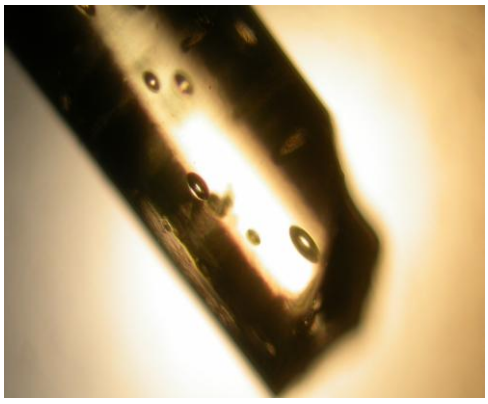
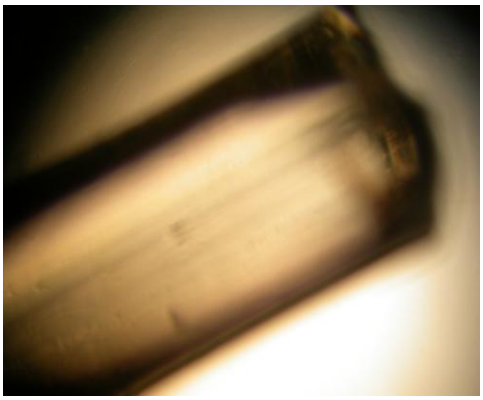
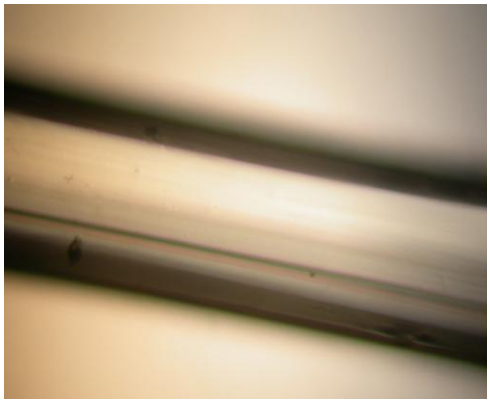
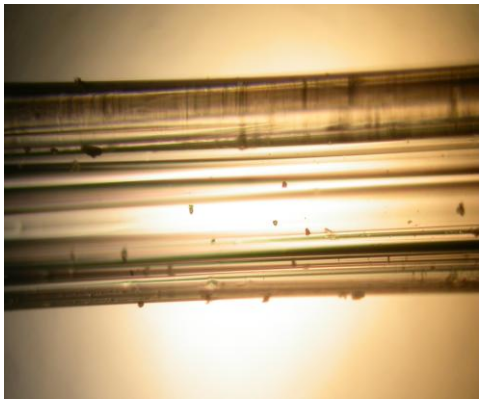
Procedure:-

A batch of 50gm sample containing polymer to drug in the ratio of 70:30 was prepared. The amount of Eudragit EPO and drug taken was 35gm and 15gm respectively. DCPT139 and DCPT140 accurately weighed 12gm and 3gm respectively to maintain the drug combination ratio 4:1 (DCPT139 to DCPT140). The weighed polymer and the drug was than pass through 40 mesh sieve alone in order to get the uniform particle size of polymer and the drug. The polymer and drug was than dried in oven to remove any type of moisture present in the sample for 1 to 2 hour at 60°C. The polymer and the drug was finally mixed and subjected to hot melt extrusion process. During the hot melt extrusion process screw speed, barrel temperature and die zone temperature was varied to obtain extrudates.

Table 3.30: Batches prepared with different set parameters of hot melt extrusion process

Parameters	**Batches Prepared with Eudragit EPO to drug ratio 70:30**			
	E.B 18	**E.B 19**	**E.B 20**	**E.B 21**
Screw Speed(rpm)	80	100	100	100
Temperature Barrel 2	100	100	90	80
Temperature Barrel 3	100	100	90	80
Temperature Barrel 4	100	100	90	80
Temperature (Die Zone)	110	110	100	90

Table 3.31: Photographs of extrudates from batch E.B 18 to E.B 21 observed under 10X magnification

 E.B 18	 E.B 19
 E.B 20	 E.B 21

RESULT: - On 80 rpm screw speed yellowish extrudates (E.B 18) were obtained in the temperature range of 100°C to 110°C. As the temperature decreased by 10°C keeping screw speed at 100 rpm transparent extrudates (E.B 19 & E.B 20) were obtained. Further decrease in temperature by 10°C at the same screw speed leads to crystallization of the drug in the extrudate.

CONCLUSION: - Transparent extrudates of batch (containing Eudragit EPO to drug ratio 70:30) was obtained keeping screw speed at 100 rpm and temperature range between 90°C to 100°C. Batch E.B 20 was selected for the determination of percentage drug content, solubility studies and dissolution studies.

Batch E.B 20 Evaluation:-

1. Drug Content Determination:

Procedure-

Extruded strands of batch E.B 20 were triturated in mortal pastel, the obtained powder was passed through sieve number 40. As per 70:30 ratio accurately weighed 66.7 mg extrudate powder (i.e. equivalent to 20 mg of combination drug DCPT 139 and DCPT 140), and mixed with 50ml of methanol. Allowed to stand for 10 min with occasional swirling add methanol to produce upto 100 mL. Absorbance of the resulting solution was measured at 240 nm and 259 nm respectively. Drug content was determined from simultaneous equation.

RESULT- The percentage drug content in E.B 20 batch was found to be (DCPT 139) 93.5% w/v and (DCPT 140) 95.7 %w/v.

2. Solubility Studies:

Procedure-

The solubility of DCPT 139 and DCPT140 (batch E.B 20) in water was determined by taking excess quantity of powdered exrudates (passed through 40mesh sieve), added into 5mL glass vials filled with water. The vials were shaken for 24 hour on lab roller. The solution was filtered through Whatmann filter paper and the drug concentration was determined by taking absorbance at 240 nm and 259nm respectively.

RESULT- The solubility of DCPT 139 and DCPT 140 in water was found to be 31.49 mg/ml and 27.73 mg/ml respectively.

3. Dissolution Studies:-

Procedure-

The dissolution studies of Batch E.B 20 were carried out using USP dissolution apparatus Type I (Basket type) at 100 rpm. Dissolution medium (900 mL) consisted of (0.1 N HCL containing 0.5% sodium lauryl sulphate) was used and 5 mL of dissolution medium was withdrawn at (5, 15, 20, 30, 40, 50, 60 min). As per percentage drug content weigh accurately 870.60 mg extrudate powder (i.e. equivalent to 250 mg of combination drug DCPT 139 and DCPT 140). The amount of dissolved drug was determined using UV spectrophotometric method at 240nm and 259nm.

Table 3.32: Invitro release profile of DCPT 140 and DCPT 139 of batch E.B 20

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
5	0.1235	0.088	0.00086	0.00490	0.043	0.245	0	0
15	0.1684	0.145	0.00110	0.00934	0.055	0.467	0.043	0.245
20	0.286	0.2	0.00199	0.01095	0.100	0.547	0.098	0.712
30	0.3673	0.25	0.00258	0.01333	0.129	0.667	0.197	1.260
40	0.485	0.308	0.00346	0.01526	0.173	0.763	0.326	1.926
50	0.577	0.355	0.00415	0.01694	0.208	0.847	0.499	2.689
60	0.613	0.38	0.00441	0.01830	0.220	0.915	0.707	3.536

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
7.698	44.118	7.698	44.118	15.395	22.059
9.861	84.072	9.904	84.317	19.807	42.158
17.922	98.545	18.020	99.257	36.040	49.628
23.191	120.004	23.389	121.263	46.777	60.632
31.185	137.313	31.511	139.239	63.022	69.619
37.390	152.434	37.890	155.123	75.780	77.562
39.651	164.671	40.358	168.207	80.716	84.103

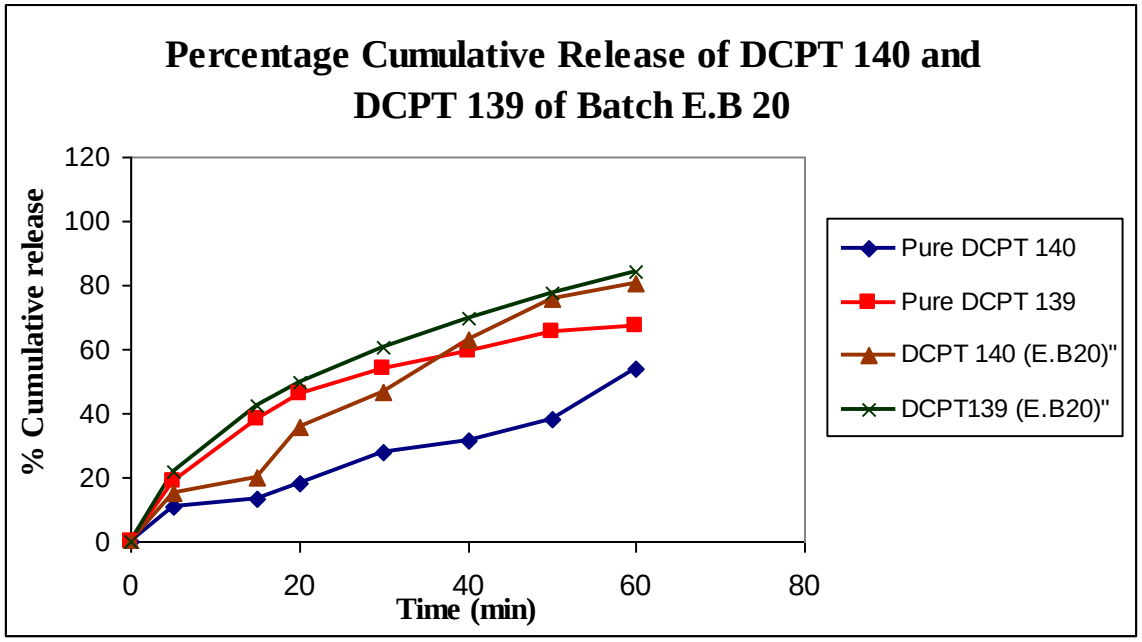


Fig. 3.13: Percentage cumulative release of DCPT 140 & DCPT139 of batch E.B 20

RESULT- The percentage cumulative release of DCPT 139 and DCPT 140 batch (E.B 20) was found to be 84.10% and 80.71% respectively within 60 minute.

3.9.2 POLYMER TO DRUG RATIO 60:40

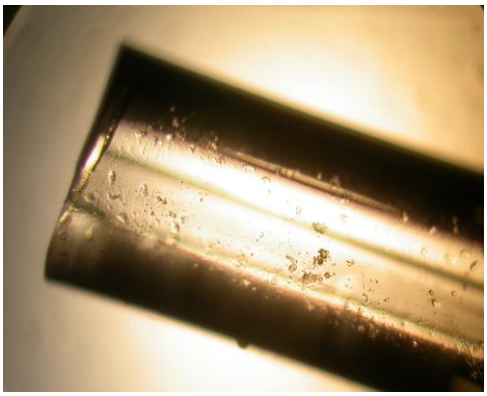
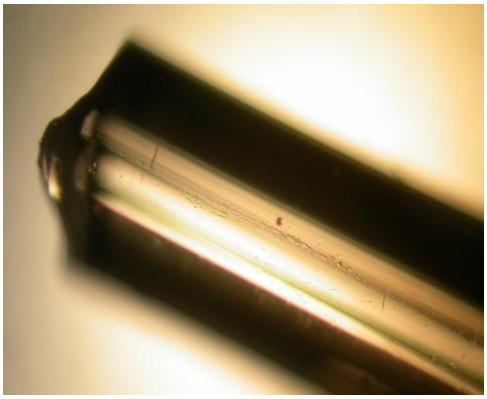
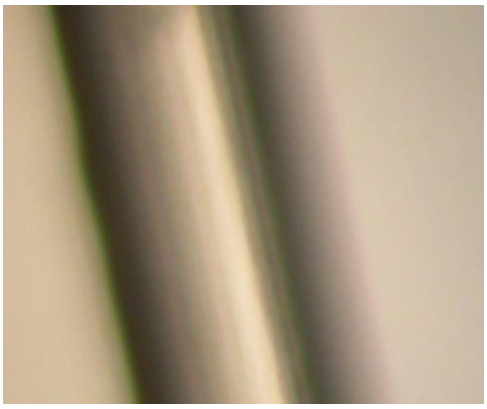
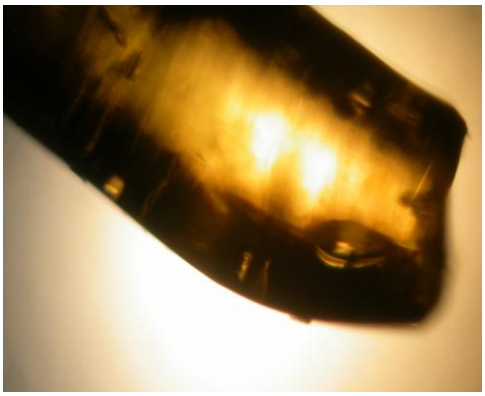
Procedure:-

A batch of 50gm sample containing polymer to drug in the ratio of 60:40 was prepared. The amount of Eudragit EPO and drug taken was 30gm and 20gm respectively. DCPT139 and DCPT140 accurately weighed 16gm and 4gm respectively to maintain the drug combination ratio 4:1 (DCPT139 to DCPT140). The weighed polymer and the drug was than pass through 40 mesh sieve alone in order to get the uniform particle size of polymer and the drug. The polymer and drug was than dried in oven to remove any type of moisture present in the sample for 1 to 2 hour at 60°C. The polymer and the drug was finally mixed and subjected to hot melt extrusion process. During the hot melt extrusion process screw speed, barrel temperature and die zone temperature was varied to obtain extrudates.

Table 3.33: Batches prepared with different set parameters of hot melt extrusion process

Parameters	Batches Prepared with Eudragit EPO to drug ratio 60:40			
	E.B 22	**E.B 23**	**E.B 24**	**E.B 25**
Screw Speed(rpm)	100	100	100	100
Temperature Barrel 2	80	90	100	110
Temperature Barrel 3	80	90	100	110
Temperature Barrel 4	80	90	100	110
Temperature (Die Zone)	90	100	110	120

Table 3.34: Photographs of extrudates from batch E.B 22 to E.B 25 observed under 10X magnification

 E.B 22	 E.B 23
 E.B 24	 E.B 25

RESULT: - On 100 rpm screw speed in the temperature range of 80°C to 90°C crystallization of the drug in the extrudate (E.B 22) was observed. As the temperature increased by 10°C keeping screw speed at 100 rpm transparent extrudates (E.B 23 & E.B 24) were obtained. Further increase in temperature by 10°C at the same screw speed gives dark brown extrudate (E.B 25) due to degradation of sample.

CONCLUSION: - Transparent extrudates of batch (containing Eudragit EPO to drug ratio 60:40) was obtained keeping screw speed at 100 rpm and temperature range between 90°C to 110°C. Batch E.B 24 was selected for the determination of percentage drug content, solubility studies and dissolution studies.

Batch E.B 24 Evaluation:-

1. **Drug Content Determination:**

Procedure-

Extruded strands of batch E.B 24 were triturated in mortal pastel, the obtained powder was passed through sieve number 40. As per 60:40 ratio accurately weighed 50 mg extrudate powder (i.e. equivalent to 20 mg of combination drug DCPT 139 and DCPT 140), and mixed with 50ml of methanol. Allowed to stand for 10 min with occasional swirling add methanol to produce upto 100 mL. Absorbance of the resulting solution was measured at 240 nm and 259 nm respectively. Drug content was determined from simultaneous equation.

RESULT- The percentage drug content in E.B 24 batch was found to be (DCPT 139) 94.75% w/v and (DCPT 140) 96.40 %w/v.

2. Solubility Studies:

Procedure-

The solubility of DCPT 139 and DCPT140 (batch E.B 24) in water was determined by taking excess quantity of powdered exrudates (passed through 40mesh sieve), added into 5mL glass vials filled with water. The vials were shaken for 24 hour on lab roller. The solution was filtered through Whatmann filter paper and the drug concentration was determined by taking absorbance at 240 nm and 259nm respectively.

RESULT- The solubility of DCPT 139 and DCPT 140 in water was found to be 29.70 mg/ml and 27.93 mg/ml respectively.

3. Dissolution Studies:-

Procedure-

The dissolution studies of Batch E.B 24 were carried out using USP dissolution apparatus Type I (Basket type) at 100 rpm. Dissolution medium (900 mL) consisted of (0.1 N HCL containing 0.5% sodium lauryl sulphate) was used and 5 mL of dissolution medium was withdrawn at (5, 15, 20, 30, 40, 50, 60 min). As per percentage drug content weigh accurately 659.28 mg extrudate powder (i.e. equivalent to 250 mg of combination drug DCPT 139 and DCPT 140). The amount of dissolved drug was determined using UV spectrophotometric method at 240nm and 259nm.

Table 3.35: Invitro release profile of DCPT 140 and DCPT 139 of batch E.B 24

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
5	0.112	0.08	0.0008	0.0045	0.039	0.223	0	0
15	0.181	0.155	0.0012	0.0100	0.059	0.498	0.039	0.223
20	0.275	0.201	0.0019	0.0115	0.095	0.573	0.098	0.721
30	0.376	0.2601	0.0026	0.0141	0.131	0.705	0.193	1.293
40	0.462	0.296	0.0033	0.0148	0.165	0.741	0.324	1.998
50	0.554	0.343	0.0040	0.0165	0.199	0.825	0.488	2.738
60	0.621	0.375	0.0045	0.0175	0.225	0.874	0.688	3.563

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
6.976	40.196	6.976	40.196	13.952	20.098
10.620	89.550	10.659	89.773	21.318	44.887
17.012	103.067	17.110	103.787	34.220	51.894
23.634	126.842	23.827	128.135	47.654	64.068
29.640	133.293	29.963	135.291	59.927	67.646
35.845	148.415	36.334	151.153	72.668	75.576
40.421	157.296	41.109	160.859	82.218	80.429

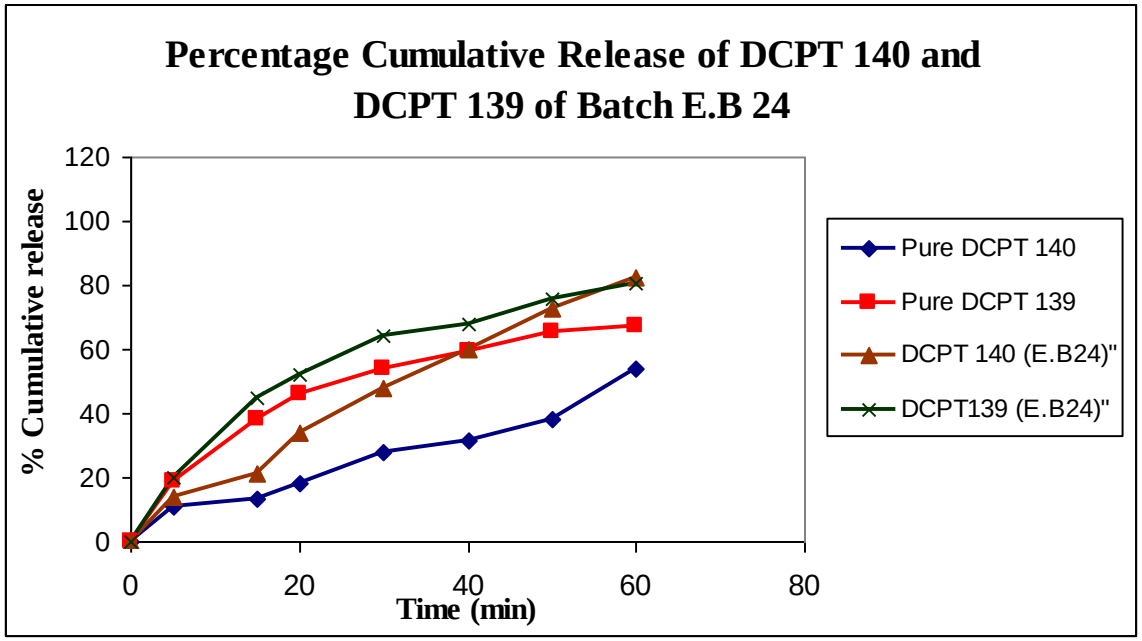


Fig. 3.14 Percentage cumulative release of DCPT 140 & DCPT139 of batch E.B 24

RESULT- The percentage cumulative release of DCPT 139 and DCPT 140 batch (E.B 24) was found to be 80.42% and 82.21% respectively within 60 minute.

CONCLUSION: From the above results of percentage drug content, solubility and dissolution studies obtained with different batches it can be concluded that batch S.B 5, K.B 13 and E.B 24 are the optimized batches. These three batches were further evaluated with respect to each other for the extrusion of DCPT 139 and DCPT 140.

3.10 EVALUATION PARAMETERS OF HOT MELT EXTRUDATES OF OPTIMIZED BATCHES:-

1. X-Ray Diffraction (XRD)

XRD is used to characterize the crystalline properties of hot-melt extruded dosage forms. Crystallinity is reflected by a characteristic fingerprint region in the diffraction pattern. The X-Ray Diffraction analysis of batch (S.B 5, K.B 13 and E.B 24) was done and compared with XRD profile of pure drug.

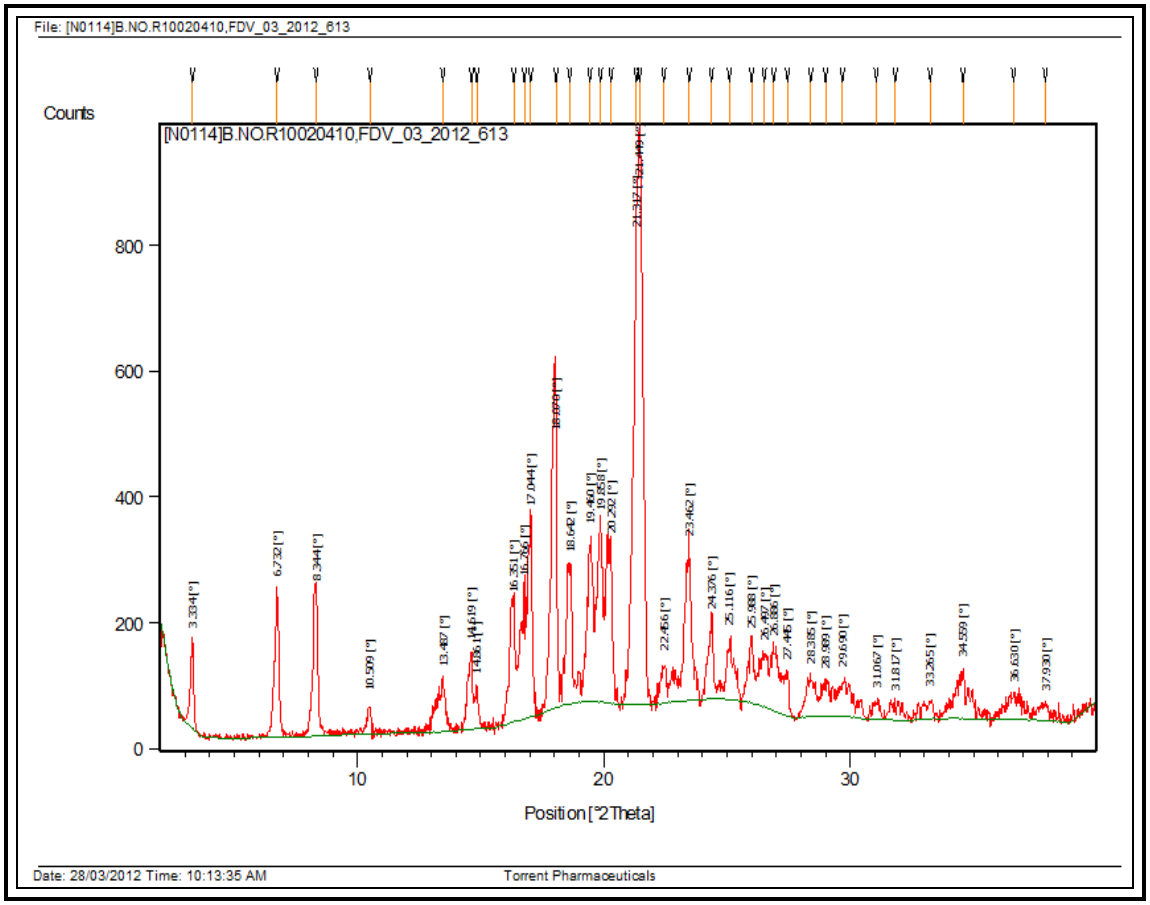


Fig. 3.15: X-Ray Diffraction profiles of DCPT 140

Table 3.36: Peak list X-Ray Diffraction profiles of DCPT 140

Pos. [° 2 Th.]	**d- spacing [Å]**	**Rel. Int [%]**
3.33	26.48	15.40
6.73	13.11	25.94
8.34	10.58	25.10
10.50	8.41	4.87
13.48	6.55	8.43
14.61	6.05	13.09
16.35	5.41	20.13
16.76	5.28	22.55
17.044	5.19	34.61
18.07	4.95	46.59
18.64	4.75	24.04
19.85	4.46	31.39
20.29	4.37	27.39
21.31	4.16	82.34
21.44	4.13	100
22.45	3.95	6.44
23.46	3.78	26.48
24.37	3.64	13.16
26.88	3.31	10.47
27.44	3.24	7.11
28.38	3.14	6.69
28.98	3.07	5.56
29.69	3.00	6.01
31.81	2.81	2.46
33.26	2.69	3.07
34.55	2.59	8.20
36.63	2.45	3.91
37.92	2.37	2.64

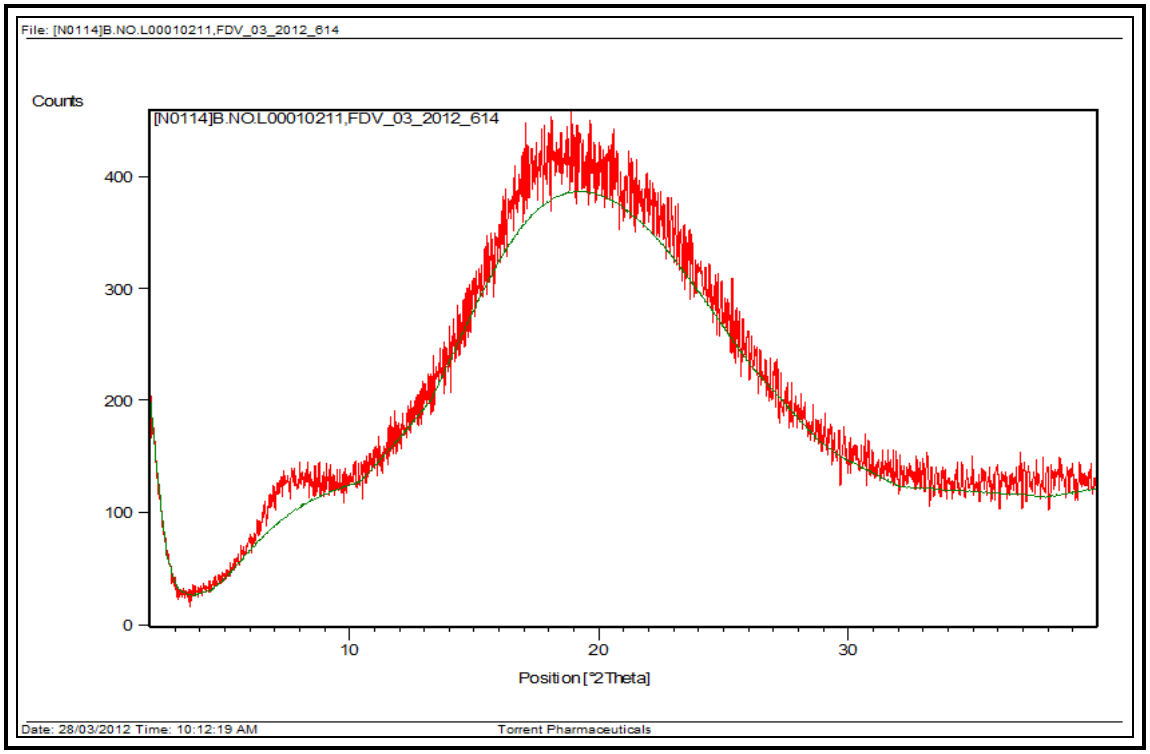


Fig. 3.16: X-Ray Diffraction profiles of DCPT 139

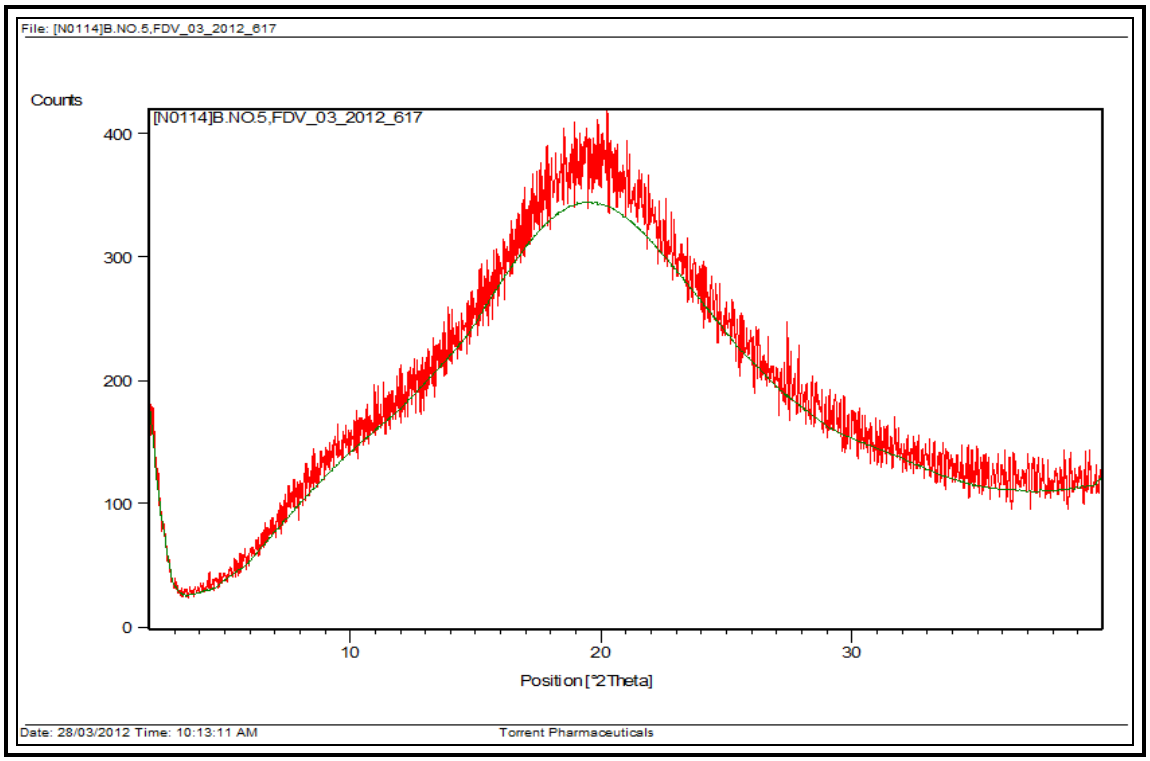


Fig. 3.17: X-Ray Diffraction profiles of batch S.B 5

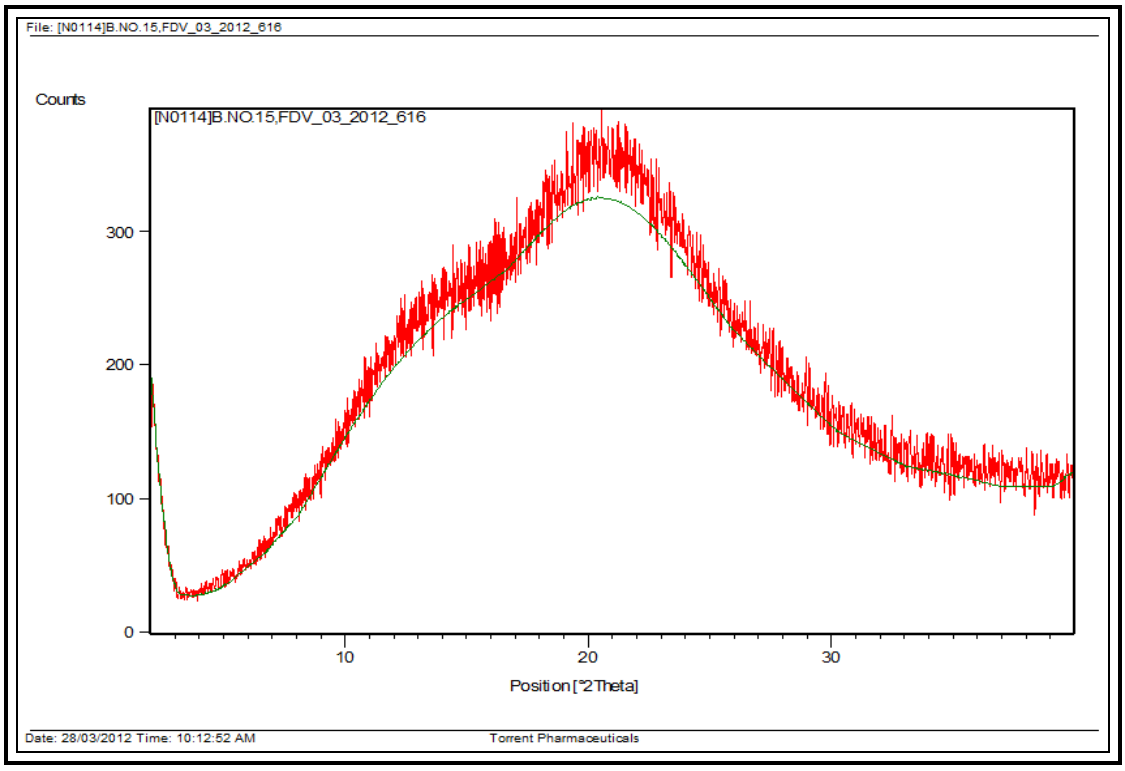


Fig. 3.18: X-Ray Diffraction profiles of batch K.B 13

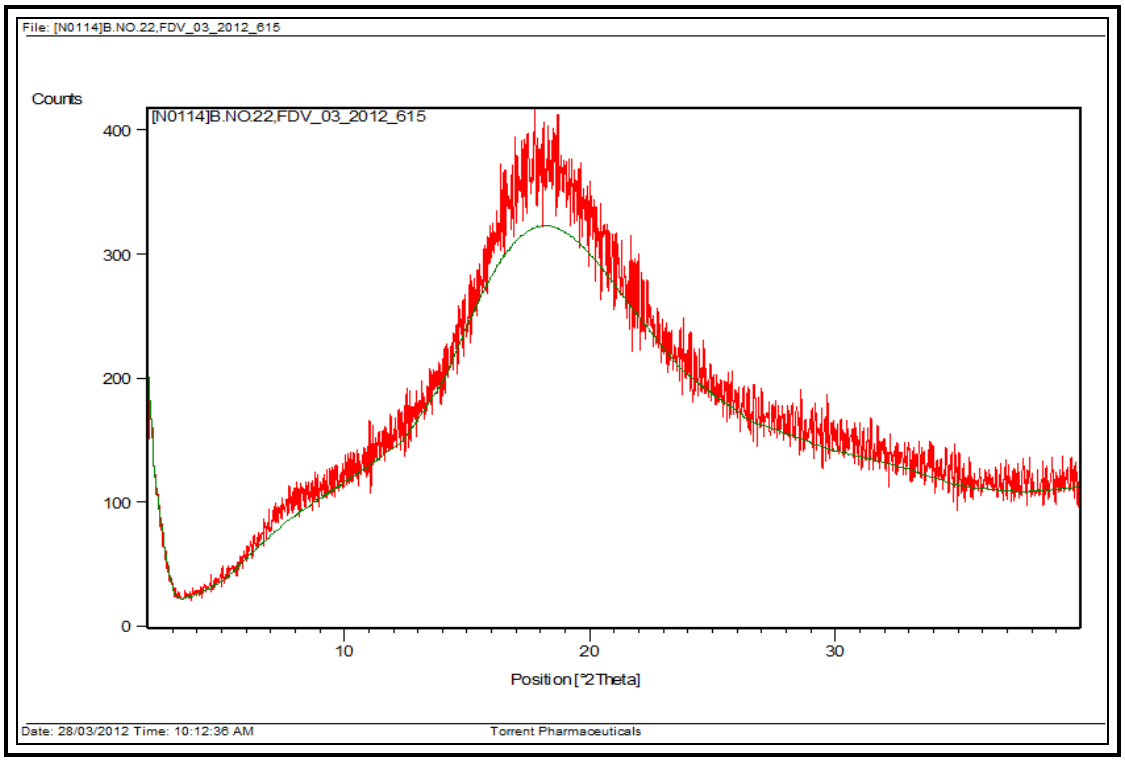


Fig. 3.19: X-Ray Diffraction profiles of batch E.B 24

RESULT: In the XRD Profile of DCPT 140 sharp speaks were observed due to crystallinity, whereas in case of DCPT 139 and all extrudate batches no sharp peaks were observed in the XRD profile.

CONCLUSION: From the above XRD profiles it can be concluded that the drug in the extrudate (batch S.B 5, K.B 13 and E.B 24) is completely converted into amorphous form.

2. DISSOLUTION STUDIES

Invitro release profiles comparison of DCPT 140 and DCPT 139 of batch (S.B 5, K.B 13 and E.B 24) in capsule –

Procedure:-

Percentage cumulative release of DCPT 140 and DCPT 139 of batch (S.B 5, K.B 13, and E.B 24) were carried out using USP dissolution apparatus Type II (Paddle type) at 50 rpm. Dissolution medium (900 mL) consisted of (0.1 N HCL containing 0.5% sodium lauryl sulphate) was used and 5 mL of dissolution medium was withdrawn at (10, 20, 30, 40, 50, 60 min). Accurate amount of the extrudate powder equivalent to 250 mg of combination drug (DCPT 139 and DCPT 140) was taken into 00 size capsule, diluent (microcrystalline cellulose) and super disintegrant (sodium starch glycollate) 5% and 2% of total weight was taken respectively. The amount of dissolved drug was determined using UV spectrophotometric method at 240nm and 259nm. The dissolution profile of DCPT 140 and DCPT 139 of each batch was generated in triplicate.

Capsule Filling:

Table 3.37: List of ingredients to be added into 00 size capsule for dissolution studies

Ingredients	**Batches**		
	S.B 5	**K.B 13**	**E.B 24**
Extrudate powder equivalent to 250 mg drug	657.37	653.75	659.28
Microcrystalline cellulose (5%)	35.34	35.14	35.44
Sodium starch glycollate (2%)	14.13	14.05	14.17
Total weight(mg)	706.34	702.94	708.89

Table 3.38: Invitro release profile of DCPT 140 and DCPT 139 of batch S.B5 in capsule
Set – 1

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.151	0.11	0.0010	0.0062	0.052	0.312	0	0
20	0.384	0.256	0.0027	0.0134	0.135	0.668	0.052	0.312
30	0.559	0.364	0.0040	0.0185	0.198	0.927	0.187	0.980
40	0.66	0.414	0.0047	0.0202	0.236	1.011	0.386	1.908
50	0.7	0.434	0.0050	0.0209	0.252	1.045	0.622	2.918
60	0.73	0.449	0.0053	0.0214	0.263	1.071	0.874	3.963

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
9.351	56.242	9.351	56.242	18.701	28.121
24.382	120.328	24.434	120.640	48.868	60.320
35.714	166.876	35.901	167.857	71.803	83.928
42.567	181.949	42.953	183.856	85.906	91.928
45.277	188.107	45.899	191.026	91.798	95.513
47.308	192.727	48.182	196.690	96.365	98.345

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (S.B 5 in capsule) was found to be 98.34% and 96.36% respectively within 60 minute.

Table 3.39: Invitro release profile of DCPT 140 and DCPT 139 of batch S.B5 in capsule Set – 2

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.163	0.12	0.0011	0.0069	0.056	0.344	0	0
20	0.411	0.27	0.0029	0.0139	0.146	0.694	0.056	0.344
30	0.5764	0.37	0.0041	0.0186	0.205	0.928	0.202	1.038
40	0.664	0.411	0.0048	0.0198	0.239	0.988	0.407	1.966
50	0.6909	0.433	0.0050	0.0211	0.248	1.056	0.646	2.954
60	0.722	0.447	0.0052	0.0215	0.260	1.074	0.893	4.010

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
10.062	61.915	10.062	61.915	20.123	30.957
26.198	124.963	26.254	125.307	52.508	62.653
36.961	166.973	37.163	168.011	74.325	84.006
42.965	177.783	43.372	179.749	86.744	89.874
44.570	190.101	45.216	193.055	90.431	96.527
46.716	193.407	47.609	197.417	95.218	98.709

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (S.B 5 in capsule) was found to be 98.70% and 95.21% respectively within 60 minute.

Table 3.40: Invitro release profile of DCPT 140 and DCPT 139 of batch S.B5 in capsule
Set – 3

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.176	0.117	0.00124	0.00609	0.062	0.305	0	0
20	0.416	0.274	0.00294	0.01413	0.147	0.706	0.062	0.305
30	0.556	0.363	0.00394	0.01854	0.197	0.927	0.209	1.011
40	0.66	0.415	0.00473	0.02032	0.236	1.016	0.406	1.939
50	0.7	0.44	0.00501	0.02154	0.251	1.077	0.643	2.955
60	0.725	0.445	0.00522	0.02117	0.261	1.058	0.893	4.032

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
11.184	54.831	11.184	54.831	22.367	27.416
26.499	127.167	26.561	127.472	53.121	63.736
35.498	166.893	35.707	167.904	71.414	83.952
42.542	182.905	42.948	184.844	85.897	92.422
45.124	193.845	45.767	196.800	91.534	98.400
47.008	190.522	47.901	194.554	95.803	97.277

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (S.B 5 in capsule) was found to be 97.27% and 95.80% respectively within 60 minute.

Table 3.41: Mean cumulative percentage release of DCPT 139 of batch S.B5

DCPT139 % C.P.R Set- 1	DCPT139 % C.P.R Set-2	DCPT139 % C.P.R Set-3	Mean % C.P.R	Std. Deviation	% R.S.D
0	0	0	0	0	0
28.121	30.957	27.416	28.831	1.875	6.502
60.320	62.653	63.734	62.235	1.745	2.803
83.928	84.005	83.950	83.961	0.040	0.047
91.928	89.874	92.419	91.407	1.350	1.477
95.513	96.527	98.398	96.812	1.463	1.512
98.345	98.708	97.274	98.109	0.745	0.760

Table 3.42: Mean cumulative percentage release of DCPT 140 of batch S.B5

DCPT140 % C.P.R Set- 1	DCPT140 % C.P.R Set-2	DCPT140 % C.P.R Set-3	Mean % C.P.R	Std. Deviation	% R.S.D
0	0	0	0	0	0
18.701	20.123	22.367	20.397	1.848	9.062
48.864	52.506	53.117	51.496	2.300	4.465
71.799	74.323	71.410	72.511	1.582	2.181
85.902	86.742	85.893	86.179	0.488	0.566
91.794	90.429	91.530	91.251	0.724	0.793
96.361	95.216	95.799	95.792	0.572	0.598

RESULT: - The mean percentage cumulative release of DCPT 139 and DCPT 140 batch (S.B 5 in capsule) was found to be 98.10% and 95.79% respectively within 60 minute.

Table 3.43: Invitro release profile of DCPT 140 and DCPT 139 of batch K.B 13 in capsule

Set – 1

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.135	0.09	0.00095	0.00470	0.048	0.235	0	0
20	0.42	0.299	0.00291	0.01664	0.145	0.832	0.048	0.235
30	0.6	0.382	0.00428	0.01898	0.214	0.949	0.193	1.067
40	0.687	0.422	0.00495	0.02009	0.247	1.005	0.408	2.016
50	0.715	0.44	0.00515	0.02100	0.257	1.050	0.655	3.021
60	0.72	0.442	0.00519	0.02103	0.259	1.052	0.912	4.071

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
8.572	42.303	8.572	42.303	17.144	21.151
26.185	149.778	26.233	150.013	52.466	75.007
38.554	170.798	38.748	171.865	77.496	85.933
44.536	180.846	44.943	182.862	89.887	91.431
46.331	188.983	46.986	192.003	93.971	96.002
46.682	189.274	47.594	193.345	95.189	96.672

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (K.B 13 in capsule) was found to be 96.67% and 95.18% respectively within 60 minute.

Table 3.44: Invitro release profile of DCPT 140 and DCPT 139 of batch K.B 13 in capsule

Set – 2

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.141	0.094	0.0010	0.0049	0.050	0.245	0	0
20	0.413	0.296	0.0029	0.0166	0.143	0.829	0.050	0.245
30	0.598	0.383	0.0043	0.0192	0.213	0.958	0.193	1.074
40	0.673	0.416	0.0048	0.0200	0.242	0.998	0.406	2.032
50	0.703	0.434	0.0051	0.0208	0.253	1.040	0.648	3.030
60	0.713	0.44	0.0051	0.0211	0.256	1.054	0.901	4.069

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
8.953	44.183	8.953	44.183	17.906	22.091
25.698	149.179	25.748	149.424	51.496	74.712
38.368	172.403	38.561	173.477	77.122	86.738
43.562	179.647	43.968	181.679	87.936	90.839
45.518	187.135	46.166	190.165	92.332	95.082
46.170	189.631	47.071	193.700	94.141	96.850

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (K.B 13 in capsule) was found to be 96.85% and 94.14% respectively within 60 minute.

Table 3.45: Invitro release profile of DCPT 140 and DCPT 139 of batch K.B 13 in capsule

Set – 3

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.133	0.096	0.0009	0.0054	0.046	0.270	0	0
20	0.4212	0.3	0.0029	0.0167	0.146	0.835	0.046	0.270
30	0.6235	0.389	0.0045	0.0189	0.224	0.944	0.192	1.105
40	0.6896	0.423	0.0050	0.0201	0.248	1.005	0.416	2.049
50	0.7119	0.437	0.0051	0.0208	0.256	1.040	0.664	3.054
60	0.7219	0.4414	0.0052	0.0209	0.260	1.045	0.920	4.094

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
8.258	48.689	8.258	48.689	16.517	24.344
26.256	150.346	26.302	150.616	52.604	75.308
40.267	169.874	40.459	170.979	80.917	85.490
44.720	180.960	45.135	183.009	90.270	91.504
46.157	187.119	46.822	190.173	93.643	95.086
46.850	188.084	47.770	192.178	95.541	96.089

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (K.B 13 in capsule) was found to be 96.08% and 95.54% respectively within 60 minute.

Table 3.46: Mean cumulative percentage release of DCPT 139 of batch K.B 13

DCPT139 % C.P.R Set- 1	DCPT139 % C.P.R Set-2	DCPT139 % C.P.R Set-3	Mean % C.P.R	Std. Deviation	% R.S.D
0	0	0	0	0	0
21.151	22.091	24.344	22.529	1.641	7.284
75.007	74.712	75.308	75.009	0.298	0.397
85.933	86.738	85.490	86.053	0.633	0.736
91.431	90.839	91.504	91.258	0.365	0.400
96.002	95.082	95.086	95.390	0.530	0.555
96.672	96.850	96.089	96.537	0.398	0.412

Table 3.47: Mean cumulative percentage release of DCPT 140 of batch K.B 13

DCPT140 % C.P.R Set- 1	DCPT140 % C.P.R Set-2	DCPT140 % C.P.R Set-3	Mean % C.P.R	Std. Deviation	% R.S.D
0	0	0	0	0	0
17.144	17.906	16.517	17.189	0.695	4.046
52.464	51.494	52.602	52.187	0.604	1.157
77.494	77.120	80.915	78.509	2.092	2.664
89.885	87.934	90.268	89.362	1.252	1.401
93.969	92.330	93.641	93.313	0.868	0.930
95.187	94.139	95.539	94.955	0.728	0.767

RESULT: - The mean percentage cumulative release of DCPT 139 and DCPT 140 batch (K.B 13 in capsule) was found to be 96.53% and 94.95% respectively within 60 minute.

Table 3.48: Invitro release profile of DCPT 140 and DCPT 139 of batch E.B 24 in capsule

Set – 1

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.1156	0.0825	0.0008	0.0046	0.040	0.230	0.000	0.000
20	0.3833	0.261	0.0027	0.0139	0.134	0.696	0.040	0.230
30	0.444	0.286	0.0032	0.0144	0.158	0.720	0.174	0.926
40	0.562	0.355	0.0040	0.0175	0.201	0.874	0.332	1.646
50	0.5879	0.369	0.0042	0.0180	0.211	0.902	0.533	2.520
60	0.629	0.392	0.0045	0.0190	0.226	0.950	0.744	3.422

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
7.202	41.420	7.202	41.420	14.404	20.710
24.199	125.336	24.239	125.566	48.477	62.783
28.446	129.566	28.620	130.492	57.241	65.246
36.184	157.297	36.516	158.943	73.033	79.471
37.911	162.289	38.445	164.809	76.890	82.404
40.633	170.960	41.377	174.381	82.754	87.191

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (E.B 24 in capsule) was found to be 87.19% and 82.75% respectively within 60 minute.

Table 3.49: Invitro release profile of DCPT 140 and DCPT 139 of batch E.B 24 in capsule

Set – 2

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.1291	0.0878	0.00091	0.00468	0.045	0.234	0	0
20	0.389	0.265	0.00273	0.01415	0.136	0.707	0.045	0.234
30	0.4575	0.293	0.00326	0.01465	0.163	0.733	0.181	0.941
40	0.567	0.3569	0.00406	0.01750	0.203	0.875	0.344	1.674
50	0.5776	0.3696	0.00412	0.01847	0.206	0.923	0.547	2.549
60	0.6322	0.394	0.00454	0.01909	0.227	0.955	0.753	3.472

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
8.153	42.111	8.153	42.111	16.306	21.056
24.555	127.313	24.600	127.547	49.201	63.774
29.354	131.883	29.535	132.825	59.071	66.412
36.538	157.493	36.882	159.167	73.765	79.583
37.068	166.202	37.615	168.751	75.230	84.375
40.839	171.835	41.593	175.307	83.186	87.654

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (E.B 24 in capsule) was found to be 87.65% and 83.18% respectively within 60 minute.

Table 3.50: Invitro release profile of DCPT 140 and DCPT 139 of batch E.B 24 in capsule

Set – 3

Time (min)	Abs.1	Abs.2	DCPT140 (g/100ml)	DCPT139 (g/100ml)	DCPT140 (mg/5ml)	DCPT139 (mg/5ml)	Error DCPT140	Error DCPT139
0	0	0	0	0	0	0	0	0
10	0.122	0.085	0.00085	0.00464	0.0425	0.2319	0	0
20	0.3775	0.2644	0.00263	0.01450	0.1314	0.7248	0.0420	0.2319
30	0.436	0.292	0.00307	0.01532	0.1536	0.7661	0.1734	0.9567
40	0.579	0.364	0.00415	0.01782	0.2073	0.8911	0.3270	1.7228
50	0.59	0.376	0.00421	0.01870	0.2106	0.9350	0.5343	2.6139
60	0.639	0.397	0.00459	0.01917	0.2295	0.9583	0.7449	3.5489

DCPT140 (mg/900ml)	DCPT139 (mg/900ml)	Cumulative DCPT140	Cumulative DCPT 139	DCPT140 % C.P.R	DCPT139 % C.P.R
0	0	0	0	0	0
7.6532	41.7356	7.6532	41.7356	15.3064	20.8678
23.6457	130.4678	23.6877	130.6997	47.3754	65.3499
27.6499	137.8970	27.8232	138.8537	55.6464	69.4269
37.3226	160.3925	37.6496	162.1153	75.2991	81.0576
37.9024	168.3021	38.4368	170.9160	76.8735	85.4580
41.3102	172.4994	42.0551	176.0483	84.1101	88.0242

RESULT: - The percentage cumulative release of DCPT 139 and DCPT 140 batch (E.B 24 in capsule) was found to be 88.02% and 84.11% respectively within 60 minute.

Table 3.51: Mean cumulative percentage release of DCPT 139 of batch E.B 24

DCPT139 % C.P.R Set- 1	DCPT139 % C.P.R Set-2	DCPT139 % C.P.R Set-3	Mean % C.P.R	Std. Deviation	% R.S.D
0	0	0	0	0	0
20.710	21.056	20.868	20.878	0.173	0.830
62.783	63.773	65.349	63.968	1.294	2.023
65.246	66.412	69.426	67.028	2.157	3.218
79.471	79.583	81.057	80.037	0.885	1.105
82.404	84.375	85.457	84.079	1.548	1.841
87.191	87.653	88.023	87.622	0.417	0.476

Table 3.52: Mean cumulative percentage release of DCPT 140 of batch E.B 24

DCPT140 % C.P.R Set- 1	DCPT140 % C.P.R Set-2	DCPT140 % C.P.R Set-3	Mean % C.P.R	Std. Deviation	% R.S.D
0	0	0	0	0	0
14.404	16.306	15.306	15.339	0.952	6.204
48.477	49.201	47.375	48.351	0.919	1.901
57.241	59.071	55.646	57.319	1.713	2.989
73.033	73.765	75.299	74.032	1.157	1.562
76.890	75.230	76.874	76.331	0.953	1.249
82.754	83.186	84.110	83.350	0.693	0.831

RESULT: - The mean percentage cumulative release of DCPT 139 and DCPT 140 batch (K.B 24 in capsule) was found to be 87.62% and 83.35% respectively within 60 minute.

Table 3.53: Mean cumulative percentage release of DCPT 139 with different polymer batch

Time (min)	DCPT139 (S.B 5) Mean % C.P.R	DCPT139 (K.B 13) Mean % C.P.R	DCPT139 (E.B 24) Mean % C.P.R
0	0	0	0
10	28.831	22.529	20.878
20	62.235	75.009	63.968
30	83.961	86.053	67.028
40	91.407	91.258	80.037
50	96.812	95.390	84.079
60	98.109	96.537	87.622

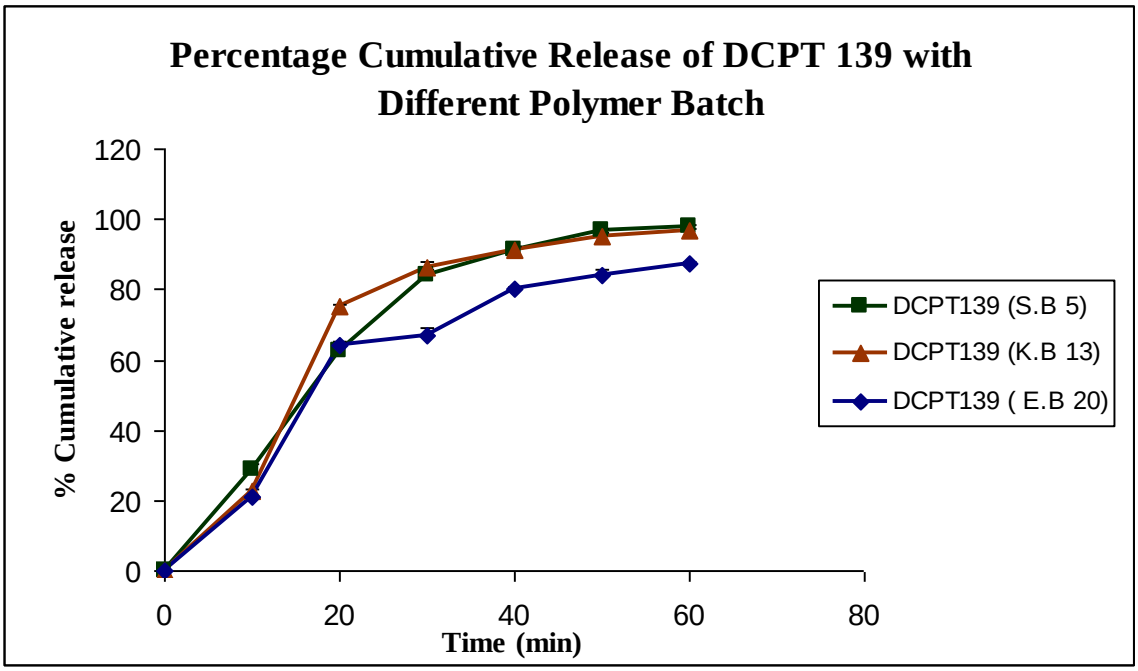


Fig. 3.20: Invitro Release profile comparison of DCPT 139 with different polymer

RESULT: The percentage cumulative release of DCPT 139 in batch S.B 5, K.B 13 and E.B 24 was found to be 98.01%, 96.53% and 87.62% respectively within 60 minute.

CONCLUSION: The percentage cumulative release of DCPT 139 in batch S.B 5 was greater with comparison to K.B 13 and E.B 24.

Table 3.54: Mean cumulative percentage release of DCPT 140 with different polymer batch

Time (min)	DCPT140 (S.B 5) Mean % C.P.R	DCPT140 (K.B 13) Mean % C.P.R	DCPT140 (E.B 20) Mean % C.P.R
0	0	0	0
10	20.397	17.189	15.339
20	51.496	52.187	48.351
30	72.511	78.509	57.319
40	86.179	89.362	74.032
50	91.251	93.313	76.331
60	95.792	94.955	83.350

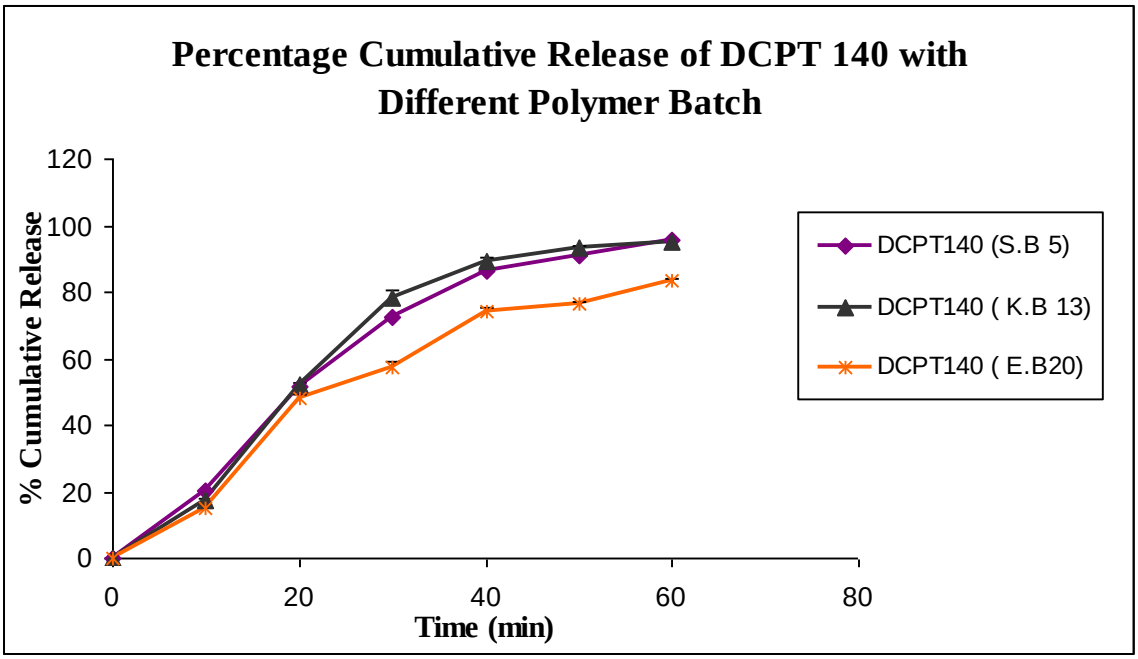


Fig. 3.21: Invitro Release profile comparison of DCPT 140 with different polymer

RESULT: The percentage cumulative release of DCPT 140 in batch S.B 5, K.B 13 and E.B 24 was found to be 95.79%, 94.95% and 83.35% respectively within 60 minute.

CONCLUSION: The percentage cumulative release of DCPT 140 in batch S.B 5 was greater with comparison to K.B 13 and E.B 24.

3. DRUG CONTENT COMPARISON

Table 3.55: Percentage drug content comparison of batch (S.B 5, K.B 13 and E.B 24)

Batch	**% Drug content**	
	DCPT 139	**DCPT 140**
S.B 5	95.43% w/v	94.19% w/v
K.B 13	96.49% w/v	93.77% w/v
E.B 24	94.75% w/v	96.40% w/v

RESULT AND DISSCUSION: The percentage drug content in the batch (S.B 5, K.B 13 and E.B 24) was found to be almost similar indicating equal amount of drug dispersion in all the batches.

4. SOLUBILTY STUDY COMPARISON

Table 3.56: Solubility comparison of batch (S.B 5, K.B 13 and E.B 24)

Sample	**Aqueous solubility**	
	(DCPT 139)	**(DCPT 140)**
Pure Drug	0.09 mg/ml	0.06 mg/ml
S.B 5	61.99 mg/ml	58.77 mg/ml
K.B 13	55.98 mg/ml	49.90 mg/ml
E.B 24	29.70 mg/ml	27.93 mg/ml

RESULT AND DISCUSSION: The aqueous solubility of DCPT 139 and DCPT 140 changes drastically from practically insoluble class to become soluble class after hot melt extrusion process. The highest amount of solubility is obtained in case of batch S.B 5.

The solid dispersion prepared through hot melt extrusion process shows increase in solubility and hence increase in dissolution rate with comparison to pure drug. The antiretroviral drug combination (DCPT 139 and DCPT 140) both are practically insoluble in water, whereas the solubility of the solid dispersion prepared of the combination drug from practically insoluble class get changed to soluble class. The percentage cumulative release of pure DCPT 139 and DCPT 140 are 67.35% and 54.10% respectively within one hour, after formulation of solid dispersion of DCPT 139 and DCPT 140 the percentage cumulative release get increase upto 98.10% and 95.79% respectively. In summary it can be concluded that solid dispersion through the hot melt extrusion process for fixed dose combination of antiretroviral drug DCPT 139 and DCPT 140 can be formulated for the solubility and dissolution enhancement.

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