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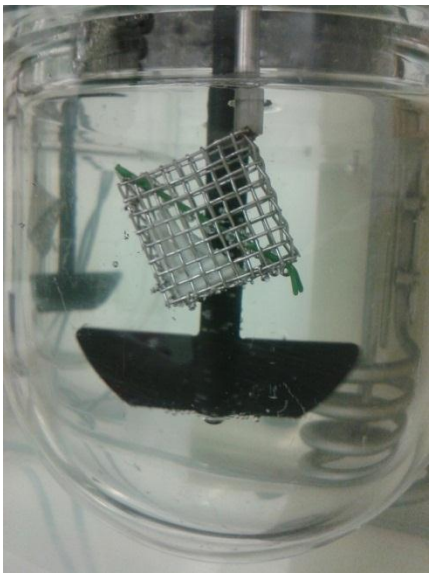

Hot-melt Extrusion of Modified Release Pellets

Influence of the formulation and extrusion process on extended- and enteric release profile

Master of Science Thesis in the Master Degree Programme, Biotechnology

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Cover:
Dissolution testing of pellets in a USP bath (left), see page 20
Example of an extrudate and cut pellets (right)

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Abstract

The interest in hot-melt extrusion in the pharmaceutical industry has increased rapidly during the last years because of its many advantages over traditional production techniques. In hot-melt extrusion, a blend of active substance (API), polymer and plasticizer in powder form is transferred by a rotating screw through the heated barrel in the extruder. Hot-melt extrusion is capable of preparing pellets with a compact structure that can resist rapid water penetration, thereby enabling the production of pellets with modified release. The aim of this project was to design two types of modified release pellets, enteric pellets with delayed release and extended release pellets, which are suitable for production by hot-melt extrusion. Two enteric polymers, HPMCAS and Eudragit L100-55, were used together with 20% TEC and different content of drug (5% Naproxen, 25% Naproxen or 5% AZD1305) to evaluate the influence of the formulation on the drug release profile. Drug loaded polymeric strands were extruded using a Haake Minilab extruder with five minutes recirculation and a 2 mm die. The extrudates were manually cut into pellets and the pH-dependent drug release was tested by exposing the pellets to an acid phase (pH1) for 2 hours followed by a neutral buffer phase.

The formulation and extrusion process influenced the release rate during both acid and buffer phase. Both Eudragit L100-55 and HPMCAS formulations produced by hot-melt extrusion had excellent enteric properties, with significantly less than 10% drug release after 2 hours in acid phase for both the acidic Naproxen and the basic AZD1305. Both polymers managed to keep the delayed release properties when the drug load was increased to 25% although the theoretical percolation limit was exceeded. Fitting the drug release data to the power law indicated that both diffusion- and swelling/erosion mechanism are involved in the drug release. The translucent appearance of the extrudates and DSC results suggest that the API is molecularly dispersed in the polymer. The evaluated formulations show a promising modified release behavior with great potential as enteric pellets indicated by the very low drug release in the acid phase.

Keywords: Hot-melt extrusion, modified release, enteric pellets, delayed release, drug delivery, formulation, HPMCAS, Eudragit L100-55, Naproxen and AZD1305.

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List of Acronyms

5-ASA	5-AminoSalicylic Acid
API	Active Pharmaceutical Ingredient
ATBC	Acetyl TriButyl Citrate
CA MH	Citric Acid MonoHydrate
CA	Cellulose Acetate
CR	Controlled Release
DSC	Differential Scanning Calorimetry
QbD	Quality by Design
ER	Extended Release
GMP	Good Manufacturing Practice
HME	Hot-Melt Extrusion
HPMC	HydroxyPropyl MethylCellulose
HPMCAS	HydroxyPropyl MethylCellulose Acetate Succinate
MP	Methyl Paraben
MR	Modified Release
PAT	Process Analytical Technology
PEG	PolyEthylene Glycol
PEO	PolyEthylene Oxide
SR	Sustained Release
TEC	TriEthyl Citrate
USP	United States Pharmacopeial convention

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1. Introduction

Widespread research has been performed with modified release drug delivery systems during the last decades. There are many advantages with these systems such as improved patient compliance and more constant levels of drug in the blood, which can increase the efficacy and reduce side effects [1]. Nowadays, exact control of the level and location of drug in the body is possible. The most common modified release dosage form has been slowly eroding matrix tablets. These tablets are usually manufactured with wet granulation and direct compression techniques. However, the wet granulation technique is both labor- and equipment-intensive, uses solvents and other additives and the compression techniques have uniformity problems [2]. A lot can be gained if a new method is developed: one such promising method is hot-melt extrusion which is one of the most common processing techniques in the plastic industry. In hot-melt extrusion, a blend of active substance, polymer and plasticizer is transferred by a rotating screw through the heated barrel in the extruder, causing the drug to be uniformly dispersed in the molten polymer. The material rapidly solidifies when exiting the extruder and can thereafter be processed with downstream equipment [2].

Pharmaceuticals have a high demand of consistency and almost superior quality because the precise delivery of active substance to a specific site in the body is critical and variations in delivery could either reduce the effectiveness of the drug or lead to toxic doses. Medical products agencies such as the Food and Drug Administration (FDA) have enabled continuous processing of pharmaceutical products as long as it is done according to the Quality by Design principle (QbD). It states that products with an inherent high quality are made through extensive control of raw materials and process parameters to ensure accurate prediction of the quality of the final product. According to many researchers hot-melt extruders can maintain the high quality demand because it is a flexible and efficient mixing device [3]. Hot-melt extrusion has a potential of continuous processing, better inline monitoring, automation and thereby reduction in capital- and labor costs. There are however, problems to be solved. Significant effort need to be devoted to finding optimal processing conditions, extensive characterization and optimization of formulations to meet the quality requirements, gain regulatory approval and marketing authorization [3]. The interest in hot-melt extrusion has increased rapidly in the pharmaceutical industry during the last years which has led to a demand in developing new pharmaceutical polymers and modified release formulations suitable for hot-melt extrusion. Pellets formulations are especially of great interest since the biopharmaceutical benefits of this type of formulation are better compared to single unit systems such as tablets.

The overall goal with this project is to acquire knowledge about how a formulation should be designed to create an extruded pellet product with a desired release profile. Specifically, this project aims to design two types of modified release pellets, enteric pellets with pH-dependent release and extended release pellets, which are suitable for production by hot-melt extrusion.

The objectives are:

- Study the effect of different composition of drug, plasticizer and polymer
- Study the effect of process parameters, such as temperature
- Study the release rate and release profile of the pellet
- Study the homogeneity and composition of the pellet i.e. the solid properties of the drug

The hypothesis was that by using appropriate components in combination with optimization of the extrusion process (parameters and equipment), the extruded pellets will have a uniform drug distribution and an extended or enteric release profile.

2. Background

This section covers pharmaceutical concepts such as formulation, composition and manufacture of dosage forms, advantages with pellets as a drug delivery system, the concept of solid dispersions and modified release formulations. Hot-melt extrusion is discussed extensively, both the process itself and its uses in the pharmaceutical industry. At the end, a small literature review covering examples of extended release and delayed release extrudates is presented.

2.1. Drug delivery systems

Drug delivery systems with modified release characteristics are preferred nowadays mainly because of the improved patient compliance. The term modified release (MR) can be used to describe all dosage forms that continuously release drugs at a rate which are adequately controlled, in order to obtain periods with prolonged therapeutic action following one single dose [4]. In general, the concentration of active pharmaceutical ingredient (API) increases after administration of a single dose, as can be seen in Figure 1. The concentration reaches maximum and decreases when the elimination is larger than the absorption.

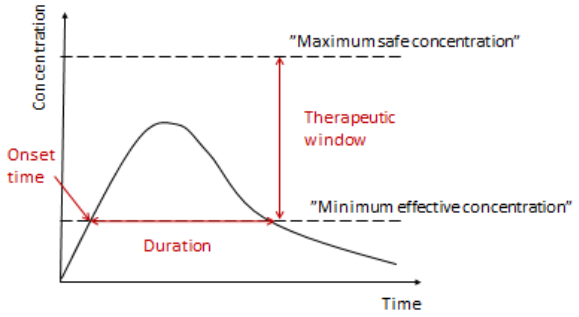


Figure 1. Concentration of API in blood after administration of a single dose (Reproduced from [5], Figure 19.2).

The most common dosage regimen is that an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the desired duration of the treatment [6]. This can be achieved with immediate release dosage forms if the dose size and frequency of administration is correct. However, there are many limitations with immediate release dosage forms: the concentration of drug in the plasma and at the site(s) of action fluctuates and will not remain in “steady-state”, leading to over- or under-medication of the patient. Another limitation is that very frequent doses might be required for some drugs. The limitations with immediate release dosage forms have led to the development of modified release formulations with an extended release behavior, to reduce the fluctuations in drug concentration. Modified release (MR) dosage forms are defined by USP (United States Pharmacopeial Convention) as those whose drug release characteristics are chosen to accomplish therapeutic objectives not offered by conventional forms.

Thus, all of the following terms can be considered modified release formulations [4]:

- *Extended release (ER,* Figure 2*):* Dosage forms that release drug slowly so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (8-12 h).

- *Delayed release* (Figure 2): The drug is not released immediately following administration but at a later time, e.g. enteric-coated tablets and pulsatile-release capsules.
- *Prolonged release:* The drug is provided for absorption over a longer period of time than from a conventional dosage form but with a slower onset time because of the slow release.
- *Sustained release (SR):* There is an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period of time.
- *Controlled release (CR):* Dosage forms that release drug at a constant rate and provides plasma concentrations that remain invariant with time.

It should be noted that USP uses the terms controlled release, prolonged release, and sustained release interchangeable with extended release. As of now, there are no internationally accepted definitions.

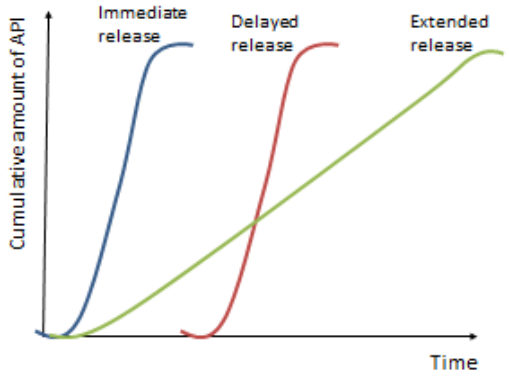


Figure 2. Schematic view of the cumulative amount of API released from an immediate, delayed and extended release dosage form. (Reproduced from [7], Figure 31.20)

To achieve modified release, much more is required than an active pharmaceutical ingredient: the physicochemical properties of the API, the formulation, the dosage form, the route of administration and extent of drug absorption are important factors in order to achieve a suitable therapeutic effect. The API needs to reach its site(s) of action and stay there long enough to be able to exert its pharmacological effect. However, the concentration of a drug in blood plasma depends on numerous factors: the amount of an administered dose that is absorbed and reaches the systematic circulation, the extent of distribution of the drug between the systematic circulation and other tissues, and the rate of elimination of the drug from the body [5]. The drug can be eliminated unchanged or be metabolized and biochemically transformed. The characterization of the time course of drug absorption, distribution, metabolism and elimination is called pharmacokinetics, as opposed to pharmacodynamics which is the effect of the drug on the body, the mechanism of drug action and the relationship between drug concentration and effect. All these issues are important to consider when designing and formulating a pharmaceutical product.

2.1.1. Formulation of dosage forms

Formulation is the process of combining different constituents such as the API, polymers and other substances in an optimal composition to produce a pharmaceutical product. Formulation is a very important concept, aiming to ensure that the API is delivered to the correct part of the body, in the right concentration and at the right rate [8]. The goal with the formulation process is to optimize

bioavailability, minimize toxicity and side effects, and improve stability [9]. When designing a formulation, the properties of the API as well as possible interactions with other ingredients, added to improve processibility and product properties, must be taken into account because it may result in chemical or physical instability.

Choosing a dosage form and a delivery route are important steps when formulating a drug. Dosage form design is the process of achieving a predictable therapeutic response of a drug in a formulation. The dosage forms should also be suitable for large-scale manufacture with reproducible product quality[8]. There are many different dosage forms in which a drug can be incorporated for efficient treatment of a disease: tablets, pellets, capsules, suspensions, solutions and emulsions. The different dosage forms can administrate the drug by alternative delivery routes. The most common delivery routes are to take a drug orally or by injection, as well as application to the skin or inhalation. The oral route is the most frequently used route for drug administration, and it is the only route discussed in this thesis. Oral dosage forms are usually intended for systemic effects, the drug must therefore avoid degradation by the enzymes in the gastrointestinal tract and by the low pH in the stomach and thereafter be absorbed into the blood. Solid oral dosage forms are the simplest and most convenient way of drug administration [8].

2.1.2. Composition of solid oral dosage forms

Drugs are not administered alone but in formulations involving other substances, called excipients. These are added to facilitate the preparation, patient acceptability and functioning of the dosage form as a drug delivery system [10]. Except for the active ingredient, several excipients are normally included in a tablet or pellet to ensure that quality requirements are uphold and the function of the dosage form decides which excipients should be included. Common excipients include: fillers to ensure a suitable size, disintegrants to accomplish fragmentation of the tablet to promote rapid drug dissolution, binders to generate sufficient mechanical strength, and lubricants to ensure that tablet formation can occur with low friction. Other common excipients are emulsifying agents, flavouring agents, colouring agents and chemical stabilizers [10]. The content of the tablet/pellet decides the rate of drug release. A way to classify solid oral dosage forms is based on the drug release patterns: immediate release, delayed release or extended release. Immediate release is the most common type, aiming for a fast drug release when the tablet disintegrates. The two latter is called modified-release dosage forms.

2.1.3. Pellets

Pellets have been used in many different industries as fertilizers, animal feed and pharmaceutical dosage units. In the pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. Pellets can also be used to describe small rods with approximately the same length as diameter [11].

There is a growing interest in multiple-unit dosage forms, such as pellets, that provide modified drug release. This is because of their beneficial pharmacokinetic properties that allow maximized drug absorption and minimized API plasma level fluctuations. Tailored release profiles can be obtained by blending pellets containing different drugs with varied release rates. The modified release behaviour is achieved by the functional coat in reservoir-type pellets and by the dissolution properties of the

matrix material in matrix pellets. The production of matrix pellets is advantageous because of the fewer production steps compared to reservoir-type pellets [12].

Although pellets have been used in the pharmaceutical industry since the late 1970s, its advantages over single-unit systems such as tablets were realized with the arrival of controlled release technology. Pellets are very flexible in its design because the dose strength can be changed without changing the formulation, incompatible APIs can be delivered simultaneously, and different release profiles can be achieved at the same and/or at different sites in the gastrointestinal tract depending on which pellets are used [11]. The main biopharmaceutical advantages are more even gastric emptying, controlled dissolution and larger dosage flexibility.

2.1.4. Manufacture of tablets

Tablets have traditionally been manufactured with wet granulation and direct compaction techniques. There are several quality issues to consider when manufacturing tablets: consistent and elegant appearance, uniform and consistent drug dose, controlled drug release, sufficient mechanical strength, stability and biocompatibility during the entire lifetime of the tablet.

Tablets are usually prepared by forcing particles into close proximity to each other which enables the particles to cohere into a porous solid sample of controlled geometry, a process known as powder compression (Figure 3). Powder compression is defined as the reduction in volume of a powder due to the application of a force [7]. The process can be divided into three stages: die filling, tablet formation and tablet ejection. The compression takes place in a die by the action of two punches, the lower and the upper. In direct compaction, the tableting procedure is only followed by a powder mixing step, reducing the number of steps and production cost. The disadvantage is less homogeneity due to the large particle sizes and thereby requiring more quality tests.

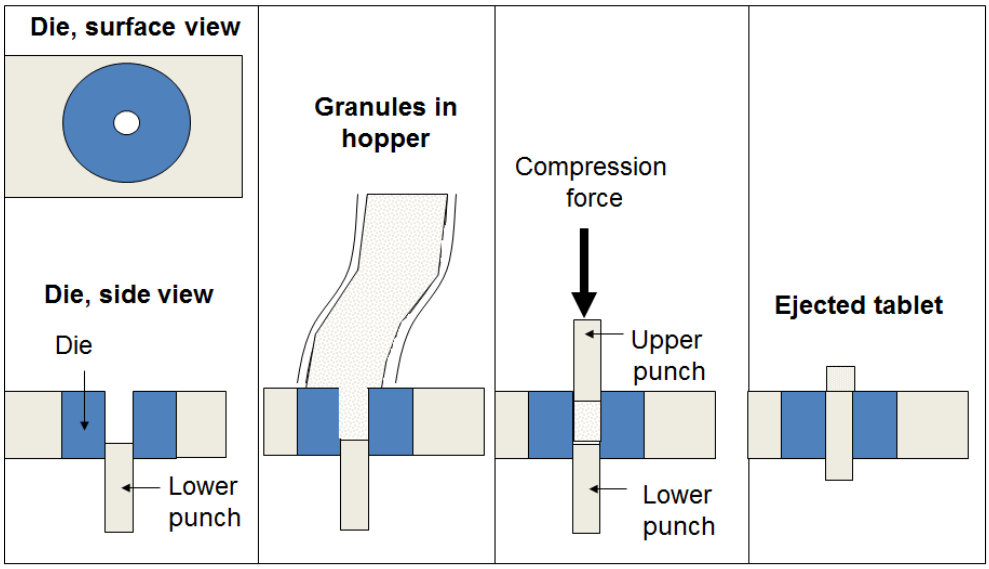


Figure 3. Formation of a tablet by powder compression (Reproduced from [7], Figure 31.1).

Wet granulation is the process of agitation of a powder in the presence of a liquid, followed by drying. The ingredients are first dry-mixed to achieve a good homogeneity. After wet mixing, the wet mass is dried in a separate drier. Granulation in a connective mixer is not a well-controlled process and large granules (above 1 mm) are formed. A second step of milling is therefore added to reduce

the size of the granules. After dry-mixing, the granules are compacted into tablets. Several problems can arise during the tableting procedure such as dose variation and low mechanical strength of the tablets. The solution binder effectively improves the compactability of the powder as well as the homogeneity [7]. However, tablets prepared by powder compression are generally quite porous which leads to a fast drug release rate. It might therefore be more difficult to achieve extended and delayed drug release with compressed tablets.

2.1.5. Manufacture of pellets

The most commonly used pelletization process is extrusion-spherononization, a multi-step process involving dry mixing, wet granulation, cold extrusion, spheronization and drying [11]. The extruded strands are transferred to a spheronizer where they are broken into short cylindrical rods and the ends are thereafter rounded off when in contact with the rotating friction plate. Pellets are usually filled into hard capsules to produce modified-release behaviour. Capsules are edible packages made from gelatin or other suitable material which is filled with medicines to produce a unit dosage. Capsules disintegrate fast when entering the body, the gelatin dissolves and the shell will split within one minute. The formulation of the content will therefore be the rate-controlling step [13]. Pellet formulations are of great interest since the biopharmaceutical benefits of this type of formulations are essentially better compared to single unit systems. It is the only dosage form that will be produced in this project. Development of a standard extrusion/spheronization process allow for hot-melt extrusion to be used instead of cold extrusion [11]. There are many limitations with the traditional manufacturing methods for solid oral dosage forms. The wet granulation technique is both labor- and equipment-intensive, uses solvents and other additives and the compression techniques have uniformity problems [2]. A lot can therefore be gained if a new method for production of solid oral dosage forms, such as pellets, is developed.

2.2. Hot-melt extrusion

Extrusion can be defined as the process of forming a new material, the extrudate, by forcing a material through a die under controlled conditions [14]. The raw materials are pumped through the die by a rotating screw under elevated temperatures, see Figure 4 [15]. Extruders provide extensive mixing and agitation that causes de-aggregation of the suspended particles in the molten polymer resulting in a uniform dispersion. Hot-melt extrusion (HME) is used for mixing, melting, and reacting of materials, thereby combining several separate batch operations into one unit and increasing manufacturing efficiency [14]. Most extruders consist of three parts: a conveying system for material transport and mixing, a die system that forms the extrudate and down-stream supplementary equipment such as cooling, cutting or collecting the products.

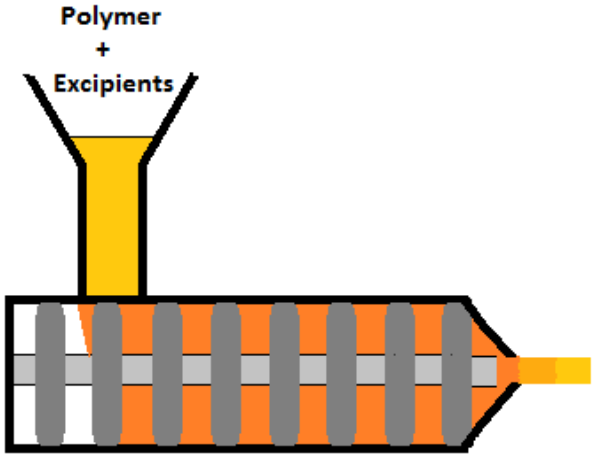


Figure 4. Schematic view of the extrusion process

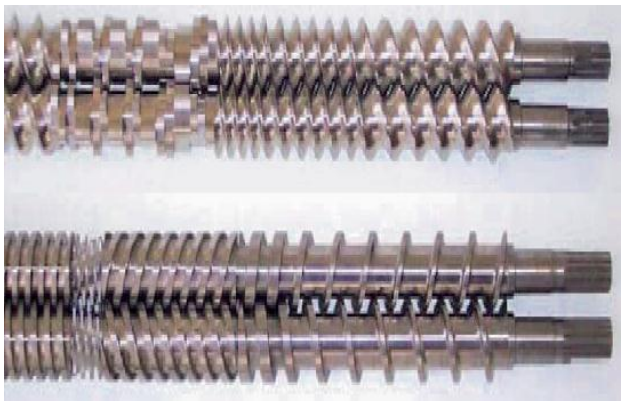


Figure 5. Example of twin-screw design: co-rotating (top) and counter-rotating (bottom) twin-screws [15].

There are two types of extruders: single-screw and twin-screw extruders. The single-screw extruder has been the most widely used [15]. Twin-screw extruders use two side-by-side screws either co-rotating or counter-rotating (Figure 5). There are several advantages of twin-screw extruders over single-screw extruders such as easier material feeding and dispersion capacities, less tendency to over-heat and shorter transit times [15]. However, single-screw extruders are more simple and cheaper.

2.2.1. History

Extrusion is a well-known processing technology that has been developed during the last century. It has been used in many diverse industrial fields, mostly with the processing of foods and the manufacturing of plastics [14]. The first industrial use of single-screw extruders was in the early 1930s with the extrusion of thermoplastic materials [16]. However, an early single-screw extruder was designed by Sturges in 1871 for the purpose of pumping soap [17]. Early twin-screw extruders were attributed to Wiegardin in 1874 [18] and Pfleiderer in 1881 [19]. The first commercially available twin-screw extruders came to the market in the 1940s [14]. Both single-screw and twin-screw extruders were initially developed within a similar time frame, at the end of the 1800s, but the commercialization and the widespread use of single-screw system occurred earlier than that of twin-screw systems [14]. This can be explained by several engineering issues for twin-screw extruders that were not overcome until the 1940s [14].

2.2.2. Process

In hot-melt extrusion, a blend of polymer and excipients in powder form is transferred by a rotating screw through the heated barrel in the extruder. The molten mass is continuously pumped through the die at the end of the extruder and rapidly solidifying when exiting the machine [2]. The screw itself is divided into three parts; feeding, melting and metering (Figure 6). In the feeding section, the material is transported from the hopper into the barrel. The large channel depth facilitates mass flow and when the depth is decreased in the melting zone, the pressure increases. The polymer softens and melts, moving by circulation in a helical path. In the metering zone, the pulsating flow is reduced to ensure a uniform delivery rate through the die cavity which is attached at the end of the barrel. The shape of the extrudate is determined by the shape of the die. The cross-section of the extrudate increases when leaving the extruder, a phenomenon called die swelling. The extent of swelling depend on the viscoelastic properties of the material, a lower viscosity leads to less extensive polymer swelling [15].

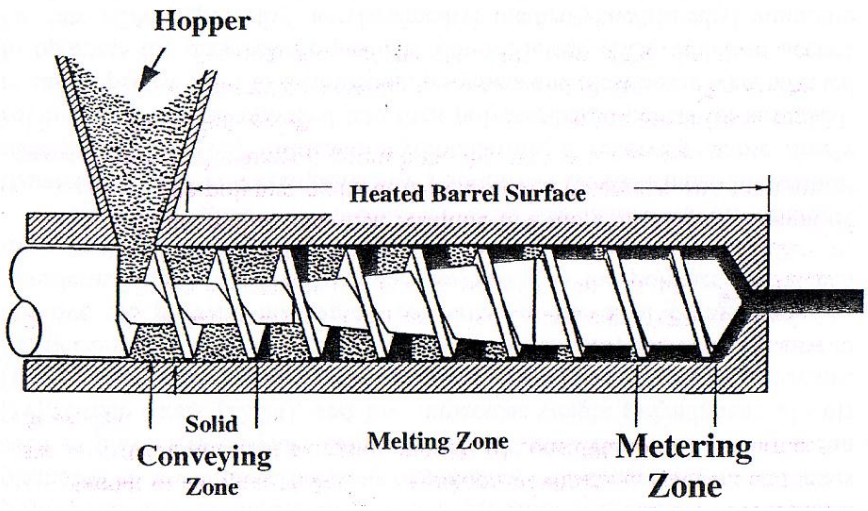


Figure 6. Schematic illustration of an extruder with different functional zones: hopper, conveying zone, melting zone, metering zone and die [2].

When the material moves through the barrel, thermal energy is generated by shearing imposed by the rotating screw and from conduction from the barrel via electrical heating bands. The pumping efficiency is dependent on the friction coefficient between the feed materials and the surface of the barrel and the screw. Material transfer should be as efficient as possible to ensure an increase in pressure in the extruder and an efficient output of the extrudate. The temperature of the melting zone is usually set 15-60°C above the melting point of semi-crystalline polymers or the glass transition temperatures of amorphous polymers [15]. The efficiency of the melting process is dependent on the polymer and extruder design; polymers with low melt viscosity and high thermal conductivity display a more efficient melting process.

The processing parameters affect the properties of the extrudate. Adjustable parameters include screw speed, processing temperature and feeding rate which impact the shear stress and mean residence time and in the long term also dissolution rate and stability of the final product. Since the processing conditions depend on the polymer used, its chemical stability and physical properties should be determined to establish appropriate processing parameters. Mixing also plays an important role during extrusion and can be classified as distributive mixing where the particular ingredient is uniformly distributed and dispersive mixing where the particle size is reduced and distributed [20].

2.2.3. Hot-melt extrusion in the pharmaceutical industry

Hot-melt extrusion has been used as an industrial application since the 1930s and can therefore be considered as being a well elaborated manufacturing technology. Hot-melt extrusion is, however, a relatively new technology in the pharmaceutical industry but has emerged as a viable technique for the development of complex drug delivery systems.

Extrusion can be used as a continuous process achieving a consistent product flow, ideally with high throughput rates. Continuous extrusion produces consistent and repeatable products with good content uniformity. The hot-melt extrusion process is easily monitored which provide comprehensive documentation and simplifies quality control [21]. HME has a potential for automation, with reduction of capital investment and labor costs [15]. In addition, solvents are not

required in hot-melt extrusion which makes the process environmentally friendly [22]. There are few drawbacks with hot-melt extrusion in the pharmaceutical industry. It has higher energy input compared to other methods and some thermolabile compounds might not be appropriate due to high processing temperatures. Melt-extruded dosage forms usually have good long-term stability, but there have been reports of recrystallization of the active substance during storage. The physical and chemical stability of the extrudate depend on the nature of the API, polymers and excipients, the physical state of the API in the final dosage form, storage and packing conditions [20].

Over the past 20 years, hot-melt extruders have been adapted to the specific needs of the pharmaceutical industry. Although the equipment is the same, there are certain criteria that need to be met in order to uphold good manufacturing practices (GMP) [20]. Extruders used in pharmaceutical processes must be adapted to meet the regulatory requirements in the pharmaceutical industry: contact parts cannot be reactive with the product and the equipment should be constructed for the cleaning and validation requirements in a pharmaceutical environment [15]. FDA has enabled continuous processing as long as it is done according to the Quality by Design (QbD) principle: products with an inherent high quality are produced by extensive control of raw materials and process parameters, thereby enabling an accurate prediction of the quality of the final product. This allows for continuous manufacturing of pharmaceuticals with lower production costs due to more effective usage of equipment and fewer analysis of the final product. Process analytical technology (PAT) has gained a lot of attention in the pharmaceutical industry and it has already been introduced for hot-melt extrusion at the laboratory scale [20]. It is used to monitor, analyze and characterize the hot melt process and products in-line. A schematic representation of an extruder setup including in-process monitoring is seen in Figure 7. Several factors can be measured immediately downstream of the extruder to provide real time quality assessment of the product. Analytical technologies such as Raman spectroscopy and near-infrared spectroscopy have been incorporated into this system. PAT helps to optimize design, analysis and control within the manufacturing process [20].

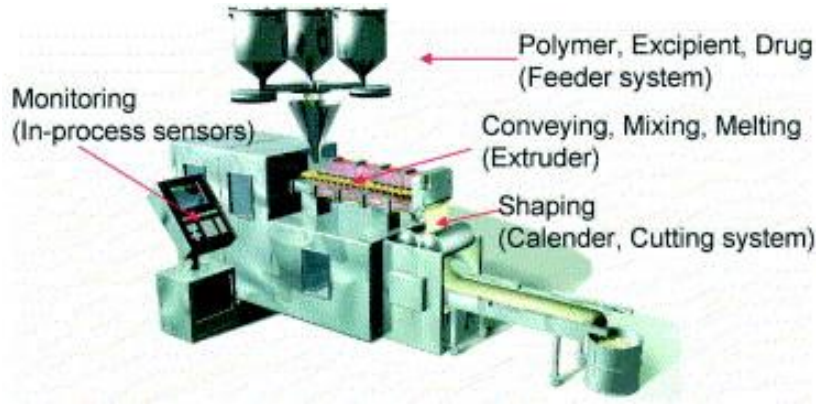


Figure 7. A schematic view of a extruder setup: feeder system, extruder, shaping and in-process monitoring [21].

Hot-melt extrusion in the pharmaceutical industry involves a premixing step where dry powders, drug, and excipients are mixed by conventional blenders and thereafter fed into the extruder. The blend of active substance, polymer and excipients in powder form is transferred by the rotating screw through the heated barrel in the extruder. Most extruders manufactured for pharmaceutical needs are twin-screw extruders because of the advantages of this type of extruder: more extensive mixing and a more stable melting process [22]. Circular holes of typically 0.5-2.0 mm diameter are

used as a die to form cylindrical extrudates [21]. A wide assortment of die shapes and sizes are available; flat dies are used for film production, circular dies are used for pelletization and spheronization whereas the annular dies are used for medical devices and tubing [20]. It has been shown that hot-melt extrusion is a viable approach in the production of many different pharmaceutical drug delivery systems such as pellets, granules, immediate and modified release tablets, transdermal and transmucosal delivery systems, and implants as visualized in Figure 8 [20].

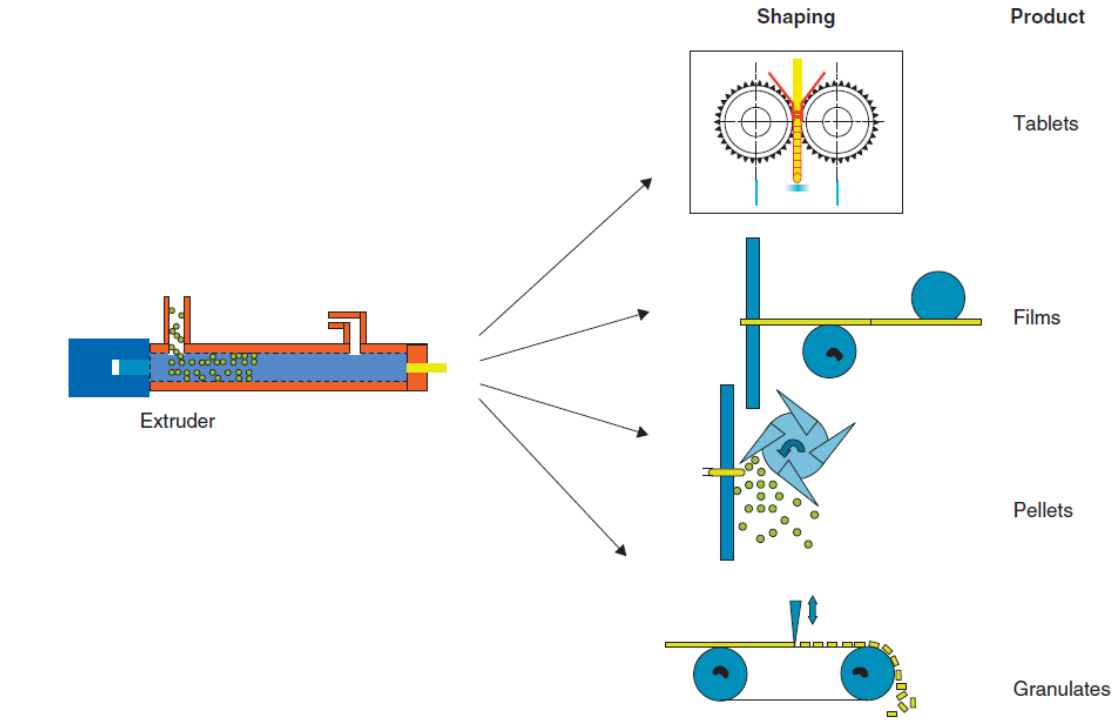


Figure 8. Schematics of different dosage forms that can be produced by hot-melt extrusion [20].

2.2.4. Pharmaceutical materials

There are a few properties that must be met in order for a pharmaceutical material to be used in hot-melt extrusion: it must be easily processed in the extruder, solidify upon exit and meet at least the same levels of purity and safety as those prepared by traditional methods [15]. Most materials in HME pharmaceuticals are already approved materials that have been used in the production of solid dosage forms. Hot-melt extruded dosage forms are a mixture of many different constituents: active substance, matrix carrier, release modifying agents, antioxidants and other additives. The drug release can be changed by incorporating functional excipients, the dissolution rate of the active substance can be increased or decreased depending on the properties of the rate-modifying agent [20]. Thermal stability of all individual compounds is a prerequisite for the process.

In hot-melt extruded drug delivery systems, the active compound is embedded in a carrier formulation. The properties of the active substance often limit the formulation and processing conditions, which makes it important to assess the thermal, chemical and physical properties of the drug before extrusion. The selection of the polymer is also important since it dictates the processing conditions and its physical and chemical properties can control the release of the active compound from the final dosage form [15]. Typical examples of polymeric carriers include polyethylene oxide (PEO), polyethylene glycol (PEG), acrylates (Eudragit), and cellulose derivatives such as hydroxypropyl methylcellulose (HPMC), HPMC acetate succinate (HPMCAS) and cellulose acetate

(CA) [22]. Incorporating plasticizers can lower the processing temperatures, which is advantageous because drug and carrier degradation might be avoided. A plasticizer is typically a low molecular weight compound that softens the polymer to make it more flexible, decreases the glass transition temperature and lowers the melt viscosity [15]. The plasticizer occupies sites along the polymer chain, providing more mobility for the polymer chains resulting in a softer, more easily deformable mass. Altogether this improves the processing conditions and the properties of the final product. Typical plasticizers are PEGs, triacetin, citrate esters and citric acid but several APIs have been shown to be effective plasticizers in certain cases [22]. Since the drug and polymer are exposed to elevated temperatures, high pressure and extensive mixing during hot-melt extrusion it is important to monitor the stability of the active ingredient and polymer to avoid degradation.

2.2.5. Solid dispersions in pharmaceutical applications

Due to high-throughput screening in drug discovery, up to 50% of the discovered new drug candidates have very poor solubility and therefore low bioavailability [20]. Improvement of solubility, dissolution rate and absorption of drugs with low water-solubility are challenging aspects in the development of pharmaceutical products [23]. Solid dispersions is an approach to increase the solubility of the API and increase bioavailability, which is partly explained by a reduction in particle size [20].

Classification of solid dispersions can be divided into molecular or particulate dispersions, based on the drug solubility in the carrier [24]. If the drug is dispersed at the molecular level, the terms molecular dispersion or solid solution are used. However, if the drug is dispersed at the particulate level, the terms particulate dispersion or solid suspension are used. In a molecular solid dispersion, the active ingredient is molecularly embedded in an inert carrier. A true solid solution can be formed if complete miscibility between the components is achieved, leading to the API being molecularly dispersed throughout the polymer [23]. The drug exists in a thermodynamically unstable amorphous form. Factors to consider when forming solid solutions are the solid-state solubility of the API in the carrier, the interaction between them and the stability of the formulation [24]. To form a particulate dispersion, the drug should have limited solubility in the polymer carrier. The polymer/drug ratio can be much less compared to molecular dispersions due to the lower amount of polymers necessary to coat the particles. The polymer intermixes itself between adjacent drug crystals leading to a more thermodynamically stable crystalline form. Although particulate dispersions are more stable than molecular dispersion, the improved dissolution rate and absorption might not be as large [24].

One of the advantages with hot-melt extrusion is that it can disperse drugs in a matrix down to the molecular level, forming a solid solution. At elevated temperatures in the extruder, the solubility of the drug in the polymer carrier is increased, resulting in the formation of a solid solution if the compounds are miscible. Depending on the processing conditions and miscibility of the components, a solid particulate dispersion might also be formed where the drug is only partly dispersed and a physical mixture of drug and carrier exist [15]. Solid dispersions have been described to increase dissolution, absorption and therapeutic efficacy of drugs. However, there are very few products on the pharmaceutical market that are solid dispersion systems [21]. Problems that limit the commercial application of solid dispersions are the method of preparation, reproducibility, formulation into dosage forms and scale up. All of these problems might be overcome by hot-melt extrusion.

2.2.6. Mechanism of release

The release of the active substance from an extruded dosage form depends on the solid state of the drug in the extrudate, for example if a solid solution has been formed. It also depends on the properties of the polymers and other excipients. All modified release formulation uses some sort of barrier, either physical or chemical to provide slow release of the maintenance dose. During the last years this idea has been used in solid oral dosage forms, which slowly release the drug in the gastrointestinal tract after being swallowed. These tablets/pellets have several different mechanisms of drug release: diffusion-controlled, dissolution-controlled or erosion-controlled. In a diffusion-controlled release system, the transport by diffusion of dissolved drugs in pores or in a polymer is the release controlling process. These systems can be divided into matrix systems (also called monolithic systems) where diffusion takes place in pores within the bulk of the release unit, and reservoir systems where diffusion occur in a thin water insoluble film or membrane on the surface of the release unit. In dissolution-controlled systems, the rate of dissolution of the drug in the gastrointestinal juices is the release-controlling process whereas in erosion-controlled release system, the erosion of the matrix where the drug is dispersed controls the release process [7]. The differences between these release-mechanisms are illustrated in Figure 9.

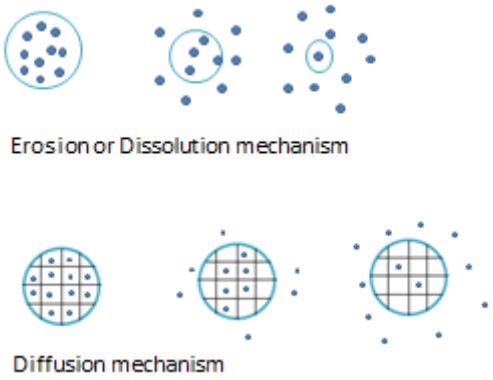


Figure 9. Schematic illustration of the Erosion/Dissolution mechanism and Diffusion mechanism.
(Reproduced from [7], Figure 31.14 and 31.16)

In this study, modified release matrix pellets will be prepared with hot-melt extrusion. The polymers HPMCAS and Eudragit L100-55 will be combined with the plasticizer triethyl citrate and an active substance in different compositions, potentially forming a solid solution when processed in the extruder. However, it is not apparent that the goal is to form a solid solution in order to achieve an extended or delayed release. Depending on the properties of the API, if it has poor solubility or high solubility, it might be just as good with a solid suspension with the active substance in particle form. Formation of a solid solution during extrusion indicates a well-mixed extrudate but the effect on the drug release rate is not obvious and must be studied further.

3. Literature review: Modified release extrudates

As can be recalled from chapter 2.1, the term modified release (MR) can be used to describe all dosage forms that continuously release drugs at a rate which are sufficiently controlled in order to obtain periods with prolonged therapeutic action following one single dose. During the past two decades, researchers have investigated many different applications of hot-melt extrusion in drug delivery systems such as oral, transdermal, transmucosal drug delivery systems and implants. Many different APIs and approved excipients have been used to develop efficient drug delivery systems for immediate, extended or targeted drug release. Hot-melt extrusion is capable of preparing matrix tablets/pellets with a compact structure that can resist rapid penetration of dissolution medium, thereby providing the pellet with both enteric and sustained-release properties [25]. This chapter

will review literature on extruded oral dosage forms with extended release and enteric formulations with delayed release.

3.1. Extended release extrudates

Extended release dosage forms release drug slowly so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (8-12 h). HME has been showed to be a viable method for production of extended release (also called sustained release) systems [20]. The release of drugs from hot-melt extruded pellets is mostly controlled by the permeability and dissolution behavior of the carrier and by the amount of soluble components in the formulation. As opposed to pellets produced by other methods, the porosity of the pellet is minimized thereby reducing the initial effect of diffusion through pores [12]. For example, Crowley *et al.* achieved sustained release characteristics with ethyl cellulose tablets containing 30% guaifenesin produced with hot-melt extrusion but not for tablets produced with direct compression because of the increased porosity of the compressed tablets [26].

In the mid-1990s, Follonier *et al.* thoroughly investigated the possibility to use hot-melt extrusion in order to produce sustained release pellets [27]. Four polymers were examined, ethyl cellulose, cellulose acetate butyrate, poly(EVAC) and Eudragit RS PM, together with the model drug diltiazem. The rate of the drug release was dependent on the type of polymer and the drug load but all formulations yielded sustained release profiles with an initial burst release due to dissolution of the drug at the surface, followed by a slow diffusion controlled phase. Later, the same group demonstrated release modification of diltiazem from extruded pellets by incorporation of hydrophilic polymers to obtain complete drug release, swelling agents to reduce the initial burst and functional agents such as superdisintergrants to vary the dissolution rate [28]. Since then, further research with extended release dosage forms has been performed [29-31]. However, during the last decade, some of the interest in modified release dosage forms produced by hot-melt extrusion has shifted to enteric formulations with delayed release properties.

3.2. Delayed release enteric extrudates

Enteric pellets are examples of a delayed release dosage form i.e. the drug is not released immediately following administration but at a later time. Enteric polymers have pH-dependent dissolution profiles and are therefore used in pharmaceutical products intended for delayed drug release, especially targeted drug delivery to the small intestine since these polymers are not degraded in the acidic environment in the stomach. These properties originate from certain polymers called enteric polymers, such as polymethacrylates (Eudragit) and cellulose derivatives (HPMCAS), which have very low solubility in acidic conditions due to free carboxylic acid groups which remain unionized at low pH. When the pH increases to a specific value which depend on the enteric polymer used, the functional groups will become ionized and the hydrophilicity and solubility will thereby be increased. Enteric polymers can be used to protect acid sensitive active substances from the acidic environment in the stomach, but also protect the stomach from gastric irritation caused by some drugs [32].

According to the United States Pharmacopeial Convention (USP), the drug release from enteric dosage forms are limited to no more than 10% in acidic medium pH 1.2 (0.1 N HCl) over 2 hours (see section 4.2.2). This requirement is not always easy to fulfill. Drug at the pellet surface is exposed to the dissolution medium and most release profiles therefore have an initial burst release [12]. High

drug loads and small pellet size increase the fraction of API in the matrix to be controlled by the enteric polymer, sometimes resulting in failure of the USP requirement. The thermal properties of most enteric polymers remain a challenge, the temperature span between glass transition temperature and thermal degradation is often small, making the use of plasticizer necessary. However, plasticizers with aqueous solubility may leach from the pellet, promoting water penetration into the matrix thus resulting in increased drug release by diffusion through the pores [12].

3.2.1. Development of method to produce enteric matrix pellets

Until recently, enteric dosage forms with pH-dependent release have focused on enteric coatings to obtain delayed drug release. In 2005, Mehuys *et al.* developed an alternative technique to enteric coatings by producing hollow cylinders with hot-melt extrusion containing the enteric polymers PVAP (polyvinyl acetate phthalate) and HPMCAS [33]. A laboratory scale co-rotating twin-screw extruder with several temperature zones and an annular die was used. The hollow cylinders were filled with model drug and both ends of the cylinder were closed yielding hot-melt extruded enteric capsules which showed excellent gastro-resistance since no drug release was observed after 2 h in 0.1 N HCl. This technique, however, was not continuous and quite time-consuming. A simpler method to produce enteric matrix tablets using HME technology was identified by Andrews *et al.* in 2008, thereby introducing a way to produce oral dosage forms with enteric properties in a fast, continuous way [34]. Eudragit L100-55 was pre-plasticized with triethyl citrate (TEC) and mixed with the model API 5-aminosalicylic acid (5-ASA) which was thereafter hot-melt extruded as cylinders using a Randcastle microtruder extruder with four different temperature zones and an 8 mm die. The cylinder was cut into small tablets (results discussed in next section). Note that researches use the terms tablet and pellet quite intermixed and when extruded cylinders are cut, it is mainly the size that determines which term is used i.e. pieces with larger diameter are called tablets and smaller diameters are called pellets.

3.2.2. Comparison of extruded and compressed tablets

In the study made by Andrews and coworkers, a comparison of the melt-extruded tablets was made with tablets produced by compression of powder made from milled extrudates [34]. The cut tablets showed excellent gastric resistance in the acidic environment, releasing less than 5% of the drug, compared to the compressed tablets which had significantly higher release rate (more than 10%). Andrews *et al.* concluded that the drug release rate depended on the concentration of plasticizer, the presence of citric acid (as a solid-state plasticizer) and the presence of a gelling agent. Including a gelling agent reduced the matrix erosion but the enteric properties were lost due to channel formation within the matrix. Yang *et al.* prepared enteric matrix tablets by cutting extrudates and compressing powder from milled extrudates with Eudragit L100 as a carrier, the acidic Ketoprofen as API and diethyl phthalate as a plasticizer [25]. A co-rotating twin-screw extruder with several temperature zones was used (unknown die-size). Surprisingly both tablet types released less than 3% in 0.1 N HCl and both showed a sustained release in the buffer phase (6 to 12 hours). As can be recalled, these results differed from Andrews *et al.* who had compressed tablets that released much more drug than the cut tablets in the acid phase. Yang *et al.* concluded that the release mechanism for the cut tablets was erosion-controlled.

3.2.3. Influence of polymer

Schilling *et al.* made an extensive study with the objective to investigate hot-melt extruded matrix pellets with a size below 1 mm and their ability to delay the release of Theophylline as a basic, water-soluble model drug [35]. A Haake Minilab extruder with co-rotating screws and a 500 µm die was used to produce enteric pellets containing five different enteric matrix polymers, the cellulosic polymers, HPMCAS LF and HPMCAS HF, and the polymethacrylates, Eudragit L100-55, Eudragit L100 and Eudragit S100. All formulations showed an initial burst effect with a relatively high release after 15 min in acid phase explained by release of drug at the surface of the pellets. The cellulosic pellets (HPMCAS, 20% TEC, 5% Theophyllline) had high release rate in acid, releasing more than 20% after two hours, thereby failing the 10% USP requirement. On the other hand, the methacrylic polymers exhibited excellent gastric protection with less than 4% drug released after two hours. These formulations, however, exhibited worse processibility with higher extrusion temperatures and the Eudragit L100-55 formulation could not be extruded through the 500 µm die. In the neutral buffer phase, Theophylline was rapidly released from the HPMCAS based pellets (>95% after 2h in buffer) versus the more sustained release profile from the Eudragit formulations (~65% after 2h in buffer).

3.2.4. Influence of drug load

Schilling *et al.* also examined the influence of drug load (10-40% Theophylline) for the Eudragit S100 formulation with 40% TEC based on the polymer content [35]. The increase of TEC from 30% to 40% increased the permeability of the matrix in both media, increasing the API release from 3.76% to 6.10% in acid phase, and from 66.56% to 83.52% in the neutral buffer phase. All drug loadings showed a pH-dependent biphasic release profile with less than 10% drug release in the acid phase and 100% drug release after 6 hours in buffer, with a slightly faster drug release rate with the 40% Theophylline formulation. The Theophylline powder did not melt during extrusion and increasing the concentration of non-melt compound led to declining processing conditions which according to Schilling *et al.* might limit the drug load. Another group, Bruce *et al.*, prepared hot-melt extruded enteric tablets using Eudragit S100 for the colonic delivery of 5-aminosylic acid using a Randcastle Microtruder extruder fitted with a 6 mm die [36]. Tablets with 25% 5-ASA showed excellent gastric protection releasing less than 10% after two hours in acid and showed controlled release in pH 7.4 phosphate buffer medium. Interestingly they found that by increasing the concentration of the acidic 5-ASA in the tablets (from 25 to 50%), a delay in tablet drug release was seen due to lowering of micro-environmental pH by the increased amount of acidic compound in the formulation [36]. The release of API was found to follow both diffusion and surface erosion models.

3.2.5. Influence of plasticizer

Schilling *et al.* also examined the effect of plasticizer type [35]. Pellets plasticized with 20% PEG (polyethylene glycol) or CA MH (citric acid monohydrate) failed to provide gastric protection, releasing much more than 10% during the acid phase which could be explained by their high aqueous solubility and formation of channels through the pellet. The other plasticizers examined, namely MP (methyl paraben), ATBC (acetyltributyl citrate) and TEC (20%) showed low drug release rates with 3.85%, 5.84% and 7.14% drug release after two hours in acid suggesting that leaching of plasticizer was negligible. In buffer, pellets that were most efficiently plasticized (MP and TEC) released Theophylline at higher rates than pellets with ATBC or no plasticizer, which Schilling *et al.* explained by faster water penetration into the pellet [35]. Bruce *et al.* found that increasing TEC content in the tablets (from 12 to 23%) resulted in an increase in drug release rates due to leaching of the plasticizer from the tablet matrix [36].

3.2.6. General considerations for HME enteric pellets

Not all studies have shown enteric tablets/pellets with good gastric protection. For example Young *et al.,* produced spherical pellets containing Eudragit L100-55 (20% Theophylline) with a Randcastle Microtruder (1.2 mm die), Randcastle Pelletizier and Calevea Spheronizer [37]. These spherical pellets released more than 25% drug in 2 hours at pH 1.2 probably due to the high surface area to volume ratio. Preparation of small diameter pellets with increased surface area, high drug loadings, and high concentration of hydrophilic substances (APIs and plasticizers) which can act as pore formers and thereby increase drug release rate, are still problems to consider when producing enteric pellets.

Although several successful studies have produced enteric matrix dosage forms with good gastric protection, they have been performed in a laboratory environment oftentimes using small scale extruders. It is hard to say if the delayed release characteristics of these enteric dosage forms will remain if the experiments are scaled up to pilot or industry scale. A lot of research remains before these extruded enteric pellets can be commercialized.

3.3. Hot-melt extruded commercialized products

Oral pharmaceutical products produced by hot-melt extrusion have been approved in the USA, European and Asian countries [21]. As of now, there are only a few commercialized products produced by hot-melt extrusion on the pharmaceutical market. However, the interest in hot-melt extrusion is increasing, with over a hundred research papers and increasing number of HME patents [20]. Many pharmaceutical companies are optimizing the technology and introducing HME produced products. A heat stable Norvir® (Abbot Laboratories) tablet which does not require refrigeration was approved by the FDA. This was followed by Kaletra®, another melt extruded tablet produced by Abbot, which has significant advantages over the older soft gelatin capsules in terms of dosing frequency and stability. Other melt extruded products include Implanon® (Organon), Isoptin SR (Abbot Laboratories) and the contraceptive NuvaRing®. The latter is an intravaginal thermoplastic ring produced by co-extrusion of drug and poly(ethylene vinyl acetate), pEVA, forming the core while the crystalline pEVA on the exterior act as a rate-limiting membrane to control the drug release [20]. There are also a number of HME produced pharmaceutical products and medical devices in the pipeline.

4. Experimental

In this section, the properties of the materials used will be described as well as theory and method descriptions for all methods used.

4.1. Materials

A detailed list of all the materials used including company and lot number can be found in Appendix I.

4.1.1. HPMCAS

HPMCAS (Hydroxypropyl methylcellulose acetate succinate) (Shin-Etsu) is an enteric polymer which was used as a matrix carrier in half of the formulations in this study. Its structural formula is shown in Figure 10. HPMCAS is often used as an enteric coating agent in solid oral dosage forms and as a solubilizing modified release agent via formation of solid dispersions. HPMCAS is insoluble in gastric

fluids but will swell and dissolve rapidly in the upper intestine. The glass transition temperature is 113 ± 2°C [38].

HPMCAS is available in several subclasses, according to the pH at which the polymer dissolves: low (L), medium (M) and high (H), and its particle size: fine powder (F) or granules (G) [38]. HPMCAS-LF was used in this study. The exact pH value at which the polymer starts to swell and dissolve depends on the buffer type and ionic strength but the grade LF is soluble above pH 5.5 [39]. HPMCAS is included in the FDA Inactive Ingredients Database for use in oral preparations [38].

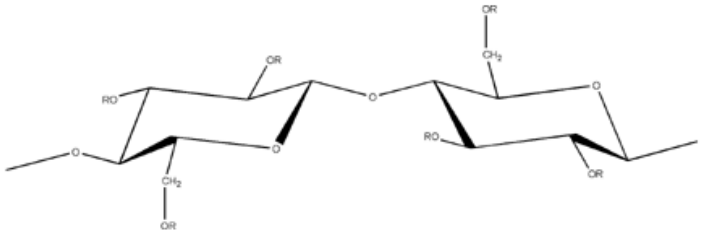


Figure 10. Structural formula of HPMCAS where -OR represents hydroxyl, methoxyl, 2-hydroxypropoxyl, acetyl, or succinoyl [38].

4.1.2. Eudragit L100-55

Eudragit L100-55 (Methacrylic acid-Ethylacrylate copolymer) (Degussa) was used as carrier polymer in half of the formulations in this study. Eudragit is a tradename of several types of polymethacrylates. The chemical name of Eudragit L100-55 is Poly(methacrylic acid, ethyl acrylate), a copolymer with a ratio of 1 : 1. The structural formula is shown in Figure 11.

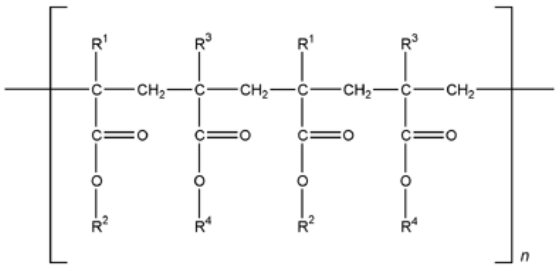


Figure 11. The structural formula for Eudragit L100-55 where R^1, R^3 = H, CH_3, R^2 = H and R^4 = CH_3, C_2H_5 [40].

Eudragit L100-55 is a modified-release agent, solubilizing agent and tablet binder. Polymethacrylates are most commonly used as oral capsule and tablet formulations as an enteric film-coating agent. Eudragit L100-55 is insoluble in gastric media but soluble in intestinal fluid above pH 5.5. Polymethacrylates are included in the FDA Inactive Ingredients Database for oral capsules and tablets [40].

4.1.3. TEC

TEC (Triehtyl citrate) (Fluka) was used as a plasticizer for all formulations. TEC is a water soluble liquid-state plasticizing agent and have, as many other plasticizers, a low-molecular weight (Figure

12). TEC is often used to plasticize polymers in formulated pharmaceutical coatings, especially extended release and enteric formulations.

Triethyl citrate is a suitable plasticizer for polymethacrylate polymeric film coatings where it is typically used at concentrations of 10-20% although higher concentrations may be needed depending on the properties of the polymers and drug used in the formulation. It is also appropriate for ethyl cellulose aqueous dispersions (10-35%) and HPMCAS (20-40%). TEC is a suitable plasticizer for polymers processed by hot-melt extrusion, it has a boiling point of 294°C. TEC is GRAS listed, accepted for use as a food additive in Europe and included in the FDA Inactive Ingredients Database for oral capsules and tablets [41].

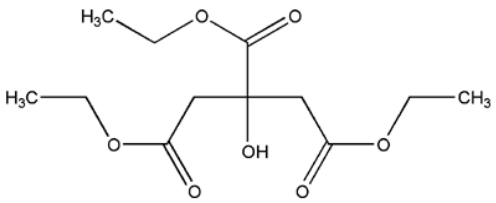
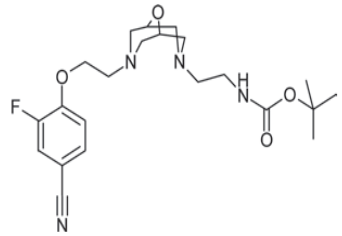


Figure 12. Structural formula of Triethyl citrate [41].

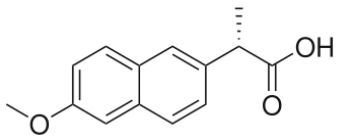
4.1.4. APIs

Two different APIs were used in this study: Naproxen (ICN Biomedicals, Inc.) as an acidic model drug and AZD1305 (not a commercialized product, kind gift from Astra Zeneca, Sweden) as a basic model drug.



AZD1305 is a water-soluble investigational antiarrhythmic agent for restoration and maintenance of sinus rhythm in atrial fibrillation patients. AZD1305 is a crystalline oxabispidine, Figure 13. In its neutral form it is a base with pK_a 9.9 and the melting point is around 90°C [42].

Figure 13. Structure of AZD1305 [42]



Naproxen is a nonsteroidal anti-inflammatory drug commonly used for the reduction of pain, fever and inflammation (Figure 14). Naproxen is a weak acid with pK_a 4.2-4.4 and its melting point is around 152-158°C.

Figure 14. Structure of Naproxen [43].

4.1.5. Buffers

Three different buffers were used in this study (full description in Appendix II). A pH7.0 phosphate buffer containing 1M NaH_2PO_4 (Fluka Chemica) and 0.5 M Na_2HPO_4 (Fluka analytical) was used for the dissolution test of extended release dosage forms. For enteric dosage forms, two buffers were used. In the acid phase, a pH1 0.1M HCl (Kebo-lab) buffer was used and in the neutral buffer phase, a 0.2 M tribasic phosphate (Na_3PO_4, Aldrich Chemistry) buffer was added to the acid buffer.
2 M NaOH (Aldrich Chemistry) was used to adjust the pH of the dissolution medium to about pH 6.9.

4.2. Methods

The underlying theory of the methods is described in short, followed by a description of the methods used.

4.2.1. Hot-melt extrusion

Powder blends for extrusion (8 g) were prepared by mixing polymer, plasticizer and active substance in a beaker. The polymer type and composition of excipients were varied and these formulations were processed in the extruder and evaluated (Appendix III). The miscibility of polymer and plasticizer was an important factor to consider. HPMCAS and TEC were not easily mixed and HPMCAS formulations were also hard to feed into the extruder. This formulation was therefore preheated, melted and formed into a string which was cut into small pieces, simplifying the loading extensively.

A mini extruder with co-rotating screws and a 2 mm die (Haake Minilab, Rheomax CTW5) was used for the extrusion of drug loaded, polymeric strands (Figure 15). The Haake Minilab extruder is a small lab-scale extruder requiring only 7 cm^3 sample. It has an integrated backflow channel, making recirculation of the melt possible and thereby achieving improved mixing. Approximately 8 g of powder was repeatedly fed into the extruder in small portions, to avoid problems with the air pressured feeding device. Once inside, the molten mass was circulated for five minutes before it was flushed. The extrudate was collected when exiting the die. All processing conditions were monitored during extrusion, the speed was kept constant at 80 rpm for all experiments and the temperature settings depended on which polymer was used: 120°C or 160°C for HPMCAS and 140°C or 165°C for Eudragit L100-55. Torque and pressure were also monitored and the maximum values were recorded (Appendix III).

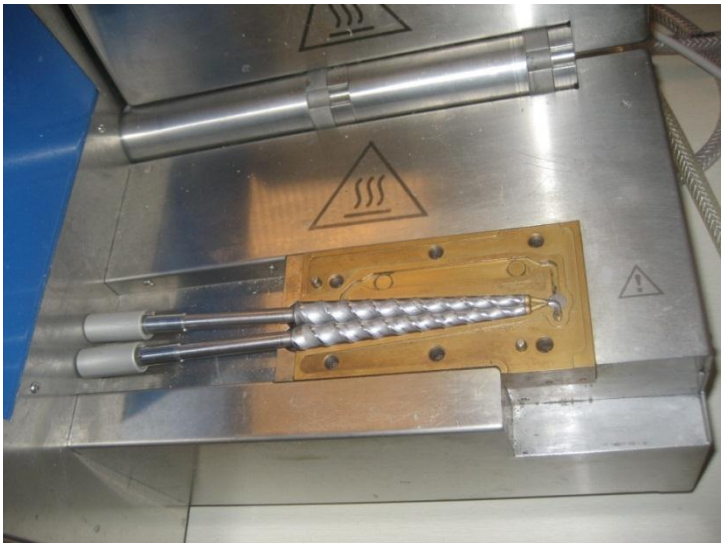


Figure 15. Haake Minilab extruder with co-rotating twin-screws.

For each formulation, 2 batches were prepared. When the first batch had been extruded, the machine was set on recirculation with the motor running and the second identical powder blend was fed into the extruder. Some of the left-over material in the extruder from the first batch could therefore be salvaged, leading to a longer extrudate the second time. Each batch were cut into pellets and divided into three replicates before dissolution testing. The total weight of material in each replicate were approximately the same, but differed a little bit between formulations depending on the amount of extrudate available after extrusion. The diameters of the extruded strands were measured with a manual micrometer (Digimatic micrometer, Mitutoyo Corporation, Japan) and the strands were thereafter manually cut to small cylindrical pellets, approximately 0.5 cm for Eudragit L100-55 and 1 cm for HPMCAS.

4.2.2. Dissolution testing

In vitro dissolution testing is done to evaluate the drug release profile of the pharmaceutical product. Although this method is called dissolution testing in the literature, it is the amount of drug released, not dissolved, that is measured. Release testing might be a more appropriate term, but in this thesis, the term dissolution testing will be used. However, in the rest of the report, recall that it is the drug release that is evaluated.

Two analysis methods are described by USP (United States Pharmacopeial Convention) for dissolution testing of enteric products, methods A and B. The method A procedure states that enteric dosage forms should be tested in 750 ml of 0.1 N hydrochloric acid at 37°C for 2h followed by the addition of 250 ml of 0.2 M sodium phosphate buffer and any further pH adjustments required to reach the specific pH. This should be done within 5 minutes but preferable as fast as possible to achieve effective mixing and neutralization. A rapid addition of the buffer medium results in increased stirring and turbulence resulting from the high momentum of the buffer medium into the stationary acid media [32]. With method B, the enteric dosage form is tested in 1L of 0.1 N hydrochloric acid for 2h, the buffer is thereafter drained and switched to 1L of pH 6.8 phosphate buffer. The performance of an enteric dosage form is evaluated during both the acid and buffer phases. In order to pass the USP requirements, less than 10% should be released during two hours in the acid phase and at least 80% drug release within 45 min (or the specified time for the particular pharmaceutical) following the addition of buffer medium [32]. The meaning of the *in vitro* test is to mimic the passage through the gastrointestinal tract, the entrance of the dosage form in the acidic stomach and thereafter the more neutral pH environment in the small intestine.

In this study, dissolution studies were carried out in a standard USP paddle apparatus (Prolabo, France) according to the method described for delayed release articles USP chapter <724>, method A (Figure 16). Pellets (500-1000 mg) were placed in the baskets and submerged in 675 ml 0.1 M hydrochloric acid (pH1). The paddle apparatus was run at 37°C and 50 rpm. 1 ml samples were collected at time 0 and every 30 min during the acid phase[1]. After 2 hours the pH was increased to around pH 6.9 by adding 225 ml 0.2 M tribasic phosphate buffer and adjusting with diluted sodium hydroxide solution (2 M) to the desired pH. At the start of this buffer phase, new samples were collected and the pH was monitored. Samples were then collected every 20 or 30 min until the pellets were completely dissolved.

Dissolution studies for non-enteric dosage forms were performed in USP paddle apparatus in 900 ml phosphate buffer (pH 7.0) for at least 4 hours, until the pellets were completely dissolved. Pellets (~500 mg) were placed in the baskets and submerged in the dissolution media, the paddle apparatus was run at 37°C and 50 rpm. 1 ml samples were collected at time 0, 20 min, 40 min, 60 min and then every 30 min until the pellets were dissolved.

[1] 1 ml dissolution media was added each time a sample was collected to keep the volume constant. The loss of active substance in the dissolution media, from the samples collected, were accounted for during post laboratory calculations.

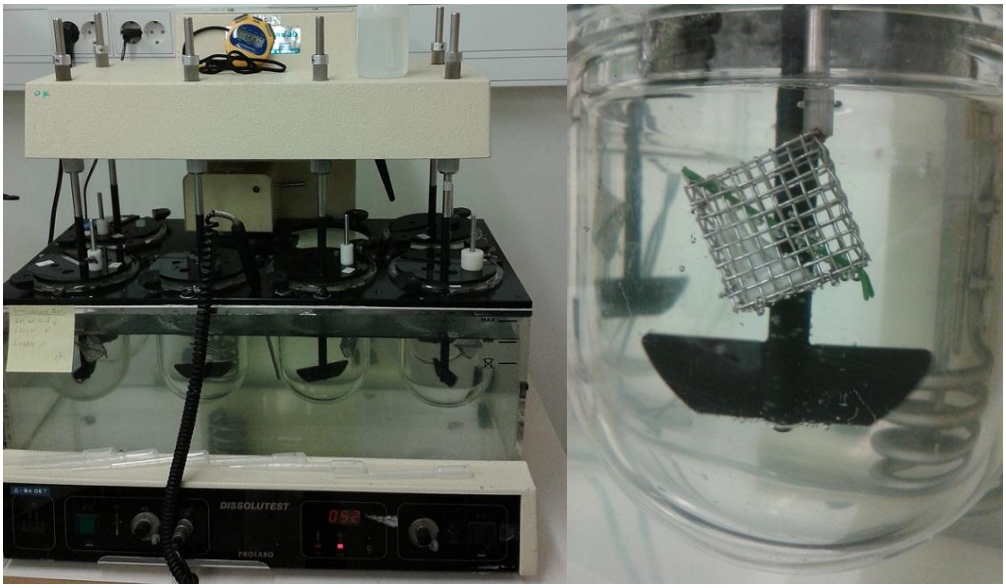


Figure 16. The experimental setup for dissolution testing: USP paddle apparatus (left) and basket with pellets submerged in dissolution medium (right).

4.2.3. UV-Vis Spectroscopy

Spectroscopy is the study of matter and radiated energy. Ultraviolet-visible (UV-Vis) spectroscopy refers to absorption spectroscopy in the ultraviolet-visible range. UV-Vis spectroscopy measures the intensity of light passing through a sample (I) and compares it to the intensity of the incident light (I_0). The method is often used in a quantitative way to determine concentrations of an absorbing species in solution by using the Beer-Lambert law:

$$A = \log\left(\frac{I_0}{I}\right) = \varepsilon c l \qquad \textbf{Equation 1}$$

A is the measured absorbance, I_0 is the intensity of the incident light at a given wavelength, I is the transmitted intensity, *l* is the path length through the sample (usually 1 cm) and c is the concentration of the absorbing species. For each species and wavelength, ε is a constant called the extinction coefficient (or molar absorptivity). The Beer-Lambert law states that the absorbance of a solution is directly proportional to the concentration of the absorbing species in the solution and the path length. UV-Vis spectroscopy can therefore be used to determine the concentration of the absorbing species in a solution, when the extinction coefficient is known.

The content of active substance in the samples collected from the dissolution tests were quantified using UV-Vis spectroscopy (Cintra 40, GBC Scientific Equipment Ltd.). However, due to technical problems, the last experiment was evaluated using a different UV-Vis spectrometer (Lambda 14, Perkin Elmer). A standard curve of Naproxen was made by dissolving a known amount of Naproxen in phosphate buffer, diluting to 4 different concentrations within the acceptable absorbance range (0.2-1.5), scanning the samples between 200-600 nm, measuring the corresponding absorbance at 271.6 nm and calculating the extinction coefficient (see Appendix IV). The absorbance of the samples from the dissolution tests were then measured and converted to concentration. The drug release percentage was plotted against time. All graphs were normalized to 100%.

4.2.4. Mechanism of drug release: Higuchi equation and power law

The mechanism of release of modified release systems can be either purely diffusion- or erosion-controlled or a combination. In 1961, Higuchi developed an equation based on Fick's law of diffusion to describe the release rate of drugs from matrix systems [44]:

$$\frac{M_t}{M_\infty} = K\sqrt{t} \qquad \textbf{Equation 2}$$

where M_t is the cumulative absolute amount of drug released at time t, M_∞ is the absolute cumulative amount of drug released at infinite time (which should be equal to the absolute amount of drug incorporated into the system) and K is a constant. This means that the fraction of drug released is proportional to the square root of time. However, this equation has some limitations, for example the swelling and/or erosion of polymers is assumed to be negligible [45]. A more comprehensive but still simple equation to describe drug release from polymeric systems is the so-called power law:

$$\frac{M_t}{M_\infty} = kt^n \qquad \textbf{Equation 3}$$

where M_t and M_∞ are the absolute cumulative amount of drug released at time t and at infinitive time, respectively. k is a constant and n is the release exponent which indicates the mechanism of release [45]. As can be seen, the classical Higuchi equation represent the special case of the power law when n=0.5. The power law (sometimes called the Korsmeyer-Peppas model) is used to analyze drug release from pharmaceutical dosage forms when the release mechanism is not well known or if more than one mechanism is involved. The exponent, n, is called the release exponent and it was first studied by Peppas and coworkers [46]. For thin films it was found that when n=0.5, the drug release is controlled by Fickian diffusion whereas when n=1, the drug release is independent of time and controlled by a swelling mechanism. A zero-order release rate is also known as case-II transport. For systems with n-values between 0.5 and 1, a combination of mechanisms control the drug release and this is called anomalous (non-Fickian) transport. The values of n for a cylindrical system were later determined: n=0.45 (Fickian diffusion), 0.45<n<0.89 (anomalous transport) and n=0.89 (case-II transport) [47]. The same authors also stated that when determining the n exponent, only the portions of the curve where $\frac{M_t}{M_\infty} \leq 0.6$ should be used.

Normalized drug release data were fitted to the power law for all enteric formulations evaluated in this study. A representative example is shown in Figure 17. Only data points in the buffer phase were used because no substantial dissolution or release is achieved in the acid phase. 3 or 4 data points per formulations were used with a cutoff limit at 70% drug release.

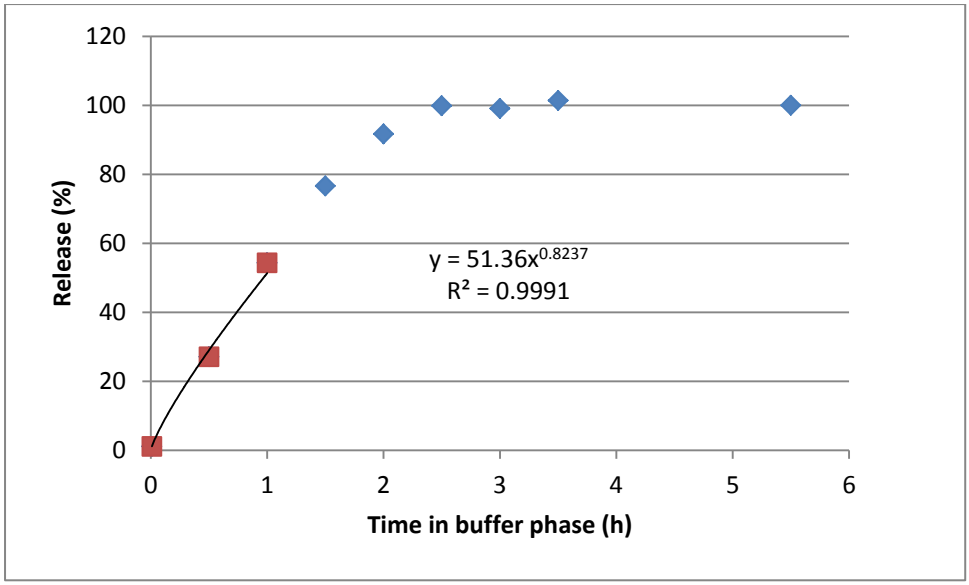


Figure 17. Example of model fitting to drug release data.

4.2.5. Differential scanning calorimetry

Differential scanning calorimetry (DSC) is a thermal analytical technique that is used to detect phase transitions and physical properties of the sample. DSC measures the difference in the amount of heat required to increase the temperature of a sample compared to a reference. The energy difference is then plotted as a function of sample temperature (Figure 18). When a sample undergoes a phase transition, more or less heat is required compared to the reference to keep both at the same temperature. DSC can be used to detect phase transitions such as melting, crystallization and glass transitions [48].

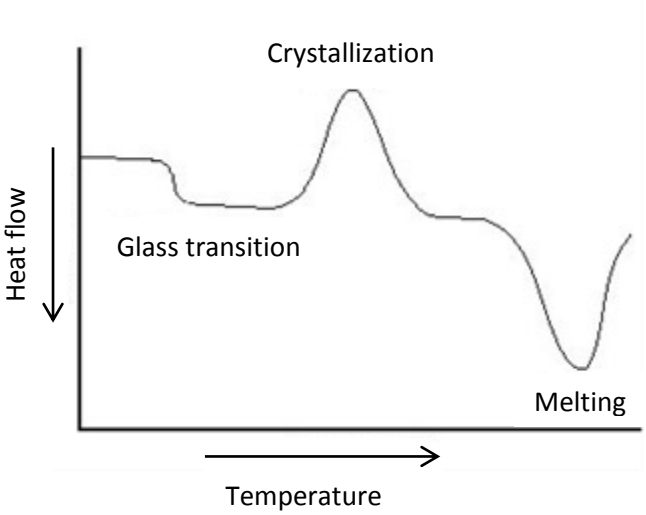


Figure 18. A typical DSC graph undergoing a glass transition, crystallization and melting.

Eudragit L100-55, HPMCAS, Eudragit L100-55 +20% TEC and HPMCAS + 20% TEC were analyzed one at a time by differential scanning calorimetry to determine the glass transition temperature. 5-10 mg of the sample were placed in the metal pan and the reference pan was kept empty (air-filled). The powder was equilibrated at 50° for 1 min and thereafter heated to 140° at 5°C/min using a differential scanning calorimeter (DSC7, Perkin Elmer). After 1 min equilibration, the sample was cooled to 50° at 10°C/min. For samples containing a mixture of polymer and plasticizer, a second run

was performed. The glass transition temperature should be measured during the second cycle at the midpoint of the step transition in the plot of heat-flow versus temperature.

DSC measurements were also performed to evaluate the composition of extrudates. If the API is molecularly dispersed in the polymer carrier, the characteristic melting point of the drug is not observed in the graph. Both APIs and the plasticizer were analyzed, as well as several extrudates to evaluate the formation of a solid dispersion. The melting point of AZD1305 is around 90°C so samples including this API were heated to 140°C. However, the melting point of Naproxen is higher, around 155°C so these samples were heated to 170°C. All samples were measured during two runs, with a heating rate of 5°C/min and a cooling rate of 10°C/min.

5. Results and Discussion

At first, results from extended release extrudates are displayed with focus on the effect of the extrusion temperature on the release profile. Then the results of the enteric pellets with delayed release are shown, focusing on the influence of the extrusion process and the formulation (polymer, plasticizer, API) on the release profile.

5.1. Extended release pellets

Pellets with extended release properties were produced with hot-melt extrusion. The two different polymers Eudragit L100-55 or HPMCAS were used in formulations which also included 5% of the API Naproxen and 20% TEC as plasticizer. Pellets were produced at two different temperatures to evaluate the effect of the temperature on the release profile, one temperature above the melting point of Naproxen (~155°C) and one below. Differential scanning calorimetry measurements were performed in order to find the glass transition temperature for the polymer blends and thus being able to select two appropriate temperatures for each formulation (Data not shown). However, it was very hard to observe the glass transition temperature for the powder blends so the process temperatures were mainly chosen relying on literature values. The T_g of HPMCAS has been reported to be 113±2°C [38], 119°C [35] and 120°C [33]. The T_g of Eudragit L100-55 has been reported to be 124.4±1.6°C [49] and around 120°C, with a reduction to 93°C when 10% TEC was included in the formulation [34]. The T_g is significantly reduced when a plasticizer is added meaning that the T_g of the polymer blends with 20% TEC will be lower than the values listed here.

The formulation with Eudragit L100-55 as a carrier was extruded at 140°C and 165°C and the HPMCAS formulation was extruded at 120°C and 160°C. The composition, extrusion parameters and average diameter for these extrudates are displayed in Table I. All extrudates were translucent when exiting the extruder but the appearance differed depending on the polymers used: the Eudragit L100-55 extrudates were whitish and hard and the HPMCAS extrudates were brownish and much more ductile. No further characterization was made. The extrudates were manually cut into pellets and the drug release properties were tested by dissolving the pellets in phosphate buffer (pH7). The drug release profile for the Eudragit L100-55 and HPMCAS pellets are seen in Figure 19 and Figure 20, respectively.

Table I. Polymer type, extrusion parameters and diameters of extrudates containing 5% Naproxen, 20% TEC, different polymers at two different temperatures.

	Polymer	Temperature (°C)	Torque (Ncm)	Diameter ± SD (mm)
E140°	Eudragit L100-55	140	130	3.61 ± 0.22
E165°	Eudragit L100-55	165	80	3.08 ± 0.21
H120°	HPMCAS	120	55	2.49 ± 0.15
H160°	HPMCAS	160	20	1.73 ± 0.25

As can be seen in Table I, there is an apparent trend where a higher temperature leads to lower torque and a smaller diameter. A higher temperature reduces the viscosity of the material, making it flow easier in the extruder and the torque is thereby reduced. Also, since the viscosity determines the amount of swelling when the extrudate exits the die, a lower viscosity will lead to less extensive polymer swelling and a smaller diameter. Recall that the die is 2 mm which means that the Eudragit L100-55 formulation exhibits more extensive swelling than does the HPMCAS formulation. This is explained by the properties of the materials, Eudragit L100-55 is more viscous than HPMCAS. H160° was very easily processed in the extruder but exited the extruder very fast and because it was very soft, it stretched out leading to a diameter smaller than the die.

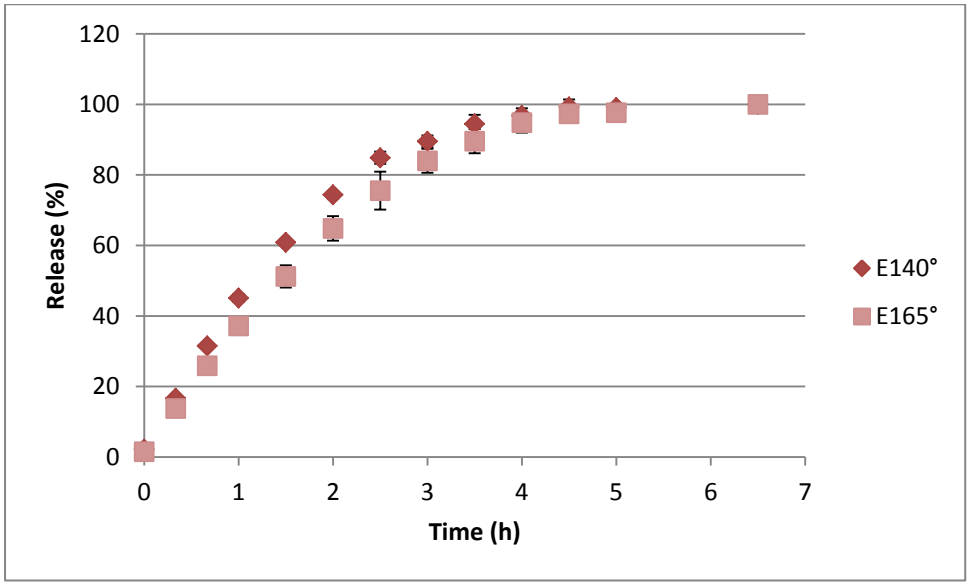


Figure 19. Naproxen release profile of Eudragit L100-55 pellets extruded at 140°C (diamond) and 165°C (square) with 5% Naproxen (Average of 3 replicates). Standard deviation error bars in black. Release: 900 ml phosphate buffer (pH 7.0) until the pellets were completely dissolved.

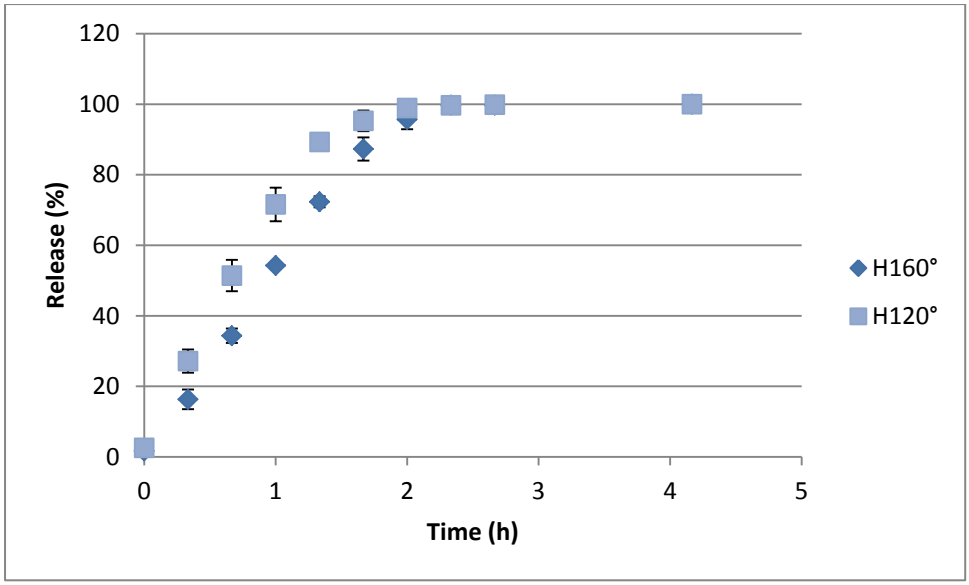


Figure 20. Naproxen release profile of HPMCAS pellets extruded at 120°C (square) and 160°C (diamond) with 5% Naproxen (Average of 3 replicates). Standard deviation error bars in black. Release: 900 ml phosphate buffer (pH 7.0) until the pellets were completely dissolved.

As seen in Figure 19 and Figure 20, both formulations (at both extrusion temperatures) exhibit an extended release. According to USP, at least 80% drug should be released within 45 minutes for immediate release dosage forms. However, all formulations released less than 80% API after 45 minutes. It is apparent that the HPMCAS formulation had a much faster release rate compared to the Eudragit L100-55 formulations. E140° released 45% Naproxen after 1h in phosphate buffer but E165° surprisingly released less API after 1 hour in buffer, only 37% (Figure 19). The same pattern was seen for the HPMCAS formulations, H120° released 72% Naproxen and H160° released 54% Naproxen after 1 h in phosphate buffer (Figure 20).

Increased temperatures promote melting of the active substance which leads to a higher solubility of the API in the polymer which should lead to an increased release rate as discussed in section 2.2.5. However, increased temperature also lead to a less porous structure compared to lower temperatures which might be an explanation to the slower release rate for the water-soluble Naproxen when processed at higher temperatures. This observation was also made by Crowley *et al.* when they studied the release of Guaifenesin from hot-melt extruded tablets based on ethyl cellulose [26]. A single-screw Randcastle extruder with four temperature zones and a 6 mm die was used. The extrudates were manually cut into tablets (recall that cut extrudates with a large diameter usually is referred to tablets in the literature). The Guaifenesin release rate decreased as the extrusion temperature increased because of less pore formation in these tablets. DSC measurements showed small melting transitions of the API in the extrudates processed at the low temperatures which were absent in extrudates processed at the higher temperatures. This indicates that a solid dispersion was formed at the higher temperature. Crowley *et al.* also performed SEM to investigate the surface morphology and at low extrusion temperatures, individual particles were visible which might be responsible for the weak melting transitions found in DSC measurements. The surprising results displayed in Figure 19 and Figure 20 might then be explained by that fewer pores are formed at higher extrusion temperatures leading to a slower drug release rate for water-soluble drugs.

From this point, the lower extrusion temperatures were used for all formulations i.e. 120° for HPMCAS formulations and 140° for Eudragit L100-55. These temperatures were chosen since they are below the melting point of the active substance and still achieved good process conditions in the extruder. Lower process temperatures are advantageous, partly because of the higher stability of the formulation that is achieved compared to higher temperatures, as long as they can provide appropriate processing conditions. These temperatures also provide a "worst-case scenario" since the release rate was slower for the higher temperatures exhibiting a more extended release behavior. This means that if some of the formulations tested onwards do not exhibit the desired modified release behavior, the extrusion temperature can be increased which should lead to a more extended release.

5.2. Delayed release enteric pellets

The preparation of enteric pellets with delayed release behavior required the use of a thermoplastic polymer with acidic groups that have low solubility in acidic conditions but dissolves in more neutral conditions. Enteric pellets with two types of such polymers, HPMCAS and Eudragit L100-55, were prepared with hot-melt extrusion. The composition of blends, the extrusion parameters (temperature, torque and pressure) and the average diameter of extruded strands for all experiments are listed in Appendix III. The temperature settings during extrusion were carefully selected to ensure melt viscosities low enough to enable the exit of the polymer strand through the 2 mm die: 120°C for HPMCAS formulations and 140°C for Eudragit L100-55 formulations. The extruded pellets were characterized with DSC measurements to evaluate the distribution of API in the extrudate. The influence of the formulation such as the influence of the polymer, influence of drug load and influence of type of API on the drug release properties was evaluated. Other aspects examined were: the influence of storage, the batch-to-batch variability and the mechanism of drug release.

5.2.1. Influence of extrusion parameters

Six pellet formulations have been prepared with HPMCAS or Eudragit L100-55 as the polymer and 20% TEC as a plasticizer. The type and amount of API was altered: 5% Naproxen (Composition 1), 25% Naproxen (Composition 2) and 5% AZD1305 (Composition 3). These formulations are given short names, for example H1.1, H1.2, E1.1 and E1.2 with the first letter describing the polymer, the first number describing the composition of drug and the second number describing the batch number. The composition, extrusion parameters and average diameter for these extrudates are displayed in Table II.

Table II. Type of polymer, type and load of API, torque and diameter of extrudates containing 20% TEC, different API and polymers.

	Polymer	API	Load (%)	Torque (Ncm)	Diameter ± SD (mm)
E1.1	Eudragit L100-55	Naproxen	5	100	3.22 ± 0.34
E1.2	Eudragit L100-55	Naproxen	5	80	2.91 ± 0.71
H1.1	HPMCAS	Naproxen	5	126	2.29 ± 0.04
H1.2	HPMCAS	Naproxen	5	83	2.16 ± 0.19
E2.1	Eudragit L100-55	Naproxen	25	36	2.52 ± 0.31
E2.2	Eudragit L100-55	Naproxen	25	42	2.50 ± 0.28
H2.1	HPMCAS	Naproxen	25	44	1.86 ± 0.35
H2.2	HPMCAS	Naproxen	25	75	1.78 ± 0.26
E3.1	Eudragit L100-55	AZD1305	5	336	4.20 ± 0.51
E3.2	Eudragit L100-55	AZD1305	5	146	3.18 ± 0.54
H3.1	HPMCAS	AZD1305	5	53	2.15 ± 0.14
H3.2	HPMCAS	AZD1305	5	106	2.19 ± 0.19

Formulations with Eudragit L100-55 were quite viscous in the extruder at 140°C and extrudates swelled extensively when exiting the extruder. HPMCAS were processed at 120°C, exhibited lower viscosity and thereby less swelling. All extrudates were translucent when exiting the extruder. In general, HPMCAS extrudates had a smaller diameter and were much more ductile compared to the Eudragit L100-55 extrudates. A trend can be observed in torque values between batches for the same formulation (Table II): the torque is usually lower for the second batch which is probably due to an increased temperature in the barrel due to shear and friction during extrusion of the second batch. The increased temperature leads to lower viscosity and in turn lower torque values. There are however a few exceptions, for experiments H2 and H3 the trend is reversed. There is no known explanation for this behavior. E2 also show this trend but the small difference between these two batches is not significant in magnitude. There is an interesting trend when the Naproxen amount is increased to 25%, the torque values drop (100 to 36 Ncm, 80 to 42 Ncm, 126 to 44 Ncm and 83 to 75 Ncm). The data show that Naproxen had a plasticizing effect on the polymer blends. This was very apparent when the extrudates containing 25% Naproxen exited the extruder, they were much more ductile. This was especially true for the Eudragit L100-55 formulation which went from being completely hard to being soft and ductile. The plasticizing effect of Naproxen is also seen when the torque values of E1 and E3 is compared, the torque from E1.1 with Naproxen is 100 Ncm whereas the value for E3.1 with AZD1305 is 336 Ncm. Most diameters follows the same trend as the torque values, the diameter is smaller for the second batch. However most of the batches had quite similar diameter, reducing the impact of diameter and surface area on the drug release rate. Experiment H3, is the only time were the diameter is increased for the second batch, 2.15 vs. 2.19 mm but the small difference in diameter is not significant. However, there is a huge difference between diameter size between E3.1 and E3.2 (4.20 compared to 3.18 mm) which is explained by the big torque difference during extrusion.

5.2.2. Characterization of extrudates

All extrudates were translucent when exiting the extruder. According to Albers *et al.*, a translucent extrudate means that a glassy solid solution has been formed [50]. When the compounds in the formulations are miscible, they will form a single-phase amorphous system and the extrudate will appear in a translucent single-phase state. An opaque extrudate, on the other hand, describes a two-phase system with one or more crystalline components or a glassy suspension where the components are not miscible on a molecular level. To evaluate the uniformity of extrudates and the

solid-state characteristics of the API and the polymer, DSC measurements were performed on selected extrudates and compared to the graphs obtained from polymer/plasticizer blends and graphs of the active substances. Differential scanning calorimetry can theoretically differentiate between solid solutions, solid dispersions where the drug is only partly molecularly dispersed, and on physical mixtures of drug and carrier. If the DSC scans of the extrudates lack the endothermic melting transition, the drug is present in its amorphous form [51]. However, the graphs are not always easy to interpret.

Both APIs exhibited distinct melting transitions in the DSC graphs, at approximately 157°C for Naproxen and 87°C for AZD1305 (Figure 21). Extrudates of stored E1, E2 and H3 were examined as well as quite fresh H2, no clear melting transitions were seen. Figure 22 shows a representative DSC graph for an extrudate (H3). The absence of melting transitions of the APIs together with the translucent appearance of extrudates suggests that the API is molecularly dispersed in the polymer. However, further DSC measurements and additional characterization techniques, such as Raman spectroscopy, need to be performed to confirm these results. This was beyond the time frame of this thesis. The well dispersed API can be explained by the extensive mixing that occur in the heated barrel during extrusion, especially since these extrudates have been produced in a Haake Minilab with 5 minutes recirculation time. This increased residence time leads to a thoroughly mixed extrudate.

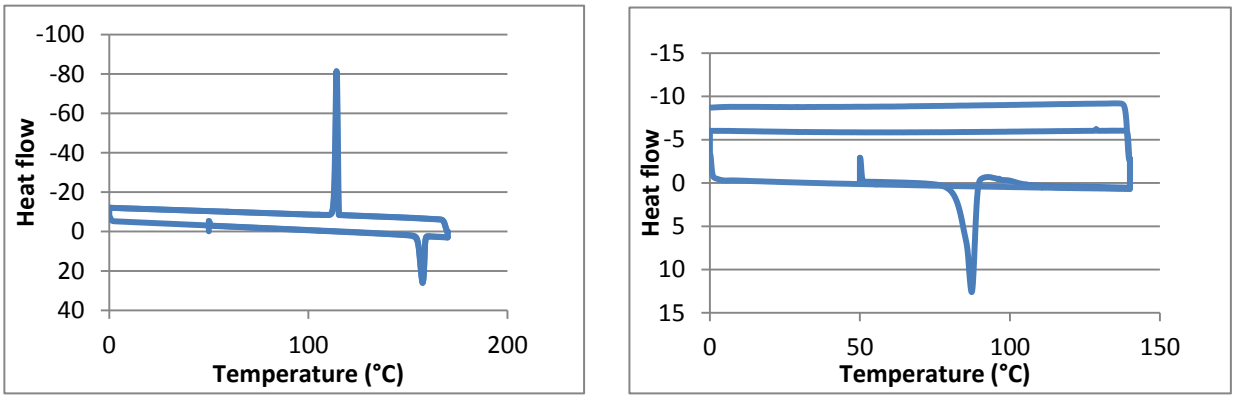


Figure 21. DSC graph of pure Naproxen (left) and AZD1305 (right).

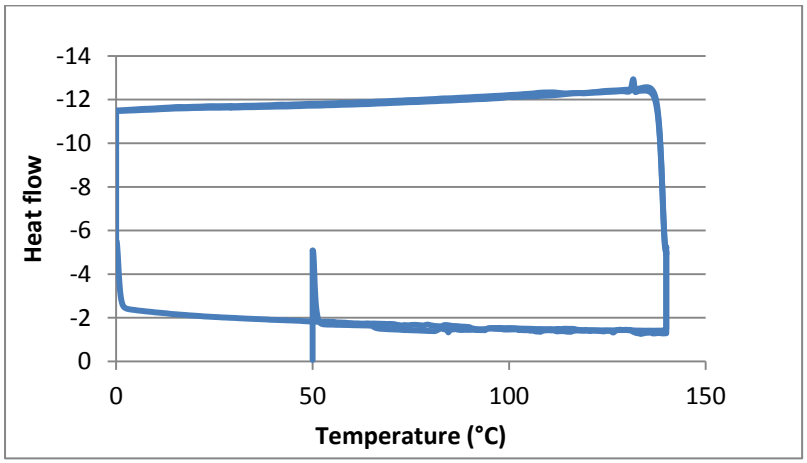


Figure 22. DSC graph of extrudate of H3.

5.2.3. Influence of polymer

To study the influence of polymer, two pellet formulations were prepared: HPMCAS or Eudragit L100-55 with 5% Naproxen as API and 20% TEC as plasticizer. The pH-dependent drug release was tested by exposing the pellets to an acid phase for two hours followed by a neutral buffer phase as described in the method (section 4.2.2). The drug release properties of extruded pellets at pH1 (first 2 hours) and pH7 (2-8 hours) are seen in Figure 23.

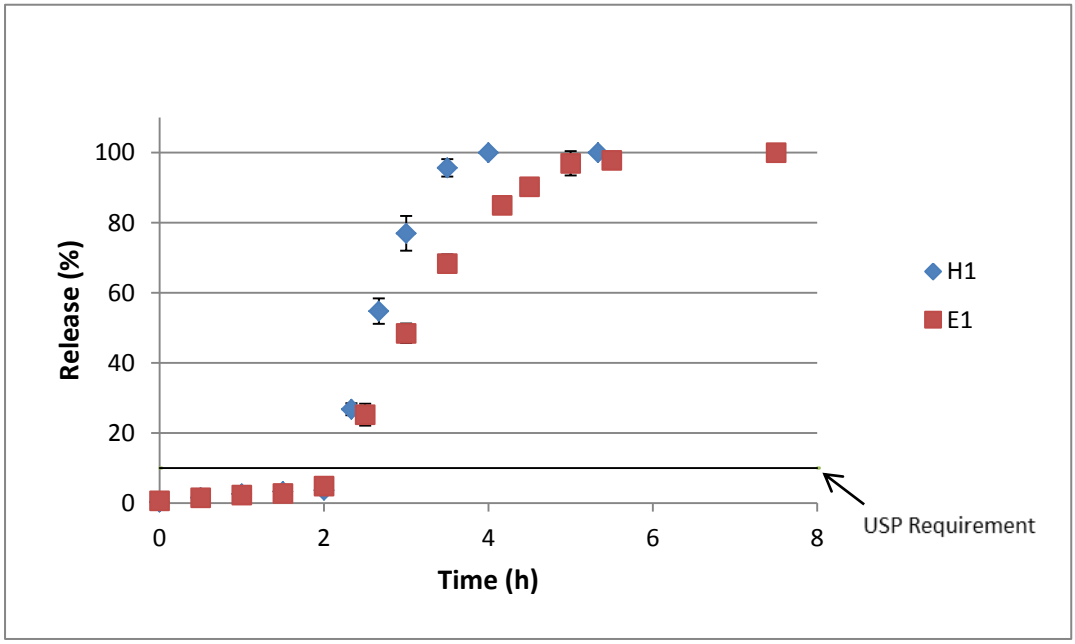


Figure 23. Influence of polymer on the release properties of enteric pellets: Naproxen release profile of Eudragit L100-55 pellets (square) and HPMCAS pellets (diamond) with 5% Naproxen (Average of 6 replicates: 2 batches, n=3). Standard deviation error bars in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

Both formulations released only about 4% Naproxen during the acid phase (considerable less than the requirement of 10% or less). Both formulations showed good gastric protection, which is indicated by the low Naproxen release in the acid phase. In the buffer phase, the HPMCAS formulation showed significantly faster dissolution and release (77% after 1h in buffer) compared to the Eudragit L100-55 formulation (48% after 1 h in buffer) which displayed a more extended release profile. The HPMCAS formulation had released 100% drug after ~4 hours compared to ~5.5 hours for the Eudragit L100-55 formulation. The difference in release rate is probably explained by the more hydrophilic character of HPMCAS compared to Eudragit L100-55 which contributed to faster water penetration and dissolution because of the increased matrix permeability. The HPMCAS pellets had a larger surface area than the Eudragit L100-55 pellets (smaller diameter and increased length). This might also have an effect on the drug release rate: larger surface area have increased contact with the dissolution medium and will therefore have a faster release rate.

The influence of polymer type was also studied by comparing two formulations with HPMCAS and Eudragit L100-55 containing 20% TEC and 5% AZD1305 as an API (Figure 24). Both formulations retained their enteric properties with less than 10% drug release in acid phase. The Eudragit L100-55 formulation released 41% API and the HPMCAS formulation released 88% API after 1 hour in the buffer phase. The HPMCAS formulation had released 100% drug after ~3.5 hours compared to

~7 hours for the Eudragit L100-55 formulation. The faster release for HPMCAS is even more apparent for these formulations. The rate of release in the buffer phase differed between the two polymers, indicating that the formulation can be selected to achieve a desired release profile.

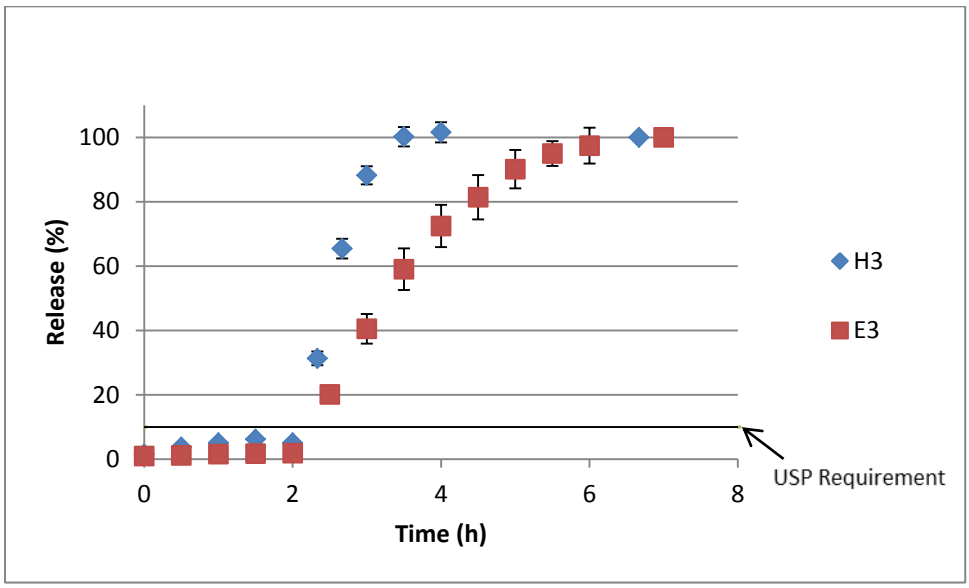


Figure 24. Influence of polymer on release properties: release profile of Eudragit L100-55 pellets (square) and HPMCAS pellets (diamond) with 5% AZD1305 (Average of 6 replicates: 2 batches, n=3). Standard deviation error bars in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

5.2.4. Influence of loading

Pellets with higher drug loading were prepared to examine the effect of increased API content on the release profile (Figure 25 and Figure 26). The amount of Naproxen was increased to 25%, the amount of plasticizer was kept constant at 20% and the polymer content decreased to 55% compared to the previous 75% (E2 and H2). This greatly affected the drug to polymer ratio as well as increased the hydrophilic content. Both these factors could change the drug release profile since the drug release rate is dependent on the integrity of the polymeric matrix and the hydrophilicity of the pellet. The maximum drug load is limited by the percolation threshold (~25%), which is defined as the critical load of soluble material that will form a percolating network when leaching from the matrix [35]. If this critical load is achieved, a continuous porous network will form during dissolution and the delayed release properties will be lost.

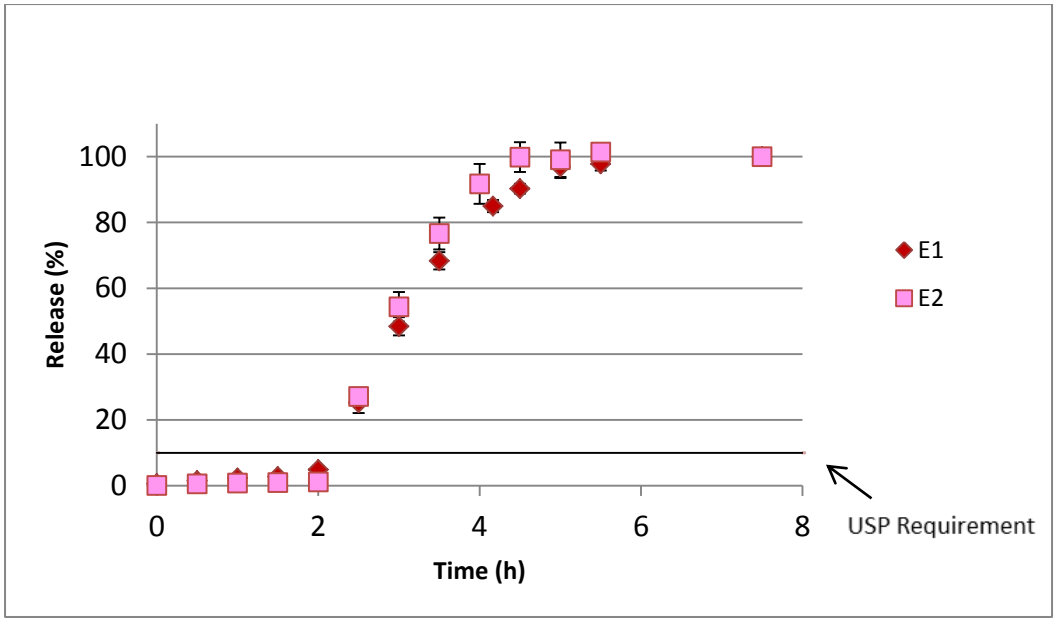


Figure 25. Influence of increased drug load on release properties: Naproxen release profile of Eudragit L100-55 with 5% Naproxen (diamond) and 25% Naproxen (square) (Average of 6 replicates: 2 batches, n=3). Standard deviation error bars in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

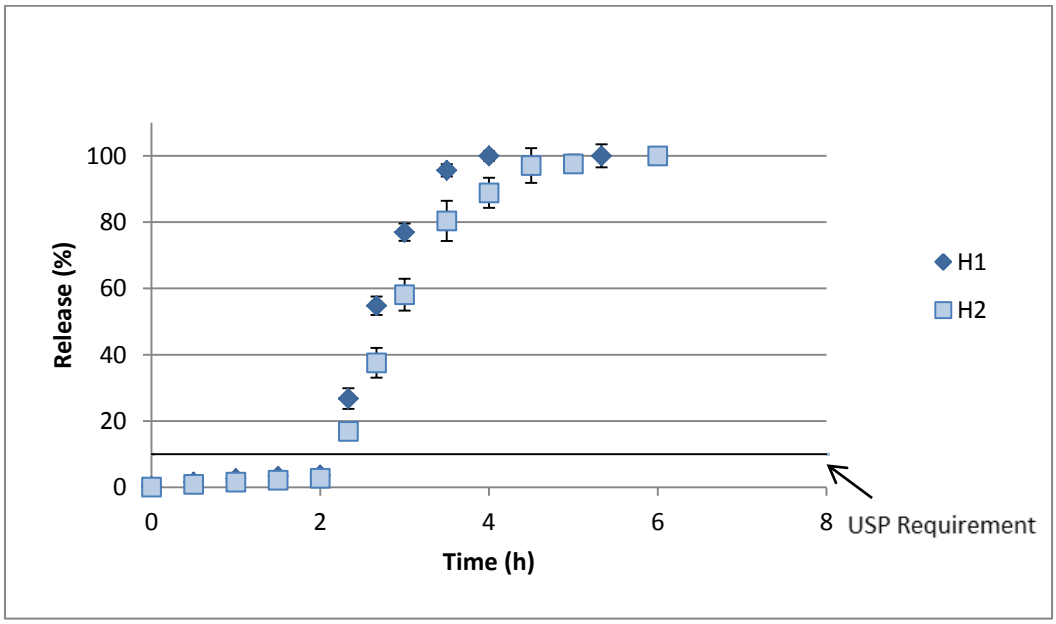


Figure 26. Influence of increased drug load on release properties: Naproxen release profile of HPMCAS with 5% Naproxen (diamond) and 25% Naproxen (square) (Average of 6 replicates: 2 batches, n=3). Standard deviation error bars in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

The formulation E2 with 25% API, see Figure 25, showed considerable less Naproxen release than required during the acid phase, only about 1% thus indicating good gastric protection. In the buffer phase, 54% Naproxen was released after 1 hour, a rate quite similar to that of the Eudragit L100-55 formulation with 5% Naproxen (48% after 1 h in buffer). 100% drug was released after 4.5 hours for

E2 compared to 5.5 hours for E1. The release profile was not changed extensively by increasing the drug load to 25%, indicating a robust formulation. An increased drug load corresponds to a higher fraction of drug on the surface which, in theory, should increase the initial release when in contact to the dissolution medium. As can be seen in Figure 25, there is no initial burst and the delayed release profile is preserved. The release rate for the pellets with 25% Naproxen had, however, a slightly faster release rate in the buffer phase than the pellets with 5% Naproxen. Schilling *et al.*, also studied the influence of drug load from enteric pellets and did not see a large difference between release rates from pellets based on Eudragit S100 containing 20, 30 or 40% API [35]. The delayed release characteristics where kept in all formulations, although a slightly faster release rate was observed for the 40% pellet formulation in the buffer phase.

The HPMCAS formulation with a higher drug load (H2) also showed excellent gastric protection, releasing only 2% Naproxen in the acid phase (Figure 26). In the buffer phase, 58% Naproxen was released after 1 hour which was significantly less than the 77% Naproxen released from H1. Also, 100% drug was released after 6 hours for H2 compared to 4 hours for H1. The slower drug release for this formulation with an increased drug load was very surprising. As discussed above, increasing the amount of hydrophilic drug should increase the drug release due to increased water penetration and matrix permeability. One explanation can be the plasticizing effect of Naproxen. The process conditions for HPMCAS at 120°C were quite good already at 5% Naproxen, increasing the amount could then have had the same effect as increasing the temperature, i.e. formation of a well-mixed blend without pores, leading to slower drug release (as discussed in section 5.1).

All formulations evaluated kept their delayed release properties. Since these formulations include 25% hydrophilic API plus an additional 20% hydrophilic plasticizer, the percolation threshold is theoretically exceeded but the drug release was not increased that much. This implies that these formulations can manage a drug load of 25%, which is a positive conclusion.

5.2.5. Influence of API

The influence of the API was also evaluated, in order to assess the robustness of the formulation. So far, the acidic API Naproxen has been used but since acidic compounds have low solubility in acid environments, there is a possibility that the inherent low solubility of Naproxen in the acid phase is one of many explanations to the excellent results obtained. A basic API (AZD1305) was therefore used with the following composition: 5% API, 20% TEC and 75% HPMCAS (H3) or Eudragit L100-55 (E3) to separate the properties of the API and the formulation. The drug release profile of Eudragit L100-55 and HPMCAS containing 5% Naproxen and 5% AZD1305 is shown in Figure 27 and Figure 28, respectively. In Figure 27, it can be seen that both formulations (E1 and E3) have low release in the acid phase, 3% vs. 2%. E3 with the basic API released only 41% drug after 1 hour in buffer phase and have a slower release compared to E1 with the acidic API (48%). Surprisingly, the opposite trend is seen in Figure 28, H3 with the basic API have a faster drug release in the buffer phase compared to H1 with the acidic API (88% vs. 77%). However, H3 has a higher drug release in the acid phase compared to H1 (6% versus 3%) which might explain the higher release in the buffer phase as well. When the drug is released in the acid phase it might form pores in the pellet which leads to increased water penetration and faster release in the buffer phase.

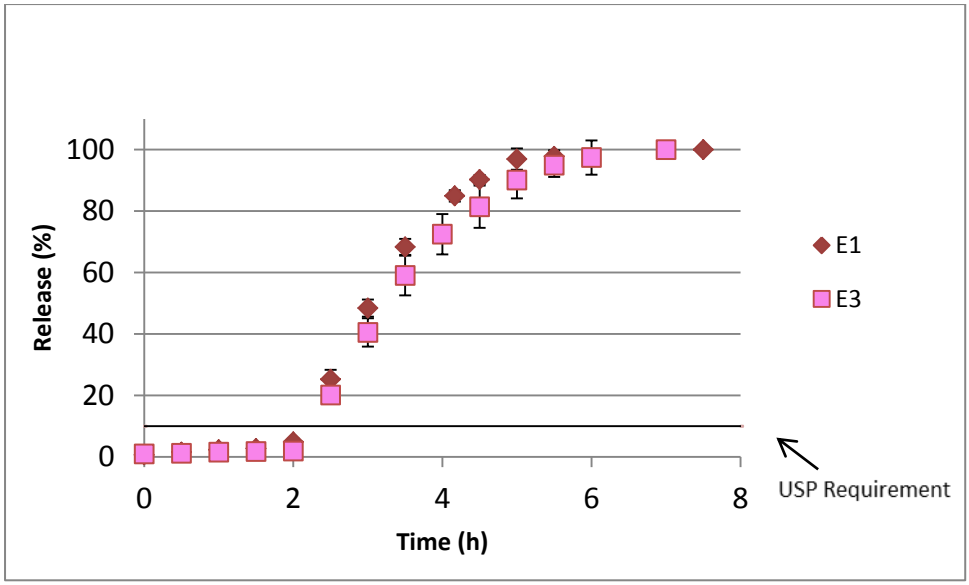


Figure 27. Influence of API on release properties: drug release profile of Eudragit L100-55 with 5% Naproxen (diamond) and Eudragit L100-55 with 5% AZD1305 (square) (Average of 6 replicates: 2 batches, n=3). Standard deviation error bars in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

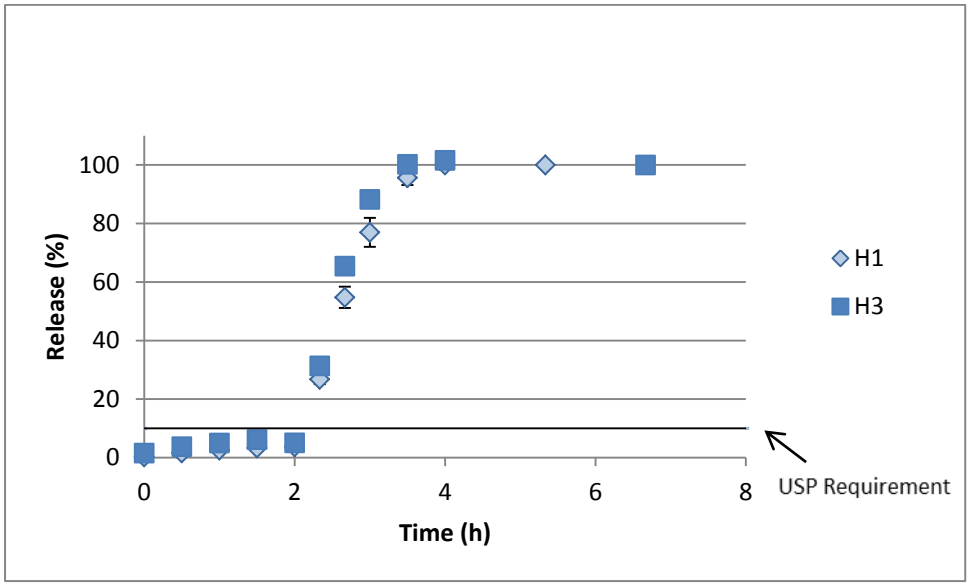


Figure 28. Influence of API on release properties: drug release profile of HPMCAS with 5% Naproxen (diamond) and with 5% AZD1305 (square) (Average of 6 replicates: 2 batches, n=3). Standard deviation error bars in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

Both formulations with the basic API AZD1305 were able to sustain the good gastric protection and passing the USP requirement of 10% drug release or less for enteric formulations. The Eudragit L100-55 formulation (E3) released only 2% AZD1305 after 2 h in acid phase whereas The HPMCAS formulation (H3) released a little bit more in the acid phase, 6% AZD1305. The higher release of the basic API from the HPMCAS formulation was consistent with results from Schilling *et al*. [35]. They prepared enteric pellets with the basic model drug Theophylline and received excellent gastric protection with formulations including Eudragit S100 (3.76% Theophylline released after 2h in acid)

and Eudragit L100 (3.85% Theophylline released after 2h in acid). However, formulations with HPMCAS could not sustain the enteric properties for a basic API, with more than 20% drug release after 2 hours because of a high initial burst effect. However, the HPMCAS formulations evaluated in this study could sustain the enteric properties for both an acidic and a basic API. The good results obtained are not explained by the solubility of the API but by the properties of the extruded formulation. The results also indicate that the Eudragit L100-55 formulation is somewhat more robust than the HPMCAS formulation but the polymers had excellent enteric properties with both acidic and basic APIs.

5.2.6. Influence of plasticizer

The type and level of plasticizer is another factor that can be tuned to change the release profile. However, in this project the plasticizer was fixed at 20% TEC as a liquid-state plasticizer. TEC is hydrophilic which means that the content should preferable not exceed the percolation threshold. For example, pellet formulations with Eudragit S100 and 20% PEG or CA MH failed to provide gastric protection because the high solubility of these plasticizers led to high porosity during dissolution and too high release rates in the acid phase [35]. Schilling *et al.* reported that pellets with 20% TEC exhibited 7.14% drug release in the acid phase with negligible leaching of the plasticizer [35]. It has however been reported that TEC can leach out into the dissolution media, thereby affecting the matrix permeability and the release rate [36]. Eudragit S100 tablets with 12 or 23% w/w TEC released less than 10% drug in the acid phase but the drug release during 12 hours was significantly increased for formulations with 23% TEC. The authors attributed the increased in drug release to increased leaching of the plasticizer leading to channel formation. This was then confirmed by measuring the amount of TEC during the 12 hours dissolution test. It was found that the rate of TEC release from the tablets corresponded to the release rate of the drug [36]. However, the amount of leaching of the plasticizer depends on the distribution of TEC in the extrudate. If TEC is well-dispersed, which is probably the case for extrudates evaluated in this project, the extent of leaching should be reduced and channel formation avoided. Even if the level of TEC was kept constant in the formulations tested in this study, the API Naproxen had a plasticizing effect which was clearly seen in the different extrusion parameters discussed in section 5.2.1. No significant impact of the plasticizing effect of Naproxen could be seen on the release properties. As discussed in section 5.2.5, the release rate seemed more dependent on the properties of the polymer and the amount of drug released in the acid phase than on the properties of Naproxen as a plasticizer. However, the plasticizer affects the processing conditions which in turn affect the release properties. This means that it will always be important to consider the plasticizer when designing a formulation with modified release properties.

5.2.7. Batch to batch variability

One important factor to consider when producing pharmaceuticals is the quality requirements: products need to be uniform and consistent. It is therefore important to evaluate the variability within and between batches. This has seldom been done in other studies concerning hot-melt extruded enteric pellets or tablets. The release profile for 2 batches of Eudragit L100-55 (E1.1. and E1.2) and HPMCAS (H1.1. and H1.2) pellets is shown in Figure 29 and Figure 30, respectively. For each experiment, two formulations were made and were extruded one at a time (Table II).

As can be seen, there is very low batch to batch variability, especially for the Eudragit L100-55 formulation (Figure 29). The variability within each batch is also small, displayed by the error bars.

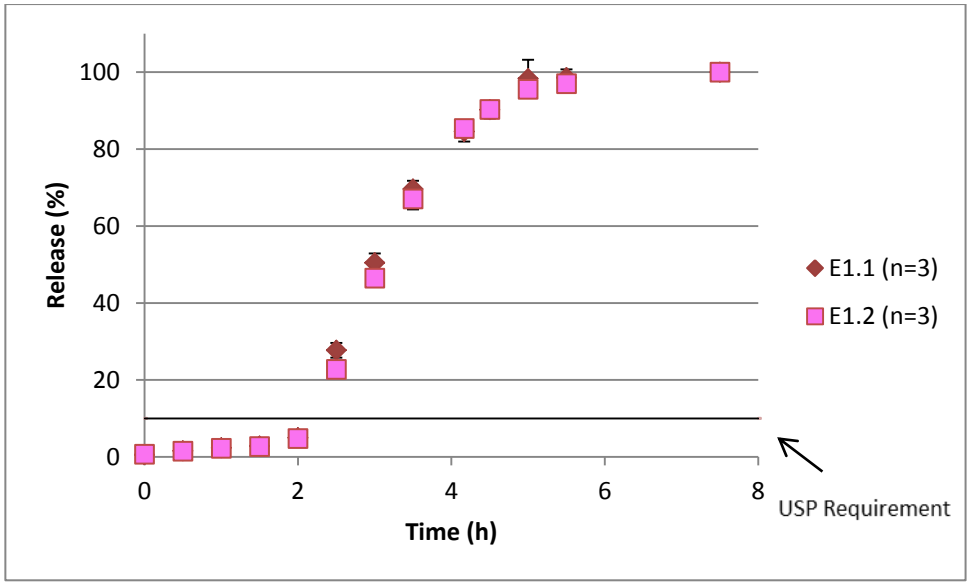


Figure 29. Naproxen release profile of Eudragit L100-55 pellets with 5% Naproxen (2 batches, n=3). Standard deviation error bars shown in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

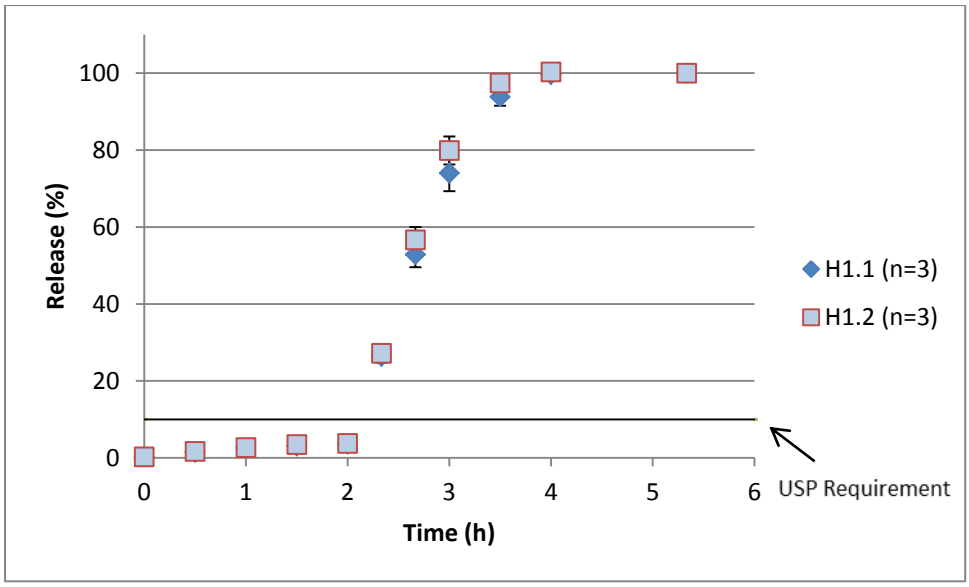


Figure 30. Naproxen release profile of HPMCAS pellets with 5% Naproxen (2 batches, n=3). Standard deviation error bars shown in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

Two batches of Eudragit L100-55 and HPMCAS with 25% Naproxen (E2.1, E2.2 and H2.1, H2.2 respectively) were also prepared. Recall the extrusion parameters and diameters in Table II. The variability within each batch is larger for the Eudragit L100-55 formulation with 25% API than for the previously discussed formulations, as can be seen in Figure 31 but there is even a larger difference for the HPMCAS formulations (Figure 32). This large standard deviation for the pellets containing 25% API might be explained by dilution errors as most of these samples had to be diluted before determining the concentration in the UV-Vis Spectrometer. It should be noted that H2 was measured with another UV-Vis spectrometer which might also explain some of the variation. There is also a quite large difference between batches for H2, an observation that is hard to explain.

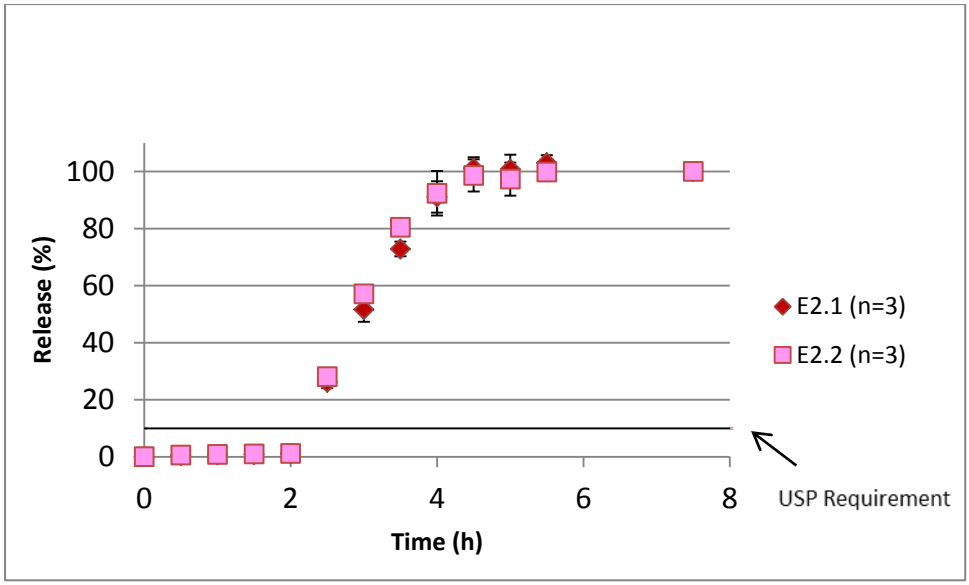


Figure 31. Naproxen release profile of Eudragit L100-55 pellets with 25% Naproxen (2 batches, n=3). Standard deviation error bars shown in black. The black line corresponds to the 10% USP limit. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

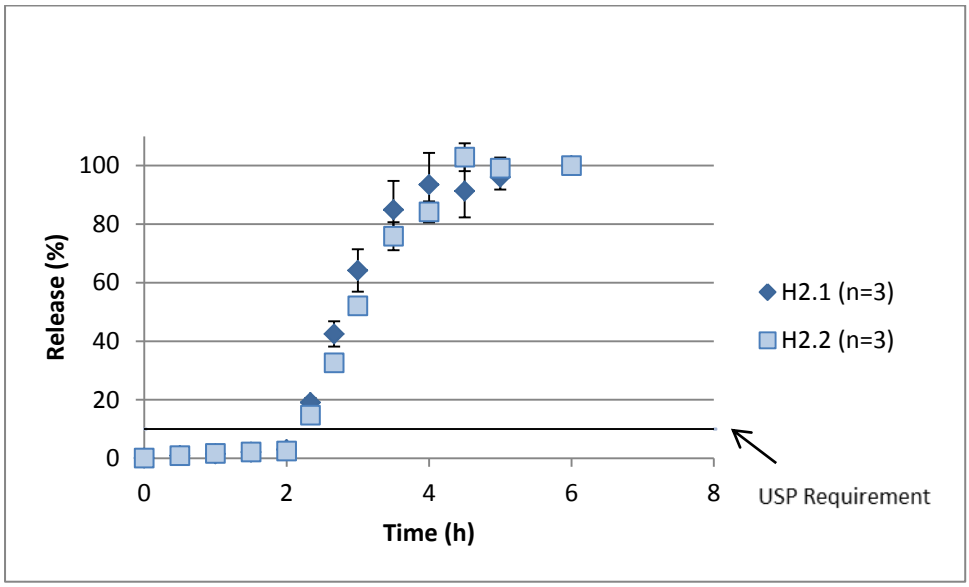


Figure 32. Naproxen release profile of HPMCAS pellets with 25% Naproxen pellets (2 batches, n=3). Standard deviation error bars shown in black. The black line corresponds to the 10% USP limit. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

The difference between batches for formulations containing AZD1305 is displayed below in Figure 33 (E3.1 and E3.2) and Figure 34 (H3.1 and H3.2). In Figure 33 there is quite a large difference between batches which might be explained by the large difference in diameter, 4.20 mm for batch 1 compared to 3.18 mm for batch 2 (Table II). It is known that pellets with a larger surface area i.e. smaller diameter, dissolves faster which generally means faster drug release. Also, as mentioned before, a larger fraction of the drug is in contact with the dissolution medium so there might be a problem with a burst release in the acid phase. This was not the case for any formulations evaluated in this study. The smaller diameter is probably the explanation to the faster release for batch E3.2. Another interesting fact is that batch E3.1 has larger standard deviation for each measurement point

which can be explained by dilution errors, since these samples where diluted before determining the concentration. As can be seen in Figure 34, there is very low variability between batches H3.1 and H3.2 which can be explained by the low variability between the diameters, 2.15 mm for H3.1 versus 2.19 for H3.2 (Table II).

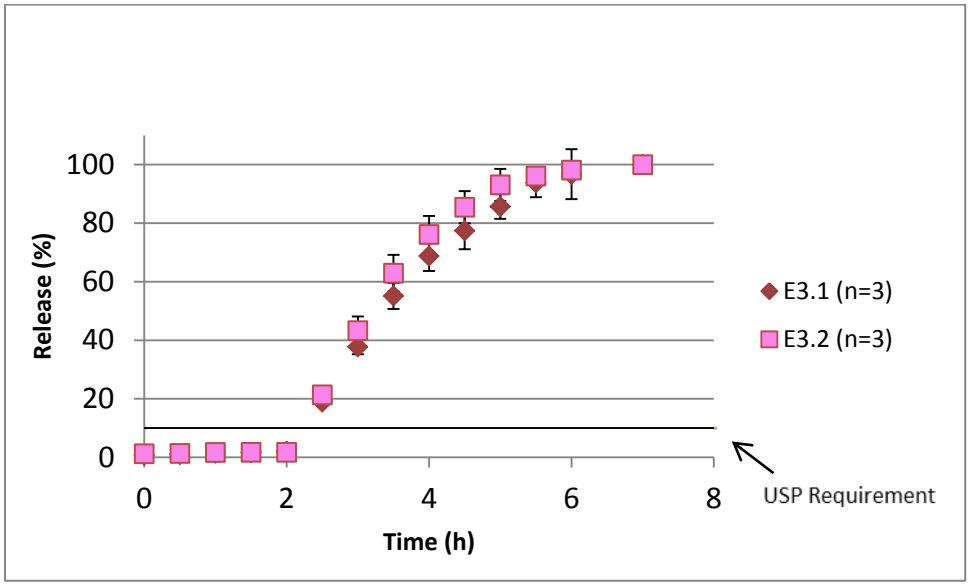


Figure 33. Drug release profile of Eudragit L100-55 pellets with 5% AZD1305 (2 batches, n=3). Standard deviation error bars shown in black. The black line corresponds to the 10% USP limit. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

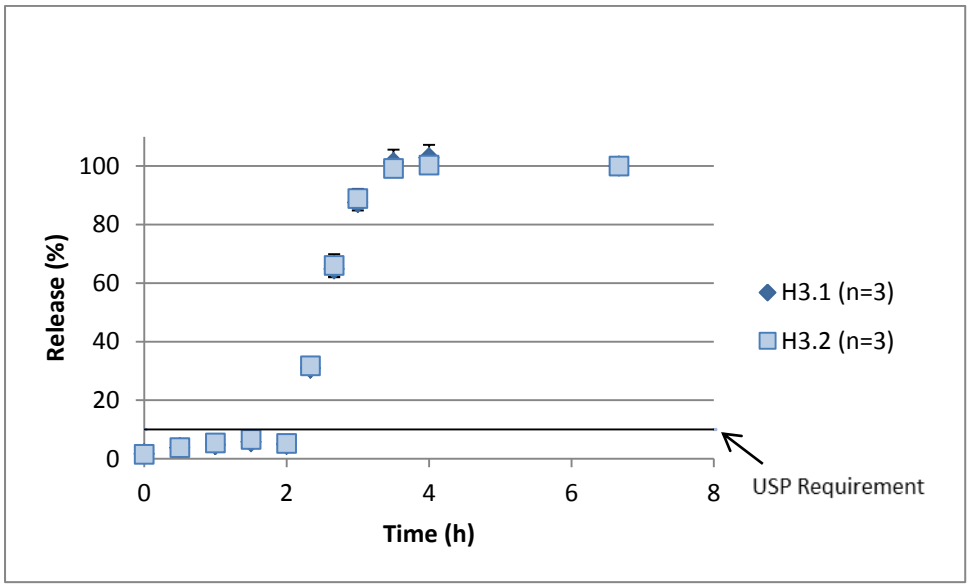


Figure 34. Drug release profile of HPMCAS pellets with 5% basic API (2 batches, n=3). Standard deviation error bars shown in black. The black line corresponds to the 10% USP limit. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

For most formulations, there was a small difference between drug release rates between and within batches. Although there were quite some differences in process parameters such as torque which was discussed extensively in section 5.2.1, this difference was not seen in release tests indicating that hot-melt extrusion is a robust production method. The diameter of the extrudate (the surface

area) seems to be the individual factor with the most effect on the drug release rate for one formulation. Hot-melt extrusion seems to be a reliable production method for enteric pellets, with consistent drug release profile.

5.2.8. Storage

All extrudates were translucent when exiting the extruder, indicating a well-mixed blend. However, the extrudate from batch E2 (Eudragit L100-55 with 25% Naproxen) turned white and brittle, an observation made after three weeks (might have occurred earlier). This means that the extrudate phase-separated forming a two-phase system. This phase-separation might be due to the API or the plasticizer. The stability of solid dispersions on storage is an important factor to consider. An instability like a change in solid-state might make the extrudate unsuitable as a pharmaceutical product if the release behavior changes. In this case the change occurred after less than three weeks which is not a long storage time and does not fulfill stability requirements. It is interesting to consider if this phase-separation changed the release properties. Therefore, a release test was done on stored E2 extrudate (E2s) with the result shown in Figure 35.

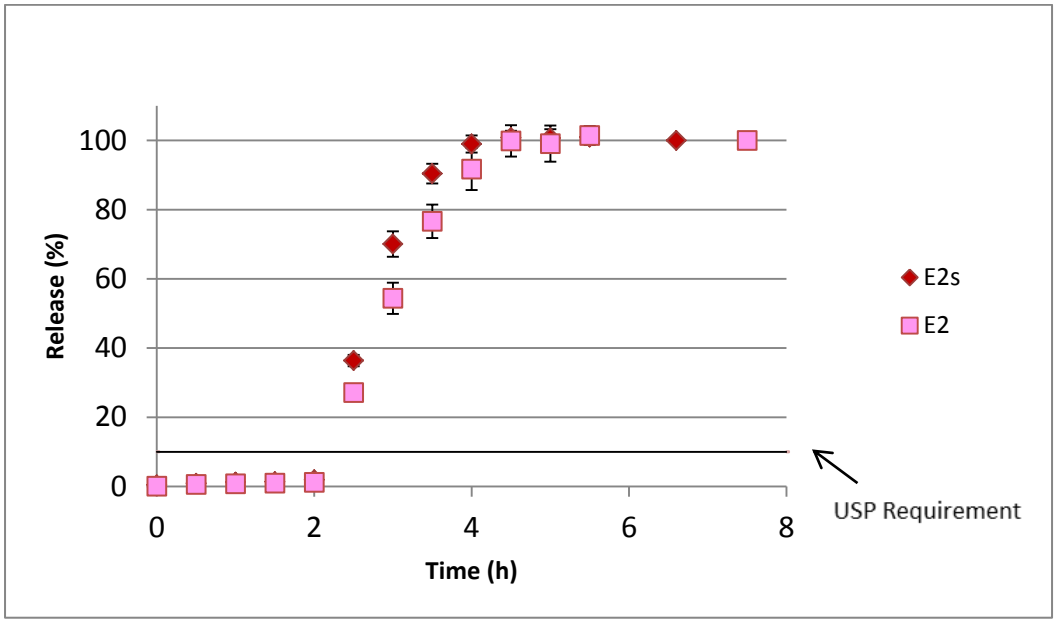


Figure 35. Influence of storage on release properties: Naproxen release profile of Eudragit L100-55 with 25% Naproxen (square) (Average of 6 replicates: 2 batches, n=3) and 2 months stored Eudragit L100-55 with 25% Naproxen (diamond) (1 batch, n=3). Standard deviation error bars in black. The black line corresponds to the 10% USP requirement. Release: 2 h in 0.1 N HCl pH1 (acid phase), thereafter pH-change to pH7 (buffer phase) by addition of 0.2 M tribasic phosphate buffer and NaOH solution.

As can be seen in Figure 35, the release in the acid phase did not change considerably, about 1% Naproxen was released after 2 hours in acid phase. After 1 hour in buffer phase, 54% Naproxen was released for the fresh extrudate compared to 70% Naproxen release for the stored extrudate (2 months). The change in drug release rate can be explained by phase-separation but it may also be due to that the batch size was significantly smaller for E2s during dissolution testing (about 1/4). Pellets in the smaller batch size have increased surface area to the dissolution medium which could lead to faster drug release.

The HPMCAS formulation with 25% Naproxen (H2) also changed its appearance, the extrudate turned opaque with a white colour but the ductility remained. This phase-separation occurred after approximately two weeks of storage. The stability of extrudates is usually high. Melt-extruded dosage forms rarely exhibit changes in matrix structure during storage since compression and intense mixing of molten materials during processing result in a product with low free volume [37]. Melt-extruded dosage forms usually have good long-term stability, but there have been reports of recrystallization of the active substance during storage. The physical and chemical stability of the extrudate depend on the nature of the polymers and excipients, the physical state of the API in the final dosage form, storage and packing conditions [20]. Inclusion of 25% Naproxen acting as a plasticizer lowers the T_g of the blend and since the glass transition temperature describe the tendency of an amorphous compound to crystallize at a certain temperature, this might lead to increased recrystallization. The extent of recrystallization increases with increasing storage temperature [48]. This might be an explanation to why formulations with 25% Naproxen phase-separated and not formulations with 5% Naproxen, who seem stable at room temperature. It should be noted that no change in appearance was observed for other extrudates during the time span of the project and that extrudates with 5% API might be considered more stable than extrudates with 25% API. It would be interesting to see how extrudates with 25% of the basic AZD1305 would behave during storage, if any phase-separation would occur and, if so, if the delayed release characteristics would be lost. It would also be interesting to evaluate the effect of a longer storage time.

5.2.9. Mechanism of drug release

All formulations showed a faster drug release than dissolution rate of the pellet, 100% of the API was released before the entire pellet had dissolved (at the last measurement). This indicates a diffusion-controlled release mechanism. However, determining the mechanism of release from matrix pellets is complex. The normalized drug release graphs were therefore fitted to the power law (Equation 3) for all different formulations with the results shown in Table III. The data points in the buffer phase up to 70% drug release were used, which included three or four data points depending on the rate of drug release. As mentioned before in section 4.2.4, only the portions of the curve below 60% drug release should be used. However, including data points up to 70% avoided the problem with only 2 data points in the region 0-60% which would not be enough to fit a power equation. About half of the drug release data fit the model very well with a correlation coefficient (R^2) above 0.99.

Table III. Power law fitting of normalized release data from hot-melt extruded cylindrical pellets in the buffer phase (up to 70% drug release).

	n	R^2
E1	0.503	0.974
H1	0.618	0.989
E2	0.824	0.999
E2s	0.773	0.999
H2	0.632	0.971
E3	0.668	0.991
H3	0.580	0.984

All formulations had an n-value between 0.45 and 0.89 indicating anomalous transport, i.e. both diffusion and swelling/erosion mechanisms determine the drug release rate. As can be seen in Table III, some of the formulations approached a diffusion-controlled release mechanism (n=0.45 for cylindrical system), for example E1 with n=0.50. A more hydrophilic formulation should lead to increased water penetration leading to swelling and erosion of the polymer. Eudragit L100-55 is less hydrophilic than HPMCAS and should therefore have a more diffusion-controlled release. This is true for E1 which has an n component of 0.50 versus H1 that have an n component of 0.62. On the other hand, both H2 and H3 have a larger component than E2 and E3. Increasing the amount of the API

implies that its properties become increasingly important in determining the rate of dissolution and release. Increasing the concentration of the hydrophilic Naproxen for a formulation should, in theory, increase the n component and switch from a diffusion-controlled release to a more erosion/swelling controlled release. Both E2 (n=0.82) and H2 (n=0.63) have a larger n component compared to E1 (n=0.50) and H1 (n=0.62) but as can be seen the difference is only significant for the Eudragit L100-55 formulation.

The solubility of the API also affects the release mechanism, a more soluble compound will have a more diffusion-controlled release mechanism. The solubility of Naproxen is 30 mg/ml in pH7.7 phosphate buffer [52]. The solubility of the stable B-form of AZD1305, which is assumed to be the contributing form in this project, is 9.3 mg/ml in phosphate buffer pH7.7 [42]. This means that H1 and E1 should have lower n component than H3 and E3, which is the case for the Eudragit L100-55 formulation but not for the HPMCAS formulation. Since these formulations are identical except for the API, it is apparent that there are other factors involved as well. The distribution of the API in the polymer should also have an impact on the release mechanism. This could be an explanation to why H1 had a larger n component than H3. It should also be noted that the "fresh" E2 has a more swelling/erosion-controlled release mechanism compared to the stored E2 (E2s) which has a combination of both mechanisms. This could be explained by increased solubility of the phase-separated extrudate.

6. Conclusions

Both Eudragit L100-55 and HPMCAS formulations produced by hot-melt extrusion had excellent enteric properties, with less than 10% drug released after 2 hours in acid phase for both the acidic Naproxen and the basic AZD1305. Both polymers managed to keep the delayed release properties when the drug load was increased to 25% even though the theoretical percolation limit was exceeded, with a hydrophilic content of 45%.

The formulation and extrusion process influenced the release rate during both phases and the subsequent release profile. There was a low batch to batch variability, which had no significant effect on the drug release profiles. The drug release mechanism was a combination of diffusion and swelling/erosion.

DSC results and the translucent appearance of the extrudates suggest that the API is molecularly dispersed. The formulations with 25% API changed to an opaque appearance (phase-separation) after approximately two weeks of storage but since no change was seen in formulations with 5% API, these can be considered more stable.

7. Future work

Examine the effect of 25% basic API on the release profile and stability of extrudates, and if a possible phase-separation would lead to loss of enteric properties due to higher solubility (compared to an acidic API) in the acid phase.

Examine the distribution of API in the extrudate, to see if a solid solution has formed, by performing further DSC measurements and additional characterization methods such as Raman spectroscopy.

Examine the effect of the recirculation during extrusion to see if this is an explanation to the good results obtained and if extrusion without recirculation (less mixing) leads to loss of enteric properties for some of the formulations.

Examine the effect of a longer storage time on the release profile and on the distribution of API in the polymers, and also at which drug load the phase-separation occurs.

Examine the effect of scale-up from laboratory scale with small batches (<10g) to a pilot scale extruder (~1000g) and see what happens to the release profile with regular screws and a “barrier flighted” screw.

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Appendices

I. Materials

Table I. List of materials used, company and lot number.

	Company	Lot number	Full name
HPMCAS (AS-LF)	Shin-Etsu	108061	Hydroxypropyl methylcellulose acetate succinate (Aqoat)
Eudragit L100-55	Degussa	B050904057	Methacrylic Acid- Ethyl Acrylate copolymer
TEC	Fluka	1228091	Triethyl citrate
Naproxen	ICN Biomedicals, Inc.	8085E	Naproxen
AZD1305	Astra Zeneca	-	$C_{22}FN_4O_4H_{31,}$ oxabispidine
NaH_2PO_4	Fluka Chemica	446321/1	Sodium dihydrogen phosphate monohydrate
Na_2HPO_4	Fluka Analytical	0001413845	Sodium phosphate dibasic dehydrate
HCl	Kebo-lab	3.3790-1	Hydrochloric acid, 37%
Na_3PO_4	Aldrich Chemistry	MKBG2188V	Tribasic phosphate
NaOH	Aldrich Chemistry	26743-049	Sodium hydroxide

II. Buffer preparation

Phosphate buffer: Two stock solutions were prepared: 1 M NaH_2PO_4 (138 g NaH_2PO_4*H_2O/1000 ml milliQ water) and 0.5 M Na_2HPO_4 (89 gNa_2HPO_4*$2H_2O$/1000 ml milliQ water). To achieve a phosphate buffer with pH 7.0, 20 ml 1 M NaH_2PO_4 was mixed with 53 ml 0.5 M Na_2HPO_4 in a large (25 L) container and filled up to 1000 ml milliQ water. A total of 20 L phosphate buffer was prepared.

Acid phase: Hydrochloric acid buffer: A 0.1 M HCl buffer was prepared by adding 37 ml 37% HCl to 4.5 L weighed milliQ water (enough for 1 round of dissolution testing). This acid buffer had a pH around 1.0.

Buffer phase: Tribasic phosphate buffer: A 0.2 M trisbasic phosphate buffer was prepared by dissolving 32.8 g Na_3PO_4 in 1000 ml milliQ water. A total of 7.5 L tribasic phosphate buffer was prepared each time (enough for 5 rounds of dissolution testing).

Sodium hydroxide: A 2M NaOH solution was prepared by dissolving 8 g of NaOH pellets in 100 ml milliQ water. This solution was made to adjust the pH of the buffer phase (1 ml 2 M NaOH approximately raised the pH of one bath of 900 ml buffer phase 0.1 pH).

III. Experimental Setup

Table III. Composition of extrudate, process temperatures, torque, pressure and average diameter of all formulations. All extrusions were performed at 80 rpm.

	Polymer	API	Plasticizer	Temperature	Torque	Pressure	Diameter
E140° (9/2)	Eudragit L100-55	Naproxen (5%)	TEC (20%)	140°C	130 Ncm	56/43 bar	3.61 ± 0.22mm
E165° (9/2)	Eudragit L100-55	Naproxen (5%)	TEC (20%)	165°C	80 Ncm	27/14 bar	3.08 ± 0.21mm
H160° (13/2)	HPMCAS	Naproxen (5%)	TEC (20%)	160° C	20 Ncm	0/0 bar	1.73 ± 0.25mm
H120° (24/2)	HPMCAS	Naproxen (5%)	TEC (20%)	120° C	55 Ncm	15/15 bar	2.49 ± 0.15mm
E1.1 (16/2)	Eudragit L100-55	Naproxen (5%)	TEC (20%)	140° C	100 Ncm	42/40 bar	3.22 ± 0.34mm
E1.2 (16/2)	Eudragit L100-55	Naproxen (5%)	TEC (20%)	140° C	80 Ncm	30/30 bar	2.91 ± 0.71mm
H1.1 (24/2)	HPMCAS	Naproxen (5%)	TEC (20%)	120° C	126 Ncm	69/33 bar	2.29 ±0.04mm
H1.2 (24/2)	HPMCAS	Naproxen (5%)	TEC (20%)	120° C	83 Ncm	35/20 bar	2.16 ±0.19mm
E2.1 (6/3)	Eudragit L100-55	Naproxen (25%)	TEC (20%)	140° C	36 Ncm	0/0 bar	2.52 ±0.31mm
E2.2 (6/3)	Eudragit L100-55	Naproxen (25%)	TEC (20%)	140° C	42 Ncm	1/0 bar	2.50 ±0.28mm
H2.1 (8/5)	HPMCAS	Naproxen (25%)	TEC (20%)	120° C	44 Ncm	3/1 bar	1.86 ± 0.35mm
H2.2 (8/5)	HPMCAS	Naproxen (25%)	TEC (20%)	120° C	75 Ncm	17/3 bar	1.78 ± 0.26mm
E3.1 (11/4)	Eudragit L100-55	AZD1305 (5%)	TEC (20%)	140° C	336 Ncm	130/74 bar	4.20 ± 0.51mm
E3.2 (11/4)	Eudragit L100-55	AZD1305 (5%)	TEC (20%)	140° C	146 Ncm	94/67 bar	3.18 ± 0.54mm
H3.1 (24/4)	HPMCAS	AZD1305 (5%)	TEC (20%)	120° C	53 Ncm	14/13 bar	2.15± 0.14 mm
H3.2 (24/4)	HPMCAS	AZD1305 (5%)	TEC (20%)	120° C	106 Ncm	49/23 bar	2.19 ± 0.19mm

IV. UV-Vis spectroscopy: concentration determination

A standard curve of Naproxen was made by dissolving a known amount of Naproxen in phosphate buffer, diluting to 4 different concentrations within the acceptable absorbance range (0.2-1.5) and measuring the corresponding absorbance. The samples were scanned from 200-600 nm, using the phosphate buffer as a baseline, and the peak with maximum absorbance at wavelength 271.6 nm was chosen (see scan in Figure IVa). At this wavelength, there should be minimum problems with light spreading due to polymers or other additives. This was confirmed by dissolving polymer (Eudragit L100-55) and plasticizer (TEC) at the concentrations corresponding to a completely dissolved sample (see scan in Figure IVb). Minimal absorption was seen at 271.6 nm (< 0.01), however at shorter wavelengths (220 nm) considerable light spreading was seen. The extinction coefficient (ε) could then be extracted from the plot of concentration versus absorption, according to Equation 1 in section 4.2.3. Samples from the dissolution tests were measured at 271.6 nm using the UV-Vis spectrometer and the absorbance obtained was thereafter converted to concentration using the calculated extinction coefficient (ε=0.0215). A standard curve was made for the basic API and the peak with maximum absorbance at 245.6 nm was chosen (Figure IVc), the extinction coefficient was determined to be 0.0422. Some of the samples were scanned through all wavelengths to ensure that no degradation had occurred during processing. However, there was a problem with too high concentration of samples, up to 120% compared to the theoretical maximum value. All graphs were normalized to 100%.

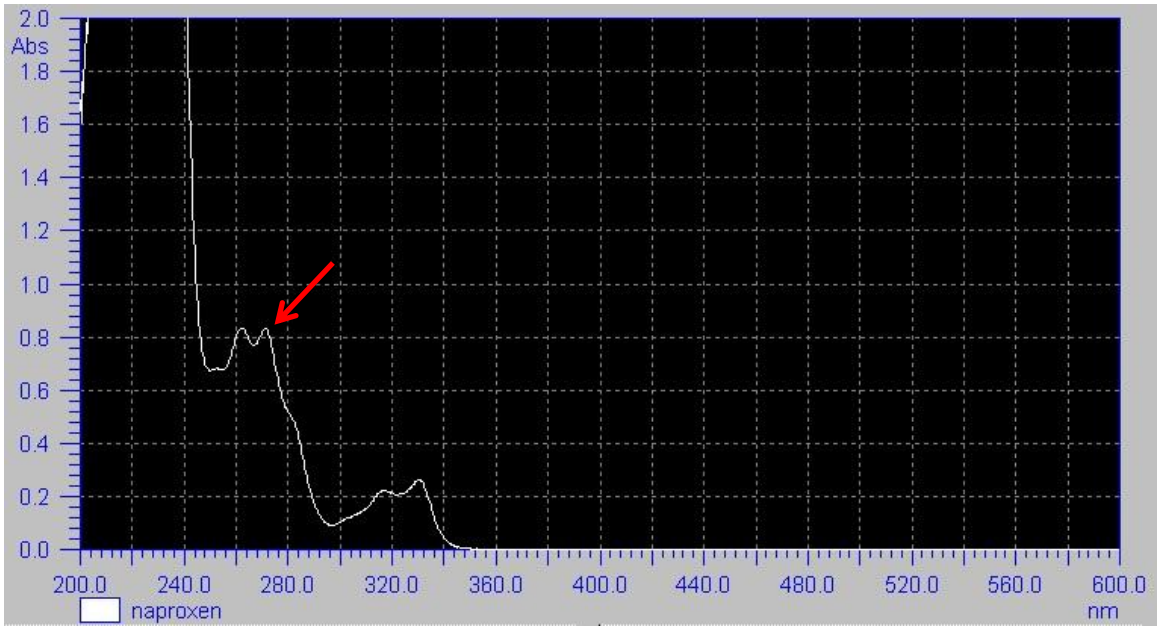

Figure IVa. Scan of a solution of naproxen in phosphate buffer (38.8 µg/ml) with a UV-Vis spectrophotometer (200-600 nm). The peak at 271.6 nm is shown by the arrow.

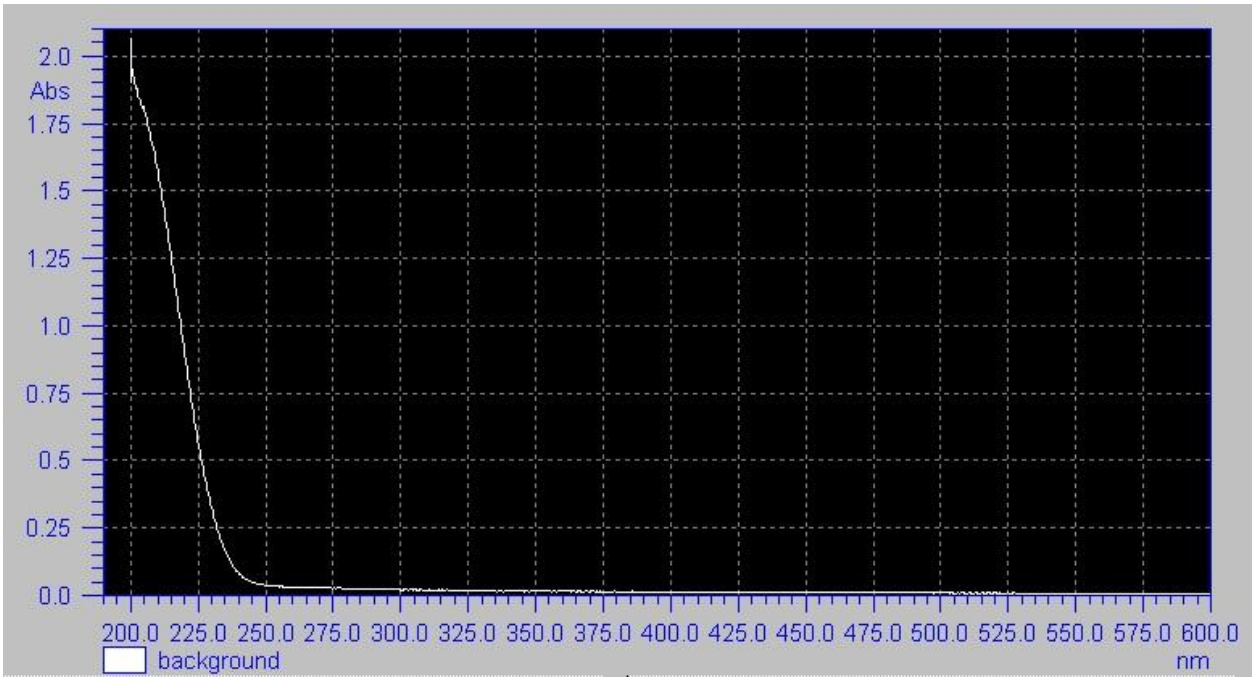

Figure IVb. Scan of a solution of Eudragit and TEC in phosphate buffer (800 and 230 µg/ml respectively) with an UV-Vis spectrophotometer (200-600 nm). Minimal light spreading is seen at wavelengths above 245 nm (<0.05).

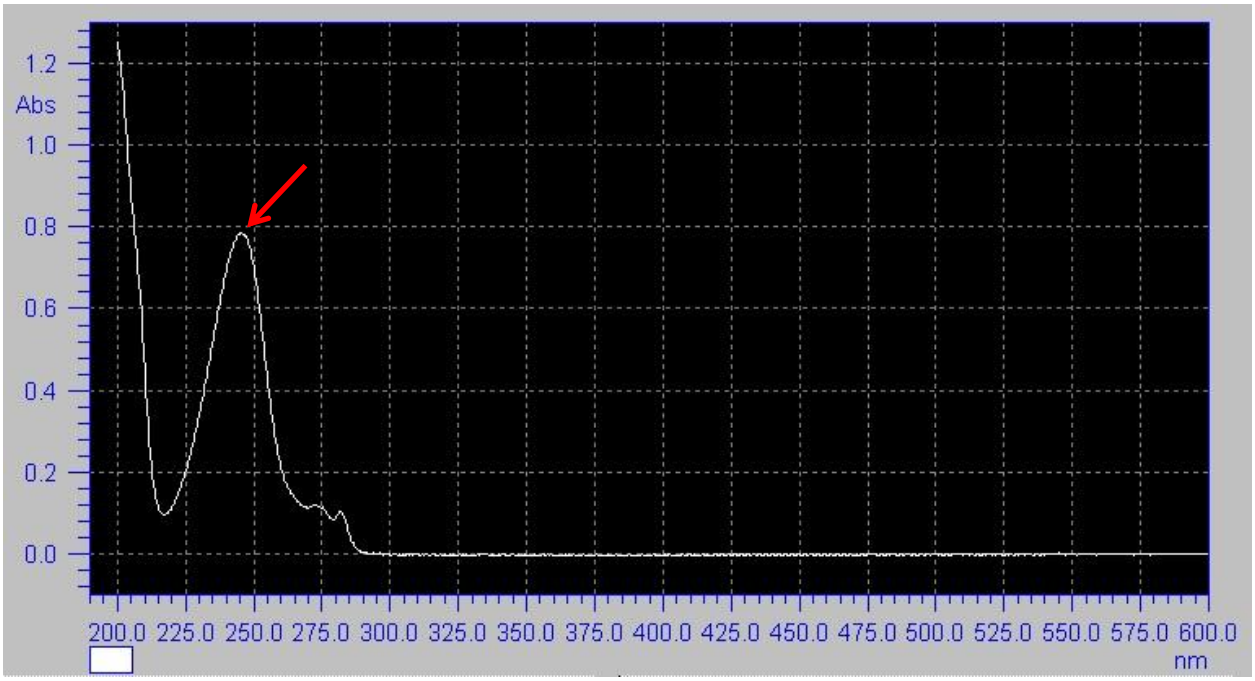

Figure IVc. Scan of a solution of the basic API in phosphate buffer (18.9 µg/ml) with a UV-Vis spectrophotometer (200-600 nm). The peak at 245.6 nm is shown by the arrow.