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Properties of Polymeric Drug Delivery Systems Prepared by Hot-melt Extrusion

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Dedication

To my dear wife, Li, son, George, and our families

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Properties of Polymeric Drug Delivery Systems Prepared by Hot-melt Extrusion

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The purpose of this research project was to investigate the physicochemical and drug release properties of polymeric drug delivery systems prepared by hot-melt extrusion containing either highly water-soluble drugs or a poorly water-soluble drug. The properties of processed materials were characterized by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), stability indicating RP-HPLC assay, dissolution studies, scanning electron microscopy (SEM), X-ray diffractometry, electronic torque rheometry, Zeta potential particle size analysis, and helium pycnometry.

Chlorpheniramine maleate (CPM), diltiazem hydrochloride (DTZ), indomethacin (IDM), and the excipients were thermally and chemically stable following hot-melt extrusion. CPM decreased the glass transition temperature (Tg) of

Eudragit® RS PO and exhibited a solid-state plasticization effect. CPM and IDM were in the amorphous state and DTZ was in the crystalline state following hot-melt extrusion processing. Triethyl citrate (TEC) facilitated the hot-melt extrusion process by decreasing the Tg and the melt viscosity of Eudragit® RS PO. However, the thermal lubricant, glyceryl monostearate (GMS), only decreased the melt viscosity of the Eudragit® RS PO. The CPM release rate constant decreased in the order from tablets prepared by direct compression, hot-melt granulation, and hot-melt extrusion. This was due to an increase in the intermolecular binding and entanglement between drug molecules and polymer molecules that occurred during thermal processing. Post-processing thermal treatment of the hot-melt extrudates had a minimal effect on decreasing the drug release rate since the hot-melt extrusion process enhanced the entanglement of the drug and polymer to a greater extent. Drug release rates from both DTZ and CPM hot-melt extrudates increased with an increase in the TEC level in the formulations, while DTZ release from the Eudragit® RS 30D coated pellets decreased with an increase of TEC in the coating layer. This could be attributed to the fact that a continuous polymeric structure was formed following hot-melt extrusion regardless of the TEC level. However, for the film coated pellets, coalescence of the polymer particles was enhanced with higher levels of TEC. Due to the lower solubility of IDM, no significant difference in drug release was observed in the IDM hot-melt extrudated granules containing 0%, 4%, and 8% TEC.

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CHAPTER ONE: INTRODUCTION

1.1. Polymeric Controlled Drug Delivery Systems Prepared by Hot-melt Extrusion

1.1.1. Significance of polymeric controlled drug delivery systems

Polymeric controlled drug delivery systems offer numerous advantages when compared with conventional dosage forms, including improved efficacy, reduced toxicity, and improved patient compliance (1, 2).

Controlled drug delivery technology represents one of the frontier areas of science, and the design and development of novel therapeutic systems involves a multidisciplinary scientific approach.

From a manufacturing point of view, oral polymeric drug delivery systems can be developed and designed by several processing methods. By modifying polymer properties, a matrix system may be fabricated for sustained or controlled drug delivery. Pharmaceutical polymeric materials with little or no toxicity serve as membranes or matrices in which the active ingredient is dispersed or dissolved. Polymers also function as carriers, and may be attached to the active ingredient.

These carriers can be used to deliver a wide variety of drugs at a controlled rate in the gastrointestinal tract.

1.1.2. Advantages of hot-melt extrusion

Hot-melt extrusion is one of the most widely applied processing techniques in the plastics industry. Film, tubing, pipes, insulation, and home siding are produced with this thermal processing. In each case, the size and shape of the extrudate is determined by the die geometry, and solidification is determined by cooling the processed material. For pharmaceutical systems, several research groups have recently demonstrated that thermal processing of pharmaceutical powders is a viable method to prepare granules, sustained release tablets and transdermal drug delivery systems.

For pharmaceutical applications, hot-melt extrusion offers many advantages over traditional processing techniques (3). Because hot-melt extrusion is a solvent-free process, there are no concerns with solvent handling or recovery after processing. Solvents are not needed for processing, therefore fewer processing steps are necessary and time-consuming drying steps are eliminated. Also, there are no requirements on the compressibility of the active ingredients. The intense mixing and agitation by the extruder screw during processing causes suspended drug particles to deaggregate in the polymer melt, resulting in a uniform dispersion of fine particles. Drug bioavailability may therefore be improved by dispersion of the drug substance at the molecular level in hot-melt extruded dosage forms. In addition, there is the possibility

of including a high dose of freely soluble drug in the extrudates without them losing their sustained release properties. This is sometimes difficult to achieve with other processing methods. The entire procedure is simple, continuous, efficient, and readily scaled-up.

1.1.3. Hot-melt extrusion process

Hot-melt extrusion equipment consists of an extruder, downstream auxiliary equipment and other monitoring tools used for performance and product quality evaluation. The extruder is typically composed of a feeding hopper, barrel, screw, die, screw driving unit and a heating/cooling device. The heart of the extruder is an Archimedean screw rotating inside a barrel. It is capable of pumping materials under a set of operating conditions at a specific rate.

During the hot-melt extrusion process, a blend of the active ingredients, the thermoplastic polymers and other processing aids is fed into the barrel of the extruder through the hopper. The materials are transferred inside the heated barrel by a rotating screw. Temperatures at different zones are controlled by several thermocouples in the barrel. The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Materials are subject to only a few minutes in the extruder (4). Depending upon the dimensions of the die cylinders, films can also be produced from the extruder.

1.1.4. Mechanism of hot-melt extrudate formation

Unlike the case of a polymer dissolved in solvent, not all of the lattice sites are occupied by a molten polymer. Some may be vacant, though as in the case of a solution, the remainder can be occupied by no more than one segment of the polymer chains. During molecular motion in a polymer melt, the vacant sites or holes can be envisaged as jumping about and effectively swapping sites with individual polymer segments. When a stress is applied to the bulk polymer melt, the mass flows in the direction that relieves the stress. At the molecular level, the probability of a molecular jump becomes higher in the direction of the stress than in any other direction and hence these stress-relieving motions predominate, leading to the observed pattern of flow. Viscous flow takes place by successive jumps of such segments until the entire macromolecule has shifted. The overall result is that in the melt the polymer molecules adopt following Gaussian configurations and behave as thermo-dynamically ideal entities (5).

From a molecular point of view, the process of hot-melt extrusion involves the high temperature transformation of a solid mass of intertwined molecules into a viscous liquid or semi-solid mass. The resulting mass emerges from the die as the result of a compelling force.

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 energy required to melt polymers in single-screw plasticating extruders is derived primarily from viscous dissipation and to a lesser

extent from heat transfer through the barrel wall. The melting-rate is highly dependent upon the physical and rheological properties of the polymer. It rises with increasing values of melt density, thermal conductivity, and melt viscosity, but decreases with increasing specific heat or heat of fusion. More viscous materials and amorphous materials melt faster (6).

1.1.5. Solid dispersions for controlled release

1.1.5.1. Solid dispersion technology

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid state in order to achieve altered solid-state properties, such as increased solubility and dissolution rate, sustained drug release, and improved stability (7).

There are many factors influencing the bioavailability of a pharmaceutical product. The two most important physicochemical properties of a drug are its solubility and permeability. As a general rule, if a drug substance has an aqueous solubility of less than 10mg/ml, dissolution is the rate-limiting step in the process of drug absorption (8). Formulation of poorly water-soluble drugs for oral delivery presents one of the most frequent and greatest challenges to pharmaceutical scientists.

The Noyes-Whitney equation describes the factors influencing drug release:

$$dC/dT = AD(Cs-C)/h \qquad (1)$$

where dC/dT is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the drug, Cs is the solubility of the drug

in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving drug.

According to this equation, the main possibilities for improving dissolution rate are to increase the surface area by decreasing the particle size of the solid drug; to increase the drug diffusion coefficient by selecting a suitable carrier; to increase its solubility by changing its physical and/or chemical structure; to ensure sink conditions by minimizing the drug concentration in the medium; and lastly to decrease the boundary layer thickness by optimizing the wetting characteristics of the drug surface.

Through application of the Noyes-Whitney equation, it can be determined that maximizing the rate of dissolution occurs by the following physical and chemical modifications.

Decreasing the particle size of the compound by milling the drug theoretically results in an increase in the available surface area for dissolution. However, in some cases the micronized powder tends to agglomerate, and may consequently become a disadvantage of the milling process. Surfactants are often incorporated into a formulation to increase drug solubility due to their amphiphilic functions. At higher concentrations, surfactant micelles will be formed and this will also enhance drug solubility. Some drugs may exist in more than one crystalline form due to different molecular arrangements. Polymorphs generally have different solubilities, melting points, and x-ray diffraction patterns, even through they are chemically identical.

Crystalline molecules of a drug form a compact crystal with high lattice energy and consequently low solubility. However, amorphous drugs have high solubility. Complexation is another method to improve drug dissolution and works via the inclusion of poorly water-soluble drugs into β-cyclodextrin. The research in this area thus far has been very promising. Chemical modifications can be utilized to increase dissolution rates. This includes making a soluble salt or a prodrug.

Methods for preparing solid dispersions

Hot melt method

Sekiguchi and Obi used a hot melt method to prepare simple eutectic mixtures. Sulfathiazole and urea were melted together at a temperature above the eutectic point, which is the lowest possible melting temperature of the mixture, and then cooled in an ice bath. The resultant solid eutectic was then milled to reduce the particle size (9).

The advantage of the hot-melt method is that it does not require finding a mutual solvent for both the drug and the polymeric carrier. For example, this hot-melt method was used to prepare probucol and polyethylene oxide (PEO) solid dispersions (10), since no mutual solvent could be found for these two components.

An important prerequisite for the manufacture of solid solutions by the hot melt method is the miscibility of the drug and the carrier in the molten state. When there are miscibility problems, this usually leads to a product that is not molecularly

dispersed. This problem can be solved by selecting a suitable carrier that shares similar physicochemical properties with the drug.

Another limitation to the hot melt method is the thermostability of the drug and the carrier. If too high a temperature is required, the drug may decompose or evaporate. In recent years, the hot melt method has enjoyed recognition in the form of hot melt extrusion. An important advantage of the hot melt extrusion method is that the drug/carrier mixture is only subjected to elevated temperatures for a few minutes, which enables both the drug and the carrier to remain thermally stable.

Solvent evaporation method

The solvent evaporation method may provide another way to solve the thermal stability problem associated with the preparation of solid dispersions.

In the solvent evaporation method, solid dispersions were prepared by dissolving both the drug and the carrier in a common solvent and then evaporating the solvent under a vacuum.

An important prerequisite for the manufacture of a solid dispersion using the solvent evaporation method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods such as freeze-drying or spray-drying. When an organic solvent is to be removed, small variations in the conditions used can lead to quite large changes in product performance. Another point to be considered is the importance of thoroughly removing all of the solvent, since most organic solvents used have toxicity issues.

With the discovery of the solvent evaporation method, many problems associated with the melt method were solved. For example, it was then possible to form solid dispersions from thermoliabile substances. Previously many polymers could not be utilized for the melt method due to their high glass transition temperature (e.g. PVP K25 has a Tg of 155°C). PVP could be considered as a carrier for solvent evaporation method. As a result, for many years the solvent evaporation method was the method of choice for many polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic solvents began to make solvent-based methods more and more problematic. For these reasons, hot-melt extrusion is the current method of choice for the manufacture of solid dispersions.

Carriers

Polyethylene glycol (PEG)

PEG is one of the most frequently used materials for the preparation of solid dispersions for three reasons. Good water solubility makes it capable of producing a fast drug release. Good solubility in many organic solvents makes it easier to be prepared by the solvent evaporation method. Also lower melting points, under 65°C, make it easier to be processed by the melt method.

However, there are a few problems with the application of PEG. For example, there are stability problems encountered during preparation by the hot-melt method. If

the dispersion is too soft it can be difficult to conduct the subsequent formulation. This is most likely to occur if a low MW PEG is used or if a drug has a plasticizing effect on the PEG.

Polyvinylpyrrolidone (PVP)

In general, the glass transition temperature of the amorphous polymer PVP is high (Tg of PVP K30 is 163°C (10)). For this reason PVP has only limited application for the preparation of solid dispersions by the hot-melt method. Due to its good solubility in a wide variety of organic solvents, it is particularly suitable for the preparation of solid dispersions by the solvent evaporation method.

Most studies of PVP solid dispersions reported in the literature have used PVP of MW of 2,500-50,000. Beyond 50,000 the aqueous solubility of PVP decreases and it has a much higher viscosity at a given concentration, which can be used for controlled release.

Polysacchrides

The glass transition temperatures of most polysacchrides are relatively high. This makes the preparation by hot melt method problematic. Also, their solubility in most solvents is poor. This makes it difficult to prepare coevaporates. Despite these drawbacks, several attempts to prepare solid dispersions using polysacchrides have been reported by other researcheres.

Characterization of solid dispersions

Whether or not a solid dispersion has achieved an improved dissolution rate can be investigated using the dissolution test. Thermal analysis methods such as thermal gravimetry analysis (TGA) and differential scanning calorimetry (DSC) can be used to investigate the thermal stability and glass transition temperature of the materials used. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous form rather than a crystal form. This result can also be confirmed by the X-ray pattern. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed. The absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions. Infrared spectroscopy (IR) is used to investigate the drug and polymer interaction. Scanning electron microscopy is another method employed to distinguish between a solid solution and a solid dispersion.

Applications of solid dispersion to enhance dissolution

Since the first report on the solid dispersion technology, several authors have published some excellent reviews on this topic (11-13).

The first report on the concept and advantages of solid dispersion formulations was published by Sekiguchi and Obi in 1961 (9). They demonstrated that a eutectic mixture of sulfathiazole and urea had a much higher dissolution rate, leading to better absorption following oral administration, as compared to

sulfathiazole administered alone. The explanation offered for this behavior was that when a mixture consisting of a poorly water-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.

In the case of a solid solution, a further reason for the improvement in the dissolution rate is that the drug is in an amorphous form rather than a crystalline structure in the solid solution.

Solid dispersions were prepared with a non-steroidal anti-inflammatory and slightly water-soluble drug, flurbiprofen (the solubility is about 30mg/ml of water at 37°C), and water-soluble polymers, hydroxypropylcellulose (HPC) or poly(ethylene oxide) (PEO), by the solvent (ethanol) method. The release rate of flurbiprofen from the flurbiprofen-PEO system was significantly larger than that from flurbiprofen powder and the flurbiprofen-HPC system. The dissolution property of the polymer greatly affected the release of flurbiprofen from the solid dispersions. In the flurbiprofen-PEO system, the release rate increased with the increasing percentage of PEO (14).

Solid dispersions of itraconazole prepared with pH-dependent hydrophilic polymers, polyvinylacetal diethylaminoacetate and Eudragit® E 100, by a spray drying method resulted in greater increases in drug solubility over those prepared

with pH-independent hydrophilic polymers, PEG 20,000, PVP, Poloxamer® 188 and HPMC. Tablets containing the solid dispersion particles prepared by spray drying showed enhanced dissolution profiles of itraconazole over the marketed product (15).

Binary solid dispersions containing a poorly water-soluble drug, atenolol and different polymers, including povidone (PVP), crospovidone (PVP-CL), polyvinilpyrrolidone/vinylacetate (PVP/VA), and Eudragit® E were prepared by the solvent (methanol) evaporation method. The drug was always present in a crystalline form in the PVP-CL and Eudragit® E systems, while with the high content of PVP and PVP/VA an amorphous atenolol was detectable. An improvement in solubility and dissolution rate of atenolol with PVP and PVP-CL was obtained (16).

Phospholipid coprecipitates containing indomethacin were prepared by the solvent method and were shown to have good industrial potential to increase the dissolution of poorly water-soluble drugs. The mechanism of improved dissolution was due to the conversion of the crystal structure of indomethacin into an amorphous form and continuous erosion of the drug from the matrix of the phospholipid (17).

Up to 50% of indomethacin can be dispersed in an amorphous state in Eudragit® E-100. Because of the good solubility of Eudragit® E-100 at pH 1.2, a fast dissolution rate of drug was observed while a marked delay was noticed at pH 7.5 where the polymer is only permeable to water. At pH 5.8 the kinetics of drug release can be modulated by the drug/polymer ratio (18).

Future perspectives

The main concerns with solid dispersions have been the ability to scale-up the manufacturing method and the physical stability of the dispersion. The application of hot melt extrusion to the production of solid dispersions is a particularly important breakthrough for the scale-up of solid dispersion manufacture. Also, researchers have shown that PVP can inhibit the recrystallization of indomethacin from the supersaturated solid solution when the storage temperature is 40-50°C below the Tg of indomethacin (19). Experience with solid dispersions over the last 40 years indicates that this is a very promising approach to improving the release rate and oral bioavailability of poorly water-soluble drugs.

1.1.5.2. Solid dispersions containing water-soluble drugs for controlled release

Solid dispersion technology is commonly used to enhance the dissolution properties of poorly water-soluble drugs by the incorporation of water-soluble materials. By dispersing a given drug into an inert carrier the drug dissolution can either be accelerated or retarded depending upon the solubility or permeability of the carrier. Recently several water insoluble polymers were used to prepare solid dispersions containing freely water-soluble drugs for controlled release purposes.

Four sustained release solid dispersion dosage forms of pilocarpine hydrochloride (PC) with ethylcellulose and/or hydroxypropylmethylcellulose phthalate were prepared by the organic solvent method. One preparation was composed of PC : ethylcellulose : hydroxypropylmethylcellulose phthalate at a

weight ratio of 1:9:10, and showed the best sustained release behavior in dissolution testing among the four preparations. This preparation was examined by powder X-ray diffractometry and differential scanning calorimetry, and was confirmed to be a solid dispersion (20).

Solid dispersion films of lidocaine hydrochloride (LDC), a highly water-soluble regional anesthetic agent, were prepared with a water-insoluble ethylcellulose (EC) and water-soluble hydroxypropylcellulose (HPC) using the solvent (ethanol) evaporation method. The controlled release profiles of LDC from the solid dispersion films of different compositions were achieved at the EC/HPC composition ratio of 5/5. The mechanism of controlled release was speculated to be that there was little release of HPC together with LDC, and the retained HPC swelled in the film by the permeating fluid. Then, the release of LDC occurred via diffusion into the swelled HPC phase, causing a marked decrease in the release rate. LDC exists as an amorphous form in the solid dispersion films containing HPC. The film for clinical use, which had the 30% LDC solid dispersion film, adhered almost completely to the buccal mucosa. These observations will provide useful information on clinical application of the LDC-EC-HPC solid dispersion film (21).

Solid dispersions containing three levels of ethylcellulose and acetaminophen (1:3; 1:1; 3:1) were prepared by the solvent evaporation method to achieve prolonged drug release. Systems composed of solid dispersions or physical mixtures containing the equivalent weight of 50 mg acetaminophen, Emcompress® as diluent and 1%

magnesium stearate as lubricant were compressed into tablets. The dissolution data showed that the drug release decreased as the level of ethylcellulose increased in the solid dispersion formulations. The drug release from tablets prepared with solid dispersions followed the diffusion controlled model for an inert porous matrix, while the drug release from tablets prepared with physical mixtures followed the first-order kinetic model (22).

1.1.5.3. Solid dispersions containing poorly water-soluble drugs for controlled release

In addition to bioavailability enhancement for poorly water-soluble drugs, solid dispersion technology has also been employed to prepare the sustained release dosage forms for these drugs.

Misoprostol is difficult to formulate due to its instability and viscous liquid form. A stable sustained release solid dispersion of misoprostol with Eudragit® RS/RL was prepared. The solid dispersion matrix formed can protect misoprostol from being degraded by water so that the stability of misoprostol is improved. In addition, misoprostol can be slowly released by diffusion from the copolymer matrix (23).

Phenacetin (PHE, water solubility is 1.31mg/ml at 37°C) solid dispersions were prepared with polyethylene oxide (PEO) and different grades of Carbopol® (CP) in the mixture of water-ethanol by the solvent evaporation method (50°C, 24 hours).

The release rate of PHE from the PHE-PEO system was larger than that from PHE powder. In the PHE-CP system, almost the same release rate was observed as PHE powder. The release rate from the PHE-PEO-CP system varied depending on the PEO/CP ratio and reached the minimum level at the PEO/CP ratio of 1/1 (w/w) (24). The release profile of PHE varied depending on the molecular weight of PEO. The minimum release rate was observed at the PEO molecular weight of 35,000. It was found that the amount of the PEO-CP complex formed by hydrogen bonding changed depending on the molecular weight of PEO (25). In another research study, they found that phenacetin existed in the amorphous state and the release of the drug was controlled by the ratio of polyethylene oxide and Carbopol® as well as the Carbopol® grade (26).

A nifedipine (NF) polyethylene glycol (PEG) solid dispersion was prepared by the melting method. Three-layer hydroxypropylmethylcellulose (HPMC) matrix tablets were prepared containing this solid dispersion. Both the high-viscosity grade HPMC (Methocel K15M) and low-viscosity grade HPMC (Methocel K100) were applied in the tablets to form the matrix. The dissolution and absorption of NF from the tablet were evaluated and the formulation had a sustained release over 24 hours (27).

In order to control the release rate of a slightly water-soluble drug, flurbiprofen, solid dispersions were prepared with a water-soluble polymer, hydroxypropyl cellulose by the solvent (ethanol) evaporation method. The release

rate of flurbiprofen from the solid dispersion granules was markedly larger than that from the flurbiprofen powder, and it was larger with a lower HPC molecular weight. X-ray diffraction study shows that flurbiprofen existed in the amorphous state in the solid dispersion (28).

Furosemide is a diuretic and antihypertensive drug, and is practically insoluble in water. In order to achieve a controlled release characteristics for this drug, Aceves and coworkers prepared furosemide solid dispersions containing Eudragit® RS/RL using the solvent (methanol) evaporation method (29). The X-ray diffraction profiles showed a transition from the crystalline to the amorphous phase for the prepared solid dispersions. Electronic microscopy analysis showed that the furosemide changed its crystalline habit from needle to a new spherical phase with a diameter around 1μ. Scanning electron microscopy showed the presence of microspheres within the polymeric matrix, and the channels formed due to the furosemide dissolution inside the Eudragit® RS/RL, thus modifying the release pattern of the furosemide system.

The poor and variable oral bioavailability of furosemide is due to the presence of a biological window in the upper gastrointestinal tract and the incomplete release of the drug from the units is related to its low water solubility. A multiple-unit floating system containing a 1:5 furosemide/polyvinylpyrrolidone solid dispersion was prepared by the solvent (methanol) evaporation method. The complete dose release over the actual gastric residence time of the system (about 8 hr) was achieved.

Physicochemical analyses suggested the predominant role of the amorphous state of furosemide is in producing enhanced drug solubility and dissolution rate, which led to the desired release profile from the floating units (30).

The dissolution behaviour of controlled release solid dispersions of indomethacin containing Eudragit® RS from different combinations of the drug in a solid dispersion form was investigated. Eudragit® RS had a retardation effect on the release of indomethacin depending upon the amount of Eudragit® RS included. Inclusion of sodium lauryl sulphate (SLS) in the solid dispersion modified the release. The kinetics of the release process was found to be best described by the Higuchi square root of time equation and the first order equation indicating that the release is a diffusion controlled process (31).

Indomethacin and Eudragit® RS coprecipitates and solid dispersions were prepared by dissolving the drug and polymers in alcohol and then precipitated using distilled water or evaporating the solvent. The IR data did not indicate a significant drug-polymer interaction. X-ray diffraction showed a reduction in crystallinity for the coprecipitates and solid dispersions. DSC revealed the conversion of indomethacin from Form I to Form II in solid dispersions and coprecipitates (32). The stability of these coprecipitates and solid dispersions was investigated by Khan *et al* (33). There was no significant change in the dissolution rates for samples stored at 4°C for 6 months. This is because the rotational motion of indomethacin at 4°C may be reduced enough to inhibit crystallization.

1.2. Additives for Hot-melt Extrusion

1.2.1. General requirements for additives used for hot-melt extrusion

In general, all additives in the hot-melt extrusion formulation should have the following features: (1). Pharmaceutical grade for safety reasons. (2). Efficient in their functions without adversely affecting the functions of the other additives. (3). Stable under the thermal processing conditions. (4). Stable during the storage of the dosage form. Migration of the additives within the drug delivery system should be avoided to maintain the performance of the dosage form.

1.2.2. Polymers

Many pharmaceutical grade polymers have been used in controlled drug delivery systems due to their different permeabilities (34). The most common materials include hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), polyvinylpyrrolidone (PVP), and polyacrylic esters. These materials can be used as both matrix and coating materials to control drug release.

To produce the pharmaceutical dosage forms via hot-melt extrusion, a pharmaceutical grade polymer must be selected that can be processed at a relatively low temperature due to the thermal sensitivity of most drugs. The molten or soft polymer melt can function as “thermal binders and/or drug release retardants” once

the material exits the extruder and solidifies. The choice of the polymer is also based on its processability and thermal stability.

HPMC, EC, and PVP have higher glass transition temperatures, which limit their use in hot-melt extrusion processing to make solid dispersions. The acrylic polymers are amorphous and have relatively low glass transition temperatures (Tg) contributing to their thermal processability. The mechanical and thermal properties of polymers are dependent on the intermolecular attraction, the spatial symmetry and the stiffness of the side chain groups. As the side chain length of the acrylic polymer increases, the polymer molecules become spaced apart and intermolecular attraction is reduced, thus decreasing the softening point of the material. However, polyacrylic materials having side chains consisting of 12 or more carbon atoms are brittle with high glass transition temperatures corresponding to the increased side chain length.

Eudragit® RS and Eudragit® RL are acrylic and methacrylic acid esters. The structure of Eudragit® RS and Eudragit® RL differs only in the amount of the quaternary ammonium substitution, with RS being much lower than RL. Their permeability to water is unaffected by pH, but water can permeate more freely into Eudragit® RL than RS, due to the presence of the ionized quaternary ammonium groups in the polymer.

Polyethylene (processing temperature: 105~120°C), polycaprolactone (processing temperature: 60~70°C), polyvinyl acetate (processing temperature: 170°C), and cellulose acetate butyrate (processing temperature: 195°C) were used in

a melt extrusion process to prepare matrix drug delivery systems containing theophylline (35).

Poly(vinyl acetate) was used as a retardant polymer to control the drug release of theophylline from matrix tablets prepared by hot-melt extrusion. Poly(vinyl acetate) is an amorphous polymer with a glass transition temperature of 32.7°C (MW 12,000) and 35.9°C (MW 45,000) (36). Due to the low glass transition temperature of Poly(vinyl acetate), the hot-melt extrusion processing temperature was approximately 70°C.

Polyacrylic acid (PAA), an amorphous polymer, was found to have a Tg of 132°C (10). Polyethylene oxide (PEO) is a semi-crystalline thermal plastic polymer and the crystalline regions melt at an onset temperature of 62°C. The Tg of the amorphous region of PEO is around –60°C (10). Depending on the molecular weight, the melting point of PEO ranges from 60°C to 75°C (37). These polymers can also be used in the hot-melt extrusion formulation.

1.2.2. Plasticizers

The use of polymeric carriers usually requires the incorporation of a plasticizer into the formulation in order to improve processing conditions during the manufacturing of the extruded dosage form or to improve the stability and physicochemical properties of the final product.

A plasticizer is a substance or material incorporated in a material (usually a plastic or elastomer) to increase its flexibility, workability, or distensibility. In addition, a plasticizer may reduce the melt viscosity, lower the temperature of a second-order transition, or lower the elastic modulus of the product (38). When a plasticizer is incorporated into a polymer, less energy is required for molecular bond rotation, and therefore polymers become capable of flow at temperatures below their decomposition temperatures.

1.2.2.1. Plasticization mechanisms

Several plasticization mechanisms have been proposed. Briefly, they involve the lubricity theory, the gel theory, the free volume theory and the polar theory (38, 39).

In the lubricity theory, a plasticizer acts as a lubricant to facilitate movement of polymer macromolecules over each other. This reduction in intermolecular or van der Waals forces along the polymer chains gives internal lubricity and makes the polymer more flexible.

The gel theory considers the plasticized polymer to be neither solid nor liquid but an intermediate state loosely held together by a three-dimensional network of weak secondary bonding forces. These bonding forces acting between plasticizer and polymer are easily overcome by applied external stresses allowing the plasticized polymer to flex, elongate, or compress.

The free volume of an amorphous material is the volume not occupied by the molecules making up the material (40). In the free volume theory, the motion of the main chain, chain ends, and side chains bring free volume for that polymer. When plasticizer molecules insert themselves between polymer molecules, they reduce, but do not eliminate polymer-polymer contacts, thus generating additional free volume.

According to the polarity theory, the intermolecular forces between the plasticizer molecules, the polymer molecules and the polymer/plasticizer molecules must be well balanced to ensure that the gel is stable. Therefore, plasticizers contain one or more of both polar and nonpolar groups which must match the polarity of the polymer. The polarity of a plasticizer molecule depends on the presence of groups containing oxygen, phophorus and sulfur. In terms of chemical structure, a plasticizer is a polar aromatic compound comprised of polar, polarizable and nonpolar portions.

1.2.2.2. Effects of plastcizers

Plasticization exhibits several effects on a polymeric pharmaceutical product: 1) facilitates thermal processing; 2) modifies drug release from the polymeric system; 3) influences mechanical properties of the polymeric system; and 4). enhances the appearance of the dosage form.

Vitamin E TPGS (TPGS, D -α-tocopheryl polyethylene glycol 1000 succinate) has been utilized for numerous applications in pharmaceutical dosage forms. Its chemical structure contains both a polar and a non-polar moiety making it similar to a conventional surface-active agent. The chemical properties of this

distinctive compound have suggested its use as a solubilizer, an emulsifier, an absorption enhancer, and a water-soluble source of vitamin E (41). This material can decrease the glass transition temperature of the mixture of HPC and PEO and acted as a plasticizer. Repka and McGinity found that the addition of Vitamin E TPGS in a mixture of HPC and PEO decreased both the pre-die pressure and the torque of the hot-melt extrusion process, suggesting that this plasticizer facilitated the thermal processing (42).

Polyethylene glycol can function as a plasticizer to improve the stability of the polymer for hot-melt extrusion processing. It was reported that when 40% of PEG 3350 was included there was no significant difference in the weight average molecular weight of PEO following the processing. Without the addition of PEG, a 15% decrease in the molecular weight of PEO was detected (37).

The influence of a plasticizer in Eudragit® RS 30D coating layer on drug release was investigated by Bodmeier *et al*. Propranolol hydrochloride beads were coated with Eudragit® RS 30D containing TEC. A U-shape drug release was found. The release rate constant was high at low plasticizer levels, then went through a minimum plateau, and increased at higher plasticizer concentrations. The U-shaped curve could be explained that at low plasticizer levels, the latex particles were insufficiently plasticized. This interfered with the coalescence or fusion of the latex particles and resulted in the faster release. At high levels of TEC, the increase in release rate constant could be explained with the leaching out of the TEC (43).

Mehta *et al* prepared a multi-unit controlled release system of a poorly water-soluble thiazole based leukotriene D_4 antagonist containing Eudragit® L 100 55 and Eudragit® S 100 by an extrusion/spheronization technique (44). When 15% triethyl citrate, based on the Eudragit weight, was incorporated into the pellet formulation with 1:1 and 1:3 ratios of Eudragit® L 100 55: Eudragit® S 100 respectively, enhanced drug release from the pellets was observed compared with the corresponding pellets without the plasticizer. The authors attributed this result to the increased dissolution rate of the plasticized polymer.

Wu and McGinity (45) investigated the influence of a non-traditional plasticizer, methylparaben, on the release of ibuprofen from beads coated with Eudragit® RS 30D containing methylparaben. The drug release rate decreased when the methylparaben levels were increased from 5% to 15%. Wu and McGinity also investigated the influence of the non-traditional plasticizer, methylparaben, on the mechanical properties of Eudragit® RS 30D coated beads. It was found that the higher levels of the methylparaben incorporated into the film resulted in a decrease in the tensile strength of the film. The decrease was attributed to an increase in the flexibility of the polymeric films when the level of methylparaben in the polymeric dispersion was increased.

1.2.3. Thermal lubricant

1.2.3.1. Thermal lubricant and lubrication mechanism

Thermal lubricants may be defined as materials which are added into the formulation to improve its procesability (46) in the hot-melt extrusion process. Thermal lubricants decrease the melt viscosity of the materials in the formulation and reduce the friction of molten materials in the extruder during thermal processing. When added in the formulation, thermal lubricants not only enhance thermal processing but also affect the dosage form performance.

External lubricants form a thin film layer between the molten polymer and the metal surfaces of the processing equipment, which helps to prevent the composition from sticking to the machinery and thus facilitates thermal processing. Such materials have a low compatibility with the polymer and often possess polar groups to enhance their affinity to metals. These materials will normally be a fluid at processing temperatures, and should have a solubility parameter at least $3Mpa^{1/2}$ different from the polymer.

The internal lubricants comprise low molecular weight materials which promote the flow of the polymer in the melt, but unlike plasticizers they have little effect on the solid state properties. Compatibility between the internal lubricant and polymer is therefore a requirement. The internal lubricants will generally have similar solubility parameters to the base polymer, but are much less viscous at processing temperatures compared with the molten polymer.

1.2.4. Anti-oxidants

Oxidation may occur with some drugs and polymers under thermal processing conditions. To prevent thermal oxidation, antioxidants need to be incorporated into the formulation to improve stability.

1.3. Characterization of Hot-melt Extruded Polymeric Drug Delivery Systems

1.3.1. Drug release mechanisms

1.3.1.1. Factors influencing drug release

Permeability of the drug through a polymeric material is a three-part process involving dissolution, migration and diffusion of the drug molecules as a function of solubility and the diffusion coefficient.

Temperature influences the drug release rate by changing the polymer microstructure. Below the glass transition temperature, there is a reduction in "free volume" and the polymer segments have little mobility. This means that not only are there less voids, but also a diffusing particle will have a more tortuous path to penetrate through the polymer.

Crystalline structures of a polymer have a much greater degree of molecular packing. The individual lamellae can be considered as almost impermeable so that diffusion can occur only in amorphous zones of imperfection. Hence, crystalline

polymers will tend to resist diffusion more than either rubbery or glassy polymers with the same chemical structure.

1.3.1.2. Mathematical models

Several mathematical models as seen in Table 1.3.1 have been proposed to investigate the drug release mechanism, including the Higuchi equation (47), zero order equation, first order equation (48), the Hixson-Crowell equation (49), the Korsmeyer-Peppas equation (50-52), and the Baker-Lonsdale equation (53). The Hixson-Crowell equation indicates an erosion-dependent release mechanism in which the release rate is controlled by the dissolution rate of the drug particles and the Higuchi equation describes a diffusion release mechanism.

Griffin proposed a dual equation combining first-order and square-root-of-time release kinetics to fit the drug release profiles from various multiparticulate controlled release dosage forms containing a lipophilic coating layer. The statistical output from nonlinear regression software suggests that this equation describes the data better than the individual equations alone (54).

It was observed that the release profiles from the extrudates containing ditiazem hydrochloride and Eudragit® RS PM were biphasic with a rapid release of the drug easily accessible at the surface of the pellets and a slow second phase where diffusion prevails. A double exponential equation $M = A_0 (1-e^{-\alpha t}) + B_0 (1-e^{-\beta t})$ was used by N. Follonier *et al* (55).

1.3.1.3. Dissolution profile comparison

The dissolution profile comparison may be carried out using a model independent method as suggested by the FDA by calculating the similarity factor f_2 value, which is a logarithmic reciprocal square root transformation of the sum of the squared differences in drug release percentage for the two delivery systems (56).

$$f_2 = 50 \times \log\left\{\left[\left(1+\frac{1}{n}\right)\sum_{t=1}^{n}(Rt-Tt)^2\right]^{-0.5} \times 100\right\}$$

where n is the number of time points, R_t is the release percentage of the reference batch at time t, and T_t is the release percentage of the test batch at time t. Two dissolution profiles are declared similar if f_2 is greater than 50.

1.3.2. Crystallinity

1.3.2.1. X-ray diffraction

X-ray diffraction can be used to study the crystallinity of materials. In X-ray diffraction, the average degree of crystalline order is measured with a lower limit of detection around 10% (57). Some drugs may exist in more than one crystalline form and exhibit polymorphic characteristics. Polymorphs generally have different solubilities, melting points, and X-ray diffraction patterns, even though they are chemically identical. Crystalline molecules of a drug form a compact crystal with high lattice energy and consequently low solubility. However, amorphous drugs have higher solubilities. Hot-melt extrusion processing can transform crystalline drugs into

amorphous forms. This is the fundamental theory for using the hot-melt extrusion technique to improve the bioavailability of poorly-water soluble drugs. The absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous form rather than a crystalline form. The presence or absence of crystallinity can be confirmed by examining the X-ray pattern of the hot-melt extrudate.

1.3.2.2. Raman spectroscopy

FT-Raman spectroscopy provides molecular information about both the crystalline and the amorphous phases. It has recently been used to quantify mixtures of polymorphs, utilizing distinct spectral peaks characteristic of each form or factor analysis techniques. One advantage of FT-Raman spectroscopy is that no sample preparation is necessary, thus, the likelihood of inducing phase changes through processing is reduced. However, sample heating is a well-known problem associated with laser Raman spectroscopy, which could result in crystallization of the sample. Non-homogeneities in mixing are another source of error in quantitating the degree of crystallinity (58).

Results from the DSC measurements should be interpreted with caution since changes in the physical state of solid dispersions may occur during heating, and the presence of the polymer may influence the melting behavior of the drug e.g. through melting point depression. Thus the Raman results are considered to be a more reliable

indicator of the solid-state modification of the drug present in the solid dispersions since they are obtained at room temperature and involve minimal sample handling.

1.3.3. Microstructures

Unique microstuctures are formed during hot-melt extrusion processing as a result of temperature and pressure on the material as it passes through the heating zones of the extruder. The microstructure of the extruded materials will influence the drug release properties of the delivery system. Scanning electron microscopy can be employed to investigate the microstructure and to distinguish between a solid solution and a solid dispersion.

1.3.4. Drug and polymer interaction

Drug and excipient interaction influences the drug release mechanisms. The adsorption phenomenon is one example of the drug and excipient interaction. Physical adsorption is due to electrostatic interactions, hydrogen bonding or van der Waals forces and is usually reversible; while in chemical adsorption, the adsorbate is attached to the adsorbent by primarily chemical bonds, including ion exchange, protonation and complexation, and is irreversible (59). The extent of adsorption depends on the physicochemical properties of both the drug and the excipient.

Eudragit® RS and Eudragit® RL are copolymers contain a low level of quaternary ammonium groups. The presence of both reversible and irreversible binding between salicylic acid and Eudragit® RL was reported, suggesting more than

one type of binding interaction (59). The reversibility of salicylic acid binding with a change in ionic conditions supported the theory that the drug interacted with these polymers primarily via ionic electrostatic interactions. Dissolution release profiles for both drugs were directly correlated to drug-polymer interactions. Decreases in pH or increases in ionic strength that minimized ionization of the drug resulted in decreased drug sorption and increased drug release from the films.

Interactions between indomethacin and Eudragit® RL were found to follow a type I Langmuir equation (60) and it is too high to get a 100% drug release (61). For Eudragit® RS 100, due to its relatively lower amount of the quaternary ammonium groups than Eudragit® RL, it was reported that no strong interaction between indomethacin and Eudragit® RS 100 was observed from the IR spectra of indomethacin, indomethacin and Eudragit RS 100 physical mixture, corecipitates, as well as solid dispersions (62).

In order to investigate the interaction between drugs and Eudragit® RL or Eudragit® RS resins under physiological conditions, molecular dynamics simulations were performed on systems containing water molecules, Eudragit® molecule fragments and furosemide, indomethacin, nicotinamide or etilefrine as model drug molecules. The interaction energies were monitored as well as the drug–Eudragit® distances to quantify and visualize the amount of drug binding. The nature of the calculated intermolecular interactions was examined by separate evaluation of H-bonding, ion–ion (electrostatic) and hydrophobic (van der Waals) interaction energies. It could be shown that van der Waals, electrostatic and H-bond energies may lead to a

great portion of furosemide and indomethacin binding to Eudragit® RL rather than to Eudragit® RS. Nicotinamide and etilefrine showed no tendency to interact with the molecule fragments of the Eudragit® resins. The calculated results were verified by experimental determinations of the amount of drug binding to Eudragit® RL and Eudragit® RS in isotonic pH 7.2 buffer solution after an equilibration period of 24 h. The amounts of drug binding to Eudragit® RL were 93.1% for furosemide and 72.4% for indomethacin, whereas the amounts of drug binding to Eudragit® RS were 31.4% for furosemide and 26.5% for indomethacin. No drug binding to the Eudragit® resins was observed for nicotinamide and etilefrine. The experimentally obtained binding rates were in excellent agreement with the calculated binding energies. This may be interpreted as an indication for the correctness of the proposed intermolecular interaction mechanisms between the four model drugs and the Eudragit® resins in the presence of water (63).

For the adsorption-desorption effect of cellulose-like biopolymers such as chitin, chitosan, and microcrystalline cellulose on indomethacin, the adsorptive capacity was ranked in the order: chitosan greater than chitin greater than microcrystalline cellulose. All the adsorption isotherms were found to follow the Langmuir and the Freundlich equations. However, chitosan-acetate gel powders and chitosan powders with pre-added acetic acid and methanol did not follow these equations, due to gel formations that led to more adsorption of indomethacin on the interlayer space of the gel. The strong adsorption of indomethacin onto chitosan might result in difficult desorption of the drug from the poymer (64).

1.3.5. Characterization of polymers

1.3.5.1. Light scattering

Light scattering is a technique widely used to characterize polymeric materials. Lasers are used as light sources in order to measure scattering at small angles to the beam. This is important since the data obtained must be extrapolated to zero concentration and zero-scattering angle using Zimm plots. The weight-average molecular weight is determined by this technique. Dynamic light scattering has been used to determine the number-average molecular weight and molecular weight distribution of polymers in solution (65, 66).

1.3.5.2. Other methods

The change in the molecular weight of Eudragit® RS in microspheres was determined by a sedimentation equilibrium ultracentrifugation technique using a Beckman ultracentrifuge. The weight average molecular weight determined was 10,000. Following irridiation this value had increased to 12,000 (67).

Colorimetric ion-pair complexation method has been developed which provides a simple and rapid way of quantifying Eudragit® RS100 and RL100 in pharmaceutical dosage forms (68). The quaternary ammonium groupings in these polymers appear to form an ion-pair complex with the dye tropaeolin OOO. When extracted into an organic phase, the optical density at 484 nm was linearly related to

polymer concentration. Good reproducibility, precision, and accuracy were demonstrated when the method was applied to a film-coated pellet formulation containing an interfering drug (promethazine hydrochloride). The method was sufficiently sensitive for the determination of polymer on a single dose unit of encapsulated beads.

1.4. Characterization of Thermal Processing

1.4.1. Plasticization efficiency

Plasticization efficiency and polymer miscibility are two considerations when selecting an appopriate plasticizer material. These two properties are depending upon their chemical structures. One way to evaluate plasticization efficiency and miscibility is to determine the glass transition temperature (Tg) of the blend of the materials by differential scanning calorimetry (DSC). The phase behavior may be conveniently determined by using the well-know single glass transition temperature criterion. When the glass transition of the mixture is intermediate to that of the individual components, this can often be used as an indication of miscibility (10). For an exacting polymer blend system where the Tg values of the two polymers are virtually coincident or similar, the aging studies are an additional useful technique to study polymer-polymer miscibility (69). Plasticization efficiency can be deteremined by measuring the glass transition temperature (Tg) as a function of plasticizer

concentration in the polymer. The glass transition temperature of two miscible materials can also be predicted by using the Gordon-Taylor equation (70).

1.4.2. Thermal processing temperatures

An attention must be paid when selecting a temperature to thermally process the drug and polymer. High processing temperatures are detrimental to the formulation components, whereas low temperatures make thermal processing hard to conduct due to the high resistence force of the unmelted or high viscosity materials exerted on the machinary. In order to maintain the thermal and chemical stability of the formulation and also the ideal thermal processibility, the type and level of thermal processing aids, including plasticizers and thermal lubricants, are needed to optimize the thermal processing temperatures. The temperature range used for extrusion is typically 50 to 100°C above the Tg of the polymer (71).

1.4.3. Melt-viscosity

High molecular weight polymers (between about 10,000 and 40,000) usually generate high melt-viscosity due to the macromolecules are linked to their neighbors at many points. Melt-viscosity of the materials in the formulation is directly related to its thermal processability. High melt-viscosity results in a greater force requirement by the machinery to process the material and can result in poor product quality or even equipment damage. If the melt viscosity of the material is too low,

however, the final extrudate will lack the desired shape, size and appearance. Measurement of the force required to process the material (torque or amp) aids in the selection of the processing conditions for appropriate melt viscosity.

In addition to the molecular weight and structure of the polymer, the rheological properties of polymer melt also depend upon processing temperature, pressure, the rate of shear, as well as upon the incorporation of various additives (46), which may provide us some solutions to enhance the thermal processing.

1.5. Pharmaceutical Application of Hot-melt Extrusion

Compared to the long history and wide application of hot-melt extrusion in the plastics industry, the use of this technology in the pharmaceutical industry is still at an early age. The pioneer research on the applications of hot-melt extrusion to prepare pharmaceutical dosage form was first reported by Speiser and coworkers in 1971 (72). They prepared sustained drug delivery systems containing some thermally stable epoxy resins by hot-melt extrusion.

Follonier *et al* investigated several ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials (73). To investigate hot-melt extrusion as a new technique for producing sustained-release polymer-based pellets with a high loading of a freely soluble drug, four polymers and diltiazem hydrochloride as the model drug were

considered for the extrusion trials. Surface appearance of various formulations was examined and the porosity assessed by means of mercury porosimetry. The pellets produced exhibited a generally smooth surface and low porosity. A distinct structure was found for the poly(ethylene-co-vinyl acetate) (ethylene-vinyl acetate copolymer; EVAC)-based pellets. The overall porosity was less than 10%. In vitro release of the drug showed a biphasic profile with a slow diffusion-controlled phase following a much faster release. The release of diltiazem hydrochloride from EVAC-based hot-melt extruded pellets of size 2x2 mm was less than 20% in 8 hours. The EVAC-based extrusion seemed most promising for further studies because of its low extrusion temperature, ease of processing, and slow release characteristics. It was concluded that hot-melt extrusion could be a simple method for producing sustained-release pellets with high loading of a freely soluble drug.

Zhang and McGinity investigated the properties of polyethylene oxide (PEO) as a drug carrier and the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets prepared by hot-melt extrusion. CPM and PEO were shown to be stable under the processing conditions. The molecular weight of the PEO, the drug loading percentage, and the inclusion of polyethylene glycol as a processing aid, were all found to influence the processing conditions and the drug release properties of the extruded tablets. Faster release of CPM from the matrix tablets was observed in acidic medium than in purified water and phosphate buffer (pH 7.4). Drug release from the matrix tablet was controlled by erosion of the PEO matrix and the diffusion of the drug through the swollen gel layer at the surface of the tablets. CPM was dispersed at

the molecular level in the PEO matrix at low drug loading level and recrystallization of CPM was observed at high drug loading levels (37).

Zhang and McGinity have also investigated the properties of hot-melt extruded theophylline tablets containing poly(vinyl acetate) and the drug release mechanism of theophylline from matrix tablets prepared by hot-melt extrusion (36). The cylindrical extrudates were either cut into tablets or ground into granules and compressed with other excipients into tablets. Due to the low glass transition temperature of the PVAc, the melt extrusion process was conducted at approximately 70°C. Theophylline was present in the extrudate in its crystalline form and was released from the tablets by diffusion. The Higuchi diffusion model and percolation theories were applied to the dissolution data to explain the drug release properties of the matrix systems. The release rate was shown to be dependent on the granule size, drug particle size, and drug loading in the tablets. Water-soluble polymers were demonstrated to be efficient release rate modifiers for this system.

Liu and McGinity have investigated the influence of formulation factors on the physical properties of hot-melt extruded granules and compressed tablets containing wax as a thermal binder/retarding agent, and compared the properties of granules and tablets with those prepared by a high-shear melt granulation method (MG) (74). Powder blends containing phenylpropanolamine hydrochloride, Precirol® and various excipients were extruded in a single-screw extruder at open-end discharge conditions. The extrudates were then passed through a 14-mesh screen to

form granules. The extrusion conditions and the optimum amount of wax to function as the thermal binder were dependent on the properties of the filler excipients. At the same wax level, drug release from tablets decreased in the order of using microcrystalline cellulose (MCC), 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. Replacing Precirol® with Sterotex® K, a higher melting point wax, resulted in slightly increased dissolution rates, when the extrusion was performed at the same temperature conditions. Hot-melt extruded granules were observed to be less spherical than high-shear melt granules and showed lower values of bulk/tap densities. However, tablets containing MCC or lactose granules prepared by hot-melt extrusion (HME) exhibited higher hardness values. Slower drug release rates were found for tablets containing MCC by HME compared with MG. 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.

An implant delivery system containing Melanotan-I, a superpotent tridecapeptide, and a biodegradable poly(D,L-lactide-co-glycolide) (PLGA) copolymer was prepared by the hot melt-extrusion method at the operating temperature of 45–70°C (75). The PLGA polymers meet the requirements needed for a matrix delivery system, including mechanical properties, biodegradability, tissue

compatibility and ease of processing. The drug released from the depot implanted subcutaneously in guinea pigs exhibited a release profile extending over one month, in agreement with data from the in vitro studies.

Hot-melt extrusion was used to prepare solid dispersions for poorly water-soluble drug to improve the drug dissolution. 17 β-estradiol hemihydrate has a water solubility of 0.2-5μg/ml. A solid dispersion of this drug with PVP and Gelucire was prepared by hot-melt extrusion. The amount of drug released in pH 1.0 hydrochloric acid water solution from a solid dispersion containing 10% of 17 β-estradiol hemihydrate, 50% PVP and 40% Gelucire 44/14 was significantly higher compared to the pure, non-micronized drug (76).

Forster *et al* reported that hot-melt extrusion can be used to enhance the bioavailability of poorly water-soluble drugs, including indomethacin, lacidipine, nifedipine and tolbutamide (77). Melt extrusion of these four poorly water-soluble drugs with PVP and PVP/VA resulted in glass solution formation depending on the temperature of the melt extrusion. When the temperature of the extrusion was too low, crystallinity was detected by powder XRD and DSC indicating incomplete melting of the drug.

Repka and McGinity have investigated the influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot-melt extrusion (78). Hydroxypropylcellulose (HPC) films containing drugs with either hydrophilic or hydrophobic plasticizers were prepared by a hot melt extrusion

process. Polyethylene glycol 8000 (PEG 8000) 2%, triethyl citrate (TEC) 2%, acetyltributyl citrate (ATBC) 2%, and polyethylene glycol 400 (PEG 400) 1% were the plasticizing agents studied. In addition, either hydrocortisone 1% or chlorpheniramine maleate (CPM) 1% was incorporated into the films as the model drug. The glass transition temperatures initially decreased with the inclusion of the drugs and plasticizers, however, after 6 months aging, films containing PEG 400 and hydrocortisone showed a marked increase in Tg. The films containing PEG 400 showed physical-mechanical instability in all parameters studied. All extruded films exhibited a marked decrease in tensile strength in contrast to a large increase in percentage elongation when testing was performed perpendicular to flow versus in the direction of flow. In addition, a consistent film of HPC in the absence of drugs or plasticizers could not be extruded due to the excessive stress on the equipment. Although the percentage of CPM on aging remained fairly constant over the processing temperature ranges in this study, the hydrcortisone levels remaining in the extruded films during storage, demonstrated as a function of time and temperature.

The influence of chlorpheniramine maleate (CPM) on the chemical and physical-mechanical properties of hydroxypropylcellulose (HPC) hot-melt extruded films containing CPM in concentrations of 1, 5, and 10 wt% was investigated. CPM functioned as an effective plasticizer, increasing percent elongation and decreasing tensile strength in a concentration dependent manner. All three concentrations of extruded films exhibited a 10- to 12-fold decrease in tensile strength in contrast to a fourfold increase in percent elongation when testing was performed perpendicular to

flow vs. in the direction of flow. The drug was also shown by XRD and DSC data to be in solution in the HPC matrix films up to the 10% level. In addition, CPM functioned as a processing aid in the extrusion of hot-melt films by stabilizing the weight-average molecular weight of HPC and allowing for film processing at lower temperatures (79).

Films containing hydroxypropylcellulose (HPC) and polyethylene oxide (PEO) were prepared with and without Vitamin E TPGS as an additive. Conventional plasticizers including polyethylene glycol 400 (PEG 400), triethyl citrate (TEC), and acetyltributyl citrate (ATBC) were also incorporated into films containing a 50:50 blend of HPC and PEO. The addition of 1, 3, and 5% Vitamin E TPGS, respectively, 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. In addition, the presence of 3% Vitamin E TPGS lowered the T_g over 11°C when compared with the HPC/PEO 50:50 blend film without TPGS, thus functioning as a plasticizer. The tensile strength decreased with increasing concentrations of TPGS, and the percentage elongation increased over 3-fold when compared with the HPC/PEO film that contained no additives. The film containing 3% Vitamin E TPGS had a similar tensile strength to that of the films containing 3% PEG 400, and a 3-fold increase in percent elongation when compared with the films containing 3% TEC and 3% ATBC. In addition, the Vitamin E TPGS facilitated the processing of the HPC/PEO films by decreasing the barrel pressure, drive amps, and torque of the extruder equipment (42).

The moisture absorption, physical-mechanical, and bioadhesive properties of hot-melt extruded hydroxypropylcellulose (HPC) films containing polymer additives were investigated. These additives included polyethylene glycol (PEG) 5%, polycarbophil 5%, carbomer 5%, Eudragit® E-100 5%, and sodium starch glycolate (SSG) 5%. Although all films studied exhibited an increase in percent water content as the percent RH increased, the SSG containing film exhibited an almost three-fold increase in percent water content compared to that of the HPC/PEG film. The temperature storage condition of 40°C/100% RH (versus 25°C/100% RH) increased the percent water content of the SSG containing film. Percent elongation was highest for films containing polycarbophil 5% (without PEG). In addition, the HPC film containing polycarbophil 5% exhibited a greater force of adhesion and elongation at adhesive failure in vivo, and a lower modulus of adhesion when compared to the HPC/PEG film (80).

The in vivo bioadhesive properties of hydroxypropylcellulose (HPC) hot-melt extruded films containing seven polymer additives on the epidermis of 12 human subjects was investigated. HPC films containing polyethylene glycol (PEG 3350) alone, Vitamin E TPGS (TPGS) 5%, sodium starch glycolate 5%, Eudragit E-100 5%, carbomer® 974P and 971P 5%, and polycarbophil 5%, all with and without plasticizer, were prepared by hot-melt extrusion. The carbomer® 971P and polycarbophil containing films were determined to have the highest force of adhesion and elongation at adhesive failure, and the lowest modulus of adhesion of all films

tested. The film containing carbomer 971P had a higher force of adhesion than the film containing 974P. In addition, films in one ethnic sub-group exhibited higher force of adhesion and elongation at adhesive failure than the other. Force–deflection profiles obtained from these experiments indicate that the force of adhesion, elongation at adhesive failure and modulus of adhesion are a function of the polymer additive in the HPC extruded films. The incorporation of carbomer® 971P and a polycarbophil into HPC films increased bioadhesion significantly when compared to the film containing HPC and PEG 3350. Differences in force of adhesion and elongation at adhesive failure were discovered between two ethnic sub-groups tested (81).

1.6. Challenges with the Hot-melt Extrusion

1.6.1. Characterization of the hot-melt extrudates

1.6.1.1. Thermal and chemical stability

During the hot-melt extrusion process, both polymeric materials and active drugs are subjected to both thermal stress and shear stress. The thermal stress is due to the high processing temperature associated with the hot-melt extrusion process. Depolymerization and thermal oxidation of the polymer may occur from high-temperature processing. The shear stress imposed on the polymer by the rotating

screw during the extrusion process could also induce a physical scission of the polymeric chains. A limitation to hot-melt extrusion processing is the thermal and chemical stability of the drug and the carrier. The drug may decompose or evaporate if processing temperatures exceeds certain temperature. To maintain the thermal and chemical stability of all components is one of the major concerns with this process and the selection of suitable plasticizers and thermal lubricants can achieve this goal.

Recently, hot-melt extrusion has been applied to the manufacture of solid dispersions. An important advantage of the hot-melt extrusion method over other thermal processing techniques is that the drug/carrier mixture is only subjected to heat for a few minutes, enabling both the drug and the carrier to remain thermally stable. The melt viscosity of acrylic polymers is more sensitive to temperature than that of most other thermoplastics. For accurate, consistent and reproducible results, good temperature control is required on all equipment.

1.6.1.2. Aging effect

The change in the physicochemical and the drug release properties of a polymeric drug delivery system can be contributed to the change of the physicochemical properties of both the drug and the polymer.

It is well known that the dispersed-phase particles tend to become larger on aging because the interfacial energy of the system is reduced by the concomitant reduction in interface area (11). The amorphous and other metastable crystalline forms of the dispersed drugs in solid dispersions are also subject to aging effect.

Significant crystallization rates of many materials from the amorphous state often occur above the glass transition temperature due to the existence of the sufficient molecular mobility to allow rapid nucleation and crystal growth. Water increases the crystallization rates of indomethacin from the amorphous state, presumably due to an increase in molecular mobility with a correspondingly marked reduction of Tg (82). Temperature was an important factor influencing the first-order transition rate of indomethacin from the amorphous form to the crystalline form (83).

For polymers in the formulation, the physical aging phenomenon results from the decrease in the free volume and accompanying decrease in molecular mobility (84).

Curing has been shown to reduce the permeability of an Eudragit® RS 30D polymeric film and to decrease the drug release rate constant of theophylline (85), demonstrating the aging phenomena of the polymer. For the hot-melt extrudated system, it is interesting to investigate the drug release from the extrudates following the post-processing thermal treatment.

1.6.1.3. Drug release mechanism

Following the thermal extrusion processing, the entanglement of the polymer was increased and the free volume of the extrudates was decreased. Therefore, the permeability of the drug through the polymeric system was decreased. Suitable drug release model should be explored to fit the drug release profiles. For example, the

release of diltiazem hydrochloride from hot-melt extrudated pellets containing Eudragit® RS PO followed a biexponential release behavior (73). This could be explained by the rapid release of the easily accessible drug at the surface of the pellets, followed by a slow second phase where diffusion prevails.

1.6.2. Problems with thermal processing

1.6.2.1. Processibility

Polymers behave very differently in the molten state than in solution, primarily due to the existence of the intermolecular interference from their neighbors in the molten state (71). A very important feature of high-molecular-weight polymers is their ability to be in a rubbery state, which is between the fluid state and glassy state.

Processibility is directly related to the rheological properties of polymer melt, which depend upon processing temperature, pressure, the rate of shear, the molecular weight and structure of the polymer, as well as upon the type and concentration of various additives (46).

Effect of temperature on viscosity

Under typical hot-melt extrusion processing conditions, polymer melts behave as pseudoplastic fluids. The melt viscosity is a measure of the frictional forces between the molecules in a liquid. The Willams-Landel-Ferry equation expresses the

viscosity at low rates of shear for amorphous polymers at temperatures less than 100°C above their Tg (86).

$$\log_{10}[\eta\ (T)/\ \eta\ (Tg)] \cong [-\ 17.44\ (T-Tg)]\ /\ [51.6+(T-Tg)]$$

where η (T) is the melt viscosity of materials at temperature T in degrees Kelvin, η (Tg) is the melt viscosity of materials at the glass transition temperature Tg in degrees Kelvin.

For polymer fluids at temperatures far above the glass transition temperature or the melting point, the viscosity follows the Andrade or Arrhenius equation:

$$\eta \cong K\ e^{E/RT}$$

where K is a constant at a given shear stress for a given polymer, E is the activation energy, R is the gas constant and T is the temperature in degrees Kelvin.

Clearly, increasing temperature is an effective means of decreasing melt viscosity in processing operation. Although the melt viscosity decreases with increasing temperature, two drawbacks are related to the increases in temperature. First, it takes time and costs money to put in and take out thermal energy. Second, excessive temperatures can lead to degradation of the polymer. There is certainly an upper limit to the processing temperature we can use for a particular polymer which depends upon the degradation temperature.

Effect of pressure on viscosity

For all fluids, viscosity increases with increasing pressure as the free volume is decreased which facilates the molecular slippage. With polymer melts, because of

their relative incompressibility, the effect becomes noticeable only at fairly high pressure (86). The pressure can be quite high in extruders and high pressure would result in slight increase in both Tg and Tm, causing the viscosity to increase tremendously as either is approached. The high viscosity due to pressure may exist, but the increase may be partly offset by viscous heating of the polymer in the equipment. The shear heating of the polymer in the equipment raises the temperature above the indicated value so that the viscosity may be lowered by an amount comparable to the increase due to the pressure. The high shear rate dependence of viscosity also obscures the effect of pressure (46).

Effect of rate of shear on viscosity

The viscosity of polymer melts is shear-rate dependent and is described by (87):

$$\eta = K\Upsilon^{n-1}$$

where η represents the viscosity of the polymer melt; Υ is the shear rate imposed on the polymer; K, an exponential function of the temperature, depends on the properties of the polymer; and n is a constant (in the range of 0.25 to 0.9 for the polymer melt) which depends only on the properties of the polymer.

A polymer melt at lower shearing rate have a higher concentration of entanglements than that at higher shearing rate. Entanglements not only increase elasticity, but they also increase the viscosity because it becomes more difficult for flow to occur by relative motion of the molecules when they are entangled (46).

Effect of molecular weight on viscosity

The relationship between the melt viscosity and the molecular weight of the polymer is governed by different equations depending upon the molecular weight of the polymer. Below a critical molecular weight, the viscosity of a molten polymer depends upon local features such as free volume, which governs the melt viscosity of small molecules and results in a practically linear dependence of viscosity on molecular weight. At molecular weight above a critical molecular weight, the entanglements of the chains with one another becomes important and the viscosity at low rates of shear depends upon weight average molecular weight to a power equal to about 3.4 or 3.5 (46, 88). A high molecular weight polymer macromolecule is linked to its neighbors at many points. The three-dimensional network is quite homogeneous, and its links can withstand high stresses without failure because the loads are statistically distributed uniformly over a large number of links (89). Therefore, higher molecular weight polymers are more viscous and difficult to extrude. For most polymers, the critical molecular weight is between about 10,000 and 40,000. For polymethyl methacrylate, the critical molecular weight is 10,400 (46).

This would make the melt processing of high molecular weight polymers an imposing task. Accordingly, hot-melt extrusion of the high molecular weight polymer is a challenge for making pharmaceutical delivery systems.

Effect of plasticizers and lubricants on viscosity

When a polymer is mixed with a plasticizer, the mixture has a Tg between the values of the two components. The W-L-F equation approximately accounts for the decrease in viscosity as a result of lowering Tg.

The function of thermal lubricants is to reduce the apparent viscosity of a polymer or to improve the surface appearance of a finished product made by extrusion.

Liquid plasticizers are used to reduce polymer Tg and processing temperature. However, difficulty in formulation mixing will occur when high levels of liquid plasticizers are used. Consequently, to enhance the thermal processibility, a solid thermal lubricant can be added to the formulation in conjunction with the liquid plasticizer to lower the melt viscosity, thereby preventing the need for high levels of a liquid plasticizer.

1.6.2.2. Miscibility

Hot-melt extrusion does not always require formulation components to be miscible, however, for the manufacture of solid solutions it is a prerequisite for the drug and the carrier to be miscible in the molten form. Poor miscibility between the drug and the carrier usually leads to a product that is not molecularly dispersed. By selecting polymeric carriers having similar solubility parameters as the drug, this problem can be solved. A single Tg determined for a blend of two materials with different Tgs indicates the thermal miscibility of the materials.

To achieve a specific drug delivery rate, sometimes more than one type of polymer needs to be incorporated into the formulation. Polymer-polymer miscibility is generally considered as a result of specific interaction between polymer segments. The specific interactions include donor-acceptor, dipole-dipole, hydrogen-bonding, ion-ion, acid-base, and ion-dipole interactions (90). It is known that proton acceptor polymer like PVP forms miscible blends with hydroxyl-containing polymers such as poly(vinyl phenol), poly(vinyl alcohol), poly(hydroxy ethyl methacrylate), etc (91). The specific interaction is hydrogen bonding. Polymer-polymer miscibility can be detected by a number of techniques such as DSC, neutron scattering, morphology studies by optical and electron microscopy, dynamic mechanical measurements, infrared spectroscopy, ultrasound, and viscometry. Miscibility characteristics of cellulose acetate phthalate (CAP) and poly(vinyl pyrollidone) (PVP) have been investigated by solution viscometric, ultrasonic, and differential scanning calorimetric (DSC) methods. The results obtained reveal that CAP forms a miscible blend with PVP in the entire composition range. Compatibility may be due to the formation of hydrogen bonding between the carbonyl group of PVP and the free-hydroxyl group of CAP (91).

CHAPTER TWO: RESEARCH OBJECTIVES

2.1. Overall Objective

The overall objective of this research project is to investigate the influence of hot-melt extrusion on the properties of polymeric controlled release drug delivery systems. This overall objective can be subdivided into the following supporting objectives.

2.2. Supporting Objectives

2.2.1. Investigate the properties of controlled release chlorpheniramine maleate tablets containing Eudragit® RS PO prepared by thermal processing

2.2.1.1. Investigate the plasticization effect of a solid drug

Eudragit® RS PO is a copolymer of acrylic and methacrylic esters with a low content of quaternary ammonium groups. It has been used to prepare matrix tablets by direct compression and wet granulation techniques. The objectives of this study were to demonstrate the influence of the *in situ* solid-state plasticization of chlorpheniramine maleate (CPM) on Eudragit® RS PO and to investigate the physicochemical properties of the resulting composite tablets.

2.2.1.2. Investigate the plasticization effect by a liquid plasticizer

A water-soluble liquid plasticizer, triethyl citrate (TEC), was selected as a candidate compound to investigate the plasticization effect on the Eudragit® RS PO by differential scanning calorimetry (DSC). These findings will be related to the results obtained from the thermal processing parameters and drug release studies.

2.2.1.3. Investigate the thermal stability

Thermal stability is a primary concern for thermal processing. The thermal stability of all the materials used in hot-melt extrusion process will be investigated by thermogravimetric analysis (TGA) and HPLC. The materials include CPM, TEC and Eudragit® RS PO.

2.2.1.4. Investigate the preparation techniques on drug release

Drug release rate is one of the most important parameters for a polymeric drug delivery system. The influences of TEC level and CPM level on the drug release from directly compressed tablets, tablets made from hot-melt granulation, and hot-melt extruded tablets will be investigated to compare the influence of processing on the rate and mechanism of drug release.

2.2.1.5. Quantitate of the TEC leached from the hot-melt extrudates during dissolution testing

Leaching of TEC from Eudragit® RS 30D film coatings has been reported in the literature, suggested that TEC may also leach from the hot-melt extrudates. Determination of the amount of TEC released from the extrudates will aid in

understanding of the drug release mechanism. A HPLC method will be developed to determine the amount of TEC released from the hot-melt extrudates.

2.2.2. Investigate the influence of post-processing thermal treatment on the properties of controlled release CPM tablets containing Eudragit® RS PO prepared by thermal processing

2.2.2.1. Investigate the post-processing thermal treatment on drug release

In addition to hot-melt extrusion and hot-melt granulation, curing or post-processing thermal treatment will be employed to facilitate the aging process. Curing at temperatures above the glass transition temperature of a coating polymer significantly enhances film formation by ensuring full coalescence of the latex particles. Curing has been shown to reduce the permeability of the film and to result in a decrease in the drug release rate constant. It was also reported that post-thermal treatment of tablets containing poly(DL-lactic acid) (PLA) at temperatures above the Tg of PLA significantly reduced the drug release rate from the matrix tablets.

High shear hot-melt granulation and hot-melt extrusion are two thermal processing techniques that utilize different temperature ranges. Both techniques will be employed to prepare the CPM tablets resulting in different polymeric structures. Curing these tablets and determining the drug release rate will facilitate in understanding of the effect of these two thermal processes on the rates and mechanisms of drug release.

2.2.2.2. Investigate the microstructures of the hot-melt extrudates

High shear hot-melt granulation and hot-melt extrusion techniques result in products having unique microstructures which influence drug release profiles. Scanning electron microscopy (SEM) was used to investigate the microstructures of the polymeric drug delivery systems after thermal processing.

2.2.2.3. Investigate the crystallinity of the hot-melt extrudates

Changes in CPM crystalline structure following thermal processing of the acrylic drug delivery systems was investigated using powder X-ray diffractometry.

2.2.3. Investigate the influence of a lipophilic thermal lubricant on the processing conditions and drug release properties of chlorpheniramine maleate tablets prepared by hot-melt extrusion

To facilitate the hot-melt extrusion thermal processing a pharmaceutical thermal lubricant, glyceryl monostearate (GMS), will first be used in hot-melt extrusion processing. The influence of GMS level on the properties of the chlorpheniramine maleate (CPM) controlled release tablets prepared by hot-melt extrusion will be studied. The melt viscosity, processing amps, and pre-die pressure will be recorded to investigate the influence of GMS on the processibility. Dissolution rate, GMS and Eudragit® RS PO compatibility, drug amorphous state and microstructure of the extrudate will also be investigated to explain the thermal lubrication mechanism and drug release properties.

2.2.4. Investigate the influence of plasticizers on the dissolution properties of a highly water-soluble drug from Eudragit® RS 30 D coated pellets and hot-melt extruded tablets containing Eudragit® RS PO

The influence of plasticizer level on Eudragit® RS PO were investigated for two thermal processes: hot-melt extrusion and film coating. Formulations containing diltiazem hydrochloride (DTZ), a highly water-soluble model drug, was hot-melt extruded. Additionally, pellets containing DTZ were film coated with Edragit® RS 30D containing different plasticizer levels in a fluidized bed coating machine. For highly water-soluble drugs, much attention should be given to minimize the burst effect, which is a fast release phenomenon during the early releasing time of the controlled release dosage forms. DSC was employed to investigate the plasticizing effect of DTZ, and TEC on Eudragit® RS PO. TGA was used to study the thermal stability of the model drug and the plasticizers. A HPLC method was qualified to measure the amount of DTZ released from the delivery systems, as well as to monitor the chemical stability of the DTZ in the hot-melt extrudates. SEM was employed to investigate the coating film formation and the microstructure of the hot-melt extrudates. X-ray diffractometry was used to investigate the crystallinity of the model drug following hot-melt extrusion.

2.2.5. Investigate the properties of polymeric delivery systems containing a poorly water soluble drug and Eudragit® RD 100 prepared by hot-melt extrusion

Formulation of poorly water-soluble drugs for oral delivery presents a challenge to pharmaceutical scientists. The solid dispersion technique is one of the most readily used methods to improve drug dissolution rate. The major concerns with solid dispersions are in the ability to scale-up the manufacturing process and to preserve the physical stability of the dispersions. The application of the hot-melt extrusion technique to produce solid dispersions is a particularly important breakthrough for the scale-up of solid dispersion manufacturing. The recrystallization of the water insoluble drug from the supersaturated solid solution can be inhibited by incorporation of some polymers, such as PVP.

Indomethacin (IDM), a poorly water-soluble, non-steroidal anti-inflammatory agent was used as a model drug to polymeric solid dispersions by hot-melt extrusion. DSC was employed to investigate the plasicizing effect of IDM on Eudragit® RL PO. Drug and polymer interaction was studied by determining the adsorption of the IDM on the polymer. Drug release mechanism was investigated. TGA was used to study the thermal stability of the model drug, and a HPLC method was developed to determine the chemical stability of the model drug following thermal processing. SEM was employed to investigate the microstructure of the hot-melt extrudates, and

X-ray diffractometry was used to investigate the crystallinity of the model drug following hot-melt extrusion.

CHAPTER THREE: MATERIALS AND METHODS

3.1. Materials

The thermal acrylic polymers that were selected for this study included Eudragit® RS PO, Eudragit® RL PO, Eudragit® RD 100, Eudragit® S 100, Eudragit® L 100, and Eudragit® RS 30D. They were donated by Röhm America, Inc. (Piscataway, NJ).

Eudragit® RS PO and Eudragit® RL PO are copolymers of acrylic and methacrylic esters. These polymers have a similar chemical structure. However, Eudragit® RS PO has a lower content of quaternary ammonium groups than Eudragit® RL PO, therefore, Eudragit® RS PO has a lower water permeability than Eudragit® RL PO. They are used for controlled drug release.

Eudragit® RD 100 contains 91% of Eudragit® RL PO and 9% of sodium carboxymethylcellulose. This material is currently used for the film coating of immediately release solid dosage forms.

Eudragit® L 100 and Eudragit® S 100 are anionic copolymers containing methacrylic acid and methyl methacrylate with a carboxyl acid functional group. The ratio of the free carboxyl groups to the ester groups is approximately 1:1 in Eudragit® L 100 and about 1:2 in Eudragit® S 100. Therefore, Eudragit® S 100 has a lower

permeability than Eudragit® L 100. Three model drugs, including chlorpheniramine maleate (CPM), diltiazem hydrochloride (DTZ), and indomethacin (IDM) were purchased from Spectrum Quality Products, Inc. (Gardena, CA). The other materials were kindly supplied by various manufactures: triethyl citrate (TEC), Morflex, Inc. (Greensboro, NC); Cab-O-Sil M-5P, Cabot Corporation (Tuscola, IL). glyceryl monostearate (GMS), Condea Vita Company (Westwood, NJ); Altalc 500V, Luzenac America, Inc. (Englewood, CO); Lactose monohydrate, Foremost Farms USA, (Baraboo, WI); PVP 90F, BASF, (Ludwigshafen, Germany). Pluronic® F68, BASF (Mt. Olive, NJ); Avicel® PH-101, FMC Corporation (Newark, DE); L-HPC LH-21, Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan).

3.2. Methods

3.2.1. Preparation of hot-melt extruded tablets

A dry powder blend of CPM, or DTZ or IDM, and Eudragit® RS PO or Eudragit® RD 100 was mixed using a Model RSI 3VG Robot Coupe Vertical Batch Processor (Robot Coupe Scientific Industrial Division, Ridgeland, MS) for 2 minutes. Varying amounts of TEC, 0%, 4%, 8% (7% TEC for CPM, since CPM had a solid-state plasticization effect on the polymer and made the polymer sticky when more than 7% TEC was used) were added to the dry powder blend at the speed of 1500rpm, and mixed for additional 2 minutes. The TEC plasticized powder blends were added to the hopper of a vertical single screw Randcastle Model RCP-0750 Microtruder®

(Randcastle Extrusion Systems Inc., NJ) with a screw diameter of 0.750 inches and a working length to diameter ratio of 24 (Randcastle Extrusion Systems Inc., NJ). The operating temperatures for DTZ, CPM and IDM at different zones of the extruder are listed in Table 3.2.1. The screw rotation speed was 20rpm and the cylindrical die diameter was 6.0mm. CPM, DTZ, and IDM hot-melt extrudates were produced at the opening of the die and were cut manually into tablets with a weight of approximately 100mg.

3.2.2. Preparation of hot-melt extruded granules

Hot-melt extruded granules containing CPM were made with a model RCP-2.0 Pelletizer (Randcastle Extrusion Systems Inc., NJ) by pelletizing the hot-melt extrudates prepared by the process described in section 3.2.1.. Granules in the 20-40 mesh range (850-425μ) were retained for further evaluation.

Hot-melt extruded granules containing IDM were reduced in size using a mortar and pestle. Granules measuring 20-40 meshes and 40-60 meshes were retained for further evaluation.

3.2.3. Preparation of high shear hot-melt granules

Granules were prepared by a high shear hot-melt granulation process using a Robot Coupe Vertical Batch Processor (Model RSI 3VG, Robot Coupe Scientific Industrial Division, Ridgeland, MS). Three S-blades were assembled in the three-liter

stainless steel chamber. The processing temperature was maintained at 60°C by circulating Thermal M fluid (100°C) (Julabo USA Inc., Kutztown, PA) in the jacket surrounding the chamber. The temperature inside the chamber was monitored using a thermal probe. The CPM and Eudragit® RS PO were blended at a speed of 1500rpm for two minutes. During this time, TEC was also incorporated into the powder blend. The blended material was heated until granules were formed between 60°C and 70°C. After mixing for 10 minutes, the granules were cooled to 25°C. Granules in the 20-40 mesh range (850-425μ) were retained for further study.

3.2.4. DTZ beads preparation

A dry powder blend of diltiazem hydrochloride (30%), lactose monohydrate (32%) and Avicel® PH-101 (35%) was mixed for 20 minutes using a twin-shell blender. 3% PVP 90F (in 10% water solution) as granulating binder was added during the wet massing process. The moistened mass was extruded using a LCI Benchtop Granulator (LCI Corp., Charlotte, NC) with a screen opening of 1.0mm. The rotation speed of the impeller was controlled at 25rpm. The extrudates were spheronized using a Caleva Model 120 Spheronizer (G. B. Caleva Ltd., Dorset, England) by setting the spheronization speed and residence time at 1000rpm and 5 minutes, respectively. The wet spheronized beads were then dried at 40°C for 48 hours. Beads in the particle size range of 14-20 mesh were used for coating.

3.2.5. Film-coating of DTZ beads

3.2.5.1. Procedures of preparing the coating dispersion

A suspension containing 15% solid materials was made by adding Eudragit® RS 30D, 50% Talc, and 10%, 15%, or 20% TEC in distilled water. The amount of TEC and Talc was based on the solid polymer weight. The suspension was mixed by using a stir bar for 60 minutes.

3.2.5.2. Film coating

250g of DTZ beads in the particle size of 14-20 mesh were coated with plasticized aqueous coating dispersion in an Aeromatic-Fielder AG Model Strea 1 coating machine with the coating conditions listed in Table 3.2.2.

The aqueous dispersion was stirred continuously during the coating process. The coated beads were dried on trays in an oven at 40°C for 24 hours. The dried coated beads were stored in a desiccator for further evaluation.

3.2.6. Compressed tablets preparation

High shear hot-melt granules, hot-melt extruded granules containing CPM as well as a dry powder blend of CPM and excipients including the plasticizer TEC (High shear blending was used for the incorporation of the TEC into the dry powder blend) were compressed into tablets (6mm die) on a Carver laboratory press (Fred Carver Inc.) with a compression force of 2000kg. High shear blending of the powder

mix with the TEC was conducted with a Robot Coupe Vertical Batch Processor for 2 minutes to ensure a uniform distribution of the TEC throughout the powder. The tablet weight was approximately 100mg.

Tablets containing IDM were prepared using a Carver laboratory press (Fred Carver Inc.). A blend of 250mg hot-melt extruded granules containing 75mg IDM, 225mg of Avicel® PH-101 and 25mg of L-HPC LH-21 was transferred to a 6mm die and compressed with a compression force of 400Kg. The prepared tablet weight was approximately 500mg with the hardness of about 15Kg.

3.2.7. Post-processing thermal treatment

Tablets containing CPM were placed in open glass vials and stored at 60°C. After storage for 0.25, 0.5, 1.0, 4.0, and 24 hours, the drug release properties of the tablets were determined.

3.2.8. Determination of the hot-melt extrusion processing parameters for Eudragit® RS PO

A Randcastle vertical single screw Microtruder® Model RCP-0750 (Randcastle Extrusion Systems Inc., NJ) with a screw diameter of 19.05 millimeters and a working length to diameter ratio of 24 was used to determine the processing parameters. The screw rotation speed was 20.0rpm and the die diameter was 6.0 millimeters. Both the drive AMPS and the pre-die pressure for Eudragit® RS PO were

determined during thermal processing for the formulations containing Eudragit® RS PO as a fuction of the level of TEC or GMS.

3.2.9. Determination of the hot-melt viscosity

The melt viscosity of the materials used was determined by using a model EPL-V5501 Electronic Plasti-Corder Torque Rheometer (C.W. Brabender Instruments Inc., South Hackensack, NJ). The processing temperatures of zone 1, zone 2, and zone 3 were set at 110°C, 130°C, and 140°C respectively. The rotation speed of the screw was 30rpm. Torque values were determined during the thermal processing for the powder blends containing Eudragit® RS PO with different level of TEC or GMS.

3.2.10. Particle size analysis

IDM, Eudragit® RD 100, Eudragit® RL PO was dispersed in distilled water separately in triplicate. The particle size of the materials was determined using a ZetaPlus Zeta potential Analyzer (Brookhaven Instruments Corporation, Holtsville, NY) with a BIC particle sizing software.

3.2.11. True density determination

Approximately 3-5g of IDM, Eudragit® RD 100, Eudragit® RL PO was weighed and a helium AccuPyc 1330 pycnometer (Micromeritics Instrument

Corporation, Norcross, GA) was employed to determine the true density of IDM, Eudragit® RD 100, and Eudragit® RL PO in triplicate.

3.2.12. Modulated differential scanning calorimetry

A modulated differential scanning calorimeter with a DSC 2920 Module Software Version 1.1 (TA Instruments, Model DSC 2920 Modulated DSC) was used to determine the solid-state plasticization effect of CPM on the Eudragit® RS PO, the plasticization effect of TEC on the Eudragit® RS PO, the miscibility of GMS with Eudragit® RS PO, the solid-state plasticization effect of DTZ on the Eudragit® RS PO, as well as the melting point of IDM and the solid-state plasticization effect of IDM and Pluronic® F 68 on the Eudragit® RL PO. Approximately 5-10mg of sample was accurately weighed and hermetically sealed in an aluminum pan. The sample was equilibrated at –10°C for 2 minutes. The temperature of the samples was then ramped from –10 to 160°C at a rate of 5.0°C/min. Modulation was set at +/- 1.0°C every 60 seconds. The samples were cycled twice to remove thermal history. The glass transition temperature was measured in the second cycle as the step transition in the plot of reversible heat flow vs temperature. The MDSC was calibrated using an indium standard prior to sample analysis.

3.2.13. Thermogravimetric analysis

A TGA 7 (Perkin Elmer) was employed to investigate the thermal stability of Eudragit® RS PO, Eudragit® RL PO, Eudragit® RD 100, Eudragit® S 100, Eudragit® L 100, CPM, DTZ, IDM, GMS, and TEC. Samples were maintained at 50°C for 1 minute and then heated to 600°C at a heating rate of 10°C/min. For the dynamic stability studies, samples were held at either 120°C, or 140°C, 160°C for 10 minutes and the percentage weight loss was recorded.

3.2.14. Chemical stability

3.2.14.1. Chemical stability of DTZ following hot-melt extrusion

10mg of the physical mixture and extrudate samples equivalent to about 3.0mg of DTZ prior to and following hot-melt extrusion were accurately weighed and transferred to a 100ml volumetric flask respectively. Samples were dissolved with 20ml ethanol first and then pH 7.4 phosphate buffer was added to volume. Samples were filtered with a 0.45μm nylon filter (Whatman Inc., Clifton, NJ) and determined using the HPLC method described in section 3.2.18.

3.2.14.2. Chemical stability of IDM following hot-melt extrusion

Samples were dissolved with 20ml ethanol in a 100ml volumetric flask, then pH 7.4 phosphate buffer was added. Samples were filtered with a 0.45μm nylon filter and determined by the HPLC method described in section 3.2.18.

3.2.15. X-ray diffractometry

An APD 3520 Philips X-ray diffractometer with a PW 1720 X-ray generator and a PW 1710 diffractometer control was employed to study the crystallinity of CPM, DTZ, IDM, and the model drug with Eudragit® RS PO or Eudragit® RD 100 in a physical mixture, hot-melt granules, and hot-melt extruded granules. The generator operating voltage and current were 40KV and 40mA, respectively. The scanning speed was 2°/min, and the 2θ scanning range was from 5° to 50°.

3.2.16. Scanning electron microscopy

Samples of hot-melt extrudates, hot-melt granules, and Eudragit® RS 30D coated pellets were coated with gold-palladium for 60 seconds under an argon atmosphere using a Pelco® Model 3 sputter coater (TED Pella Inc., Tustin, CA) in a high vacuum evaporator equipped with an omni-rotary stage. The morphologies of the samples were investigated by using a Hitachi S-4500 Scanning Electron Microscope (Hitachi, Ltd. Ibaraki-Ken, Japan) at 15KV at two magnifications (100X and 1000X).

3.2.17. Dissolution studies

The release of CPM, TEC, DTZ, and IDM from the sustained release tablets or granules were determined by using the VanKel 7000 dissolution system with a

VanKel 7500 temperature control system and a VanKel 8000 autosampler according to the USP methods with the experiment conditions listed in Table 3.2.3. Samples were passed through a 10μ filter and analyzed using UV or the HPLC methods described in section 3.2.18. The experiments were conducted in triplicate.

To investigate the influence of pH on the IDM release from hot-melt granules, a USP 24 apparatus III method was used with a VanKel Bio-Dis II with the following parameters. 250ml of different pH release media pH 1.2 (0~2h), pH 5.0 (2~4h), pH 6.8 (4~8h), pH 7.4 (8~12h) maintained at 37°C. Dipping rate was 20 dips per minute. Samples were collected and filtered through a 0.45μm filter at predetermined time intervals and analyzed by the HPLC method described above. The experiments were conducted in triplicate.

3.2.18. HPLC method for TEC

A HPLC method was used to determine the release of TEC from the hot-melt extrudates (92). The stability indicating HPLC methods for CPM, DTZ, and IDM were based on the USP methods (93).

The chromatographic system consisted of a Waters 501 HPLC pump, a Waters 486 tunable absorbance detector set at 220nm, a Waters 712 WISP sample injector, and a Waters C18 3.9×300mm μBondabpak analytical column (10μm). The experiment conditions are listed in Table 3.2.4. Linearity of the system was demonstrated over the working sample concentration range with a correlation

coefficient of 0.99. A lack of interference from the other ingredients was demonstrated, and the reproducibility of the system for multiple injections (n=6) was less than 0.5% relative standard deviation.

3.2.19. Adsorption of indomethacin on the acrylic polymers

2.5, 5.0, 10.0, and 15.0mL of 100.0μg/mL IDM pH 6.8 phosphate buffer solution and 17.5, 15.0, 10.0, and 5.0 mL of pH 6.8 phosphate buffer solution were added into each of the 4 test tubes respectively in triplicate. Either 0.20g of the Eudragit® RD 100, or 0.18g of the Eudragit® RD 100 and 0.02g Eudragit® S 100, or 0.18g of the Eudragit® RD 100 and 0.02g Eudragit® L 100 was added into each set of the test tubes. These test tubes were put into a shaking air bath thermostated at 37°C for 24 hours. Samples were filtered, diluted, and analyzed by UV at 318nm.

CHAPTER FOUR: RESULTS AND DISCUSSION

4.1. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate

Plasticizers are incorporated into pharmaceutical polymers to facilitate thermal processing (42), to modify drug release from polymeric systems (43, 45, 94, 95) and to enhance the mechanical properties (42, 45, 96, 97) and surface appearance of the dosage form (98). When incorporated into a polymeric material, a plasticizer improves the workability and flexibility of the polymer by increasing the intermolecular separation of the polymer molecules (39). This results in a reduction in elastic modulus, tensile strength, polymer melt viscosity and glass transition temperature (Tg). The polymer toughness and flexibility is improved and lower thermal processing temperatures can be empolyed (87). For instance, pharmaceutical polymers used in film coating typically require a plasticizer in order to reduce brittleness and to enhance polymer coalescence and film formation (99). The plasticizer reduces both the glass transition temperature of the polymer and the minimum film formation temperature. As a result, the temperature required for film coating is reduced.

In selecting the appropriate plasticizer for a polymeric material, the plasticization efficiency and compatibility must be considered which may be determined by measuring the glass transition temperature of the polymeric material as a function of plasticizer concentration. Differential scanning calorimetry (DSC) is typically used to measure the polymer glass transition temperature, however, this technique is not always sensitive enough to identify Tg's for certain polymers. Modulated differential scanning calorimetry (MDSC) has been shown to be more effective in separating thermal events, and provides greater resolution and sensitivity due to the application of a modulated rather than a linear temperature program (100, 101). A second run is performed to erase the different thermal histories of the samples (102).

Wu and McGinity reported that solid non-traditional plasticizers including methylparaben and drugs such as ibuprofen and chlorpheniramine maleate were able to plasticize and lower the glass transition temperature of polymeric films prepared from aqueous latex dispersions of Eudragit® RS 30 D (45). Eudragit® RS PO is a copolymer of acrylic and methacrylic esters with a low content of quaternary ammonium groups. It has been used to prepare matrix tablets by direct compression (103), and wet granulation techniques (104, 105).

Hot-melt extrusion is one of the most widely applied processing techniques in the plastics industry. For pharmaceutical systems, several research groups have recently demonstrated that thermal processing of pharmaceutical powders is a viable

method to prepare granules, sustained release tablets (3, 36, 37) and transdermal drug delivery systems (42, 79-81). For pharmaceutical applications, hot-melt extrusion offers many advantages over traditional processing techniques. Solvents and water are not needed for processing, therefore fewer processing steps are needed and time-consuming drying steps are eliminated. There are no requirements on the compressibility of the active ingredients and the entire procedure is simple, continuous and efficient (3).

The objectives of this study were to demonstrate the influence of the *in situ* solid-state plasticization of chlorpheniramine maleate (CPM) on Eudragit® RS PO and to investigate the physicochemical properties of the resulting composite tablets. Tablets were prepared by hot-melt extrusion and by direct compression. In addition, tablets were also compressed from granules prepared by a high shear hot-melt granulation technique. CPM was used as both a model drug and as a solid-state plasticizer in this study. A liquid plasticizer, triethyl citrate (TEC), was also incorporated into the formulations. Plasticization effect and the microstructure of these composites were investigated to explain the drug release mechanism from tablets prepared by the different technologies.

4.1.1. Plasticization and drug release

4.1.1.1. Influence of TEC concentration on drug release

The profiles in Figure 4.1.1 demonstrate the influence of TEC levels on the dissolution properties of directly compressed tablets formulated with a dry powder blend of CPM and excipients or granules prepared by high shear hot-melt granulation. Drug release was greater than 80% in 2 hours for tablet formulations containing no TEC. Tablets formulated using hot-melt granules containing no TEC released CPM faster than tablets of the dry powder blend. Due to the loss of surface moisture during the hot-melt granulation process, no interaction between drug and polymer was observed when TEC was not present in the formulation, resulting in a faster release rate of drug from tablets containing granules prepared by high shear hot-melt processing.

When TEC was incorporated into the formulations, the drug release rate decreased for both tablet preparations, as shown in Figure 4.1.1. The drug release data were fitted to the Higuchi equation (47), and the drug release rate constants were calculated and determined to be diffusion-controlled processes (106). The drug release rate constant decreased from 32.8% $h^{-1/2}$ to 28.1% $h^{-1/2}$ when the TEC level increased from 4% to 7% in the directly compressed tablet formulation. A decrease in the rate constant from 30.8% $h^{-1/2}$ to 27.9% $h^{-1/2}$ was found when the TEC level increased from 4% to 7% in compacts containing granules prepared by the high shear hot-melt process. The decrease in the drug release rate constant was due to the presence of TEC in the interstices of the polymer, to increase the binding of the drug to the polymer, thus facilitating the formation of a continuous matrix structure which would decrease the diffusivity of the drug from the system. The addition of TEC

further enhanced drug and polymer binding during thermal processing and, as a result, drug release rates from tablets formulated as a dry powder blend were faster than drug release rates from compressed tablets prepared from high shear hot-melt granules having 4% of TEC.

The influence of TEC levels on the dissolution release rate of CPM from hot-melt extruded tablets is seen in Figure 4.1.2. The drug release rate constant was calculated to be 11.7% $h^{-1/2}$ for tablets containing no TEC. When 4% and 7% TEC were incorporated into the powder blend formulation, the release rate constants for the hot-melt extruded tablets containing Eudragit® RS PO and 10% CPM were increased to 13.8% $h^{-1/2}$ and 18.6% $h^{-1/2}$, respectively. CPM drug release rates increased with increasing levels of TEC in the hot-melt extruded tablets, whereas in directly compressed tablets or tablets prepared from high shear hot-melt granules, a decrease in the drug release rate was seen. The high temperature and pressure of the hot-melt process converted the materials into a homogenous structure. For the directly compressed tablets and those prepared from the hot-melt granules, porous structures were formed. The TEC functioned to enhance the formation of a continuous matrix structure in the directly compressed tablet compact. The plasticizer also enhanced the adhesion of polymer particles in the granules prepared by the hot-melt granulation process. The water-soluble plasticizer, diffused from the hot-melt extruded tablets into the dissolution media, enhancing drug release as a result of channel formation in the tablet. This hypothesis was confirmed by determining the amount of TEC

released from the hot-melt extruded tablets during the dissolution study, and these results appear in Figure 4.1.3. The release of TEC from the hot-melt extruded tablets also followed the Higuchi diffusion model. TEC was completely released after 24 hours for the tablets containing 4% and 7% TEC. The diffusion of TEC into aqueous media from cast films prepared from aqueous colloidal polymer dispersions had previously been reported by Bodmeier and Paeratakul (107).

4.1.1.2. Influence of CPM concentration on drug release

The influence of CPM levels on the dissolution properties of tablets prepared by hot-melt extrusion is demonstrated in Figure 4.1.4. Drug release rates increased with increasing amounts of CPM in the formulation. When 6, 10 and 14% CPM was incorporated into the extruded formulation, the drug release rates were calculated to be 9.11% $h^{-1/2}$, 13.8% $h^{-1/2}$, and 20.0% $h^{-1/2}$, respectively. Higher level of CPM corresponding to lower level of the polymer in the tablet, resulted in an increase in the drug release rate. As more drug is released from the tablet, more channels are produced, contributing to faster drug release rates. In addition, higher drug levels in the extruded tablet formulation produced a higher drug concentration gradient between the tablet and the dissolution medium. According to Fick's first law, the mass flux of a component per unit cross sectional area perpendicular to the direction of diffusion is proportional to its concentration gradient (108), thus drug release rate was increased.

The influence of CPM levels on the dissolution profiles of CPM tablets prepared from the granules of the hot-melt extrudates was also investigated.

Compared with the results in Figure 4.1.4, drug release rates were faster from tablets prepared with hot-melt extruded granules than from tablets compressed with dry powder blends (Figure 4.1.5). Granulation of brittle hot-melt extrudates increased drug release after compression, due to the brittle nature of the polymer and the formation of internal cracks within the granules during the compaction process. The granules having poor cohesive properties resulted in soft tablets with large voids between the granules as observed by SEM. Drug was released rapidly through both the voids between the granules and the cracks within the granules.

In contrast, drug release from tablets prepared with granules made by the hot-melt granulation method, as seen in Figure 4.1.6, was slower than from tablets prepared by hot-melt extruded granules, as in Figure 4.1.5. The high shear hot-melt granules were more porous than the granules prepared from hot-melt extruded tablets, which contributed to the good adhesion properties of the granules prepared by high shear hot-melt granulation, resulting in harder tablets. Drug release rate from these tablets increased with increasing CPM concentration in the tablets.

4.1.2. Plasticization efficiency

The temperature and heat capacity calibration for MDSC was carried out utilizing Indium as the standard prior to sample analysis (100, 101, 109). The glass transition temperature of Eudragit® RS PO was determined to be 67.4 °C using MDSC. A value of 61.5°C determined by DSC using a scanning rate of 10°C/min has

been reported by other investigators (110). The difference between the two Tg values was possibly due to the different methodologies used to experimentally determine this property. The data in Figure 4.1.7 demonstrate that the glass transition temperatures of blends of Eudragit® RS PO and TEC decreased as a function of the percentage of TEC added to the formulations. Plasticizer efficiency is a function of the Tg of the plasticized polymer. A linear relationship between glass transition temperature and percent TEC in Eudragit® RS PO was observed within the TEC concentration range of 0% to 12%. The glass transition temperature decreased 2.70°C for each percentage of TEC present in the polymer. Above 12% TEC in the Eudragit® RS PO, the polymer agglomerated and could not be processed. A single glass transition temperature was observed for the mixtures of Eudragit® RS PO and TEC, indicating miscibility between the two materials.

As shown in Figure 4.1.7, the glass transition temperature of the acrylic polymer decreased as the concentration of CPM in the sample increased. A single glass transition temperature was also observed for the blends of Eudragit® RS PO and CPM, indicating miscibility. The glass transition temperature decreased approximately 1.31°C for each percentage of CPM in Eudragit® RS PO. These results indicated that the plasticization efficiency of CPM was approximately half that of the TEC. Both CPM and TEC exhibited a plasticization effect on Eudragit® RS PO, suggesting that lower processing temperatures can be used during hot-melt extrusion of a powder blend containing these materials.

4.1.3. Morphology studies on granules following thermal processing

The surface morphologies of drug and polymer physical blend as well as granules formed by the hot-melt processes are displayed in Figure 4.1.8. A SEM of a physical mixture of CPM and Eudragit® RS PO in Figure 4.1.8 (A) shows that particles of CPM were adsorbed on the surface of Eudragit® RS PO particles. When 4% TEC was incorporated into the physical mixture, CPM particles adhered to the swollen surface of the Eudragit® RS PO as shown in Figure 4.1.8 (B). The binding of the CPM to the acrylic polymer contributes to the decrease in drug dissolution rate as the TEC concentration in the directly compressed tablet formulation was increased. Figures 4.1.8 (C) and (D) show the SEM photographs at two magnifications of granules containing TEC plasticized CPM and Eudragit® RS PO blends prepared by a high shear hot-melt granulation process. The lower magnification photograph (C) shows a typical porous granule formed after high shear hot-melt granulation. At higher magnification (D), the porous structure of granules formed from the fusing of drug and polymer particles following thermal processing is shown. Figures 4.1.8 (E) and (F) show the SEM photographs of hot-melt extruded granules of TEC plasticized CPM and Eudragit® RS PO powder blends at two magnifications. These two photographs display a fused granule containing drug and polymer following hot-melt extrusion. These SEMs suggest a homogeneous distribution of the CPM in the acrylic

polymer and demonstrate that hot-melt extrusion technology is a thermal processing method that can be employed to prepare CPM-Eudragit® RS PO solid solutions.

It can be concluded from these studies, that controlled release matrix tablets containing CPM and Eudragit® RS PO were successfully prepared using hot-melt extrusion and high shear hot-melt granulation techniques. The effects of TEC levels on drug release rates were dependent on the thermal processing method used to prepare the solid composite. As TEC levels increased, the drug release rates decreased for tablets prepared by either direct compression or from granules made by high shear hot-melt granulation. In contrast, drug release rates increased with increasing TEC levels for the hot-melt extruded tablets. The CPM content in the tablets influenced the drug release rates from tablet formulations, resulting in an increased drug release rate with increasing amounts of CPM irrespective of preparation method. Granules prepared via high shear hot-melt granulation formed a porous discontinuous matrix structure, thus resulting in faster drug release rates. In comparison, CPM was homogenously dispersed in the hot-melt extruded tablets resulting in a slower and more controlled release of drug. The acrylic polymer was plasticized *in situ* by both the CPM and the TEC during thermal processing, and the plasticization efficiency of TEC was shown to be twice that of CPM. The influence of both CPM and TEC levels on the drug release rate from these polymeric drug delivery systems was shown to be a function of whether the granules or tablets were

formed by either hot-melt granulation or hot-melt extrusion, as well as the plasticization effects of both TEC and CPM on the acrylic polymer.

4.2. Influence of Thermal Processing on the Properties of Chlorpheniramine Maleate Tablets Containing an Acrylic Polymer

Polymer based drug delivery systems have received considerable attention in the scientific literature since polymeric carriers can be used to deliver a wide variety of drugs at a controlled rate in the gastrointestinal tract (111-114). Polymer based drug delivery systems prepared by thermal processing are gaining more attention in the pharmaceutical field. High shear hot-melt granulation (115-119) and hot-melt extrusion (3, 37, 72, 73, 78) are two procedures utilizing heat that can overcome the disadvantages of traditional processing technologies, including stability issues associated with wet granulation, as well as flowability and content uniformity problems associated with direct compression. Furthermore, no organic solvents are used in hot-melt granulation and hot-melt extrusion processes (36).

One of the greatest concerns for polymeric drug delivery systems is aging, which is a phenomenon that results in a change in drug release rate over time. Curing or post-processing thermal treatment is often employed to decrease the aging effect. Curing at temperatures above the glass transition temperature for a film coated pellet or tablet significantly enhances film formation by ensuring complete coalescence of the polymeric particles. Curing has been shown to reduce the permeability of an Eudragit® RS 30D polymeric film and to decrease the drug release rate constant of

theophylline (85). It was also reported that post-processing thermal treatment of tablets containing a pseudolatex dispersion of poly(DL-lactic acid) (PLA) at temperatures above the Tg of the polymer significantly retarded the drug release rate constant from the matrix tablets (120).

In the current study, chlorpheniramine maleate (CPM) tablets containing Eudragit® RS PO were prepared by direct compression, high shear hot-melt granulation, and hot-melt extrusion and the effects of thermal processing and post-processing thermal treatment on drug release were determined. In addition, the thermal stability of the materials used in the formulation and the crystallinity of CPM following thermal processing were investigated.

4.2.1. Influence of thermal treatment on the dissolution profiles of CPM tablets

The influence of post-processing thermal treatment on the dissolution properties of CPM from tablets prepared by direct compression of a dry powder blend of Eudragit® RS PO and CPM (10%, w/w) is shown in Figure 4.2.1. By fitting drug release profiles to the Higuchi equation (47, 106), the drug release rate constant was calculated and the results suggested that the mechanism of drug release from these tablets occurred by a diffusion-controlled process. The CPM direct compression tablets containing Eudragit® RS PO released more than 80% of the model drug within 2 hours. The drug release rate constants decreased dramatically when the tablets were stored at 60ºC, a temperature slightly above the glass transition temperature of the

tablet components (55.5ºC). By calculating the similarity factor f_2 value for the drug release profiles, before thermal treatment and post-processing thermal treatment for 24 hours, the f_2 value was less than 50. These dissolution profiles cannot be considered similar indicating that post-processing thermal treatment for 24 hours significantly decreased the drug release rate for the directly compressed tablets containing no TEC.

Omelczuk and McGinity (120) had previously reported that post-processing thermal treatment of tablets containing a pseudolatex of PLA significantly retarded the release of theophylline from matrix tablets. The retardation in theophylline release was attributed to increased tablet hardness due to increased bonding between granules. Generally, amorphous solids are not in a stable thermodynamic equilibrium at temperatures below their glass transition temperature. These materials tend to undergo slow processes to establish equilibrium indicating that even below the Tg, molecular mobility is not zero (121). This contributes to the aging phenomenon that occurs in polymeric drug delivery systems. This gradual approach to equilibrium affects many properties of the tablet, including the dissolution rate and the mechanical properties. The influence of thermal effects on the drug release profiles from polymeric dosage forms can be explained by the free-volume theory, since the transport of materials in a closely packed system depends primarily on the degree of the entanglement, or the free volume of the system (121). The free volume of an amorphous material is the volume not occupied by the molecules making up the material (40). Post-processing thermal treatment of the tablets will increase the degree

of the entanglement of tablet ingredients, and decrease the free volume of the system to cause a decrease in permeability of the polymer.

The dissolution profiles of tablets that contained 4% (w/w) TEC in the Eudragit® RS PO and 10% (w/w) CPM blend are shown in Figure 4.2.2. The addition of the plasticizer enhances the Brownian motion of the polymer segments and weakens the interaction between chains, thus increasing the interchain distance (122). The presence of the plasticizer enhances the drug and polymer intermolecular entanglements and resulted in a decrease in the drug release rate as shown in Figure 4.2.2. Thermal treatment of the tablets above the glass transition temperature of the plasticized polymer enhanced intermolecular binding and entanglement between drug and polymer molecules, thus decreasing the diffusivity of the drug from the matrix tablet. This effect was enhanced as the time of post-processing thermal treatment time was increased. After 24 hours of storage at 60ºC, the drug release rate constant was reduced from $36.2\%h^{-1/2}$ to $30.0\%h^{-1/2}$. Dissolution profile comparison also demonstrated that post-processing thermal treatment decreased the drug release rate significantly for the directly compressed tablets containing 4% TEC.

Previous research has demonstrated that TEC can leach from the CPM - Eudragit® RS PO hot-melt extrudates, resulting in an increase in the drug release rate from these extrudates (123). However, for directly compressed tablets, the influence of TEC on the entanglement of CPM in the Eudragit® RS PO system was more dramatic than the effect of the leaching of TEC, since the drug release rate constant of

the CPM from directly compressed tablets decreased from 36.2%$h^{-1/2}$ to 32.4%$h^{-1/2}$ due to the inclusion of 4% TEC. Thermal treatment of the tablets containing 4% TEC at 60ºC for 24 hours further increased the entanglement of CPM in the Eudragit® RS PO system, and decreased the drug release rate constant to 31.3%$h^{-1/2}$.

Eudragit® RS PO is a copolymer of acrylic and methacrylic esters with a low content of quaternary ammonium groups(124). Since it is a thermoplastic material, it will soften and become pliable when heated above its glass transition temperature. When the granules prepared by high shear hot-melt granulation and hot-melt extrudates of Eudragit® RS PO were cooled, the granules and extrudates solidified and retained their shape. For compressed tablets composed of 4% TEC, 10% CPM and Eudragit® RS PO granules prepared by high shear hot-melt granulation, the drug release rate constant was 30.8%$h^{-1/2}$ as shown in Figure 4.2.3. The drug release rate constant was calculated to be 30.8%$h^{-1/2}$. This is lower than the directly compressed tablets rate constant, 32.4%$h^{-1/2}$. The drug release rate decreased since the high shear hot-melt granulation process further enhanced Eudragit® RS PO intermolecular entanglement inside the granules.

Figure 4.2.3 shows the effect of post-processing thermal treatment on the dissolution profiles of CPM tablets prepared by high shear hot-melt granulation. Drug release rate constants decreased from 30.8%$h^{-1/2}$ to 26.9%$h^{-1/2}$ following 24 hours of thermal treatment, which represents a reduction of 12.6% from the tablets prior to storage at 60°C.

Powders processed by hot-melt extrusion are subjected not only to elevated processing temperatures but also to high pressure. Thus, the free volume of the system is reduced, which further retards molecular mobility (84). The drug release rate constant was decreased dramatically from 30.8%$h^{-1/2}$ to 13.8%$hr^{1/2}$ after granules composed of 4% TEC, 10% CPM and Eudragit® RS PO were prepared by hot-melt extrusion, when compared to tablets compressed from the granules processed by high shear hot-melt granulation. Hot-melt extrusion process had already decreased the free volume of the polymeric drug delivery system to a greater extent than direct compression and high shear hot-melt granulation.

The profiles in Figure 4.2.4 demonstrate the influence of post-processing thermal treatment on the dissolution properties of CPM from hot-melt extruded tablets. Post-processing thermal treatment exerted a minimal influence on the drug release rate constant of tablets prepared by hot-melt extrusion and after 24 hours curing at 60°C, the drug release rate constant decreased from 13.8%$hr^{1/2}$ to 12.8%$hr^{1/2}$. Hot-melt extrusion requires high temperature and pressure to process the powder blend into the extruded tablets. Thus, curing had minimal effects on enhancing drug and polymer entanglement and decreasing the polymer free volume. The results of this study indicated that the matrix systems prepared by hot-melt extrusion exhibited a slower drug release rate constant and post-process curing at elevated temperature had little effect on drug release. These findings suggest that tablets prepared by hot-melt extrusion will exhibit less aging effects during storage.

4.2.2. Thermal stability studies of CPM, Eudragit® RS PO and TEC

Thermal events, including melt crystallization and glass transition, do not cause a change in the mass of the sample, while other thermal changes, such as decomposition, sublimation, reduction, and vaporization are accompanied by mass changes (125). These changes are related to the thermal stability of the material. The thermogravimetric profiles of CPM, Eudragit® RS PO and TEC in Figure 4.2.5 demonstrate the change in mass of the samples as a function of temperature. For methyl methacrylate copolymers, previous research has shown that scission of polymer chains at elevated temperatures results in a monomeric product (126). The depolymerization of poly(methyl methacrylate) is a free-radical process that is initiated from the ends of the chain. Each initiated chain unzips rapidly to yield monomer formation. Thus, at any instant the system contains only unreacted polymer and monomer (127). The USP requires the determination of the content of the following monomers: methacrylic acid and either methyl methacrylate or ethyl acrylate (93). The total amount of the monomers cannot be more than 0.3%. The boiling point of methyl acrylate at 608mmHg is 70°C, which is an indication of the volatility of the monomer. As shown in Figure 4.2.5, the remaining weight percentage of Eudragit® RS PO at the temperature higher than 450ºC was zero, which is further evidence for the volatility of the monomer. As monomers are the sole volatile decomposition products of the methacrylic copolymer, determination of the change in

weight of the polymer is a precise indication of the thermal stability of the polymer. In this study, all materials were stable up to 160ºC. When the temperature was increased to 200ºC, the TEC either volatilized or degraded and the weight percentage decreased dramatically. When the temperature reached 260ºC, no TEC remained in the analyzed sample. The CPM began to decompose at about 180ºC, and the weight percentage decreased very rapidly to about 20% of its initial weight. Eudragit® RS PO was more stable and did not begin to decompose until heated to 330ºC.

The thermal stability of CPM, Eudragit® RS PO and TEC was investigated at a temperature close to the thermal processing temperature for hot-melt extrusion. Dynamic thermal stability studies were conducted and the mass change of the samples as a function of time in the isothermal mode was measured. Figure 4.2.6 illustrates the dynamic thermal stability of CPM, Eudragit® RS PO and TEC held at 120°C for 60 minutes. There was no change in mass of CPM and Eudragit® RS PO at 120ºC for one hour. When processed by hot-melt extrusion, the procedure would hold the composite blend of ingredients at 115°C for less than 3 minutes. TEC has a higher tendency to evaporate or decompose than CPM and Eudragit® RS PO at 120°C. These findings suggest that a short processing time or a low processing temperature would minimize the evaporation of the TEC.

For the hot-melt extrusion of the Eudragit® RS PO itself, the die temperature should be above 160°C to make the polymer soft enough to be processed. The dynamic thermal stability profiles of CPM, Eudragit® RS PO and TEC held constant

at 160°C for 60 minutes are shown in Figure 4.2.7. A linear decrease in the weight percentage remaining as a function of time was found, with the acrylic polymer being the most stable. This study revealed that if a processing temperature of 160°C and a processing time of 60 minutes were employed for hot-melt extrusion, this would be detrimental for materials in the formulation. However, for the hot-melt extrusion process, only 2 to 3 minutes are required for the materials to pass through the extruder. In addition, the presence of TEC as a plasticizer in the powder blend will reduce the processing temperatures and stabilize components in the formulation.

4.2.3. Plasticization compatibility

The X-ray diffraction patterns of CPM, Eudragit® RS PO, the physical mixture, high-shear hot-melt granules and hot-melt extruded granules of 14%CPM and Eudragit® RS PO are shown in Figure 4.2.8. The CPM exhibited two sharp peaks (2θ=19.35, 2θ=20.30) indicating a crystalline structure, while the pure Eudragit® RS PO polymer was shown to be an amorphous material due to the absence of complete steroregularity and the presence of bulky side groups in the polymer. When CPM (14%) was blended with Eudragit® RS PO, the physical mixture exhibited the crystalline characteristics of the CPM. After high shear hot-melt granulation, there was a decrease in the peak intensity representing a decrease in crystallinity of the drug substance. In contrast, no crystalline peaks were observed with the hot-melt

extruded samples indicating that the CPM was in the amorphous state following hot-melt extrusion.

The concentration of drug in the hot-melt extrudates did not affect the degree of crystallinity, as shown in Figure 4.2.9. As the CPM level increased from 14% to 30%, the model drug remained in the amorphous state. These results demonstrate that CPM and Eudragit® RS PO are miscible when up to 30% of CPM was incorporated into the polymer, suggesting that a solid solution was formed during hot-melt extrusion processing.

It may be concluded from this study, that the drug release rate constants from the controlled-release matrix tablets containing CPM and Eudragit® RS PO prepared by direct compression (DC), high shear hot-melt granulation (HMG) and hot-melt extrusion (HME) were 36.2%$h^{-1/2}$, 30.8%$h^{-1/2}$, and 13.8%$h^{-1/2}$, respectively. The drug release rate was decreased for tablets prepared by thermal processes. The post-processing thermal treatment of tablets at 60°C for 24 hours further decreased drug release rate constants to 30.0%$h^{-1/2}$ (DC), 26.9%$h^{-1/2}$ (HMG), and 12.8%$h^{-1/2}$ (HME). Post-processing thermal treatment at 60°C for 24 hours had a minor influence on the drug release rate from tablets prepared by hot-melt extrusion due to its minimal effect on drug and polymer entanglement. During hot-melt extrusion, the free volume and the mobility of the polymer and drug mixture were reduced, thus decreasing the permeability of the drug from the polymer. Eudragit® RS PO, CPM and TEC used in this investigation were thermally stable during thermal processing as illustrated by

thermogravimetric analysis. Finally, the X-ray diffraction patterns following hot-melt extrusion demonstrated that CPM was dispersed homogeneously at a molecular level in Eudragit® RS PO. The CPM was in the amorphous state and miscible with the polymer at concentrations up to 30%.

4.3. Influence of a Lipophilic Thermal Lubricant on the Processing Conditions and Drug Release Properties of Chlorpheniramine Maleate Tablets Prepared by Hot-melt Extrusion

Hot-melt extrusion has recently been demonstrated to be a viable method to prepare granules, sustained release tablets (37) and transdermal drug delivery systems (42). However, due to the thermal stress and shear stress involved in this thermal processing, several concerns should be paid on the processibility, thermal and chemical stability of the ingredients in the formulation in order to achieve the processable and stable pharmaceutical products.

The hot-melt extruder is typically composed of four heating zones: feed zone, compression zone, metering zone, and die (55). Temperatures at different zones are controlled by several thermocouples in the barrel. The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. The melt viscosity of a polymer, a measure of the frictional forces between the molecules in a liquid, is an important parameter for the indication of processibility.

When molecular weights exceed a critical point (between about 10,000 and 40,000), higher molecular weight polymers are more viscous and difficult to extrude. Since a higher molecular weight polymer macromolecule is linked to its neighbors at

many points (89), the entanglements of the chains with one another becomes important and the viscosity at low rates of shear depends upon weight average molecular weight to a power equal to about 3.4 or 3.5 (46, 88). For polymethyl methacrylate, the critical molecular weight is 10,400 (46). This would seem to make the hot-melt extrusion of the Eudragit® RS PO, a copolymer of acrylic and methacrylic esters with the molecular weight of 150,000, a challenge for preparing pharmaceutical delivery systems by this thermal processing.

In addition to the molecular weight and structure of the polymer, the rheological properties of polymer melt also depend upon processing temperature, pressure, the rate of shear, as well as upon the incorporation of various additives (46), which may provide us some solutions to solve the above problem.

Changing temperature is an effective means of controlling melt viscosity in the processing operation as revealed by the Willams-Landel-Ferry equation and the Andrade or Arrhenius equation (86). However, two drawbacks are related to the increases in temperature. First, it is not economical to put in and take out thermal energy. Second, excessive temperatures can lead to degradation of the polymer and the active drug in the formulation. There is certainly an upper limit to the processing temperature we can use for a particular polymer and a drug which depends upon the degradation temperatures of the materials.

The effect of pressure on polymer melt viscosity becomes noticeable only at fairly high pressure due to their relative incompressibility (86). The viscosity of

polymer melts is shear-rate dependent (87). Both fairly high pressure and high shearing rate can theoretically decrease the melt viscosity of the polymer. However, they are impractical in the hot-melt extrusion processing for the pharmaceutical application. Therefore, the use of the formulation method to improve the thermal processing would be more interesting to pharmaceutical scientists.

Several plasticizers have been used in the hot-melt extrusion process to prepare drug delivery systems (37, 42). Plastcizers function by lowering the glass transition temperature of the polymer in the formulation thus facilitating thermal processing. Most of the pharmaceutical grade plasticizers used are liquid plasticizers. The shortcoming of liquid plasticizers in pharmaceutical application is that they cannot be used at high levels due to the difficulty of mixing the polymers with the liquid plasticizers. Consequently, to enhance the thermal processibility, a solid thermal lubricant can be added to the formulation in conjunction with the liquid plasticizer to lower the melt viscosity, thus preventing the need for high levels of a liquid plasticizer. For the application of the thermal lubricant, D. Henrist and J.P. Remon included the glyceryl monosterate in a starch based theophylline delivery system produced with a twin screw co-rotating extruder (128). However, the authors did not investigate the mechanism of a thermal lubricant facilitating the thermal processing.

In this study glyceryl monostearate (GMS) was selected as a lipophilic thermal lubricant. The melt viscosity of the formulation containing GMS was determined to investigate its effect on the thermal processibility. The drug release,

microstructure and the crystallinity of the extrudate were also evaluated to investigated the properties of the chlorpheniramine maleate (CPM) controlled release tablets containing Eudragit® RS PO and GMS prepared by hot-melt extrusion.

4.3.1. Thermal stability studies of CPM, Eudragit® RS PO and TEC

The thermal stability of CPM, Eudragit® RS PO, GMS and TEC as determined by TGA is shown in Figure 4.3.1. These data indicate that with the exception of TEC, the remaining materials were stable at 120°C for 60 minutes. CPM, Eudragit® RS PO and GMS were quite stable, while 10.55% of TEC evaporated indicating the volatile properties of TEC. However, the powder composite takes only 2 to 3 minutes to pass from the hopper through to the die. The loss of TEC during this short period of time in the hot-melt extrusion process was less than 0.5% as determined by the dynamic thermal study.

4.3.2. Hot-melt extrusion processing parameters for Eudragit® RS PO

Eudragit® RS PO is a copolymer synthesized from acrylic and methacarylic acid esters and contains a low level of quaternary ammonium groups. It has been used to prepare matrix tablets by direct compression (103), and wet granulation techniques (104, 105). Due to its low glass transition temperature, this acrylic polymer can be used to formulate controlled release tablets containing CPM by hot-melt extrusion (123).

During the hot-melt extrusion, the drive AMPS and the pre-die pressure are two parameters indicating the resistance of the melt materials within the extruder, as well as the processibility of the formulation. The drive AMPS is related to the torque of the screw. The torque is defined as the force of resistance on the screw to maintain a specific speed. The pressure gage indicates the pressure at the location of the probe, which is present at the end of the barrel just before the die. The pre-die pressure is determined by the shape of the die, the temperature of the polymer melt, the flow rate through the die, and the rheological properties of the polymer melt (87).

Table 4.3.1 shows the thermal processing parameters for Eudragit® RS PO. At a screw rotation rate of 20rpm and with temperature settings in Zone 1, Zone 2, Zone 3, and Zone 4 being 120°C, 160°C, 180°C, and 190°C, respectively, the melt Eudragit® RS PO cylinders can be extruded smoothly from the die as the acrylic polymer molecules became flexible at these temperatures. With a decrease in processing temperature (die) from 190°C to 150°C, the polymer molecules become more rigid. Therefore, the drive AMPS was increased from 2.0AMPS to 3.66AMPS, indicating higher power consumption and poor processability of the polymer at the lower processing temperature. Eudragit® RS PO could not be processed when the die temperature was lower than 140°C due to the high resistance of the unmelted polymer on the extruder.

4.3.3. Effect of TEC on the hot-melt processing parameters

When Eudragit® RS PO was processed by hot-melt extrusion, it required a die temperature as high as 190°C. Lower temperatures consumed higher screw driving energy and also generated higher pre-die pressure. When 4% TEC was incorporated into the Eudragit® RS PO, the acceptable processing temperature at the die was reduced to 150°C. With the same processing temperature setting in each of the heating zoon, the hot-melt processing parameters for TEC plasticized Eudragit® RS PO are shown in Table 4.3.2. Without TEC in the polymer, the drive AMPS for Eudragit® RS PO was 3.66 AMPS. When 4% or 8% TEC was incorporated into the Eudragit® RS PO, the drive AMPS decreased to 1.92 AMPS and 1.14AMPS respectively. The pre-die pressures were also decreased with an increase in TEC. This clearly demonstrated that TEC can facilitate thermal processing, suggesting an improvement in the processability of the polymer with the addition of TEC. This can be attributed to the fact that TEC can lower the glass transition temperature of Eudragit® RS PO as described in a previous report (123). This finding can also be explained based on melt viscosity data.

The melt viscosity of the materials is a measure of the frictional forces between the molecules in a liquid and can be used to reflect the processability of the thermal processing and is directly related to the torque values. The toque was determined by using an Electronic Torque Rheometer at specific temperature settings and screw rotation rates. The torque is the force of resistance on the screw to maintain

a specific speed. The torque values of the Eudragit® RS PO powder containing different levels of TEC were determined during thermal processing and as seen in Figure 4.3.2, the torque decreased with an increase in plasticizer concentration. It was reported that the melt viscosity of polyethylene oxide was significantly decreased with the addition of polyethylene glycol (37). The reduction in the torque value was due to a decrease in frictional shear between the powder blend and the machinery. Processing the powdered blend at lower temperatures will also help to stabilize both the active drug and other materials in the formulation.

4.3.4. Effect of GMS on the hot-melt processing parameters

The influence of glyceryl monostearate (GMS), a thermal lubricant, on hot-melt processing parameters was also investigated and the results are shown in Table 4.3.3 with processing variables as follows: a screw rotation rate of 20rpm and the temperatures in Zone 1, Zone 2, Zone 3, and Zone 4 (die) being set at 110°C, 130°C, 140°C, and 150°C, respectively. With a melting point of 67.5°C, when GMS was incorporated into the Eudragit® RS PO powder blend and processed at the above temperatures, it melted completely and resulted in decreased drive AMPS as shown in Table 3, demonstrating that the GMS improved thermal processibility, lowered the thermal processing temperatures and served as a thermal lubricant.

The melt viscosity of the powder blend of Eudragit® RS PO and GMS was also determined by using an Electronic Torque Rheometer as seen in Figure 4.3.3.

The torque values were found to decrease with an increase in GMS levels. GMS improved the Eudragit® RS PO processibility by decreasing the melt torque values. This explained the observation of the GMS facilitating thermal processing.

4.3.5. Miscibility studies

The DSC profile on the top left corner of Figure 4.3.4 shows the melting behavior of GMS with a melting point of 67.5°C. To the right, is shown the thermal transition of Eudragit® RS PO with a glass transition temperature of 64.33 °C. The two diagrams on the lower half of Figure 4.3.4 show the combination of the melt behavior plus a glass transition of the polymer, indicating GMS was immiscible with Eudragit® RS PO when 8% and 16% of GMS powder were blended with Eudragit® RS PO due to the hydrophobic properties of GMS.

4.3.6. Morphology studies on the hot-melt extrudates

Previous studies have shown that in the absence of GMS in the powder blend, CPM, Eudragit® RS PO, and TEC were quite compatible with each other due to their similar solubility properties (123). GMS was immiscible with Eudragit® RS PO following hot-melt extrusion as shown in Figure 4.3.5. The morphology of the granules formed by the hot-melt process and the results of the miscibility study clearly showed that GMS was a thermal lubricant and not a plasticizer for the acrylic polymer. The inclusion of GMS in the formulation formed a coating on the polymer

during processing resulting in smoother extrudates which minimized the sticking of the molten polymer to the machinery, thus improving the thermal processibility.

4.3.7. Dissolution studies

Drug dissolution profiles from the hot-melt extruded tablets containing the thermal lubricant GMS are shown in Figure 4.3.6. The GMS increased the drug release rate from tablets containing Eudragit® RS PO prepared by hot-melt extrusion. This is due to the fact that the GMS weakened the polymeric structure of Eudragit® RS PO and increased the drug diffusivity from the polymer. Another explanation is that as the GMS level in the formulation was increased less polymer was present in the extruded tablet. Additionally, the incorporation of GMS decreased the pre-die pressure and resulted in the extrudates with higher free volumes in the polymeric delivery systems. Therefore, release rate of CPM increased with an increase of GMS in the extrudates.

4.3.8. Crystallinity of the hot-melt extrudates

The X-ray diffraction patterns of CPM, GMS, Eudragit® RS PO, the physical mixture and hot-melt extrudates of 14% CPM, 10% GMS and Eudragit® RS PO are shown in Figure 4.3.7. CPM exhibited two sharp peaks at 2θ equal to 19.35°, and 20.30°. Crystallinity was also seen with the GMS which exhibited two peaks at 2θ equal to 19.65° and 23.40°. The Eudragit® RS PO polymer was shown to be an

amorphous material due to the absence of complete steroregularity and the presence of bulky side groups in the polymer. The physical mixture containing 14% CPM, 10% GMS, and Eudragit® RS PO showed a crystalline character due to the presence of the drug and the thermal lubricant. The hot-melt extrudates of the formulation also show a decreased peak intensity, indicating a decreased crystallinity of the CPM in the extrudates. It was reported for the indomethacin/PVP system following hot-melt extrusion that indomethacin was converted into the amorphous form at higher processing temperatures while the crystallinity of the drug was detected from the extrudates processed at lower temperature (77). Zhang and McGinity reported that the crystalline state of the theophylline was maintained in the extruded granules containing poly(vinyl acetate) with the extruder die temperature of 75°C (36). In another study, even though diphenhydramine hydrochloride and Eudragit® E 100 have the same solubility parameter which indicates possible miscibility, however, the crystalline drug was observed following the hot-melt extrusion due to the fact that the processing temperature of 80-130°C was much lower than the melting point of diphenhydramine hydrochloride (166-170C°) (129). Previously, it has been found that CPM could form a solid solution with Eudragit® RS PO at a level up to 30% of CPM. In the present study, the appearance of the crystallinity of CPM in the hot-melt extrudates may be due to the incomplete melt of the drug. CPM was partially transformed into an amorphous form since a lower processing temperature was used as the result of the incorporation of TEC and GMS.

In summary, Eudragit® RS PO, CPM, GMS, and TEC were found to be thermally stable as shown by the TGA study. TEC decreased the glass transition temperature and the melt viscosity of Eudragit® RS PO and facilitated the thermal processing. Both DSC and SEM studies demonstrated that GMS was not miscible with Eudragit® RS PO. GMS facilitated the hot-melt extrusion process by decreasing only the melt viscosity of the Eudragit® RS PO, by acting as a thermal lubricant. With an increase in the GMS content, the release rates of CPM from Eudragit® RS PO hot-melt extruded tablets increased. CPM was partially in the crystalline state after hot-melt extrusion processing with Eudragit® RS PO and GMS. The incorporation of a thermal lubricant such as GMS into a powder blend will decrease the thermal processing temperatures and potentially allow more drugs and polymers to be processed by hot-melt extrusion.

4.4. Influence of Plasticizer Level on the Drug Release from Sustained Film Coated and Hot-melt Extruded Dosage Forms

Plasticizers are materials incorporated in a polymer to increase its workability and flexibility(38). Plasticizers decrease the glass transition temperature (Tg) of the polymer. Therefore, less energy is required for molecular bond rotation. In pharmaceutical applications, hot-melt extrusion and aqueous polymeric coating are two thermal processes with different heat intensities. Plasticizers are typically used in the formulation to facilitate the polymers become capable of flow at lower temperatures for hot-melt extrusion and to lower the minimum film formation temperature and enhance the polymer particle coalecence during the film coating process.

In addition to the ability to enhance the thermal processing, the effect of the plasticizers on drug release rate is another major concern in the design of drug delivery systems. The influence of plasticizer level on drug release from aqueous polymeric film coated tablets or pellets was already investigated by several research groups. Wu and McGinity (45) investigated the influence of a non-traditional plasticizer, methylparaben, on drug release. For ibuprofen beads coated with Eudragit® RS 30D containing methylparaben, the drug release rate decreased when the methylparaben levels were increased from 5% to 15%. Bodmeier *et al*

investigated the influence of a plasticizer on drug release over a wide range of the plasticizer level. In their studies, propranolol hydrochloride beads were coated with Eudragit® RS 30D containing triethyl citrate (43). A U-shaped drug release profile was found. The release rate constant was high at low plasticizer levels, then went through a minimum plateau, and increased at higher plasticizer concentrations. At low plasticizer levels, TEC increased the coalescence or fusion of the insufficiently plasticized latex particles and resulted in a decreased drug release. At high levels of TEC, the increase in release rate constant was due to the leaching out of the water-soluble plasticizer from the coated beads.

Hot-melt extrusion has been recently demonstrated to be a viable method to prepare granules, sustained release tablets (37) and transdermal drug delivery systems (42). It offers many advantages over traditional processing techniques. Plasticizers have been used in several research studies on the hot-melt extrusion (37, 42). However, the influence of plasticizer level on the drug release mechanism from the hot-melt extrudated systems has not been explored yet. Investigation of the influence of the plasticizer level on drug release rate provides us another way to reveal the function of the plasticizer on the polymeric drug delivery system during the thermal preparation processing.

The purpose of the current research was to investigate the influence of a water soluble plasticizer, triethyl citrate (TEC), on the drug release rate from the hot-melt extrudates containing acrylic polymers and model drugs with different

physicochemical properties. The two highly water-soluble drugs selected included chlorpheniramine maleate (CPM) and diltiazem hydrochloride (DTZ). The poorly water-soluble drug selected was indomethacin (IDM). Aqueous film coating, a less heat intensive thermal process, was also employed to investigate the plasticizer level in the coating formulation on the drug release from diltiazem hydrochloride pellets coated with Eudragit® RS 30D.

4.4.1. Thermal stability

The physical stability of the materials used in the hot-melt extrusion formulations was determined by TGA under a nitrogen atmosphere as shown in Figure 4.4.1. It was indicated that there was no weight loss for diltiazem hydrochloride until a temperature of 230°C was reached. This result is consistent with the reported data by Mazzo, *et al* (130). Significant weight loss was observed beyond 250°C due to the decomposition or vaporization of the DTZ, Eudragit® RS PO and TEC. The thermal stability of CPM and IDM were determined and previously reported (123).

4.4.2. Chemical stability of DTZ following hot-melt extrusion

The drug contents before and following hot-melt extrusion were determined by using a USP stability indicating HPLC assay method as described in Table 4.4.3. The drug content decreased less than 2% following processing. No degradant peaks

were observed in the chromatograms. Follonier, *et al* who processed DTZ with Eudragit® RS PM by hot-melt extrusion at 140°C also reported that no significant difference in drug content between the reference and the DTZ extrudates was observed in samples, before and after processing (73). These results demonstrated that DTZ was chemically stable following hot-melt extrusion, indicating that the hot-melt extrusion processing conditions employed in this study were acceptable for the preparation of DTZ hot-melt extrudates.

4.4.3. Plasticization effect of DTZ on Eudragit® RS PO

In our previous research a solid-state plasticization effect by both CPM and IDM on Eudragit® RS PO was observed. In the current study, no solid plasticization effect on Eudragit® RS PO was seen with highly water-soluble drugs, including diltizem hydrochloride, propranolol hydrochloride, diclofenac sodium, and naproxen sodium. The absence of a solid-state plasticization effect of these drugs on Eudragit® RS PO was due to their higher melting points; for example the melting point of DTZ is 214.6°C (130). Diltiazem hydrochloride was selected for further investigation due to its lack of plasticization effect on Eudragit® RS PO as shown in Figure 4.4.2. In addition, good compatibility between DTZ and the aqueous colloidal dispersion, Eudragit® RS 30D, was a further reason to select DTZ as the model drug. This negates the possibility of precipitation of Eudragit® RS 30D polymer as flocculates on the surface of the DTZ beads during the coating process.

4.4.4. Influence of TEC concentration on drug release

4.4.4.1. From hot-melt extrudates containing CPM

The influence of TEC levels on the drug release from the hot-melt extrudated tablets containing CPM is seen in Figure 4.4.3. The drug release rate was increased with the increase of the TEC from the hot-melt extruded delivery system containing CPM and Eudragit® RS PO. CPM exhibited a solid-plasticization effect on Eudragit® RS PO and a solid solution with a continuous structure was formed following hot-melt extrusion as reported previously (123). However, TEC was released from the hot-melt extrudates in the dissolution test (123). The diffusion of TEC into aqueous media from cast films prepared from aqueous colloidal polymer dispersions had previously been reported (107).

4.4.4.2. From hot-melt extrudates containing DTZ

Diltiazem hydrochloride is a calcium channel blocker widely used in the treatment of angina pectoris, supraventricular tachycardias, and hypertension (131). It is a highly water-soluble drug with a solubility in the range of 588mg/ml to 678mg/ml in the pH range of 1.0 to 5.8 (132). The influence of TEC levels on the dissolution rate of DTZ from the hot-melt extruded tablets containing 30% DTZ is seen in Figure 4.4.4. The drug release rate increased with the increase of the TEC level. This finding is consistent with the effect of TEC level on the drug release of another highly water-soluble drug, CPM, from the hot-melt extrudates as reported above. Even though

DTZ did not exhibit the plasticization effect on Eudragit® RS PO, a continuous polymeric structure was formed following thermal extrusion processing.

The data in Figure 4.4.4 also reveals that a drug release burst effect from the hot-melt extrudates was eliminated as the result of the thermal processing. It was reported that for this highly water-soluble drug, DTZ was distributed in the coating polymer matrix when dichloromethane was used as the solvent and Eudragit® RS 100 as the coating material to prepare microparticles by the spray-drying technique. Microcapsules were formed when using toluene. It was reported that the initial release from microcapsules was faster due to the presence of some uncoated drug crystals (133).

4.4.4.3. From Eudragit® RS 30D coated beads containing DTZ

It is generally accepted that the film-forming process occurs in three stages: (I) evaporation of the water until the particles reach close-packing; (II) formation of particle contacts and deformation of that latex particles as the particle volume fraction goes above that of a close-packed structure; (III) gradual coalescence by interdiffusion of polymer molecules between latex particles (134). Following the aqueous polymeric coating process, without any curing on the coated pellets, the film formed has a higher permeability due to incomplete coalescence. As the film was cured, the permeability approached a minimal value and remained relatively unchanged over a period of time (135). The cured DTZ pellets were used for the dissolution studies. Figure 4.4.5 shows the influence of TEC level in the Eudragit®

RS 30D coating layer on the dissolution rate of DTZ from coated pellets with a 15% polymer weight gain. The drug release rate decreased with the increase of the TEC level. Several authors have observed the same drug release phenomena for the coated beads (45, 94, 136). The addition of a plasticizer facilitates the polymer particle coalescence. The formation of a continuous polymeric structure decreased the permeability of the film.

4.4.4.4. From hot-melt extrudates containing IDM

The influence of TEC level on the drug release from the hot-melt extrudated granules (20-40 mesh) containing a poorly water-soluble drug, IDM, and Eudragit® RD 100 is seen in Figure 4.4.6. The dissolution profiles comparison was carried out using a model independent method (56). By calculating the similarity factor f_2 values, the f_2 values between the formulations were greater than 50, which means that these dissolution profiles can be considered similar. The addition of TEC in the hot-melt extrudates formulation did not influence the drug release for a poorly-water soluble drug. This could be contributed to the low solubility of the drug and the drug release rate was controlled by intraparticle diffusion.

4.4.5. Microstructures of Hot-melt extrudates and surface morphology of coated beads

4.4.5.1. Hot-melt extrudates

The surface morphologies of the hot-melt extrudates containing 30% DTZ, 66% Eudragit® RS PO and 4% TEC are displayed in Figure 4.4.7. This SEM picture showed that a continuous polymeric structure was formed following hot-melt thermal processing, even though the DTZ was not dispersed homogeneously at the molecular level in the acrylic polymer. This will be further confirmed by the X-ray diffraction studies.

4.4.5.2. Coated beads

The surface morphologies of the Eudragit® RS 30D coated DTZ beads containing different levels of TEC in the coating layer are displayed in Figure 4.4.8. With an increase in the amount of TEC incorporated in the formulations, the surface morphology of the coated beads became smoother as the higher levels of TEC contributed to a more complete coalesence of the polymeric particles in the Eudragit® RS 30D film coatings.

4.4.6. Crystallinity follwing hot-melt extrusion

The X-ray diffraction patterns of DTZ, Eudragit® RS PO, the physical mixture, and hot-melt extrudates containing 30% DTZ and Eudragit® RS PO are shown in Figure 4.4.9. The DTZ exhibited several sharp peaks in the 2θ range from 10° to 28° indicating a crystalline structure, while the pure polymer Eudragit® RS PO was shown to be an amorphous material. When DTZ (30%) was blended with Eudragit® RS PO, the physical mixture exhibited the crystalline characteristics of the

DTZ. Crystalline peaks were also observed with the hot-melt extruded samples indicating that the DTZ was in the crystalline state following hot-melt extrusion. The crystallinity of DTZ following hot-melt extrusion is the result of the high melting point of the DTZ and the immiscibility of the drug with the polymer as revealed by the DSC data. It was reported by Zhang and McGinity (36) that the crystalline state of theophylline was maintained in the extruded granules containing poly(vinyl acetate) with an extruder die temperature of 75°C. Even though diphenhydramine hydrochloride and Eudragit® E 100 have the same solubility parameter, which signals the possible miscibility of the two materials, the crystalline drug was observed following hot-melt extrusion in a processing temperature range of 80-130°C which was lower than the melting point of diphenhydramine hydrochloride (166-170C°) (129).

In conclusion, DTZ and the excipient components of the extruded tablets were thermally and chemically stable at thermal processing temperatures of 90°C to 140°C, as shown by TGA and HPLC. No plasticization effect of DTZ on Eudragit® RS was observed. The influences of TEC levels on drug release rates were dependent on the thermal processing methods used to prepare the solid composite. An increase in the TEC level resulted in an increase in the DTZ or CPM release rate from the extruded tablets, while the drug release rate from the coated DTZ pellets decreased when the TEC level in the coating formulation was increased. DTZ was in the crystalline state

following thermal processing. Different levels of TEC in the IDM hot-melt extrudated granules produced a similar drug release profile. This could be due to the lower solubility of IDM and the drug release rate was controlled by intraparticle diffusion.

4.5. Properties of Hot-melt Extrudated Solid Solutions Containing Acrylic Polymers and a Poorly Water-Soluble Drug

There are many factors influencing the bioavailability of a pharmaceutical product. Among these factors, the two most important physicochemical properties of a drug are its solubility and permeability. If a drug substance has an aqueous solubility of less than 10mg/ml in solution at 37°C over a pH range of 1 to 7, dissolution is the rate-limiting step in the process of drug absorption (8). Therefore, a potential bioavailability problem may occur and methods for improving drug solubility should be explored. Enhancing the oral bioavailability of poorly water-soluble drugs is one of the most challenging issues in the drug development, and several techniques such as micronization and salt formation, have been investigated. These methods have limitations due to the agglomeration of the micronized powder or the reconversion of salts into aggregates of their respective acid or base forms. The first breakthrough in this area was the investigation of a solid dispersion conducted by Sekiguchi and Obi in 1961 (9). It was demonstrated that without those limitations mentioned above a eutectic mixture of sulfathiazole and urea had a much higher dissolution rate leading to better absorption following oral administration as compared to sulfathiazole administered alone.

Even though solid dispersion technology provides many advantages over the traditional techniques (11, 137), only two products, a griseofulvin-in-poly(ethylene glycol) solid dispersion (Gris-PEG, Novartis) and a nabilone-in-povidone solid dispersion (Cesamet, Lilly) were marketed due to the existence of the following problems: (a) the melt or solvent preparation methods, (b) the reproducibility of the physicochemical properties, (c) formulation into dosage forms, (d) the scale-up of manufacturing processes, and (e) the physical and chemical stability of drug in the solid dispersions (12). In recent years, solid dispersion technology was gained recognition due to the application of hot-melt extrusion in the pharmaceutical field (13). An important advantage of the hot-melt extrusion is that the drug/carrier mixture is subjected to an elevated temperature for only a few minutes, which allows both the drug and the carrier to be both thermally and chemically stable. Due to the simplicity of manufacturing and scale up processes, the physicochemical properties of solid dispersions are not expected to change significantly during the scale-up. For this reason, the application of hot-melt extrusion will grow rapidly in the preparation of solid dispersions.

To enhance the bioavailability of poorly water-soluble drugs, highly water-soluble carriers were used to prepare the solid dispersions. When a mixture consisting of a poorly water-soluble drug and an inert highly water-soluble carrier is dissolved in an aqueous medium, the drug release mechanism causes the carrier to 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

improve bioavailability. For the purpose of preparing a sustained solid dispersion delivery system containing the poorly water-soluble drugs, the same hot-melt extrusion process can be employed. The only difference is the selection of polymers with suitable permeability. Solid solutions can improve the drug solubility to the greatest extent. In order to prepare solid solutions, an important prerequisite is the miscibility of the drug and the carrier in the molten state. When there are miscibility problems, this usually leads to a product that is not molecularly dispersed.

Furosemide is a diuretic and antihypertensive drug that is practically insoluble in water. Controlled drug release tablets were prepared by compressing the granules of solid dispersions containing furosemide and Eudragit® RS/RL PO made by the solvent (methanol) method (29). Flurbiprofen is a non-steroidal anti-inflammatory drug with a slight water solubility (30mg/ml in water at 37°C). Solid dispersion granules containing flurbiprofen (FP) and poly(ethylene oxide) (PEO) or HPC were prepared by solvent (ethanol) method (14). The release rate of the drug from the FP-PEO system was significantly larger than that from FP powder and the FP-HPC system. The dissolution property of the polymer base greatly affected the release of FP from the solid dispersions. In the FP-PEO system, the release rate increased with the increasing percent of PEO.

Several acrylic polymers were evaluated to formulate the sustained indomethacin solid solutions. Eudragit® RS PO / RL PO are copolymers synthesized from acrylic and methacarylic acid esters which contain a low level of quaternary

ammonium groups. The Eudragit® RL polymer contains a greater molar ratio of these ionizable groups, which causes it to be more readily permeable than the Eudragit® RS PO. The Eudragit® RD 100 is a new product from Röhm America. It is a powder combination of 91% of Eudragit® RL PO and 9% of sodium carboxymethyl-cellulose. This material is currently used for film coating immediate release dosage forms. The Eudragit® RD 100 was selected in this study since it exhibits higher permeability compared to the Eudragit® RS PO/ RL PO.

Several researchers have reported that hot-melt extrusion can be used to enhance the bioavailability of poorly water-soluble drugs (77), but the development of the controlled release dosage forms for poorly water-soluble drugs which avoid the risk of the burst effect has not been investigated using this thermal processing. In this study, indomethacin, a poorly water-soluble drug (solubility in water is 4.0-8.8 μg/ml) (138) was selected and controlled release drug delivery systems containing several acrylic polymers were prepared by hot-melt extrusion. The thermal and chemical stability of the materials used in the formulation was evaluated through the preformulation, and formulation studies were conducted to reveal the controlled drug release mechanisms.

4.5.1. Particle size, true density, melting point and glass transition temperature

The particle size of indomethacin, Eudragit® RL PO, and Eudragit® RD 100 was determined by using a Zeta Potential Analyzer with a BIC particle sizing

software and is shown in Table 4.5.1. The average effective diameters for these three materials as received were 13.98μm, 40.96μm, and 43.11μm respectively, which represents the fine particles of these materials.

The true density of indomethacin, Eudragit® RL PO, and Eudragit® RD 100 was determined by using a helium pycnometer (139). The average true densities for these three materials as seen in Table 4.5.2 were 1.3756g/cm^3, 1.1887g/cm^3, and 1.2094g/cm^3, respectively.

Due to its different molecular arrangements and/or conformations, indomethacin has been shown to exhibit four polymorphs with different melting points (140). The melting point of indomethacin for Form I was 160-161.5°C, for Form II, III, and IV the melting points were reported to be 154.5-155.5°C, 148°C, and 134°C, respectively (138). The melting point of the indomethacin powder as received was determined to be 162.46°C using DSC at a heating rate of 10°C/min from –10 to 180°C as seen in Figure 4.5.1. This result showed that indomethacin was in the crystal Form I prior to hot-melt extrusion. Form I is the most stable polymorph and has the lowest solubility. The energy required for a molecule to escape from a crystal is much greater than the energy required to escape from an amorphous powder, which explains why the crystal form of a compound is always less soluble than the corresponding amorphous form (141). The amorphous form was formed as a result of the quenching process in the first run. A glass transition phenomenon was observed in the second run of the indomethacin using DSC and the glass transition temperature

was found to be 47.77°C, which is close to the values of 45°C (58), and 50°C, reported by Zografi *et al* (19).

4.5.2. Plasticization effect of indomethacin on Eudragit® RL PO

The solid-state plasticization effect of indomethacin on Eudragit® RL PO was determined by DSC at a heating rate of 10°C/min from –10 to 180°C. The DSC profile of the mixture of indomethacin and Eudragit® RL PO of the first run showed an endothermal peak of 157.8°C due to the melting behavior of the indomethacin. During the first run, samples underwent both heating and cooling processes, so their previous history was erased. In the second run, the glass transition temperatures (Tg) of the mixtures of Eudragit® RL PO and indomethacin were determined as shown in Figure 4.5.2. A slight decrease in the Tg was seen using 40% indomethacin in the Eudragit® RL PO mixture. Since glass transition temperatures for pharmaceuticals are generally found to be about two thirds that of the melting temperatures (142), the melting point of indomethacin is 162.5°C and chlorpheniramine maleate (130-135°C) (143), it was not surprising to see that the solid-state plasticization effect was weaker for the mixture containing indomethacin in Eudragit® RL PO compared to chlorpheniramine maleate in Eudragit® RS PO. When a compound is miscible with the polymer in the molten state, the lower the melting point, a stronger plasticizing effect will exhibit on the same polymer. Even though the solid-state plasticization effect of indomethacin on Eudragit® RL PO was weak, this study demonstrated that

indomethacin was miscible with Eudragit® RL PO and a solid solution of indomethacin was formed during the extrusion process.

The glass transition temperature of Eudragit® RL PO was 62.88°C, and for IDM it was 47.77°C as determined by DSC. After determining the Tg of the pure materials of IDM and Eudragit® RL PO, the Tg of the mixture of Eudragit® RL PO and IDM can be predicted by using the following Gordon-Taylor equation (70).

$$Tg_{,\ mixture} = [(m_1Tg_1) + (Km_2Tg_2)]/[m_1 + (Km_2)] \quad (1)$$

$Tg_{,\ mixture}$, Tg_1, and Tg_2 are the glass transition temperatures of the mixture, component 1 and component 2. m_1 and m_2 are the weight percentage of component 1 and component 2, respectively. K can be calculated from the equation (2).

$$K \approx \rho_1 Tg_1/\rho_2 Tg_2 \quad (2)$$

ρ_1, and ρ_2 are the densities of component 1 and component 2. By comparing the determined values with the predicted values as shown in Figure 4.5.2, we can see the determined values fit the Gordon-Taylor equation very well.

The Tg was decreased with an increase of IDM, as described by the Gordon-Taylor equation, demonstrating the solid-state plasticization effect of this model drug. IDM was also miscible with this acrylic polymer.

4.5.3. Plasticization effect of Pluronic® F68 on Eudragit® RL PO

Pluronic® F68 was sieved through a 30 mesh screen before blending with Eudragit® RL PO at different ratios. The DSC scanning rate was 10 °C/min over a

temperature range of –20 to 150°C. As the melting peak of Pluronic® F68 was observed both in the first run and in the second run of all the samples, and the melting points of Pluronic® F68 in these mixtures did not decrease significantly as seen in Table 4.5.3, this demonstrated that there was no plasticization effect of Pluronic® F68 on the Eudragit® RL PO.

4.5.4. Thermal stability

The thermal stability of indomethacin, Eudragit® RL PO, Eudragit® RD 100, Eudragit® S 100, Eudragit® L 100, and Pluronic® F68 was investigated at the thermal processing temperature, 140°C. Table 4.5.4 illustrates the weight percentage of these materials remaining after being kept at 140°C for 10 minutes. The loss of mass of these materials at 140ºC for 10 minutes was less than 1%, indicating that indomethacin and the other excipients had good thermal stability. The chemical stability of IDM was verified by HPLC (section 3.6). In a previous study with another acrylic polymer, Eudragit® RS PO was shown to be thermally stable at 120ºC for more than an hour (144).

4.5.5. Adsorption of indomethacin on the acrylic polymers

The adsorption of IDM onto Eudragit® RL 100 has been reported to prevent the drug from being completely released during a dissolution study (61). The adsorption of IDM in the pH 6.8 phosphate buffer solutions on the acrylic polymers,

including either the Eudragit® RD 100, or Eudragit® RD 100 with 10% Eudragit® S 100 or with 10% Eudragit® L 100, is seen in Figure 4.5.3. IDM had a strong binding with Eudragit® RD 100 due to the existence of the quaternary ammonium groups in the acrylic polymer. When 10% of Eudragit® S 100 was blended with Eudragit® RD 100, this interaction was weaker than with Eudragit® RD 100 alone. This effect is contributed to the anionic functional groups in Eudragit® S 100 and a lower amount of Eudragit® RD 100 presence in the powder blend. When there were higher amounts of the anionic functional groups contained in the Eudragit® L 100, even lower IDM and polymer binding was observed as seen in Figure 4.5.3.

4.5.6. Chemical stability of IDM in the formulation

For methyl methacrylate copolymers, previous research has shown that scission of polymer chains at elevated temperatures (300°C) results in a monomeric product (126). The depolymerization of poly(methl methacrylate) is a free-radical process that is initiated from the ends of the chain. Each initiated chain unzips rapidly to yield monomer formation. Thus, at any instant the system contains only unreacted polymer and monomer (127). The chemical stability of Eudragit® RS PO is well documented (73). Therefore, only the chemical stability of IDM in the formulations following hot-melt extrusion was determined and the results are shown in Table 4.5.5. A HPLC method was used to evaluate the chemical stability of indomethacin. By using the stability-indicating RP-HPLC, no additional peaks were detected. Results

of this study demonstrated that indomethacin was chemically stable subject to thermal and pressure stress for only a few minutes (4). Other researches have demonstrated that indomethacin was quite stable in the molten state (145). It was reported that only 1% of crystalline indomethacin was decomposed at 145°C after 48 hours. Amorphous indomethacin was less stable than its crystalline form, but it still needed several hours to begin to degrade (145). The chemical stability of IDM was reported in PVP/IDM (1:1) and PVP/IDM (4:1) systems processed at 170°C, and less than 1% of the active drug was chemically degraded (77).

4.5.7. Drug release from hot-melt extrudates

4.5.7.1. Influence of Pluronic® F68 level and tablet processing on drug release

A powder blend containing 30% IDM, 66% Eudragit® RD 100, and 4%TEC was processed by hot-melt extrusion. The extradates were ground into granules in the particle size of 20-40 mesh and the drug release properties were determined. It was found that only 36% of the drug was released after 12 hours in pH 6.8 using the USP 24 paddle method. A binding interaction between the acidic functional group in the drug and the quaternary amine group in the Eudragit® RD would account for the low level of drug release. A non-ionic surfactant, Pluronic® F68, a polyoxyethylene-polyoxypropylene copolymer with a melting point of 56.2°C, was incorporated into the formulation to replace an equivalent amount of Eudragit® RD 100. As shown in Figure 4, an increase in drug release was observed with the increase in the Pluronic®

F68 level in the granules. This effect was contributed to the lower interfacial tension between the drug and the dissolution medium increasing the wettability of the drug in the formulation. The drug release data showed a better fit with the Higuchi equation than with the first order drug release equation by comparing the linear regression coefficients. The drug release rate constants were calculated and the drug release mechanism was shown to be a diffusion-controlled process. The drug release rate constant increased from 10.24% $h^{-1/2}$, to 15.32% $h^{-1/2}$, and to 20.18% $h^{-1/2}$ when the Pluronic® F68 level increased from 0%, 5%, to 10%, respectively, in the hot-melt extrudates. The increase of nifedipine release from multiple-layer pellets containing Pluronic® F68 was reported by several researchers (146).

The dissolution of the hot-melt extrudates containing different levels of Pluronic® F68 with a particle size in the range of 40-60 mesh was also conducted, with the results reported in Figure 4.5.5. Comparing Figure 4.5.4 and Figure 4.5.5, we see that the drug release rate was increased compared with the same formulation having a particle size in the range of 20-40 mesh. From the Noyes-Whitney equation, drug dissolution rate is proportional to the surface area available for dissolution. A decrease in the particle size of the extrudate increased the surface area exposed to dissolution, resulting in an increased drug release rate, as shown in Figure 4.5.5.

Formulation of the granules of the solid solutions containing a poorly water-soluble drug prepared by the hot-melt extrusion is of practical significance. In this study, tablets containing the 50% of the granules of the solid solutions and 45% of

Avicel® PH-101 were compressed. To minimize the influence of the tablet formulation and the tableting processing on the drug release from the tablets, 5% L-HPC (LH-21), a super disintegrant, was added to the formulation to ensure a fast disintegration of the compressed tablets. At the compression force of 400 Kg, the compressed tablets had a hardness of 15Kg. The drug release profiles from these tablets are seen in Figure 4.5.6. Comparing the drug release from the tablets with the hot-melt extruded granules formed the tablets by calculating the similarity factor f_2 values, the f_2 values were greater than 50 for the three formulations, suggesting that both the tablet formulation and the tabletting compression process did not significantly influence the drug release rate from the hot-melt extruded solid solution granules.

4.5.7.2. Influence of Eudragit® L100 and Eudragit® S100 level on drug release

The dissolution profiles in both Figure 4.5.4 and Figure 4.5.5 demonstrate that a tailing effect is present with the extrudates containing the IDM. After 12 hours, there was still more than 20% drug remaining in the granules to be slowly diffused from the polymer. An approach to solving this problem was to include an enteric polymer in the formulation. Eudragit® L 100 or Eudragit® S 100 were incorporated into the powder blend. Drug release profiles from granules containing different levels of Eudragit® L 100 in the formulation are seen in Figure 4.5.7. With an increase in the amount of Eudragit® L 100 added, the drug release rate increased. The Eudragit®

L 100 is an anionic copolymer based on methacrylic acid and methyl methacrylate with a carboxylic acid functional group. This polymer exhibits higher permeability at higher pH than Eudragit® RD 100. In addition, the incorporation of Eudragit® L 100 in the formulation decreased the binding of IDM with the Eudragit® RD 100. These two factors contributed to the increased drug release rate of the polymeric systems containing of Eudragit® L 100.

The ratio of the free carboxyl groups to the ester groups is approximately 1:1 in Eudragit® L 100 and about 1:2 in Eudragit® S 100. Therefore, Eudragit® S 100 has a lower permeability than Eudragit® L 100. Drug release profiles from granules containing different levels of Eudragit® S 100 in the formulation are seen in Figure 4.5.8. The addition of Eudragit® S 100 in the formulation did not enhance the drug release rate significantly. The dissolution profiles comparison was carried out using a model independent method (56). By calculating the similarity factor f_2 values, it can be observed that the f_2 values between the top two lines and the bottom two lines were greater than 50, which means that these dissolution profiles can be considered similar. Eudragit® S 100 did not increase the drug release rate as high as Eudragit® L 100 since the release of the drug with a low solubility is primarily controlled by the relative magnitude of the rate of swelling/erosion of the polymer (147).

4.5.7.3. Influence of TEC level on drug release

Pharmaceutical polymers used in thermal processing such as film coating, hot-melt granulation, and hot-melt extrusion typically require a plasticizer in order to reduce the glass transition temperature of the polymer and to facilitate the thermal processing. The addition of a plasticizer will usually decrease the drug release rate from polymeric coated systems since the plasticizer will increase the coalescence of the polymeric particles. In a previous study it was reported that for hot-melt extrudated systems containing a highly water-soluble drug, chlorpheniramine maleate, the drug release rate increased with an increase in the plasticizer level (123). In this study, the drug release profiles from the hot-melt extrudates containing a poorly water-soluble drug, IDM, are shown in Figure 4.5.9. The dissolution profiles comparison was carried out using the method mentioned above. The f_2 values were greater than 50, which means that these dissolution profiles can be considered similar. The addition of TEC in the hot-melt extrudate formulation containing a poorly water-soluble drug did not influence the drug release, in the hot-melt extrusion process even though TEC had an effect on the formation of the structure of the drug delivery systems which governed the drug release from the polymeric delivery systems. For the poorly water-soluble drug, the drug release is also controlled by the drug solubility. Kim reported that when a high drug loading is maintained for poorly water-soluble drugs, the addition of a water-soluble excipient to a matrix does not influence the release kinetics (147). Carli *et al* demonstrated that drug release from the Eudragit® RS or Eudragit® RL system was not influenced by porosity, whereas

the drug release rate was controlled by intraparticle diffusion (148). Lovrecich, *et al* revealed that for the indomethacin and Eudragit® RS PO system, the diffusion coefficient of indomethacin through the polymer did not change with aging, although the polymer underwent local rearrangement. The driving force for water uptake was the presence of ionic groups. This proves that the physical parameters (free volume, short range order) of glassy polymers do not influence the diffusion (110).

4.5.7.4. Influence of pH on drug release from granules

The profiles in Figure 4.5.12 demonstrate the effect of pH on drug release from the hot-melt extrudated granules. Since the solubility of indomethacin was dependent on the pH of the media, the drug release rate increased with an increase in pH of the media. The pKa value of indomethacin is 4.5 (149). The drug has a lower solubility at lower pH and a higher solubility at higher pH.

The drug release profiles in Figure 4.5.11 show 10% of the Eudragit® L100 incorporated in the formulation. The drug release rate increased compared to the drug release at the same pH values shown in Figure 4.5.10, which could be contributed to the higher permeability of Eudragit® L100 compared to Eudragit® RD 100 in the corresponding pH media.

The drug release profiles in Figure 4.5.12 show 10% of the Eudragit® S100 incorporated in the formulation. The drug release rate also increased as compared with the drug release at the same pH values in Figure 4.5.10, but it increased to a

lesser extent as compared with Eudragit® L100. As described earlier, this is due to the lower permeability of the Eudragit® S 100 than that of Eudragit® L100 in the corresponding pH media.

The drug release from the delivery systems in the different pH media can be determined conveniently by using the Bio-Dis® apparatus. The Bio-Dis® apparatus (method 3) eliminates manual and tedious work in changing dissolution media, providing an advantage when dissolution testing is performed in a pH step gradient (150, 151). Figure 4.5.13 shows that the drug release rate increased with both pH and the incorporation of the Eudragit® L100 or the Eudragit® S100 for reasons described above.

4.5.8. Microstructures and crystallinity of the hot-melt extrudates

The scanning electron micrographs in Figure 4.5.14 show the microstructure of the hot-melt extrudates of IDM. A continuous single phase was observed for both formulations, demonstrating that IDM was homogenously dispersed in the hot-melt extrudates. In addition to the DSC results, the photographs in Figure 4.5.14 also demonstrate that IDM was miscible with the acrylic polymer in the molten state. A brittle structure is seen for the formulation with no TEC, in Figure 4.5.14 (A). In comparison, when 4% TEC was added to the formulation, a smoother structure with lesser brittle character is seen in Figure 4.5.14 (B).

Pluronic® F68 and indomethacin are crystalline materials as shown by the X-ray profiles with peaks in Figure 4.5.15. Eudragit® RD 100, which is composed of a mixture of sodium CMC and Eudragit® RL 100, exhibited no evidence of crystalline peaks, showing it to be an amorphous polymer. The physical blend containing 30% IDM exhibited some peaks. The X-ray profile for the extrudate showed the absence of peaks, indicating that IDM was in an amorphous form and a solid solution was formed following the hot-melt extrusion process. A related study also revealed that solid dispersions of indomethacin and Eudragit® RS prepared by the solvent method resulted in the formation of an amorphous form of IDM when present at concentration as high as 30% (w/w) (61).

Several pharmaceutical processes, including spray drying, lyophilization, and milling have been shown to transform a crystalline drug transform into different polymorphous structures. An amorphous form of drug is formed first due to a lower interfacial energy of the metastable nucleus against the amorphous matrix than that of the more stable nucleus against this matrix as explained by Ostwald (19, 152). The transformation of crystalline IDM into amorphous form as a result of thermal processing enhanced the solubility of the model drug, thus decreasing the influence of solubility of the poorly water-soluble drug on the drug release and increasing the influence of the delivery system. In addition, the formation of a molecularly distributed drug in the system also eliminates the influence of drug particle size on drug release, which is a major concern for poorly water-soluble drugs.

When 10% Eudragit® S 100 replaced the same amount of Eudragit® RD 100 in the hot-melt extrudate formulations as seen in Figure 4.5.16, the peak intensity was higher as compared with the formulation without Eudragit® S 100 (the top line in Figure 4.5.15). This is because IDM was immiscible with Eudragit® S 100 in the molten state. When more than 10% of Eudragit® S 100 was added to the formulation to replace the same amount of Eudragit® RD 100, an increase in crystallinity of IDM was found following the thermal processing.

In conclusion, IDM decreased the glass transition temperature of the Eudragit® RL PO as determined by DSC demonstrating that IDM exhibited a solid-state plasticization effect on the polymer and IDM was miscible with this polymer in the molten state. An amorphous form of IDM was converted from the crystalline form and a solid solution of IDM was formed following the hot-melt extrusion process of the formulation containing Eudragit® RD 100 as demonstrated by the X-ray diffraction, the DSC and the SEM profiles. Eudragit® RD 100/L 100/S 100 were thermally stable at 140°C for 10 minutes as shown by TGA. IDM was chemically stable in the formulations following hot-melt extrusion as determined by a USP stability indicating RP-HPLC assay. The drug and polymer adsorption study demonstrated that IDM had a strong binding with the Eudragit® RD 100 resulting in an incomplete drug release from the extrudated granules. When 10% of the Eudragit® L 100 or Eudragit® S 100 was blended with Eudragit® RD 100, a weaker

interaction was observed due to the presence of the anionic functional group in the Eudragit® L 100 or Eudragit® S 100. The drug release rate from the hot-melt extrudates solid solutions increased with a decrease in granule particle size, with the addition of the Pluronic® F68, Eudragit® L 100 or Eudragit® S 100, and also with an increase in the pH of the dissolution media due to the increased wetability and solubility of the drug, increased permeability of the polymer, or decreased drug and polymer interaction. The incorporation of TEC, the further formulation and processing of the hot-melt extrudated granules with Avicel® PH-101 and L-HPC into tablets showed no significant influence on drug release from the granules. SEM photographs showed that IDM was homogeneously distributed in the hot-melt extrudates and that the addition of TEC decreased the brittle character of the extrudate.

CHAPTER FIVE: SUMMARY AND CONCLUSIONS

The influence of *in situ* plasticization of chlorpheniramine maleate (CPM) on Eudragit® RS PO from hot-melt extruded matrix tablets, and from compressed granules prepared by thermal processing was investigated. CPM was studied as both a model drug substance and as a solid-state plasticizer for the acrylic polymer. Triethyl citrate (TEC) was incorporated into the polymer blend as a liquid plasticizer for the polymer. The influence of TEC and CPM concentration on the dissolution properties of CPM tablets was investigated. The glass transition temperature (Tg) of the samples was determined by modulated differential scanning calorimetry. The morphologies of the granules formed by hot-melt extrusion and hot-melt granulation processes were investigated by scanning electron microscopy. The addition of 12% TEC to the polymer reduced the Tg by 32.5°C, while the reduction in the Tg for the same level of CPM was 16.4°C. The effect of TEC levels on drug release was dependent on the tablet preparation method. At high TEC levels, the release rate of CPM decreased in tablets prepared by direct compression and tablets made from compressed granules that had been prepared by high shear hot-melt granulation. However, the CPM release rate increased from hot-melt extruded tablets with increasing blends of plasticizer in the extruded tablets. An increase in the CPM content in the tablets resulted in an increase in the drug release rate. During high shear hot-melt granulation, the model

drug adhered to the polymer to form a porous discontinuous structure. Following hot-melt extrusion, the drug was distributed at a molecular level in the continuous polymeric structure. The influence of both CPM and TEC levels on the drug release rate from these polymeric drug delivery systems was shown to be a function of whether the granules or tablets were formed by either hot-melt granulation or hot-melt extrusion, as well as the plasticization effects of both TEC and CPM on the acrylic polymer.

To determine the effects of thermal processing and post-processing thermal treatment on the release properties of chlorpheniramine maleate (CPM) from matrix tablets containing Eudragit® RS PO and triethyl citrate (TEC), CPM tablets containing Eudragit® RS PO with and without TEC were prepared by direct compression, high shear hot-melt granulation and hot-melt extrusion. X-ray diffraction patterns showed that the CPM was distributed in Eudragit® RS PO at the molecular level following hot-melt extrusion. The TGA profiles of CPM, Eudragit® RS PO and TEC demonstrated that these materials were thermally stable during both the high shear hot-melt granulation and hot-melt extrusion processes. The tablets were subjected to post-processing thermal treatment by storing the tablets at 60°C in open containers for 24 hours. Tablets prepared by direct compression showed the highest drug release rate constant of 36.2%$h^{-1/2}$. When 4% TEC was incorporated into the formulation, the drug release rate constant for the directly compressed tablets decreased to 32.4%$h^{-1/2}$. After high shear hot-melt granulation and hot-melt extrusion

of the powder blend containing 4% TEC, the drug release rate constant decreased to 30.8%$h^{-1/2}$ and 13.8%$h^{-1/2}$ for the respective processes. The drug release rate constants for all tablets decreased following post-processing thermal treatment. The reduction in release rate was due to an increase in the intermolecular binding and entanglement between drug molecules and polymer molecules that occurred during thermal processing. Post-processing thermal treatment of the hot-melt extrudates had a minimal effect on the drug release rate since the hot-melt extrusion process enhanced the drug and polymer entanglement to a greater extent.

To investigate the influence of a lipophilic thermal lubricant on the processing conditions and properties of chlorpheniramine maleate (CPM) tablets prepared by hot-melt extrusion, CPM tablets containing Eudragit® RS PO, triethyl citrate (TEC) and glyceryl monostearate (GMS) were prepared by hot-melt extrusion at 95°C (die). The thermal stability of CPM, Eudragit® RS PO, TEC, and GMS were determined by thermogravimetric analysis (TGA). The influence of the concentration of thermal lubricant and plasticizer level on the thermal processing parameters was determined. The effect of the GMS level on the drug release properties of CPM hot-melt extruded tablets was investigated. Differential scanning calorimetry (DSC) was used to investigate the compatibility of the drug and the functional excipients. The morphologies of the extrudates were investigated by scanning electron microscopy (SEM). In addition, X-ray diffractometry was employed to study the crystallinity of CPM in the hot-melt extrudates. Thermal stability studies showed that CPM and the

excipient components of the extruded tablets were stable at the thermal processing temperature. The incorporation of TEC or GMS in the powder blend decreased the drive AMPS and the torque values in the hot-melt extrusion process. The glass transition for Eudragit® RS PO and the melting behavior of GMS were determined with the powder mixture of GMS and Eudragit® RS PO. The results demonstrated that these two materials were not miscible in the molten state. These results were in agreement with the findings from the SEM and X-ray diffraction studies. An increase in the thermal lubricant level in the Eudragit® RS PO system resulted in an increase in the rate of drug release from the tablets. TEC and GMS facilitated the thermal processing to prepare CPM controlled-release matrix tablets containing an acrylic polymer by hot-melt extrusion. TEC lowered both the glass transition temperature and the melt viscosity of the acrylic polymer. The lipophilic lubricant only decreased the melt viscosity of the acrylic polymer and had no effect on the glass transition temperature.

In the current study, the influence of plasticizer level on drug release was investigated for two thermal processes: hot-melt extrusion and film coating. Two highly water-soluble model drugs, diltiazem hydrochloride (DTZ) and chlorpheniramine maleate (CPM), and a poorly water-soluble drug, indomethacin (IDM) were selected in the hot-melt extruded formulations containing Eudragit® RS PO or Eudragit® RD 100 and TEC. In addition, pellets containing DTZ were film coated with Eudragit® RS 30D and varying levels of TEC using a fluidized bed

coating unit. Both CPM and IDM exerted the plasticization effect on the acrylic polymers. No plasticizing effect of DTZ on Eudragit® RS PO was observed from differential scanning calorimetry (DSC). Thermogravimetric analysis (TGA) data showed the thermal stability of the DTZ, Eudragit® RS PO and TEC under the hot-melt extrusion temperature 140°C. Drug content determined by HPLC indicated the chemical stability of DTZ in the formulation following hot-melt extrusion. Drug release rates of both DTZ and CPM from hot-melt extrudates increased with an increase in the TEC level in the formulations, while DTZ release from the Eudragit® RS 30D coated pellets decreased with an increase of TEC in the coating layer. This observation could be attributed to the fact that a continuous polymeric structure was formed following hot-melt extrusion regardless of the TEC level. However, for the film coated pellets coalescence of the polymer particles was enhanced with higher levels of TEC as revealed by SEM. The addition of TEC (0% to 8%) in the hot-melt extrudate formulation containing IDM did not influence the drug release rate as the drug release rate was controlled by intraparticle diffusion for poorly water-soluble drugs.

To investigate the physicochemical and drug release properties of controlled release hot-melt extrudates containing a poorly water-soluble drug, indomethacin (IDM). IDM tablets containing Eudragit® RD 100, and triethyl citrate (TEC) were prepared by hot-melt extrusion using a Randcastle Microtruder RCP-0750 vertical single screw extruder. The crystal habit and the particle size of IDM were determined

and the true density was determined using a helium pycnometer. Differential scanning calorimetry (DSC) was employed to investigate the melting point of IDM and the plasticization effects of both IDM and Pluronic® F68 on the acrylic polymer. Thermogravimetric analysis (TGA) was used to study the thermal stability of the these materials under the hot-melt processing conditions. The chemical stability of IDM following thermal processing and the amount of drug release from the hot-melt extrudates during dissolution testing were determined by RP-HPLC. Dissolution studies were conducted according to the USP 24 apparatus 2 method at 37°C and 100 rpm in pH 6.8 phosphate buffer solution and also according to the USP 24 apparatus 3 method at pH 1.2, 5.0, 6.8, and 7.4. The influence of granule size, and the mechanism of Pluronic® F68, Eudragit® S 100, Eudragit® L 100, TEC in the extrudate on drug release was investigated. The microstructure of the hot-melt extrudates was examined by SEM. X-ray diffractometry was used to investigate the crystallinity of the model drug following hot-melt extrusion. IDM was found to be thermally stable at the hot-melt extrusion processing temperatures and displayed a plasticizing effect on the Eudragit® RL PO as revealed by a decrease in the glass transition temperatures of the polymer. The inclusion of the Pluronic® F68, Eudragit® L 100 or Eudragit® S 100 in the powder blend prior to processing increased the rate of release of the IDM from the extrudates. An increase in the media pH or a decrease in the granule particle size also increased the rate of release of IDM. The inclusion of TEC up to 8% in the granule formulation or compressing the granules

with Avicel® PH-101 and L-HPC in the tablets did not influence the drug release. IDM was transformed from the crystalline Form I into an amorphous form in the Eudragit® RD 100 granules following hot-melt extrusion. Controlled release tablets containing IDM and acrylic polymers were successfully prepared by hot-melt extrusion. The thermal processing facilitated the formation of a solid solution with a continuous matrix structure that was shown to decrease drug diffusivity from the hot-melt extrudates.

Table 1.3.1. Drug release mathematical models

Zero order	$Q_t = Q_0 + Kt$
First order	$\ln Q_t = \ln Q_0 + Kt$
Higuchi	$Q_t = Kt^{1/2}$
Hixson-Crowell	$Q_\infty^{1/3} - Q_t^{1/3} = Kt$
Korsmeyer-Peppas	$Q_t / Q_\infty = Kt^n$
Baker-Lonsdale	$(3/2)[1-(1-(Q_t / Q_\infty))^{2/3}] - (Q_t / Q_\infty) = Kt$

Q_t is the amount of drug released after time t.

Q_∞ is the total amount of drug in the dosage form.

t is the drug release time.

K is a drug release constant.

n is the release exponent, indicative of the mechanism of drug release. Zero-order and anomalous release kinetics are represented by $0.89<n<1.0$ and $0.45<n<0.89$, respectively, for a swellable cylindrical matrix.

Table 3.2.1. Hot-melt extrusion processing temperatures at different zones for CPM, DTZ, and IDM.

Drugs	Temperatures of Different Heating Zones			
	Zone 1	Zone 2	Zone 3	Zone 4 (die)
CPM	90°C	105°C	110°C	115°C
DTZ	90°C	120°C	135°C	140°C
IDM	90°C	105°C	120°C	140°C

Table 3.2.2. Film coating conditions.

Preheating temperature	35°C
Preheating time	2 minutes
Inlet temperature	35-40°C
Outlet temperature	32-34°C
Air pressure	1.5 Kg/cm^2
Spray rate	2.0g/min
Coating level	8%, 10%, 12%, and 15% based on polymer weight

Table 3.2.3. Dissolution methods for CPM, TEC, DTZ, and IDM.

	CPM and TEC	DTZ	IDM
Method	USP 24 basket	USP 24 paddle	USP 24 paddle
Dissolution medium	Distilled water, 500ml	PH 7.2 PBS, 900ml	PH 6.8 PBS, 900ml
Rotation speed	100rpm	50rpm	75rpm
Temperature	37°C	37°C	37°C
Determination method	UV, 261nm (CPM) HPLC (TEC), 220nm	HPLC, 240nm	HPLC, 254nm

Table 3.2.4. HPLC methods for CPM, DTZ, IDM, and TEC.

Model Drug	CPM	DTZ	IDM	TEC
Mobile phase (v/v)	Methanol:water: triethylamine (850:150:2)	Acetonitrile: 0.02M PBS (50:50)	Acetonitrile: 0.02 *M* PBS (60:40)	Methanol: water (70:30)
Wavelength	261nm	240nm	254nm	220nm
Retention Time	6.0min	5.0min	4.5min	5.0 min
Flow rate	1.0 ml/min	1.0 ml/min	1.0 ml/min	1.0 ml/min
Injection Volume	20 μL	20 μL	20 μL	20 μL

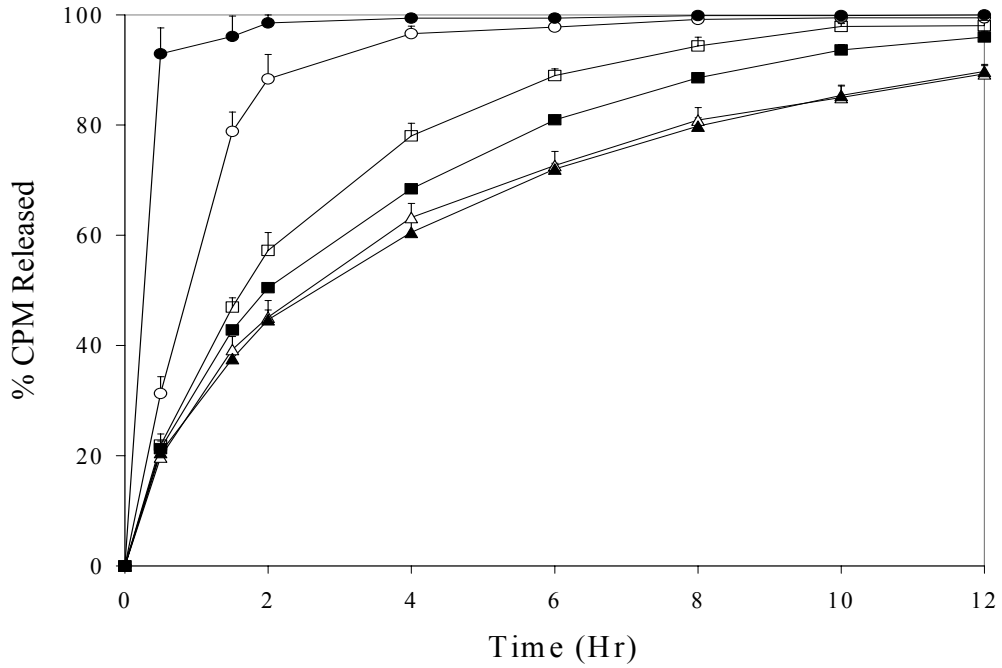


Figure 4.1.1. Influence of triethyl citrate levels on the dissolution properties of Eudragit® RS PO tablets containing chlorpheniramine maleate (10%**,** w/w), prepared by direct compression of powder blend (DC) or high shear hot-melt granules (HMG). Compression force: 2000Kg. Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (○): 0% triethyl citrate, DC; (□): 4% (w/w) triethyl citrate, DC; (Δ): 7% (w/w) triethyl citrate, DC; (●): 0% triethyl citrate, HMG; (■): 4% (w/w) triethyl citrate, HMG; (▲): 7% (w/w) triethyl citrate, HMG.

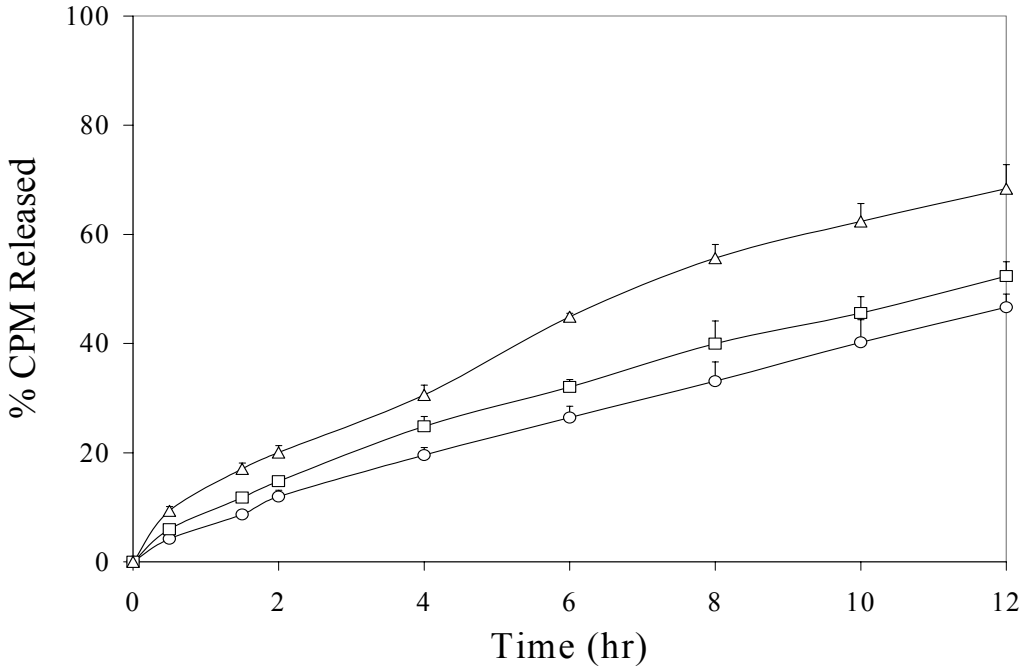


Figure 4.1.2. Influence of triethyl citrate levels on the dissolution properties of Eudragit® RS PO hot-melt extruded tablets containing chlorpheniramine maleate (10%, w/w).

Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (●): 0% triethyl citrate; (■): 4% (w/w) triethyl citrate; (▲): 7% (w/w) triethyl citrate.

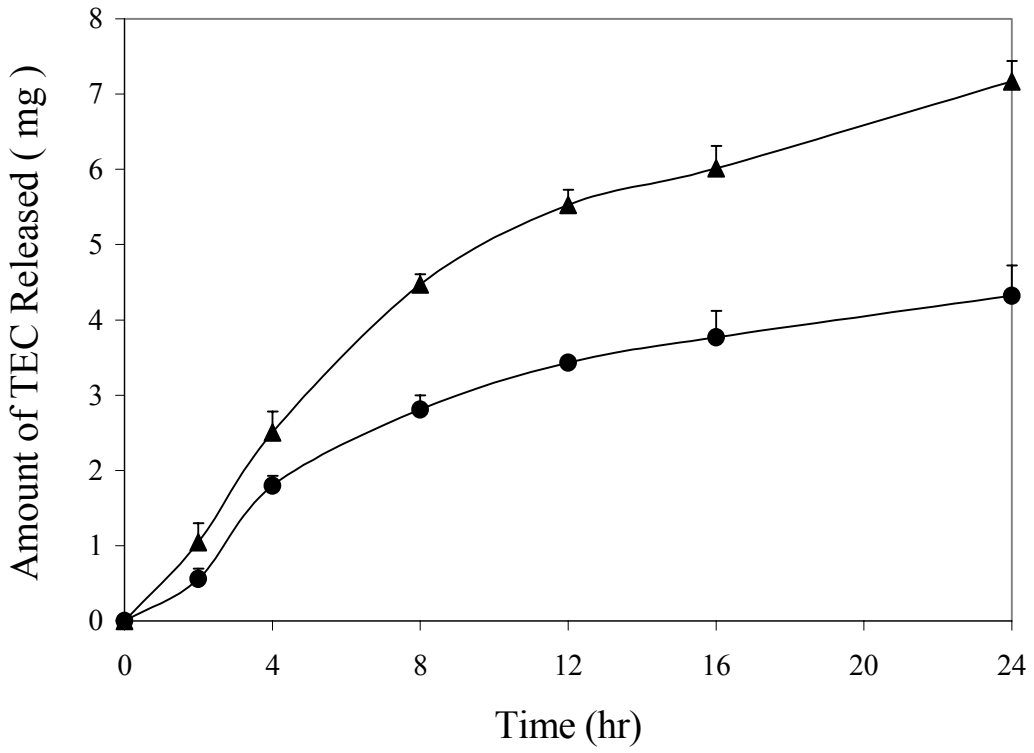


Figure 4.1.3. Release of triethyl citrate from the hot-melt extruded Eudragit® RS PO tablets containing chlorpheniramine maleate (10%, w/w) with time.
Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (●): 4% (w/w) triethyl citrate; (▲): 7% (w/w) triethyl citrate.

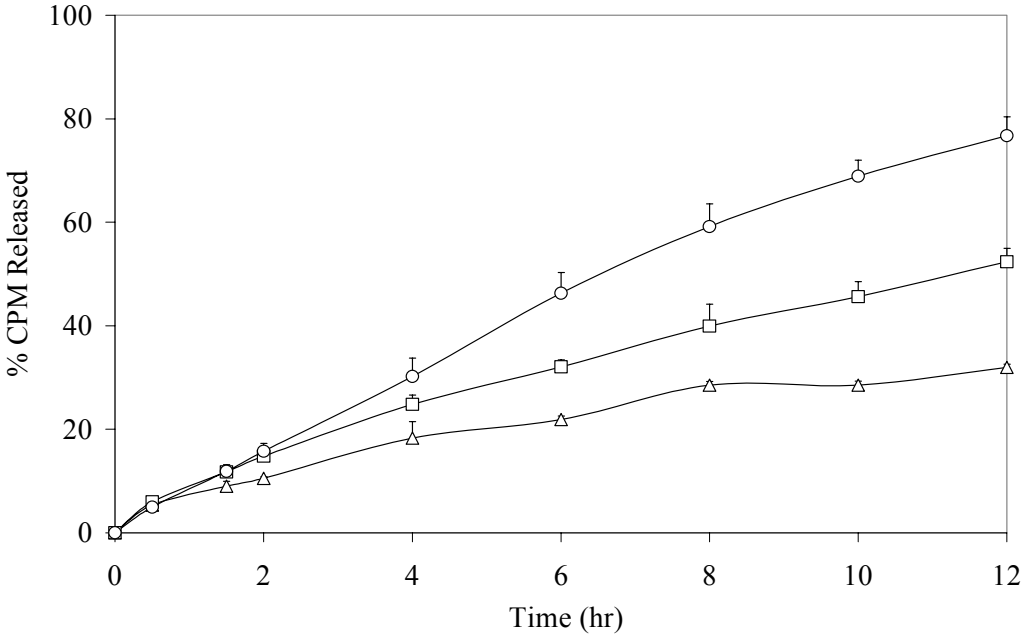


Figure 4.1.4. Influence of chlorpheniramine maleate levels on the dissolution properties of hot-melt extruded chlorpheniramine maleate tablets containing Eudragit® RS PO and 4% (w/w) triethyl citrate.

Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (Δ): 6% (w/w) chlorpheniramine maleate ; (□): 10% (w/w) chlorpheniramine maleate ; (○): 14% (w/w) chlorpheniramine maleate .

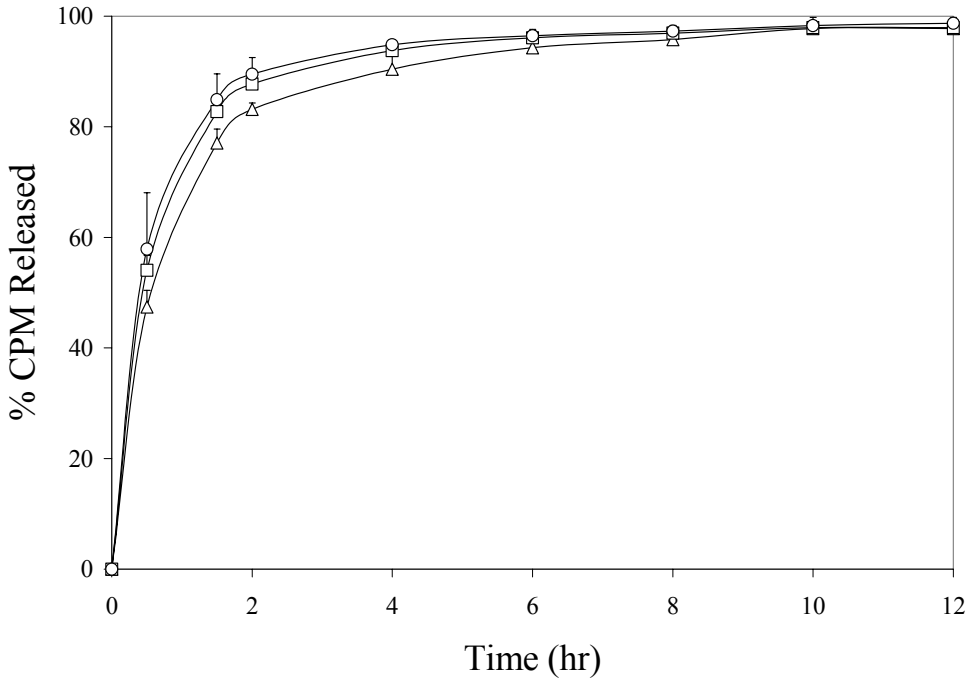


Figure 4.1.5. Influence of chlorpheniramine maleate levels on the dissolution properties of chlorpheniramine maleate tablets containing Eudragit® RS PO and 4% (w/w) triethyl citrate prepared with hot-melt extruded granules.

Compression force: 2000Kg. Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (Δ): 6% (w/w) chlorpheniramine maleate ; (□): 10% (w/w) chlorpheniramine maleate ; (○): 14% (w/w) chlorpheniramine maleate .

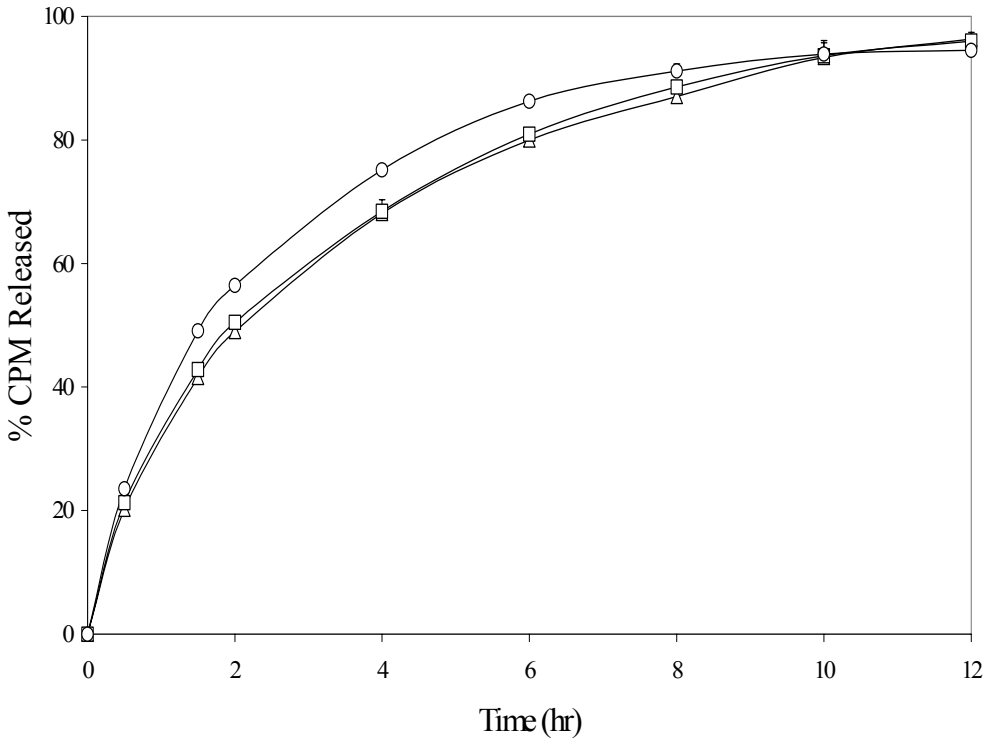


Figure 4.1.6. Influence of chlorpheniramine maleate levels on the dissolution properties of chlorpheniramine maleate tablets containing Eudragit® RS PO and 4% (w/w) triethyl citrate prepared with high shear hot-melt granules.

Compression force: 2000Kg. Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (Δ): 6% (w/w) chlorpheniramine maleate; (□): 10% (w/w) chlorpheniramine maleate; (○): 14% (w/w) chlorpheniramine maleate.

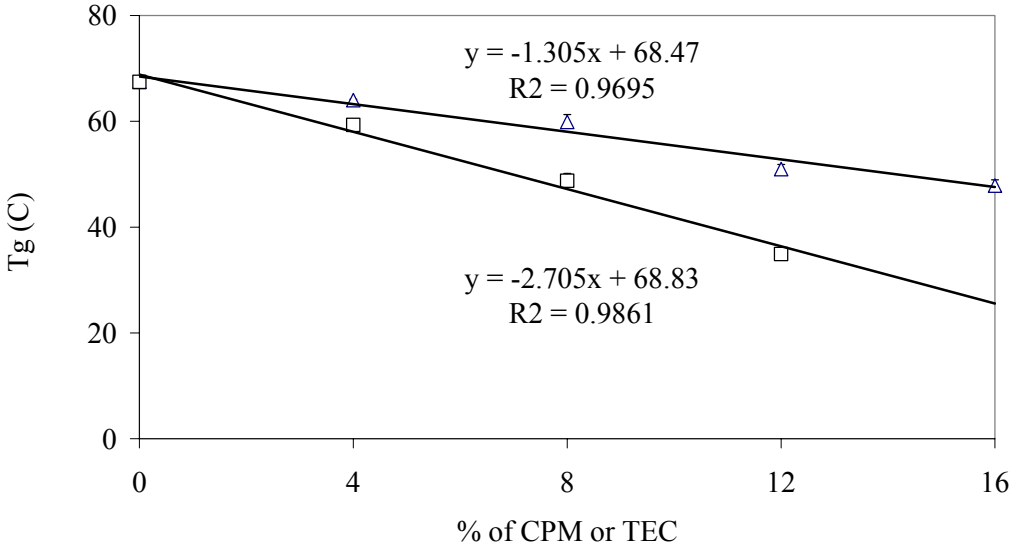
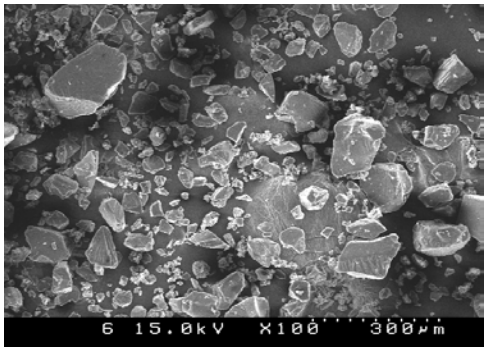
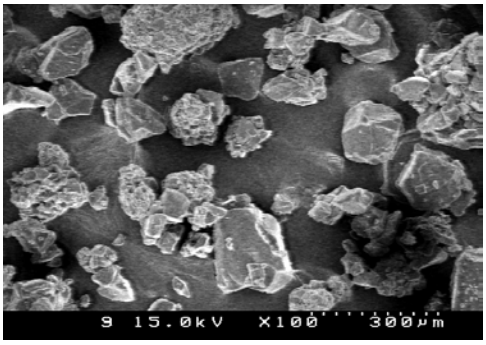


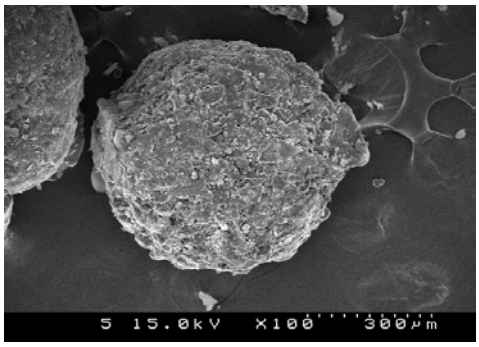
Figure 4.1.7. Glass transition temperature of Eudragit® RS PO as a function of chlorpheniramine maleate and triethyl citrate level, determined by MDSC (n=3). (Δ):chlorpheniramine maleate ; (□):triethyl citrate.



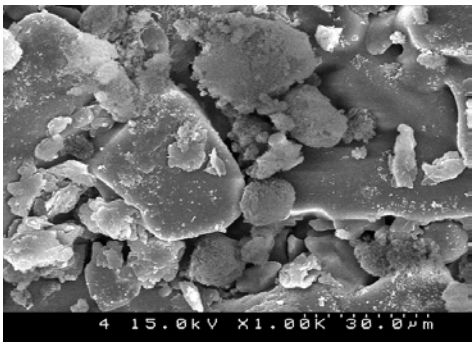
(A)



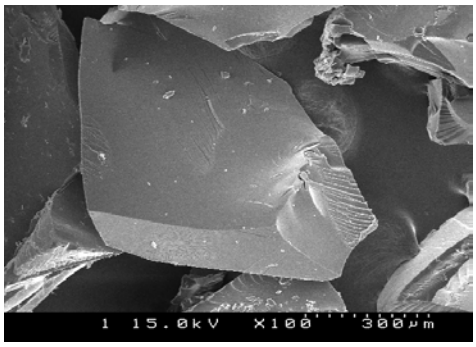
(B)



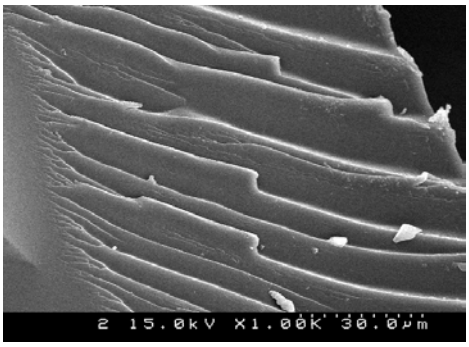
(C)



(D)



(E)



(F)

Figure 4.1.8. SEM photographs of processed CPM formulatıons.
(A), Physical mixture of chlorpheniramine maleate and Eudragit® RS PO; (B), Physical mixture of chlorpheniramine maleate, Eudragit® RS PO, and triethyl citrate; (C, D), High shear hot-melt granules containing triethyl citrate plasticized Eudragit® RS PO and chlorpheniramine maleate at two magnifications; (E, F), Hot-melt extruded granules containing triethyl citrate plasticized Eudragit® RS PO and chlorpheniramine maleate at two magnifications.

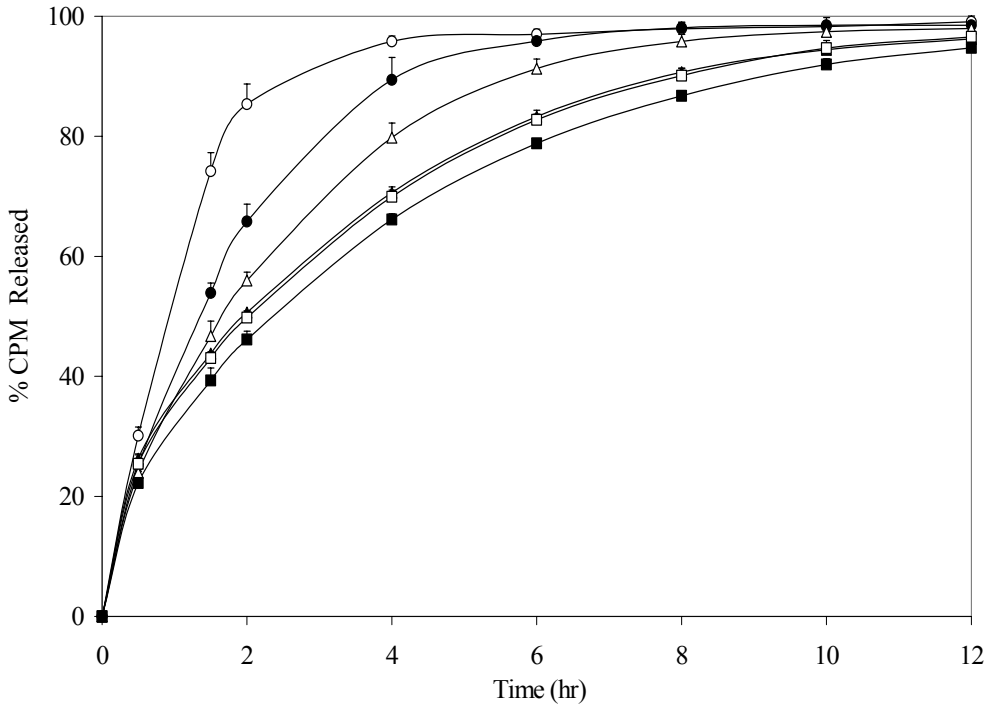


Figure 4.2.1. Influence of post-processing thermal treatment (at 60°C) on the dissolution profiles of Eudragit RS PO tablets containing CPM (10%), prepared by direct compression.

Compression force: 2000Kg. Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (○): Before treatment; (●): 15min; (Δ): 30min; (▲): 1.0 hour; (□): 4.0 hour; (■): 24 hour.

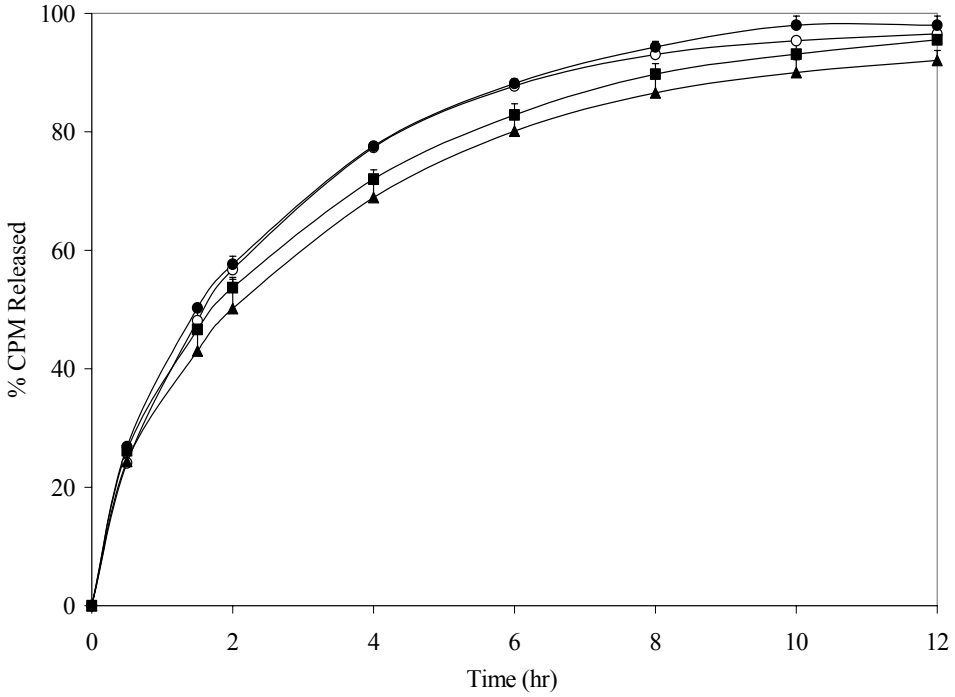


Figure 4.2.2. Influence of post-processing thermal treatment (at 60°C) on the dissolution profiles of Eudragit RS PO tablets containing CPM (10%) and TEC (4%), prepared by direct compression.

Compression force: 2000Kg. Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (○): Before treatment; (●): 1.0 hour; (▲): 4.0 hour; (■): 24 hour.

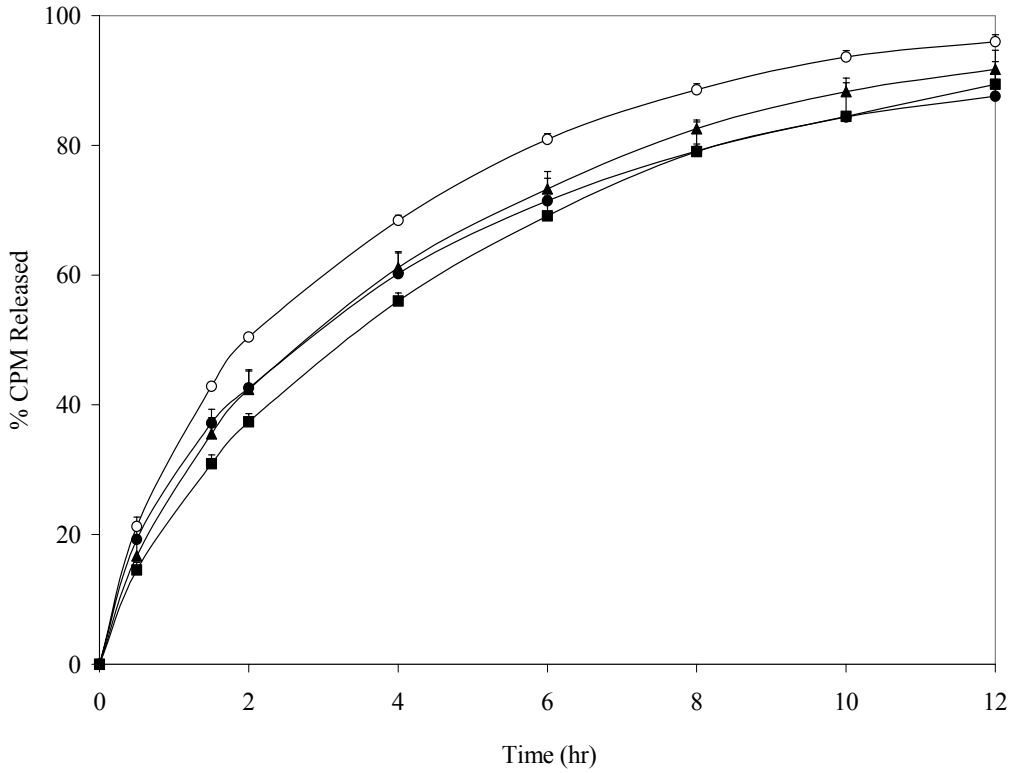


Figure 4.2.3. Influence of post-processing thermal treatment (at 60°C) on the dissolution profiles of Eudragit RS PO tablets containing CPM (10%) and TEC (4%), prepared by high shear mixer hot-melt granulation.

Processing temperatures: 60°C. Compression force: 2000Kg. Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (○): Before treatment; (●): 1.0 hour; (▲): 4.0 hour; (■): 24 hour.

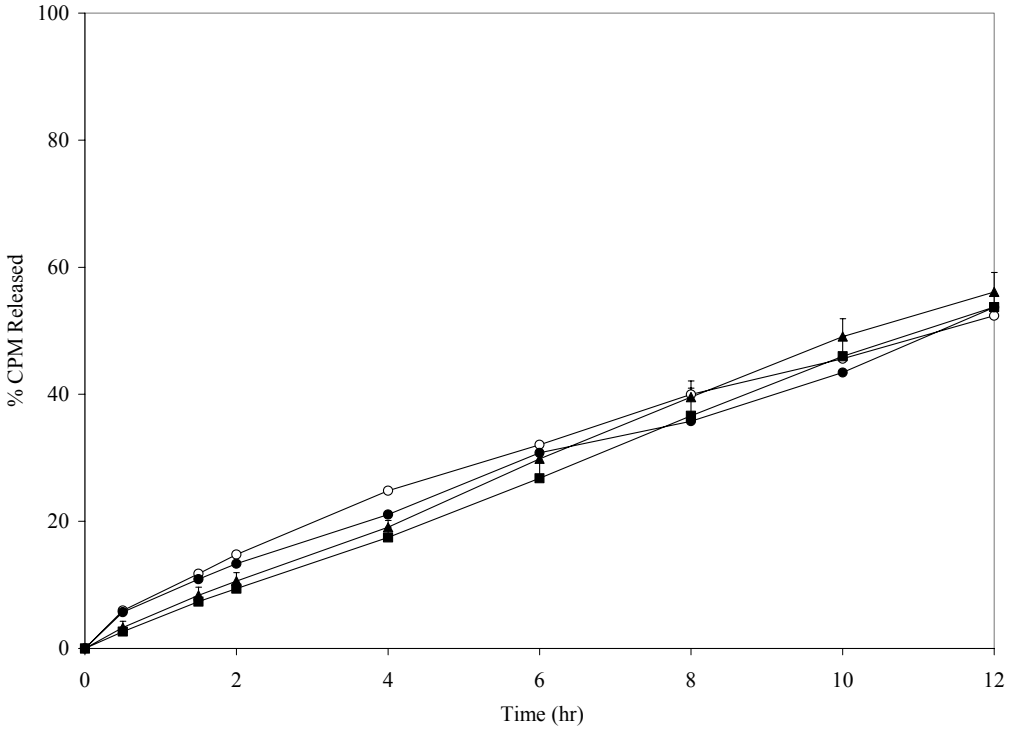


Figure 4.2.4. Influence of post-processing thermal treatment (at 60°C) on the dissolution profiles of hot-melt extruded tablets containing Eudragit RS PO, CPM (10%) and TEC (4%).

Processing temperatures: Zone 1, 2, 3, and 4 (die): 90°C, 105°C, 110°C, and 115°C respectively. Screw rate: 20 rpm. Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (○): Before treatment; (●): 1.0 hour; (▲): 4.0 hour; (■): 24 hour.

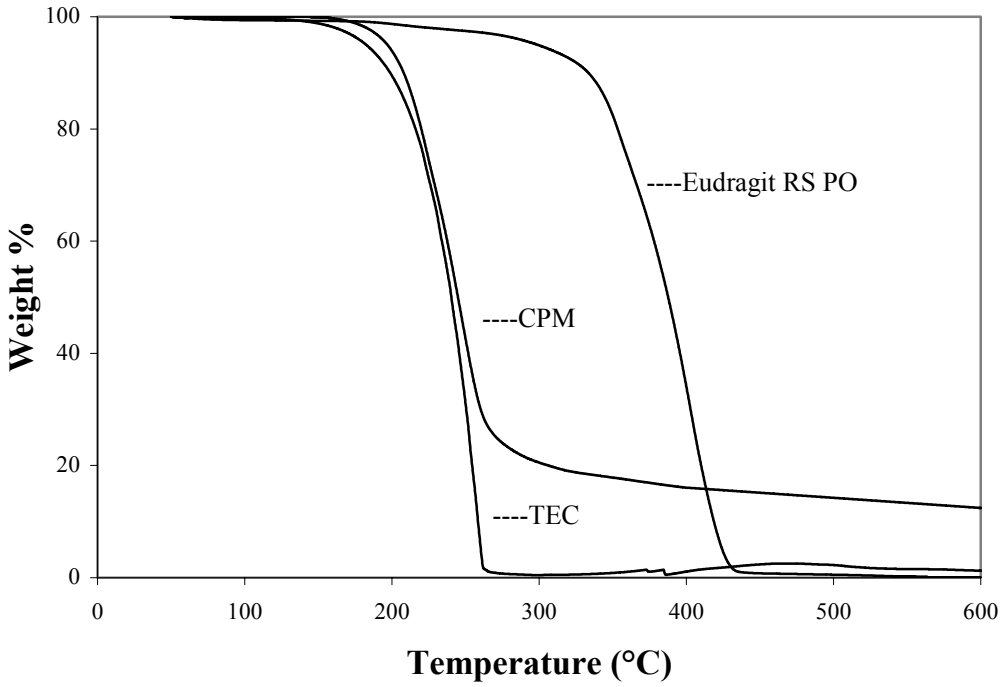


Figure 4.2.5. Thermal stability of CPM, Eudragit® RS PO and TEC was determined from 50°C to 600°C at the heating rate of 10°C /min using thermogravimetry analysis (TGA).

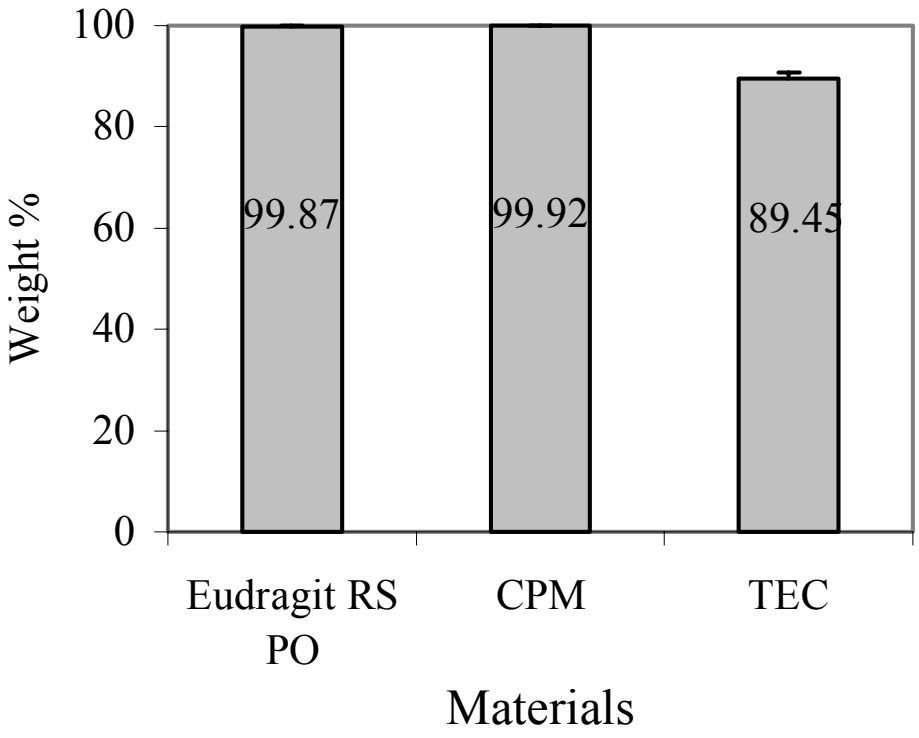


Figure 4.2.6. Dynamic thermal stability of CPM, Eudragit® RS PO and TEC were determined using thermogravimetry analysis (TGA) with temperatures held at 120°C for 60 minutes.

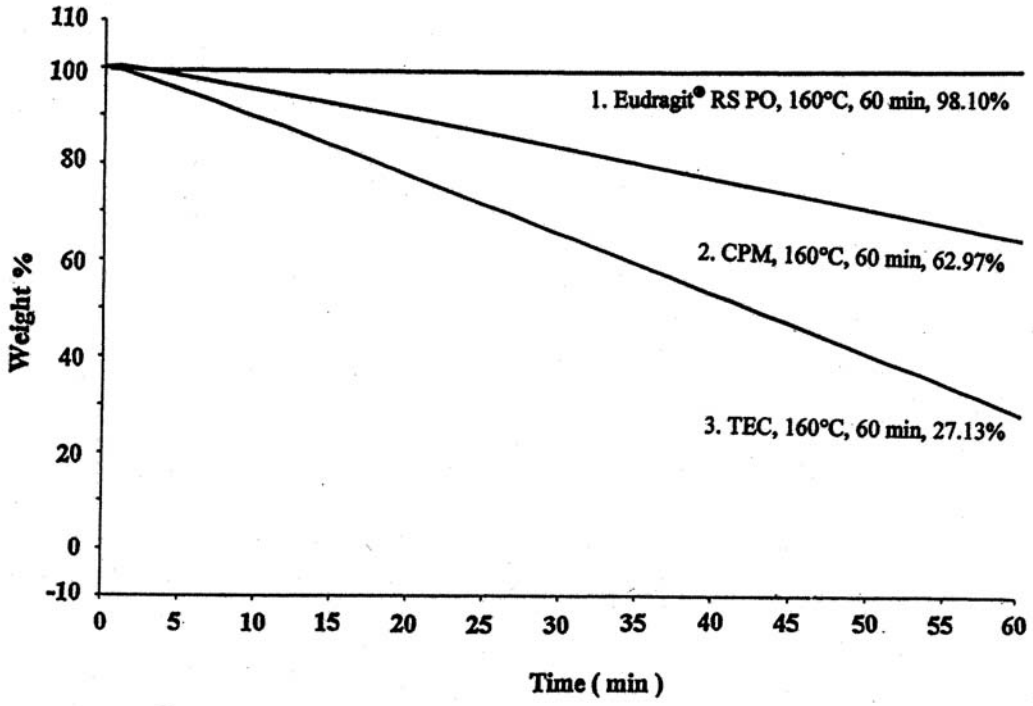


Figure 4.2.7. Dynamic thermal stability of CPM, Eudragit® RS PO and TEC were determined using thermogravimetry analysis (TGA) with temperatures held at 160°C for 60 minutes.

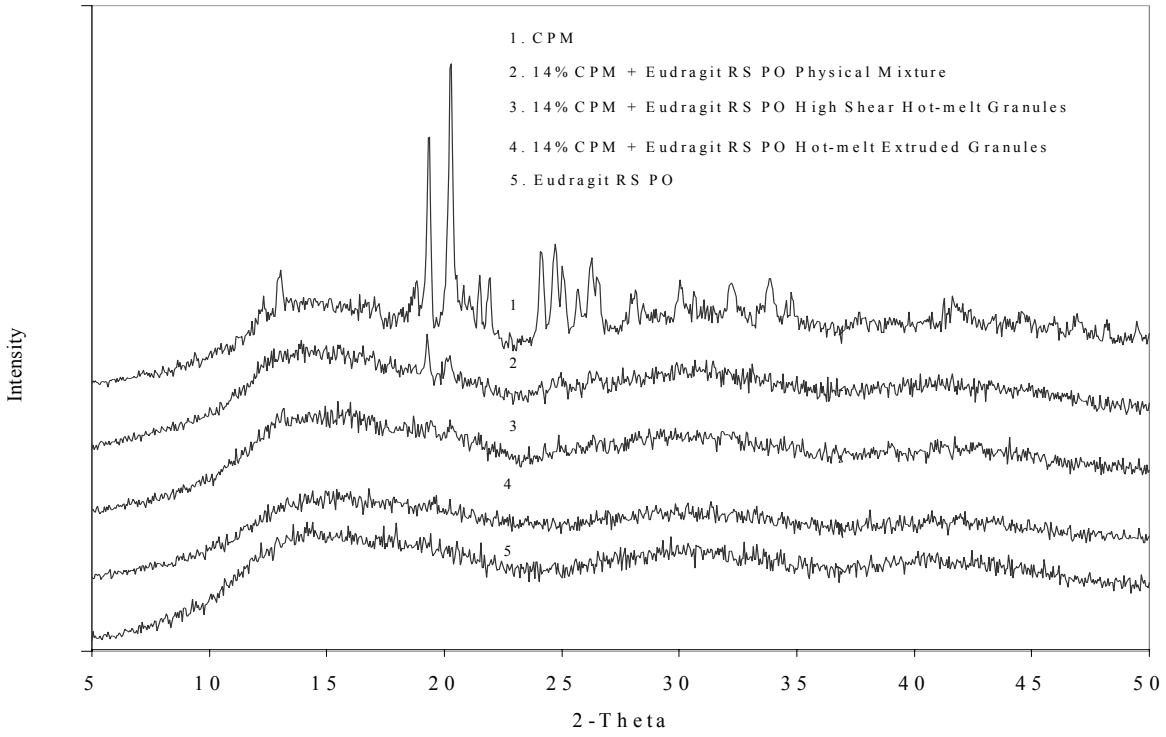


Figure 4.2.8. X-ray diffraction patterns of CPM, Eudragit® RS PO, and three treatments of these materials were determined using an X-ray diffractometer.

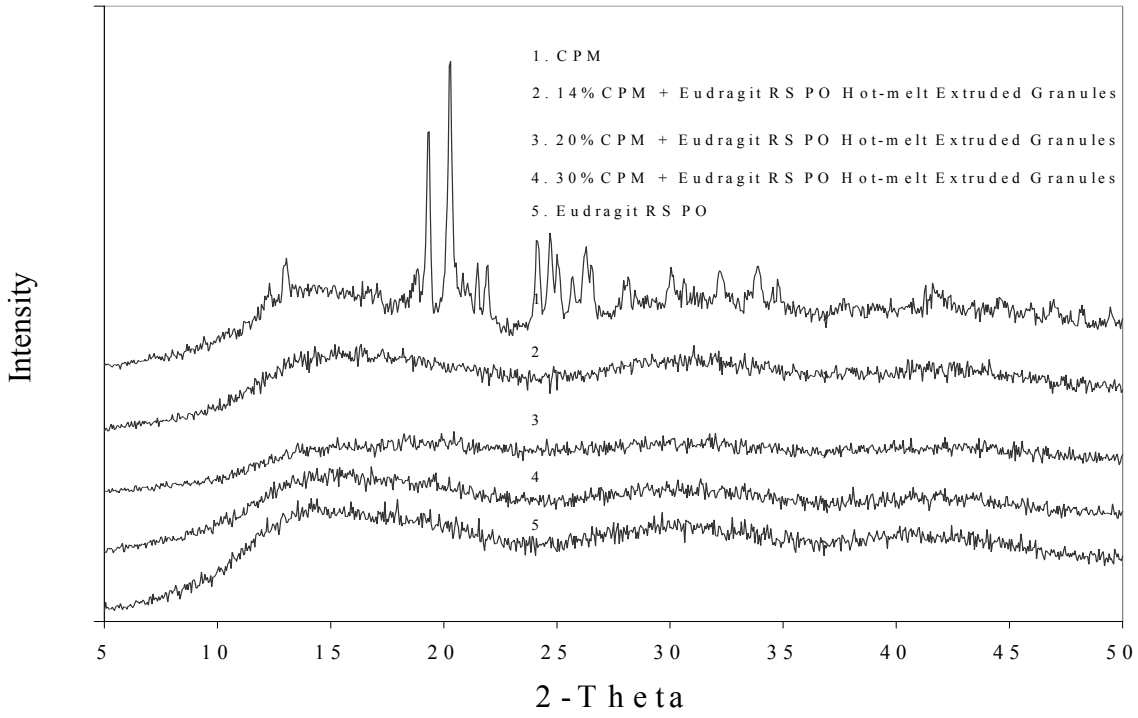


Figure 4.2.9. X-ray diffraction patterns of hot-melt extruded granules of Eudragit® RS PO were determined using an X-ray diffractometer.

Table 4.3.1. Influence of thermal processing temperature on the processing parameters for Eudragit® RS PO.

Heating Zones	Processing Temperature at Different Zones			
Zone 1	120°C	115°C	110°C	110°C
Zone 2	160°C	150°C	140°C	130°C
Zone 3	180°C	160°C	150°C	140°C
Zone 4	190°C	170°C	160°C	150°C
Drive AMPS	2.04±0.14	2.74±0.30	3.20±0.30	3.66±0.16
Pre-die Pressure	Zero PSI	Zero PSI	200 PSI	400 PSI

Table 4.3.2. Influence of TEC on the hot-melt processing parameters for Eudragit® RS PO.

Heating Zones	Processing Materials		
	Eudragit® RS PO	Eudragit® RS PO+4%TEC	Eudragit® RS PO+8%TEC
Zone 1	110°C	110°C	110°C
Zone 2	130°C	130°C	130°C
Zone 3	140°C	140°C	140°C
Zone 4	150°C	150°C	150°C
Drive AMPS	3.66±0.16	1.92± 0.18	1.14±0.06
Pre-die Pres.	400 PSI	Zero PSI	Zero PSI

Table 4.3.3. Influence of GMS on the hot-melt processing parameters for Eudragit® RS PO.

Heating	Processing Materials			
Zones	Eudragit® RS PO	Eudragit® RS PO+10%GMS	Eudragit® RS PO+20%GMS	Eudragit® RS PO+30%GMS
Zone 1	110°C	110°C	110°C	110°C
Zone 2	130°C	130°C	130°C	130°C
Zone 3	140°C	140°C	140°C	140°C
Zone 4	150°C	150°C	150°C	150°C
Drive AMPS	3.66±0.16	1.39±0.02	0.90±0.01	0.86±0.01
Pre-die Pres.	400 PSI	Zero PSI	Zero PSI	Zero PSI

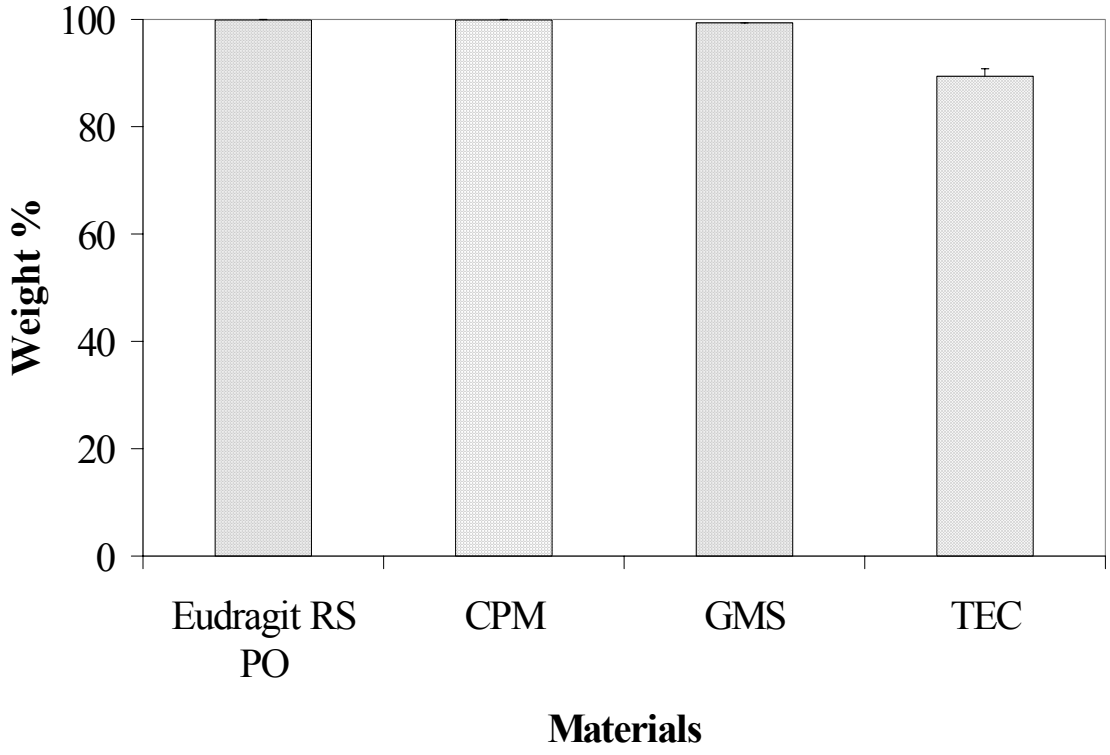


Figure 4.3.1. Thermal stability of CPM, Eudragit® RS PO, GMS, and TEC isothermal at 120°C for 60 minutes.

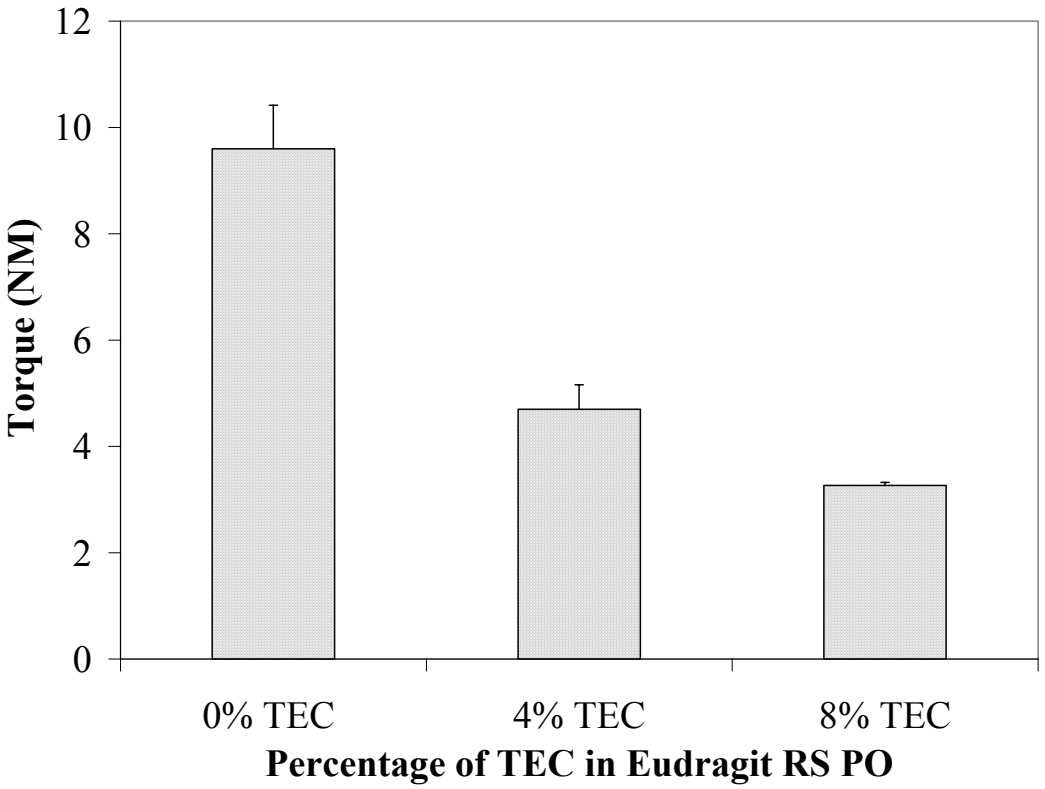


Figure 4.3.2. Influence of TEC on the reduction of hot-melt viscosity of Eudragit® RS PO.

(Temperatures for zone 1, zone 2, and zone 3: 140°C, 130°C, and 110°C. Screw rotation speed: 30rpm).

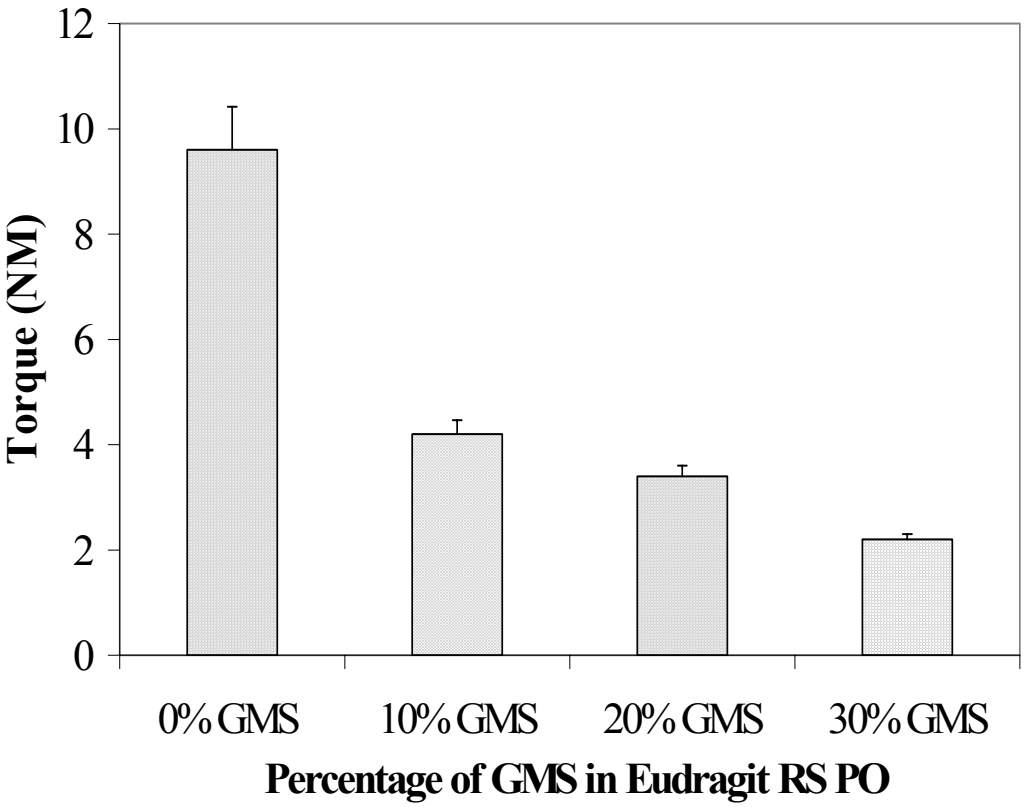


Figure 4.3.3. Influence of GMS on the reduction of hot-melt viscosity of Eudragit® RS PO.

(Temperatures for zone 1, zone 2, and zone 3: 140°C, 130°C, and 110°C. Screw rotation speed: 30rpm).

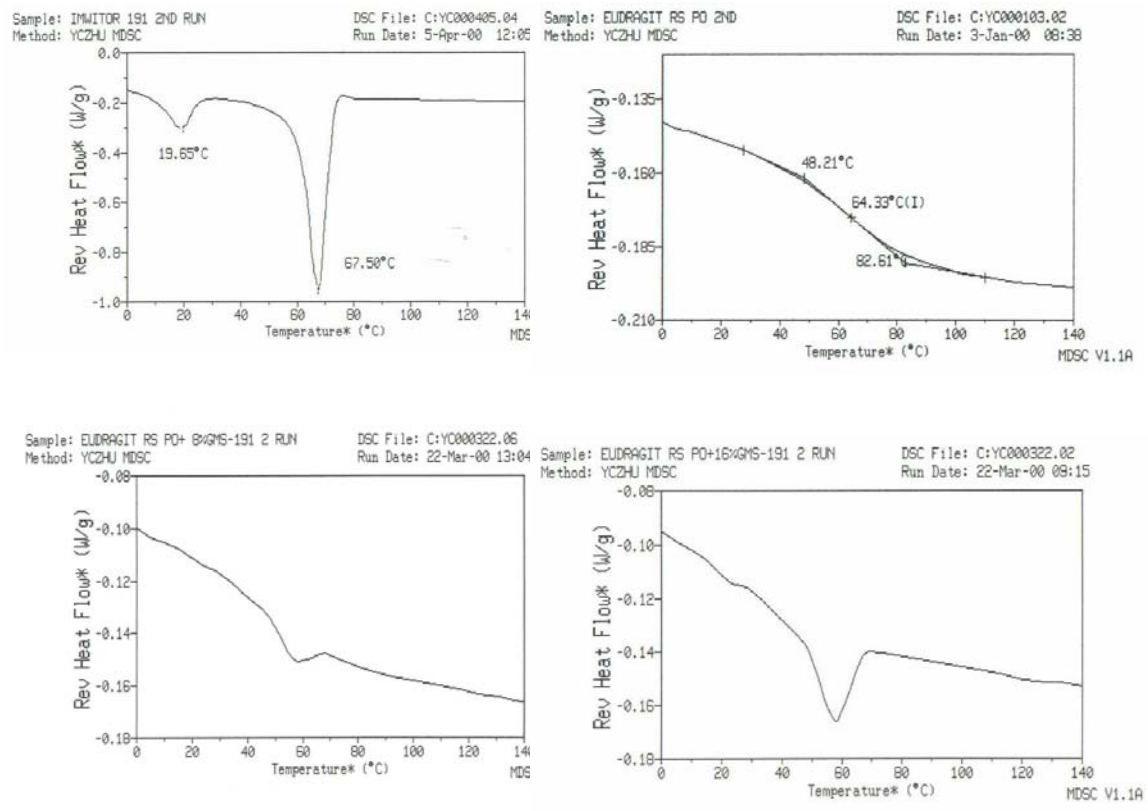


Figure 4.3.4. Thermal miscibility of GMS with Eudragit® RS PO determined by DSC.

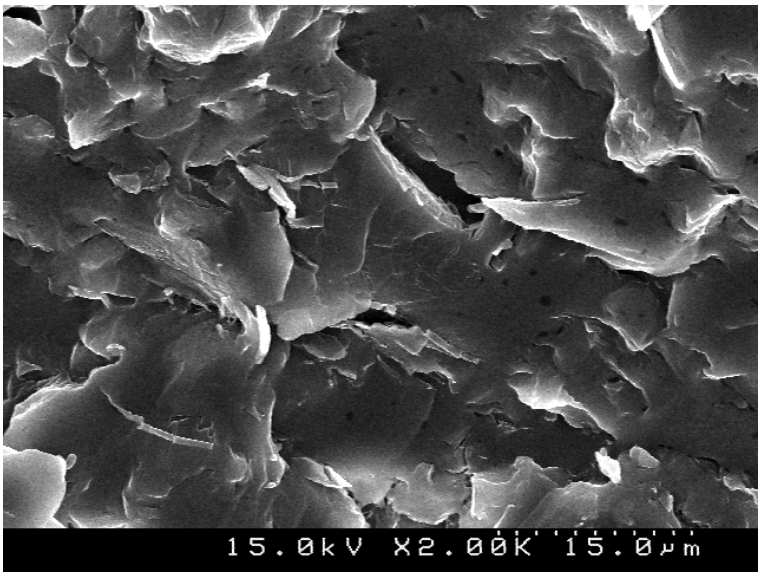


Figure 4.3.5. SEM photographs of the hot-melt extrudates containing 5% GMS. (Formulation: 14% CPM, 77%,Eudragit RS PO, 4% TEC, 5%GMS)

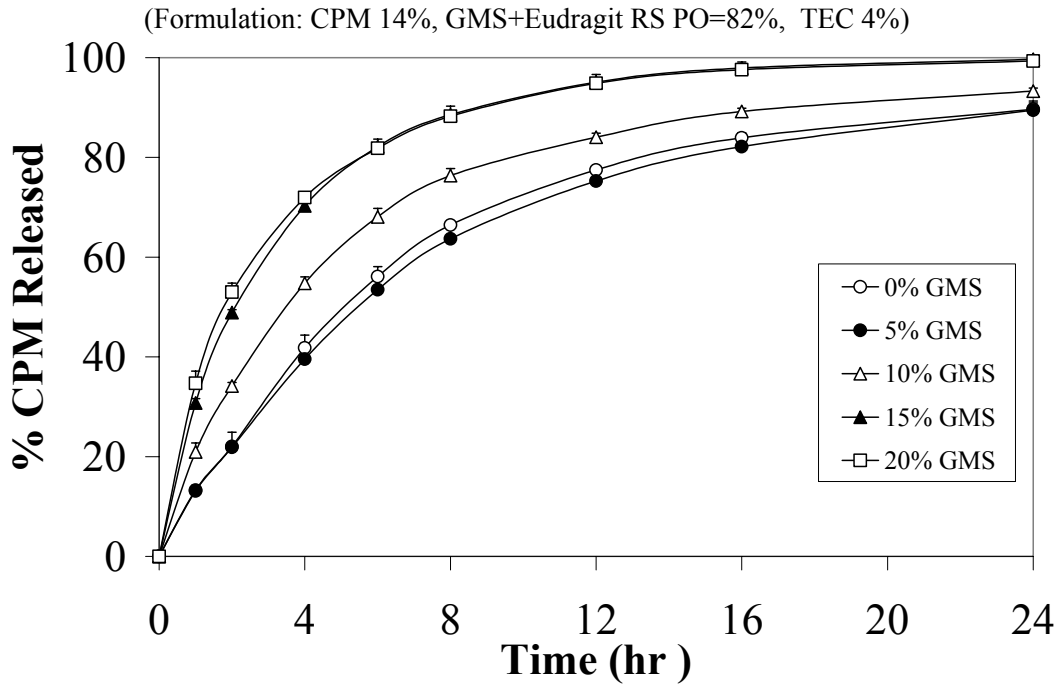


Figure 4.3.6. Influence of GMS on the drug release from hot-melt extruded tablets. Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (○): 0% GMS; (●): 5% GMS; (Δ): 10% GMS; (▲): 15% GMS; (□): 20% GMS.

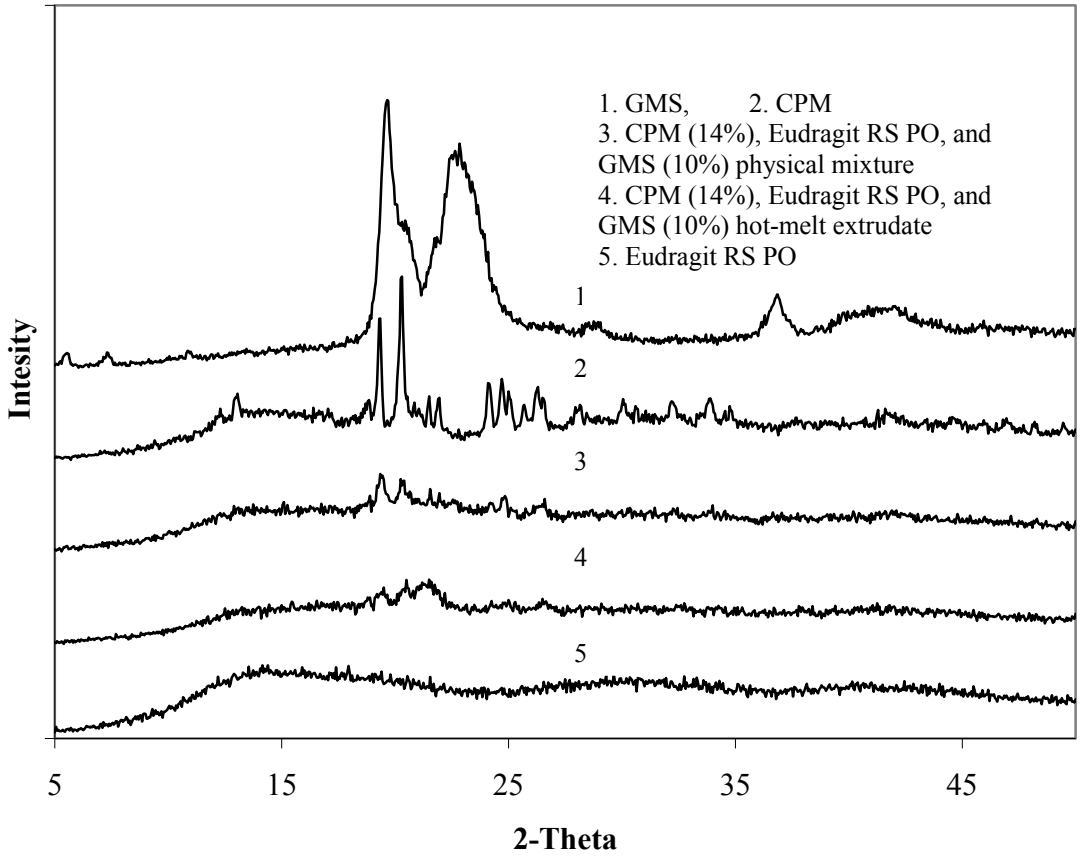


Figure 4.3.7. X-ray diffraction patterns of hot-melt extruded CPM granules containing Eudragit® RS PO, GMS and TEC.

Table 4.4.3. DTZ content in the formulation prior to and following hot-melt extrusion.

Formulations	DTZ content before hot-melt extrusion	DTZ content after hot-melt extrusion
DTZ (30%), Eudragit® RS PO (66%), TEC (4%)	99.96±2.21	97.91±1.32
DTZ (30%), Eudragit® RS PO (62%), TEC (8%)	100.4±0.21	98.93±0.56

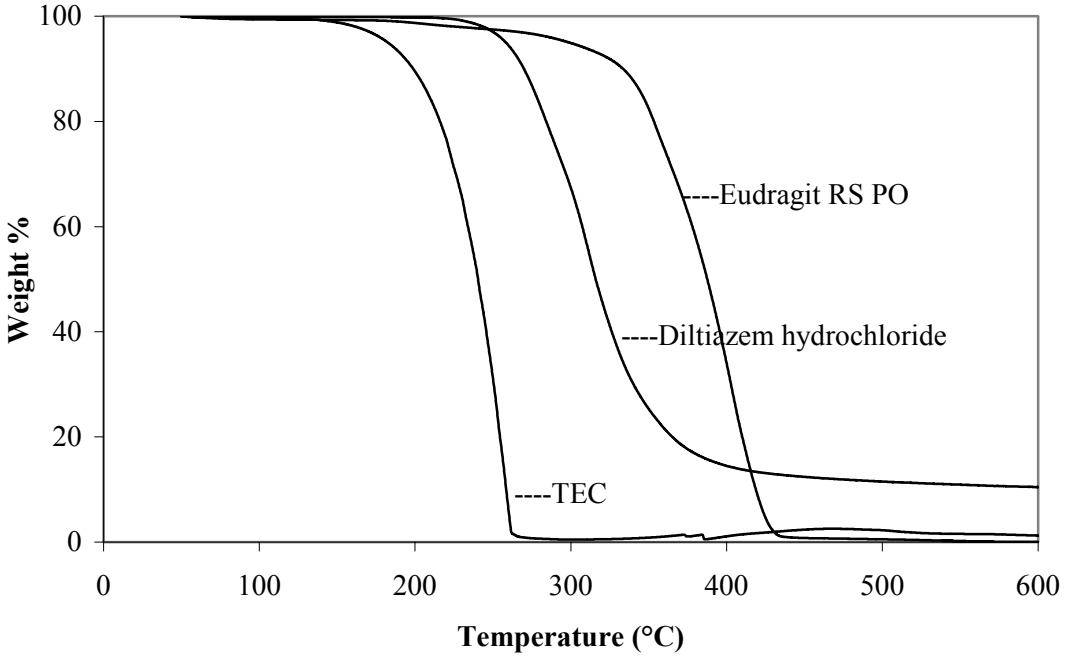


Figure 4.4.1. Thermal stability of TEC, DTZ, and Eudragit® RS PO determined from 50°C to 600°C at the heating rate of 10°C/min by using TGA.

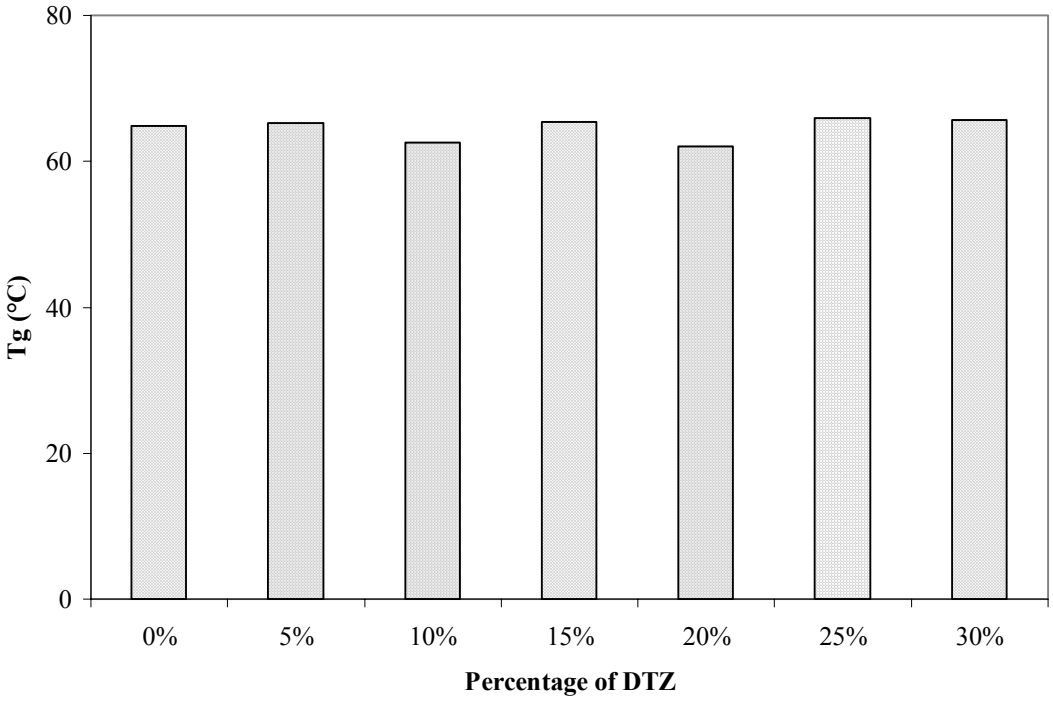


Figure 4.4.2. Glass Transition temperatures of the mixture of Eudragit® RS PO and DTZ determined by DSC from -10°C to 160°C at the heating rate of 10°C/min.

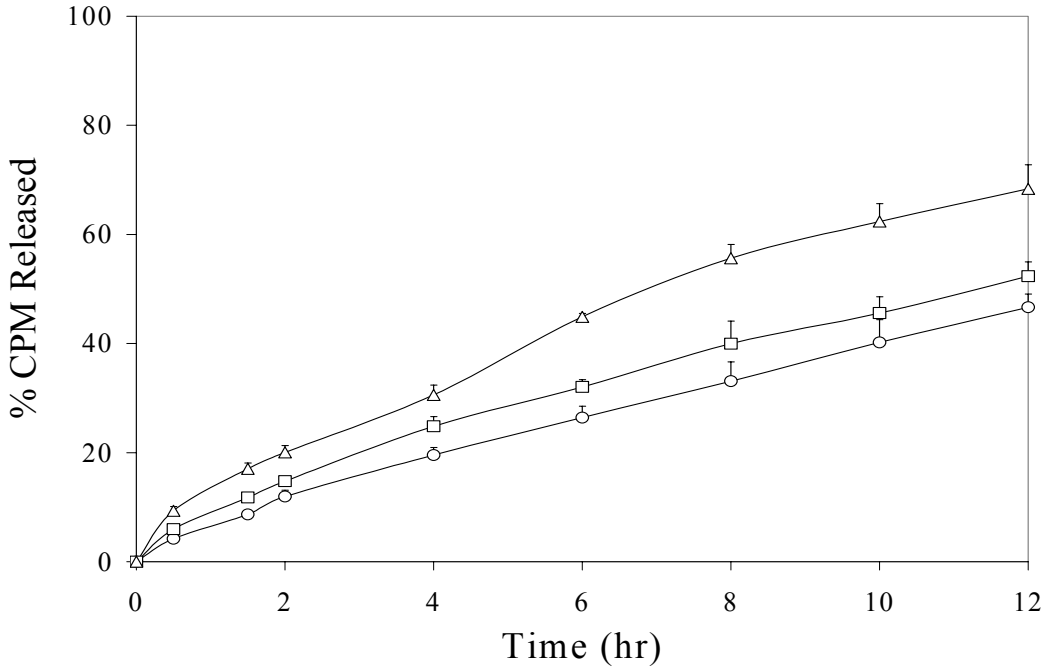


Figure 4.4.3. Influence of TEC levels on the dissolution properties of Eudragit® RS PO hot-melt extruded tablets containing CPM (10%).

Dissolution: USP 24 basket method, 100rpm, 500ml distilled water as the dissolution medium, 37°C (n=3). (○): 0% TEC; (□): 4% TEC; (Δ): 7% TEC.

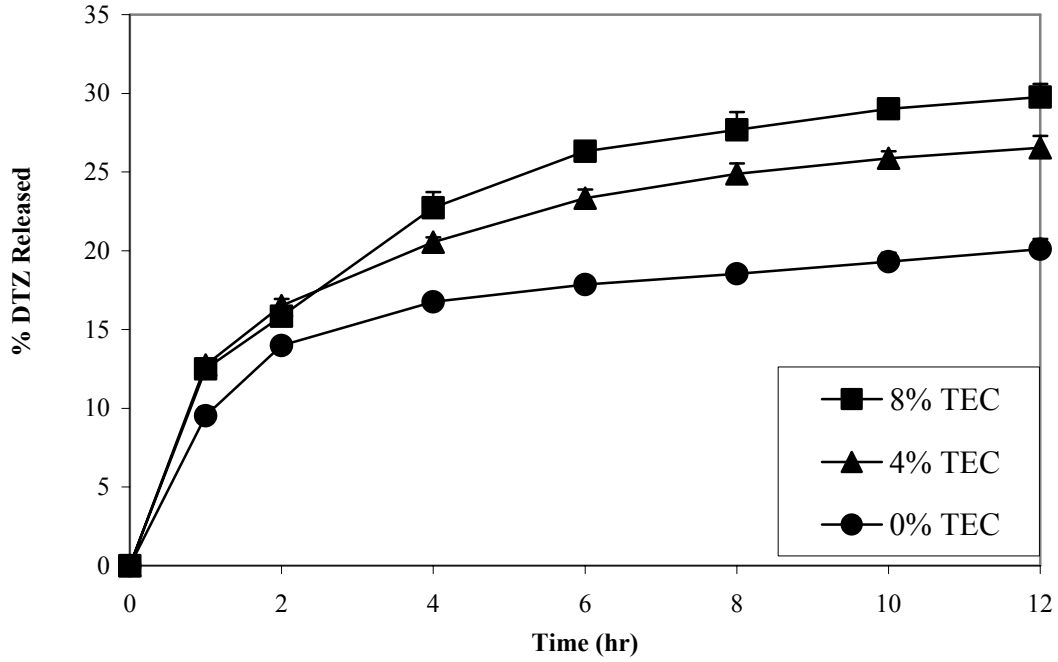


Figure 4.4.4. Influence of TEC Level on the dissolution rate of DTZ from hot-melt extruded tablets containing DTZ 30%, Eudragit RS PO+TEC=70%.
Dissolution: USP24 paddle method, 50rpm, pH 7.2 PBS, 37°C (n=3). (●): 0% TEC; (▲): 4% TEC; (■): 8% TEC.

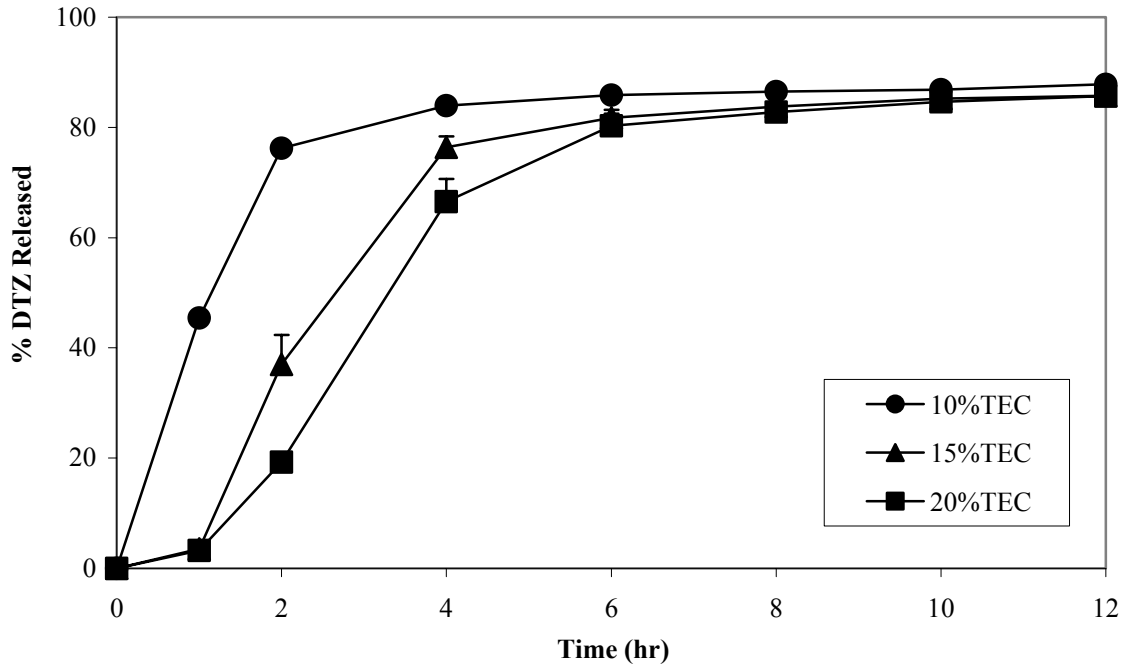
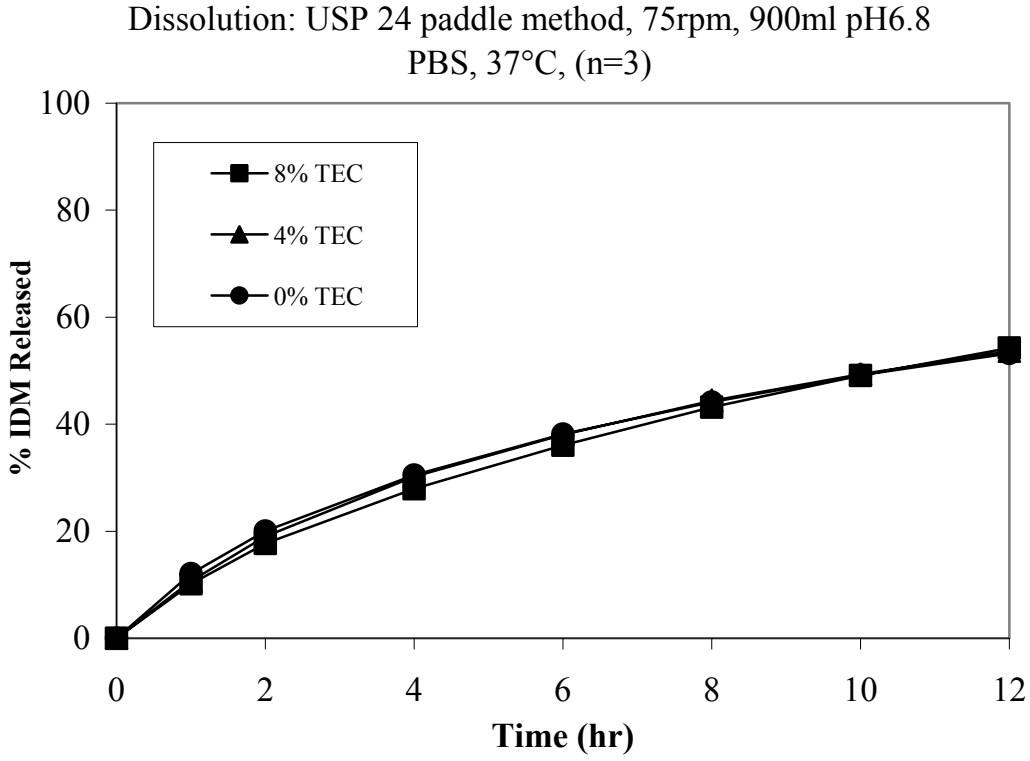


Figure 4.4.5. Influence of TEC level in the Eudragit® RS 30D coating layer on the dissolution rate of DTZ from coated pellets with a 15% weight gain.
Dissolution: USP24 paddle method, 50rpm, pH 7.2 PBS, 37°C (n=3). (●): 10% TEC; (▲): 15% TEC; (■): 20% TEC.



Fgure 4.4.6. Influence of TEC on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, Eudragit® RD 100 and 5% Pluronic® F68.

Dissolution: USP24 paddle method, 50rpm, pH 7.2 PBS, 37°C (n=3). (●): 0% TEC; (▲): 4% TEC; (■): 8% TEC.

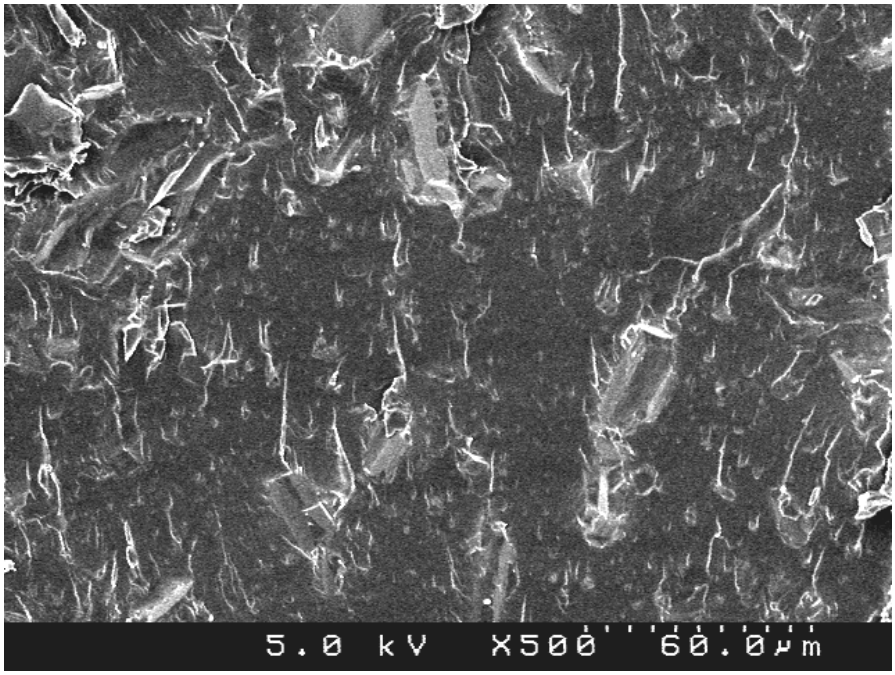
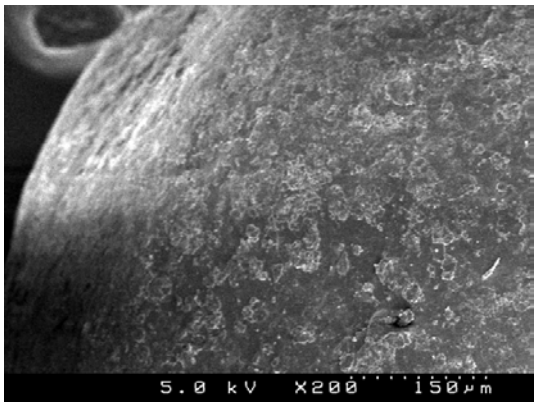
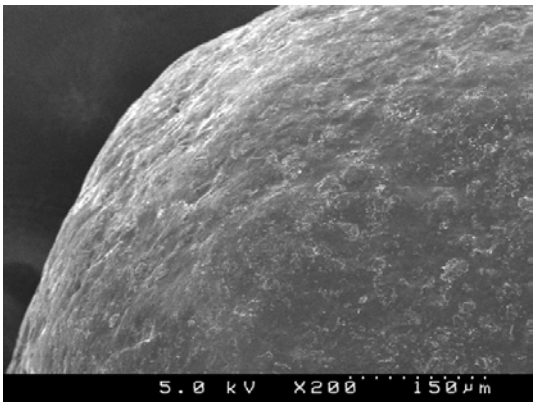


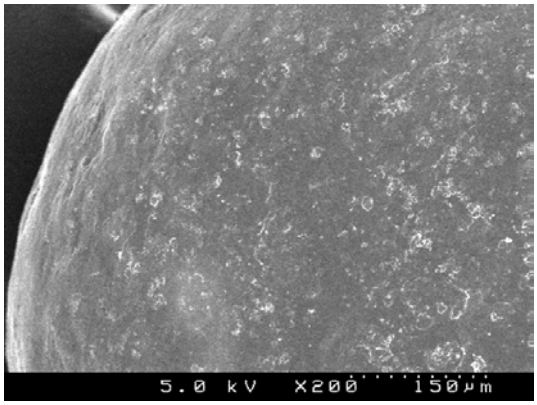
Figure 4.4.7. SEM photograph of hot-melt extrudates containing 30% DTZ, 66% Eudragit® RS PO and 4% TEC.



(A) 10% TEC



(B)15% TEC



(C) 20% TEC

Figure 4.4.8. SEM photographs of Eudragit® RS 30D coated DTZ beads containing different level of TEC in the coating layer with 15% weight gain based on solid polymer.

(A). 10%TEC; (B). 15% TEC; (C). 20% TEC.

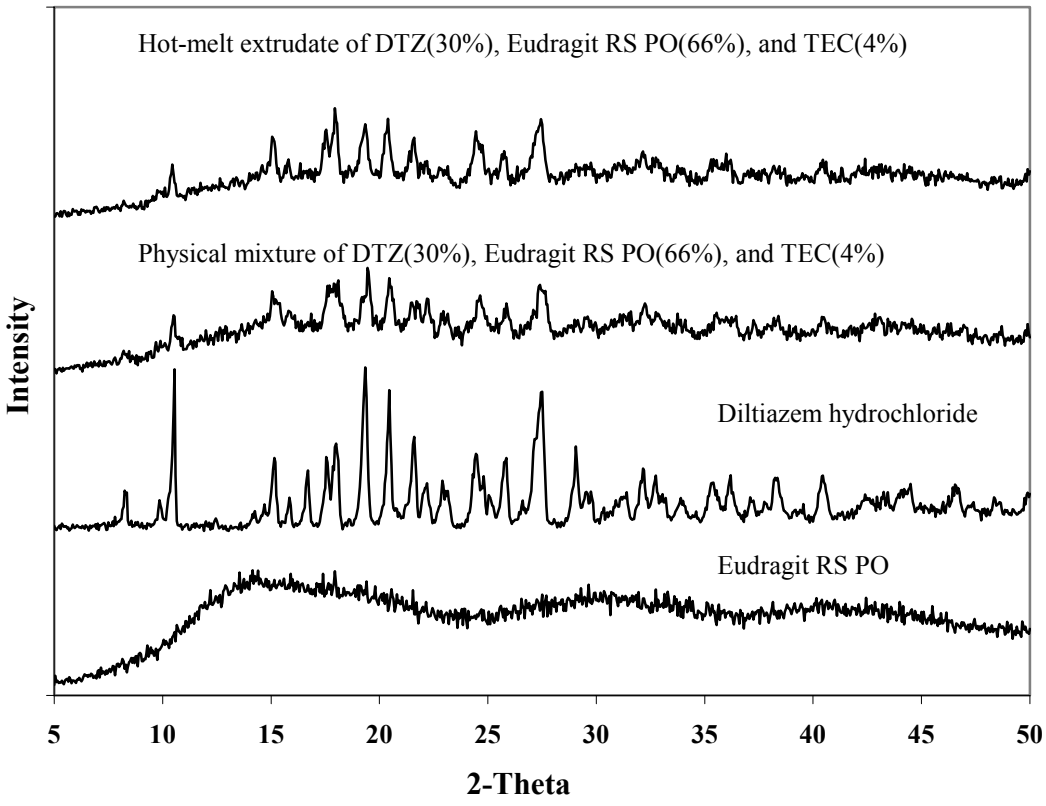


Figure 4.4.9. X-Ray diffraction patterns of DTZ, Eudragit® RS PO, and processed materials.

Table 4.5.1. Particle size of the model drug and the acrylic polymers determined by ZetaPlus Zeta potential analyzer (n=3).

Materials	Indomethacin	Eudragit® RL PO	Eudragit® RD 100
Effective Diameter (μm)	13.94	34.66	39.73
	13.29	41.90	43.25
	14.70	46.32	46.35
Average Effective Diameter (μm)	13.98	40.96	43.11
SD	0.71	5.89	3.31

Table 4.5.2. True density of indomethacin and acrylic polymers determined by AccuPyc 1330 pycnometer (n=3).

Materials	Indomethacin	Eudragit® RL PO	Eudragit® RD 100
Density (g/cm^3)	13760	1.1901	1.2148
	1.3759	1.1881	1.2074
	1.3756	1.1880	1.2061
Average Density (g/cm^3)	1.3756	1.1887	1.2094
SD	0.0006	0.0012	0.0047

Table 4.5.3. Melting points of Pluronic® F68 in the mixture of Eudragit® RL PO.

% of Pluronic® F68	First run melting point°C	Second run melting point°C
10%	54.26	55.22
20%	53.57	55.22
30%	54.26	55.70
40%	54.74	56.17
50%	53.78	54.98
100%	56.17	58.09

Table 4.5.4. Thermal stability of indomethacin and other excipients (Isothermal at 140°C for 10 minutes determined by TGA).

	Materials					
	IDM	Pluronic® F68	Eudragit® RD 100	Eudragit® RL PO	Eudragit® S 100	Eudragit® L 100
Remaining Weight %	99.8	99.9	99.3	99.8	99.8	99.8

Table 4.5.5. Chemical stability of indomethacin in the formulations containing acrylic polymers following hot-melt extrusion determined by HPLC.

Formulations	IDM content before HME	IDM content after HME
IDM (30%), Eudragit® RD 100 (61%), Pluronic® F68 (5%), TEC (4%)	97.09±0.88	97.69±0.95
IDM (30%), Eudragit® RD 100 (51%), Eudragit® L 100 (10%), Pluronic® F68 (5%), TEC (4%)	101.9±1.01	99.83±0.19
IDM (30%), Eudragit® RD 100 (51%), Eudragit® S 100 (10%), Pluronic® F68 (5%), TEC (4%)	103.5±1.57	103.3±0.24

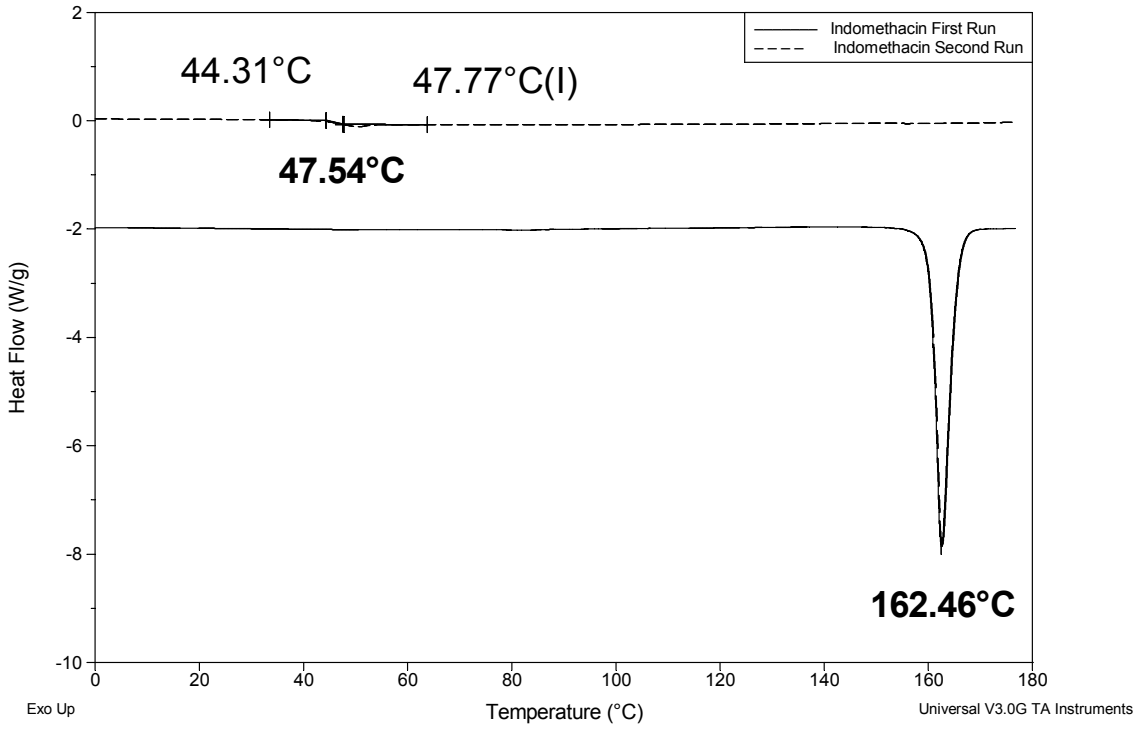


Figure 4.5.1. Thermal analysis of indomethacin by DSC.

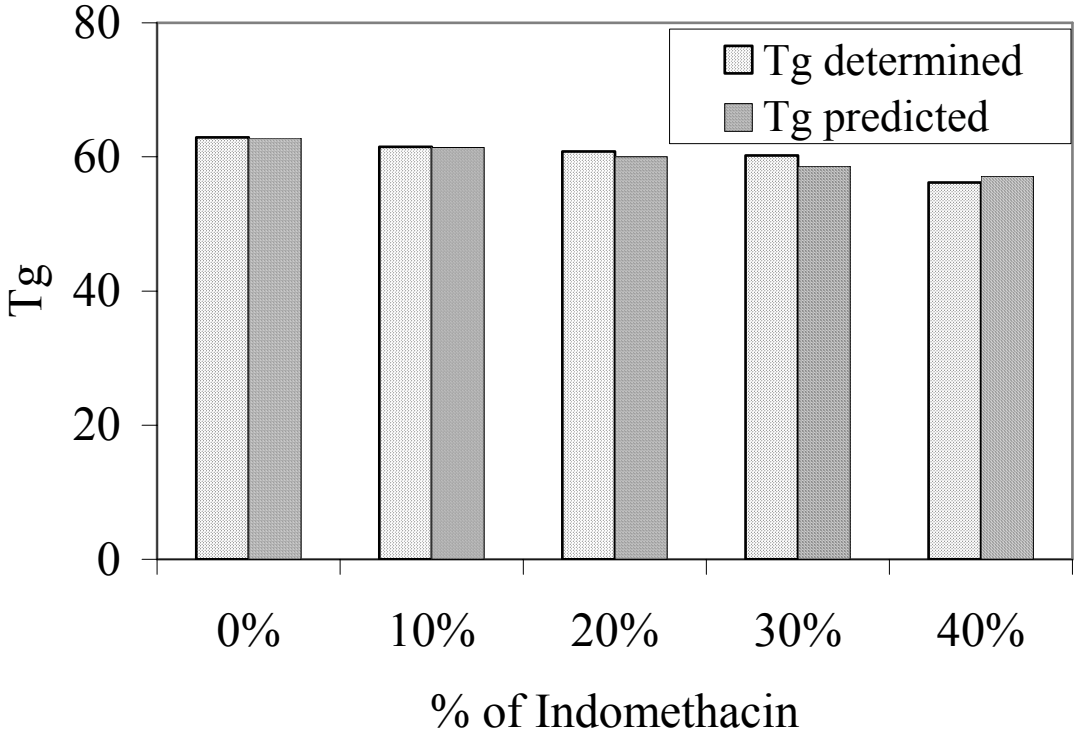


Figure 4.5.2. Glass transition temperatures of mixtures of Eudragit® RL PO and indomethacin.

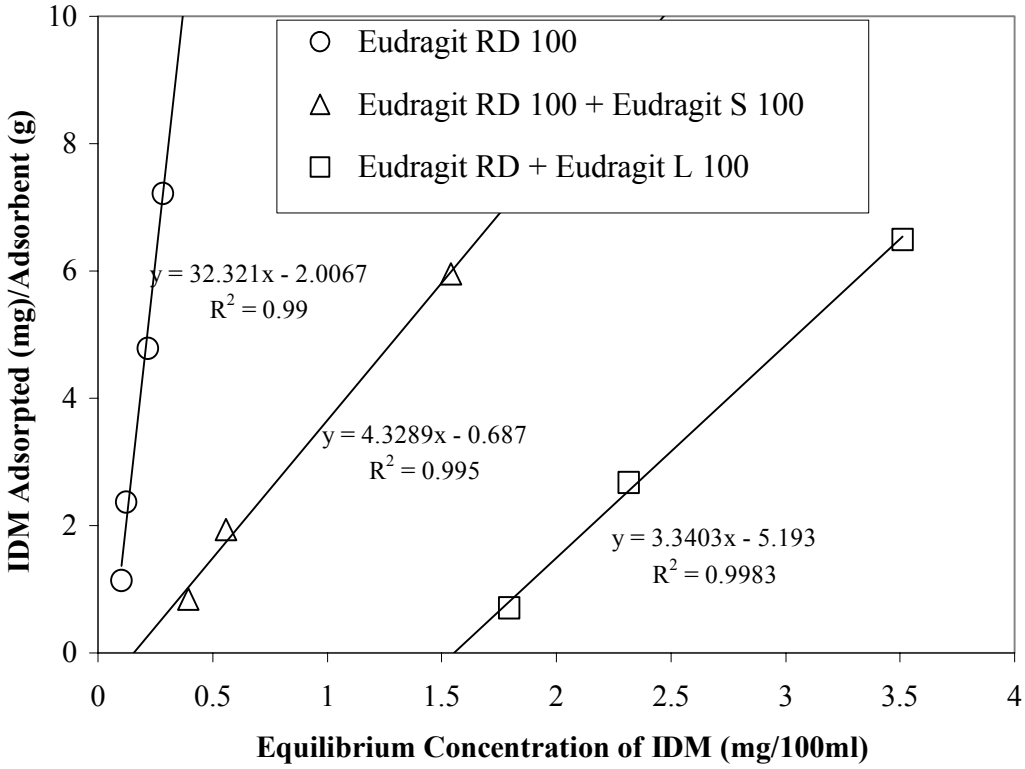


Figure 4.5.3. Adsorption of IDM in the pH 6.8 phosphate buffer solutions on the acrylic polymers.

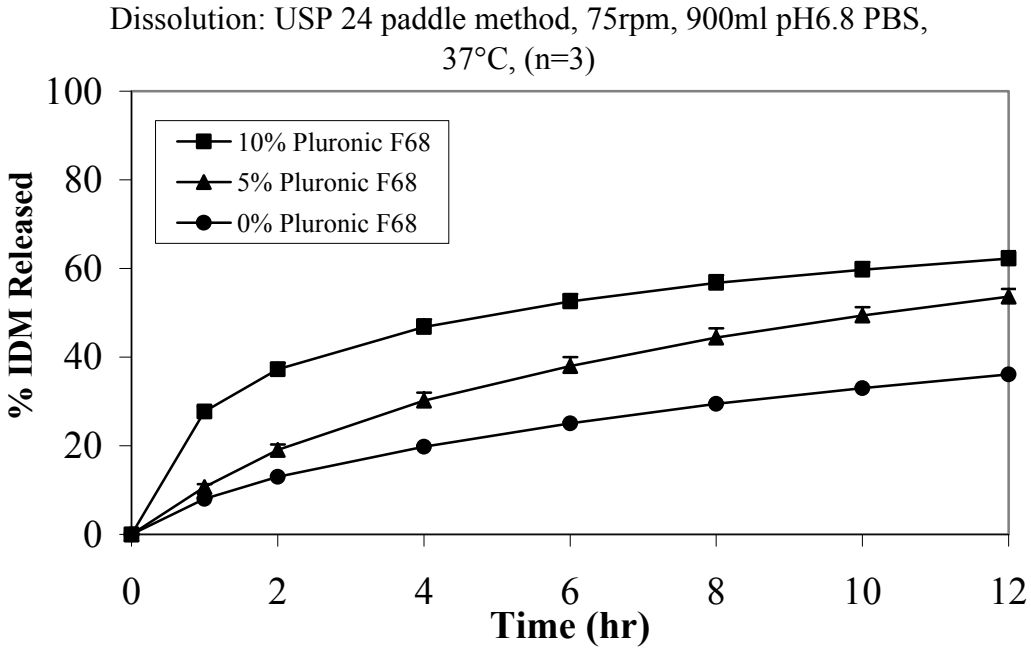


Figure 4.5.4. Influence of Pluronic® F68 on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, Eudragit® RD 100, Pluronic® F68 and 4% TEC.

Dissolution: USP24 paddle method, 75rpm, pH 6.8 PBS, 37°C (n=3). (●): 0% Pluronic® F68; (▲): 5% Pluronic® F68; (■): 10% Pluronic® F68.

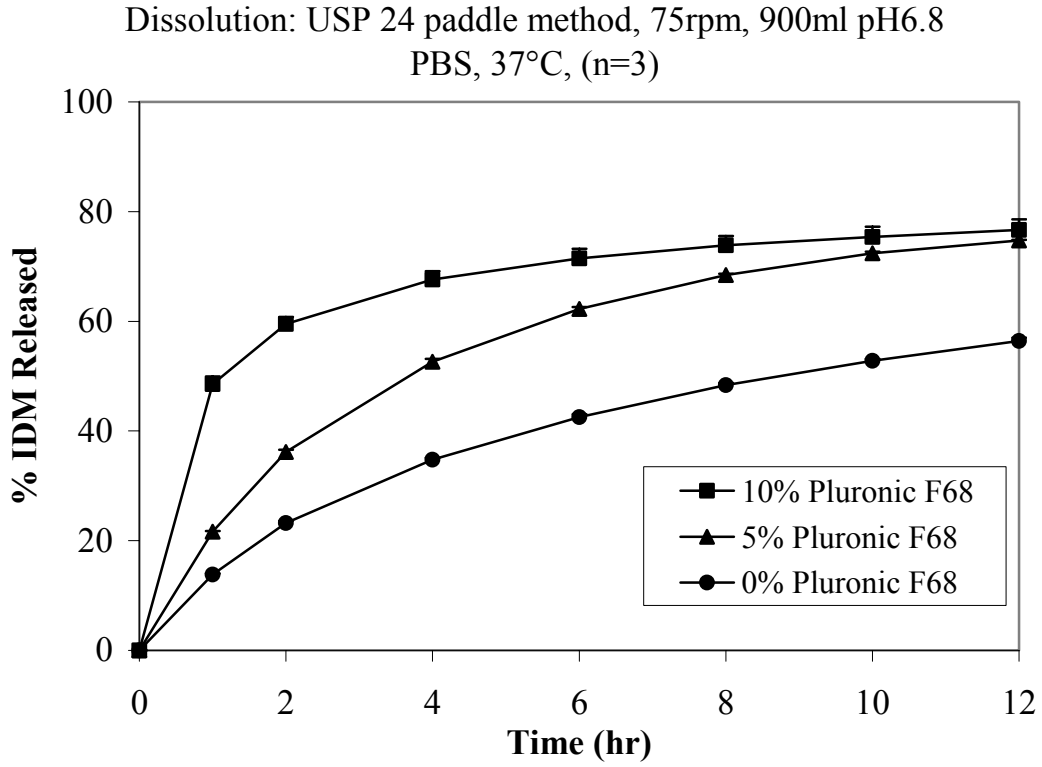


Figure 4.5.5. Influence of Pluronic® F68 on indomethacin release from hot-melt extrudated granules (40-60 mesh) containing 30% IDM, Eudragit® RD 100, Pluronic® F68 and 4% TEC.

Dissolution: USP24 paddle method, 75rpm, pH 6.8 PBS, 37°C (n=3). (●): 0% Pluronic® F68; (▲): 5% Pluronic® F68; (■): 10% Pluronic® F68.

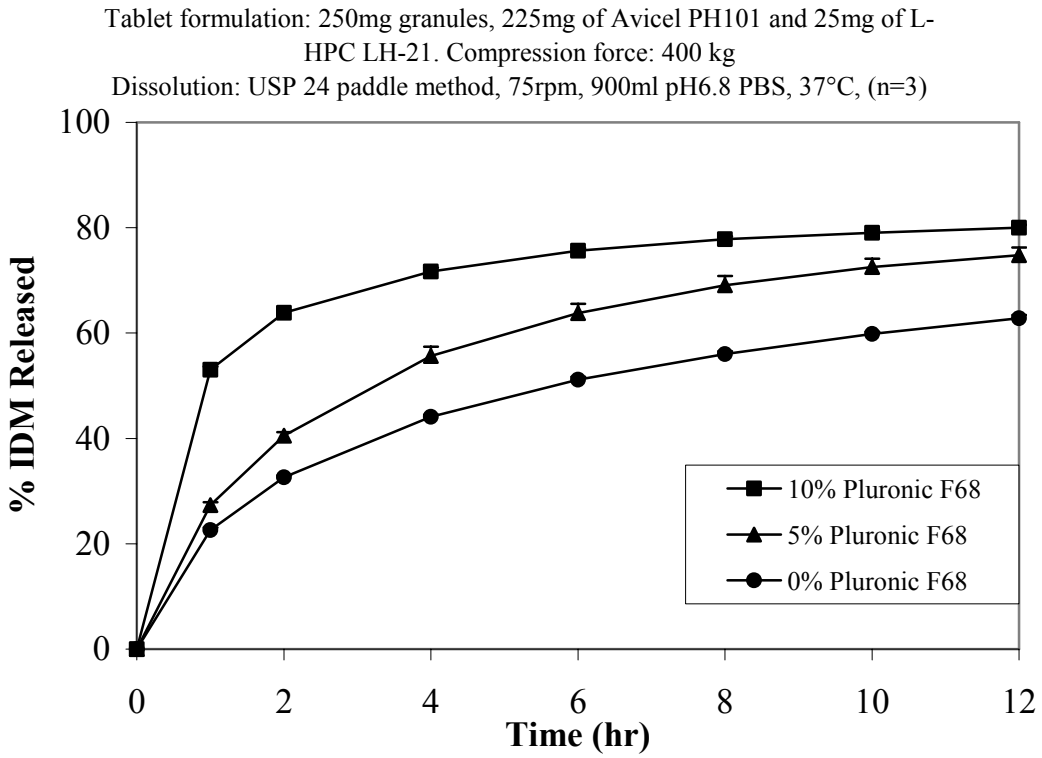


Figure 4.5.6. Influence of tableting on indomethacin release from tablets made with the granules (40-60 Mesh) containing 30% IDM, Eudragit® RD 100, Pluronic® F68 and 4% TEC prepared by hot-melt extrusion.

Dissolution: USP24 paddle method, 75rpm, pH 6.8 PBS, 37°C (n=3). (●): 0% Pluronic® F68; (▲): 5% Pluronic® F68; (■): 10% Pluronic® F68.

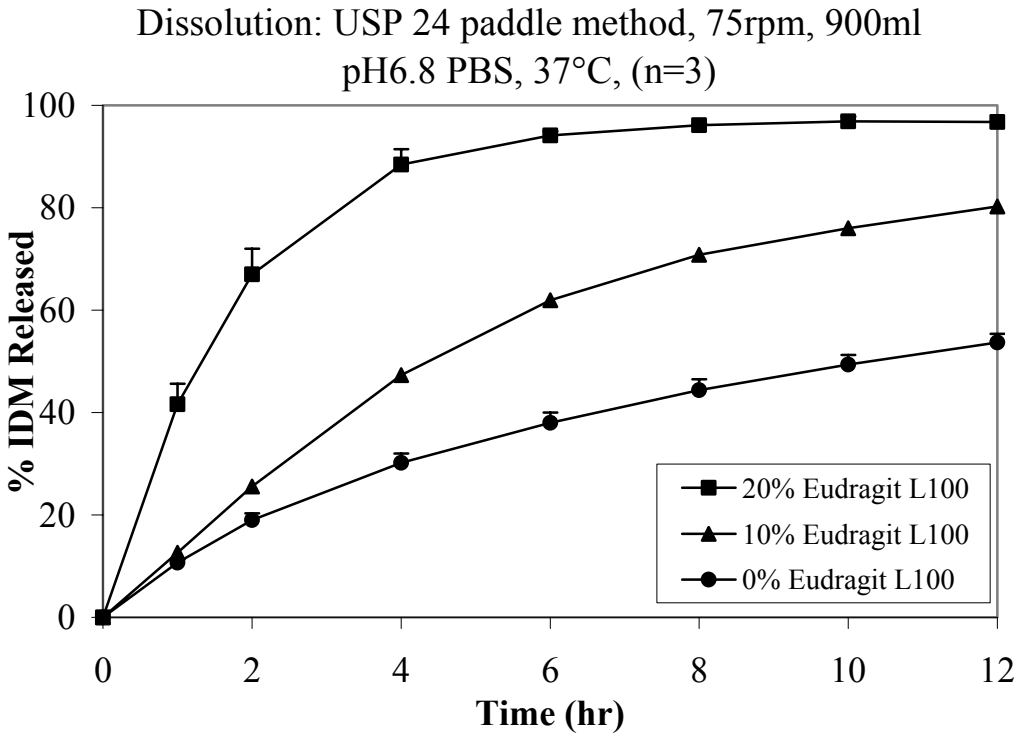


Figure 4.5.7. Influence of Eudragit® L 100 on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, Eudragit® RD 100, 5% Pluronic® F68 and 4% TEC.

Dissolution: USP24 paddle method, 75rpm, pH 6.8 PBS, 37°C (n=3). (●): 0% Eudragit® L 100; (▲): 10% Eudragit® L 100; (■): 20% Eudragit® L 100.

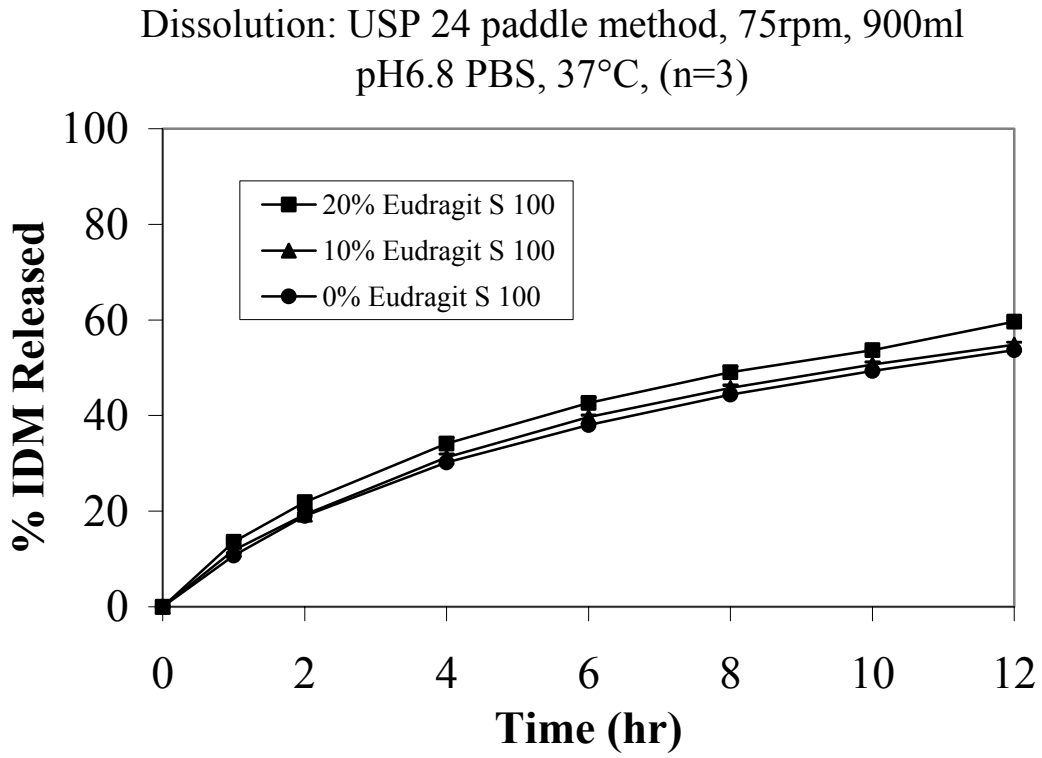


Figure 4.5.8. Influence of Eudragit® S 100 on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, Eudragit® RD 100, Eudragit® S 100, 5% Pluronic® F68 and 4% TEC.

Dissolution: USP24 paddle method, 75rpm, pH 6.8 PBS, 37°C (n=3). (●):0% Eudragit® S 100; (▲): 10% Eudragit® S 100; (■): 20% Eudragit® S 100.

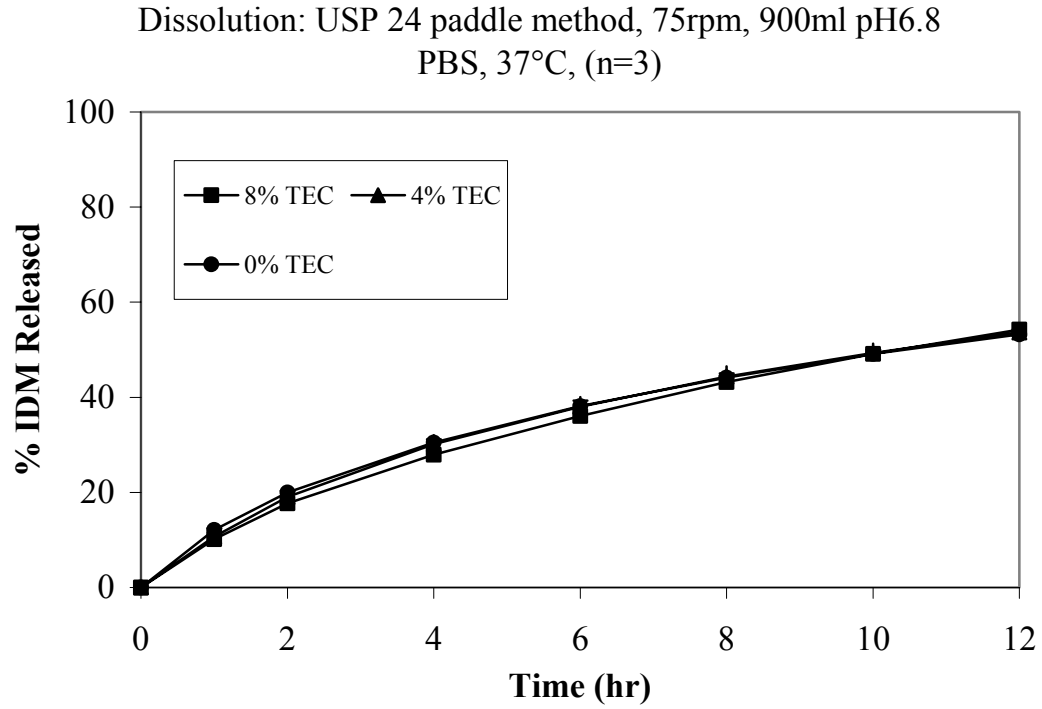


Figure 4.5.9. Influence of TEC on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, Eudragit® RD 100 and 5% Pluronic® F68.

Dissolution: USP24 paddle method, 75rpm, pH 6.8 PBS, 37°C (n=3). (●): 0% TEC; (▲): 4% TEC; (■): 5% TEC.

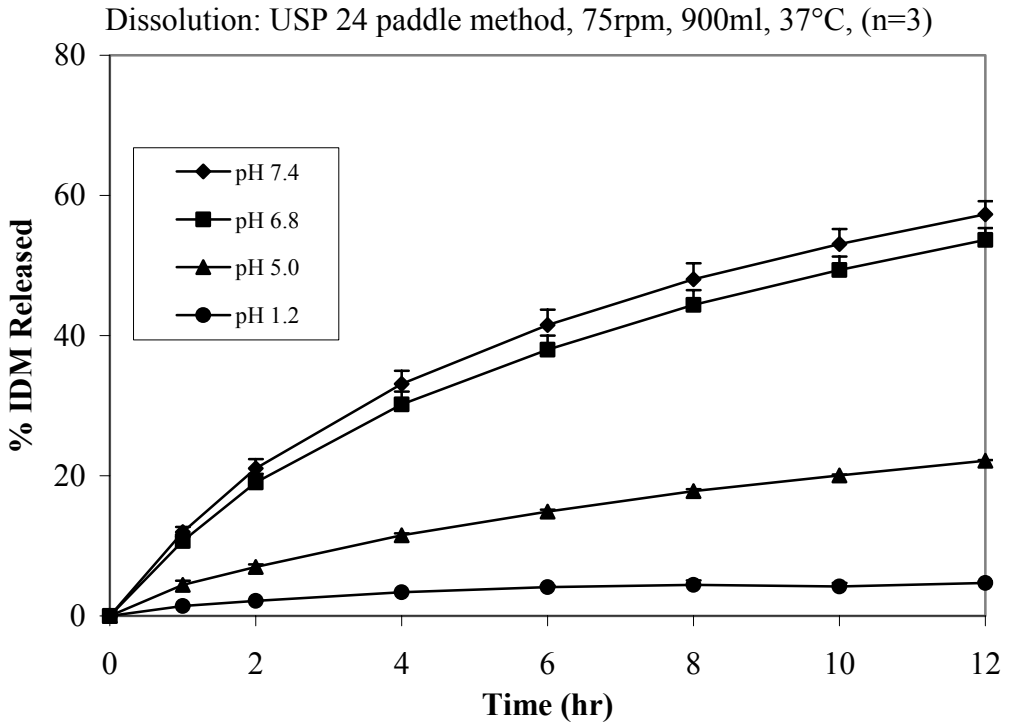


Figure 4.5.10. Influence of pH on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, 61% Eudragit® RD 100, 5% Pluronic® F68 and 4% TEC.

Dissolution: USP24 paddle method, 75rpm, pH 6.8 PBS, 37°C (n=3). (●):pH 1.2; (▲):pH 5.0; (■):pH 6.8; (◆): pH 7.4.

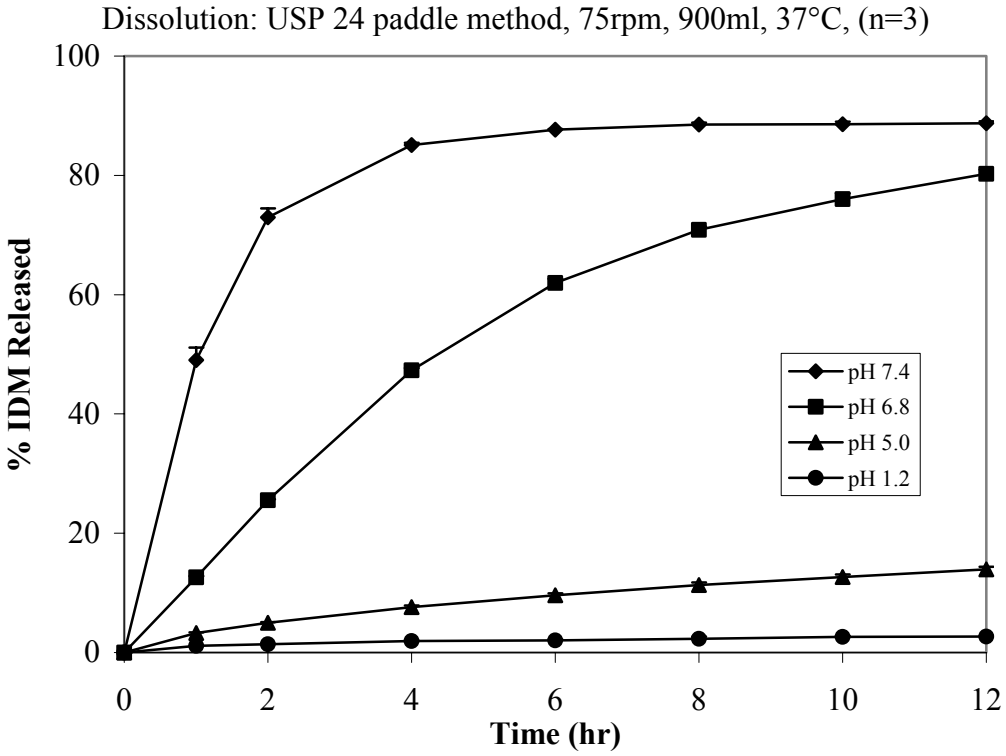


Figure 4.5.11. Influence of pH on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, 51% Eudragit® RD 100, 10% Eudragit® L 100, 5% Pluronic® F68 and 4% TEC.

Dissolution: USP24 paddle method, 75rpm, 37°C (n=3). (●): pH 1.2; (▲): pH 5.0; (■): pH 6.8; (◆): pH 7.4.

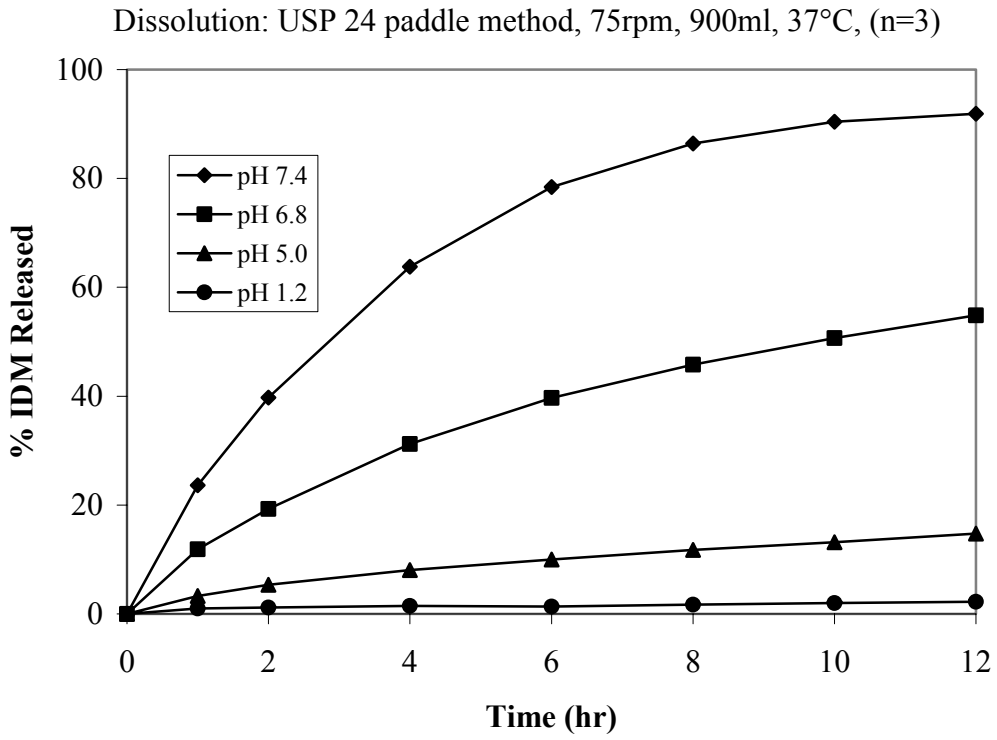


Figure 4.5.12. Influence of pH on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, 51% Eudragit® RD 100, 10% Eudragit® S 100, 5% Pluronic® F68 and 4% TEC.

Dissolution: USP24 paddle method, 75rpm, 37°C (n=3). (●): pH 1.2; (▲): pH 5.0; (■): pH 6.8; (◆): pH 7.4.

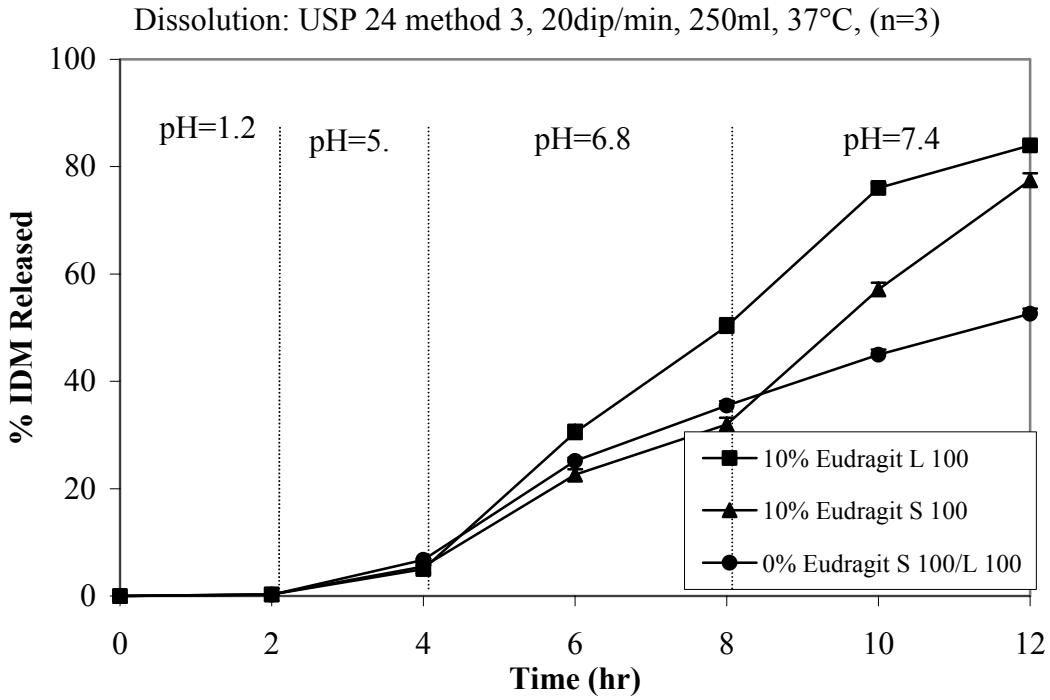
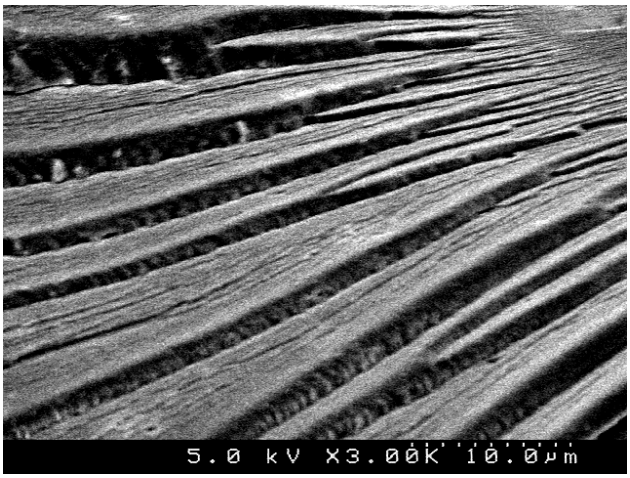
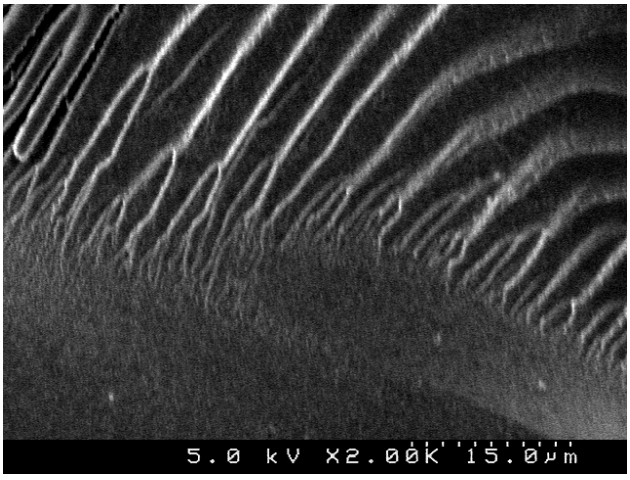


Figure 4.5.13. Influence of pH on indomethacin release from hot-melt extrudated granules (20-40 mesh) containing 30% IDM, Eudragit® RD 100, 5% Pluronic® F68 and 4% TEC.

Dissolution: USP24 method 3, 20 dip/min, 250 ml, 37°C (n=3). (●): 0% Eudragit® S 100/L 100; (▲): 10% Eudragit® S 100; (■): 10% Eudragit® L 100.



(A)



(B)

Figure 4.5.14. SEM photographs of hot-melt extrudates.

(A) 30% IDM, 65% Eudragit® RD 100, 5% Pluronic F68, and 0% TEC; (B) 30% IDM, 61% Eudragit® RD 100, 5% Pluronic F68, and 4% TEC

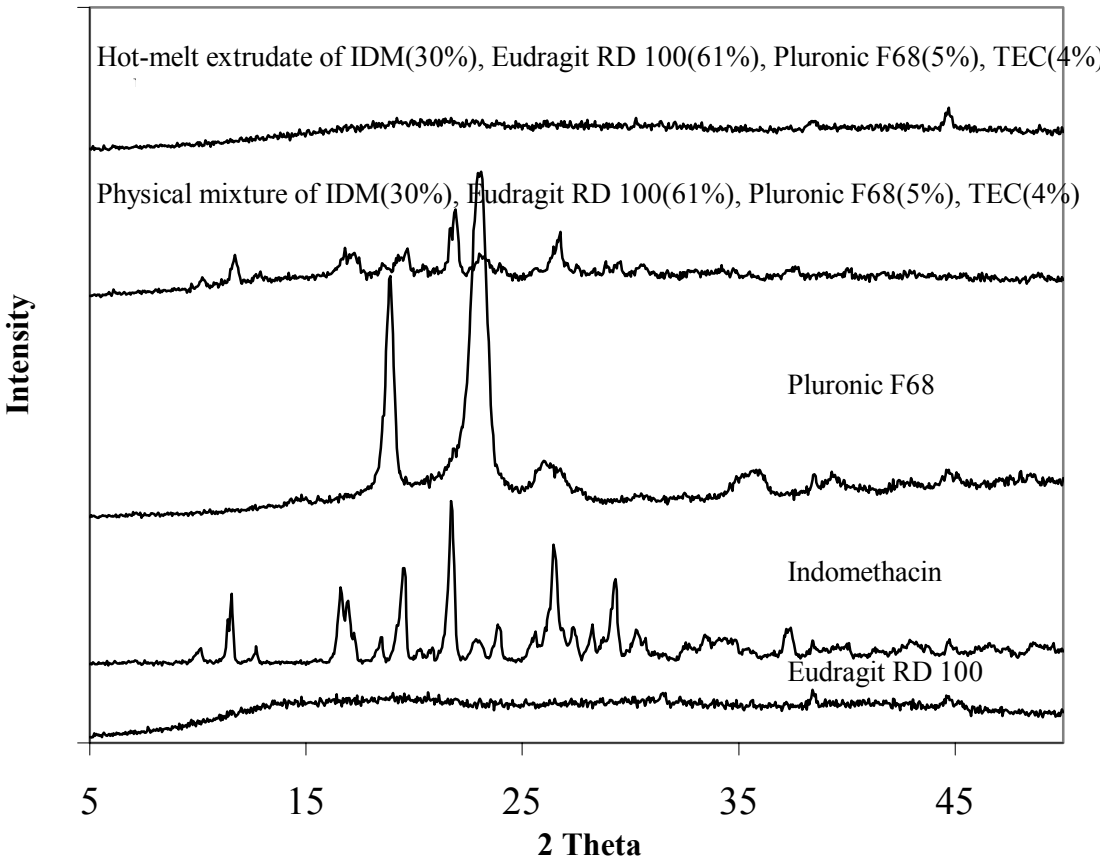


Figure 4.5.15. X-Ray diffraction patterns of IDM, Eudragit® RD 100, Pluronic® F68, and processed materials.

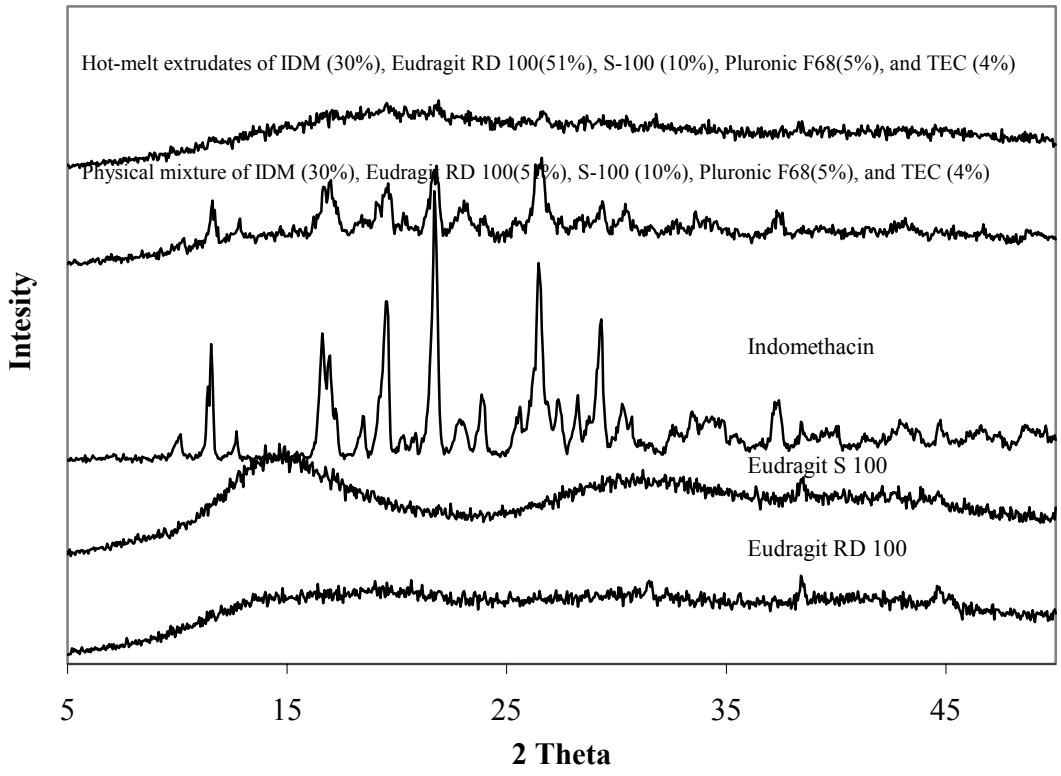


Figure 4.5.16. X-Ray diffraction patterns of IDM, Eudragit® RD 100/S100, and processed materials.

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