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HOT-MELT CO-EXTRUSION AS MANUFACTURING TECHNIQUE FOR MULTILAYER ORAL DOSAGE FORMS

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TABLE OF CONTENTS

OUTLINE AND AIMS

Co-extrusion implies the simultaneous hot-melt extrusion of two or more materials through the same die, creating a multilayered extrudate. This innovative continuous production technology offers numerous advantages over traditional pharmaceutical processing techniques. Moreover co-extrusion provides great potential for the production of fixed-dose combination products which are gaining importance in pharmaceutical industry. Except from an implant (Implanon®) and a vaginal ring (Nuvaring®), there are no co-extruded dosage forms on the market so far. The **aim of this work** was to evaluate the potential of hot-melt co-extrusion for the production of multilayer (core/coat) oral dosage forms. Possible applications are pointed out and polymers which can be combined in co-extruded dosage forms are selected.

In the **introduction**, the equipment and downstream solutions for processing co-extrudates into drug products are reviewed. Requirements and challenges in material selection, considering melt viscosity and multilayer adhesion are pointed out. Examples of medical and pharmaceutical applications are presented and some recent findings considering the production of oral drug delivery systems are summarized. **Chapter 1** gives a brief overview of the polymer characteristics relevant for hot-melt co-extrusion (including solubility, hygroscopicity, toxicity, thermal stability, melt viscosity and extrudability). In **chapter 2,** fixed-dose combination dosage forms are developed by means of hot-melt co-extrusion, the core providing sustained drug release and the coat immediate drug release. In **chapter 3**, hot-melt co-extrusion is assessed for the development of multilayered dosage forms characterized by a dual release profile of the same drug. In **chapter 4**, fixed-dose combination dosage forms are developed characterized by immediate release for both layers, the layers containing different drugs with different water-solubility. **Chapter 5** is a critical evaluation of the co-extrusion process. This chapter questions if hot-melt co-extrusion offers an added value over hot-melt extrusion.

GENERAL INTRODUCTION

Hot-melt co-extrusion: requirements, challenges and opportunities for pharmaceutical applications

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1. Introduction

Co-extrusion is defined as the simultaneous hot-melt extrusion of two or more materials through the same die, creating a multilayered extrudate [1]. The technique allows to combine the desirable properties of multiple materials into a single structure with enhanced performance characteristics. The simultaneous extrusion of graphite and presswood for making pencils was already patented in the 19th century. Since 1940 hot-melt co-extrusion was utilized predominantly in the plastic industry and to a lesser extent in the food industry. Co-extrusion of plastics started with the production of pipes, wires and cables. The first major plastic co-extrusion was the production of the multilayer garden hose (patented in 1947). Another early example of plastic co-extrusion is the multilayer drinking straw, that came on the market in 1963 [2]. Plastic co-extrusion has a lot of applications in the packaging industry which can be divided into barrier and non-barrier applications. The incorporation of a barrier layer is used to control transmission of oxygen, carbon dioxide or moisture [3-5]. Non-barrier applications include improved appearance (coloration, opacity), improved sealing characteristics, stiffness/strength adjustment and printability. Around 1984 co-extrusion became popular in the food industry to produce snacks with different colors, textures or flavors. The outer material is usually starch- or cereal-based, while the filling can be cereal-, fat-, sugar- or water-based. In comparison to plastic co-extrusion, the use of food products has additional challenges. Due to many transformations (starch gelatinization, protein coagulation, formation of amylose-lipid complexes, non-enzymatic browning) occurring during co-extrusion-cooking, large rheological changes are observed, which complicates the process [6]. Moreover the shelf life of co-extruded food is often limited, because of migration of moisture or oil from the filling to the outer material [7].

Due to the advantages of hot-melt co-extrusion over conventional solid dosage form manufacturing techniques, the pharmaceutical industry became interested in this innovative technology. Besides the continuity of the process its major advantages are fewer processing steps, no use of organic solvents/water and the possibility of improving drug solubility or sustaining drug release [8-11]. Additional benefits of this technique include its versatility, increased throughput and reduced costs. By producing multilayer products with a reduced amount of expensive polymers and increased amount of inexpensive polymers a cost-efficient process can be achieved without sacrificing performance, e.g. by placing pigment only in appearance layers and/or by using recycled material in an inner layer [12]. The technology does have a price however. Besides the investment in equipment (additional extruders), there is often need for an experienced line operator (taken into account the increased levels of process complexity). In some cases the additional process costs may offset the material cost savings.

Up until now co-extrusion has been barely applied in the pharmaceutical industry. The only two co-extruded dosage forms available on the market are Nuvaring®, a contraceptive vaginal ring, and Implanon®, a contraceptive implant [13]. So far, there are no co-extruded dosage forms for oral use on the market and only a few papers on this topic have been published during the last decade [1, 14-16].

2. Process and Equipment

Co-extrusion is the process of extruding two or more materials through a single die [17]. This technology requires the combination of at least two extruders in a single processing step. Each individual extruder provides a stream of material that is combined in the co-

extrusion die connected to the outlet of the extruders. The co-extrusion equipment is fundamentally comprised of two or more feeders, extruders and a co-extrusion die (Fig. 1). Screw extruders are typically used for pharmaceutical purposes which are available in several types that differ from one another in number of screws (single or twin), rotational direction of the screws (co- or counterrotating) and whether or not the screws are intermeshing. Twin screw extrusion has several advantages over single screw. It offers intense mixing of the components as it imparts both dispersive and distributive mixing. The two screws create an environment of controlled temperature and pressure inside the extrusion barrel. Co-rotating intermeshing twin screw extruders are primarily used in pharmaceutical manufacturing since they provide intensive mixing, a relatively short residence time and ensure complete emptying of the extruder (minimizing loss of highly valuable product). Each extruder of a co-extrusion setting is typically divided into three sections for feeding, compression and metering of the materials. Materials are introduced via the feeding section from where they are transported to the compression section. In the compression section, materials are softened, homogenized and compressed. Finally, the material enters the metering section, where the pulsating flow is reduced to ensure a uniform delivery rate through the die.

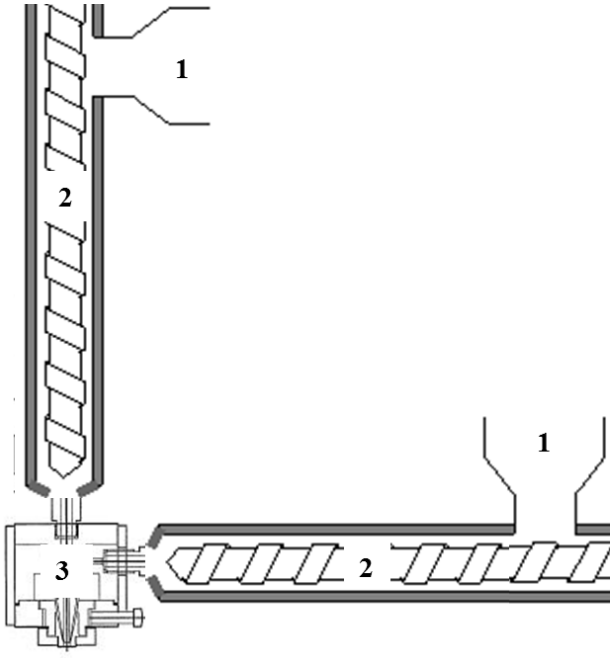

Figure 1. Schematic image of a co-extrusion equipment: 1) feeder; 2) extruder; 3) die.

In co-extrusion the die design is as critical as the selection of the materials and optimum processing conditions to provide uniform layer distribution and thickness in the co-extruded formulation. There are two systems to combine melt streams from the individual extruders: single manifold dies or multimanifold dies (Fig. 2). In single manifold dies, the different melt streams flow together through the same manifold. Prior to the die, the incoming melts form the different extruders are arranged in the proper sequence and their velocities are balanced by feedblocks. Multimanifold dies exhibit individual manifolds for each layer, which means the different melts are only combined near the die exit. Each manifold is designed to distribute its melt to the desired shape and location in the structure, before combining with the other melt streams [12]. Besides the number of manifolds, dies can also

be classified according to their shape. Flat dies are utilized for the production of films and patches, whereas e.g. circular dies are used for pelletization.

Figure 2. Schematic representation of a multimanifold die (left) and a single-manifold die (right).

After the co-extrudate has exited the die, it can be further processed into its final dosage form. Several downstream solutions are available for shaping (co-)extrudates into dosage forms such as calendaring, (co-)injection moulding and pelletizing. A major challenge at the moment is to shape the final product in a continuous way. Calendering is the process where a co-extrudate is passed through two temperature-controlled rolls, which contain tablet- or pill-shaped cavities. This technique offers an optimization towards continuous processing by allowing final shaping of the extrudates immediately after exiting the die. During injection moulding, the extruded mass is injected into a mould at high pressure. After cooling down, the product is removed from the mould. Pelletizing is another downstream solution. Note that traditional pelletizers that consist of blades on a helical rotor cannot be used for shaping (co-)extrudates, since deformed pellets would be yielded due to the softness of the extruded mass. Die face cutters are available post-extrusion for the production of spheronized micropellets [18].

3. Materials used in hot-melt co-extrusion

Proper material selection is critical to produce good quality co-extruded dosage forms. Co-extruded dosage forms are multilayer systems of which each layer consists of a mixture of one or more active pharmaceutical ingredients and functional excipients, such as matrix carriers, plasticizers and other processing aids (antioxidants, bulking agents, release modifying agents). Matrix carriers need to soften easily inside the barrel of the extruder and solidify quickly after exiting the die. The selection of appropriate carriers is important in the formulation and design of a hot-melt (co-)extruded dosage form. The carrier material properties often dictate the processing conditions necessary for the production of the dosage form. Generally, thermoplastic polymers exhibiting a low glass transition temperature or melting point are used. If the drug does not exhibit plasticizing properties, the use of polymeric carriers may require the incorporation of a plasticizer into the formulation in order to improve the processing conditions, the stability or the physico-mechanical properties of the final product. Depending on the properties of the drug substance and the other excipients in the formulation, the drug can be present as crystals (crystalline suspension), in amorphous state (glassy suspension) or molecularly dispersed in the carrier (solid solution) [11]. The state of the drug in the final dosage form influences the processability and the stability of the product.

Since melt extrusion is an anhydrous process, potential drug degradation from hydrolysis is avoided. In addition, poorly compactible drugs can be incorporated into solid dosage forms. Nevertheless materials used in hot-melt (co-)extrusion must meet the same level of purity and safety as those used in traditional dosage forms, meeting the strict regulatory requirements e.g. Generally Recognized As Safe status (GRAS), Good Manufacturing Practice (GMP) and Environmental, Health and Safety (EHS) guidelines.

Furthermore, in addition to acceptable physical and chemical stability, these materials must possess a certain degree of thermal stability, although this has to be put into perspective since Repka et al. showed that a thermally non-stable drug, hydrocortisone, could be successfully incorporated into hydroxypropylcellulose films by hot-melt extrusion [19].

In comparison to conventional hot-melt extrusion (HME), development of a co-extruded formulation is more challenging as additional technical considerations have to be taken into account when selecting polymer combinations. A successful co-extrusion process requires that the polymer melts can be processed at similar temperatures because they need to flow through the co-extrusion die under the same temperature conditions. Although both melts may be extruded at different temperature conditions in each barrel, each temperature profile needs to allow the melt to exit the co-extrusion die at the set die temperature. Furthermore, melt viscosity matching and adequate adhesion between the layers are indispensable to ensure the quality of co-extruded dosage forms.

3.1. Viscosity matching

Layer non-uniformity is an often faced problem in polymer co-extrusion and can be caused by many process factors such as melt temperature non-uniformity, pressure variations and velocity mismatch. However the key for success is the adequate choice of materials in order to match the melt viscosities of the layers. Viscosity matching is not always easy as each polymer has its own viscoelastic properties and each layer is, depending on its location in the structure, exposed to different shear rates during the co-extrusion process. As polymer viscosity is dependent on shear and temperature it is logical that melt temperature uniformity is essential to control temperature-related viscosity.

Viscosity mismatch can cause encapsulation and interfacial instability. Encapsulation happens when a low-viscosity melt flows around a high-viscosity melt and encapsulates it. The polymer viscosity ratio determines the degree of encapsulation: the larger the difference in viscosity, the higher the risk for encapsulation. Viscosity mismatch can also lead to interfacial instabilities (Fig. 3a) such as zigzag or wave patterns. If the layers are combined in a feedblock and then pass a single manifold die there is a longer contact zone inside the die and more time for the layers to relocate and cause encapsulation or instability. Multimanifold dies on the other hand can allow for a larger mismatch in polymer viscosities because the layers are only combined near the die exit. However, when feedblock technology is being used and known viscosity differences are present, modifications can be made to the feedblock geometry to correct for the viscosity mismatch using movable vanes and/or distribution pins [12].

Viscosity of thermoplastic polymers is generally assessed via melt flow index (MFI) measurements. The melt flow index is a measure of the ease of flow of the melt of a thermoplastic polymer and is defined as the weight of the polymer extruded per time unit through a capillary of specific diameter and length in a melt flow indexer by pressure applied through dead weight under prescribed temperature conditions as specified by ASTM D1238 [20]. MFI is inversely proportional to apparent melt viscosity. By performing measurements at different temperature and shear conditions, the viscosity of each polymer at specific conditions can be predicted.

Yet in case the viscosities are perfectly matched, layer rearrangement can still occur. This phenomenon is caused by secondary flows normal to the primary flow direction as a result of the viscoelastic characteristics of the polymer. The amount of layer rearrangement depends on the viscoelastic properties of the material and on the die geometry. Layer

rearrangement increases with increasing viscoelastic characteristics. With respect to the die geometry, interface deformations occur in square and rectangular dies, while they are less likely to happen in circular dies. Differences in normal forces in non-radially symmetrical channels cause secondary flows, which produce recirculation zones followed by layer rearrangement. [21, 22]. Accordingly, viscoelastic flow effects can be minimized by adequate selection of the polymers and die geometry.

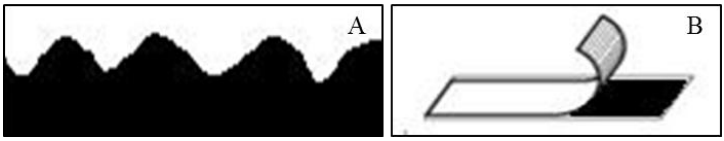

Figure 3. Typical co-extrusion problems: A) Interfacial instability; B) poor adhesion.

3.2. Adhesion

A common problem for all layered products is adhesion control. Yet adequate adhesion between the layers is essential to avoid separation during downstream processing (Fig. 3b). Adhesion is defined as the tendency of dissimilar particles or surfaces to cling to one another or as the molecular attraction that holds the surfaces of two dissimilar substances together [23]. The adhesion between polymers has been widely studied over the last two decades.

The recent adhesion literature divides adhesion mechanisms into three main categories: mechanical interlocking, molecular bonding, and thermodynamic adhesion [24]. The mechanical coupling adhesion mechanism (Fig. 4a) is based on a “lock and key” effect: the material of one layer interlocks into the irregularities of the surface of the other layer. A

second mechanism for explaining the adhesion between two surfaces in close contact is molecular bonding (Fig. 4b). It occurs when surface atoms of two separate surfaces can interact via dipole-dipole interactions, van der Waals forces and chemical interactions (i.e. ionic, covalent and metallic bonding). Chemical bonding can also occur following the formation of new compounds at the interface, which is known as reaction bonding. The third category, thermodynamic adhesion (Fig. 4c), implies that the thermodynamics of the polymer system will attempt to minimize the surface free energy. The advantage of the thermodynamic mechanism over the other mechanisms is that it does not require molecular interaction for good adhesion, only an equilibrium process at the interface [25].

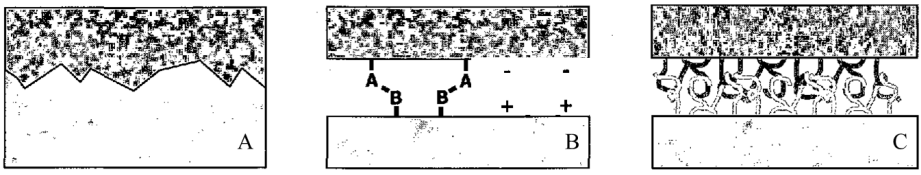

Figure 4. Adhesion mechanisms: A) mechanical interlocking; B) molecular bonding; C) thermodynamic adhesion.

Polymer compatibility influences adhesion but is not a prerequisite for adhesion. Miscible polymers will diffuse into each other at the interface, creating an interphase, by one of the mechanisms described above, while adhesion between immiscible polymers is generally weak due to limited interdiffusion. Many polymer combinations used in co-extrusion are immiscible systems. Fairly often tie layers are used which are functionalized resins that are bond to adjacent polar and non-polar resins. There are also various process

variables affecting adhesion in co-extrusion. For example, increasing the temperature and contact time usually increases adhesion since there is a longer time for the chemical reaction and chain entanglement to occur. On the other hand adhesion is decreased by high interfacial stress and shrinkage of one of the layers.

Generally, adhesion is quantified with a destructive test to evaluate the ability of an interface to resist mechanical stress. The testing methods can be divided into tensile, shear, cleavage and peel tests [26]. Tensile and shear adhesion testing methods measure the load or stress required to fail a standard junction. The main advantage of these stress-based tests is that they are simple to perform and the calculation of the stress is straightforward. Therefore, this type of adhesion testing method is most widely used. There are also a whole class of testing methods based on resistance to cleavage. These tests involve forcing a wedge at the interface, thereby creating cleavage stresses. During a peel test, a coating is pulled from its substrate. The crack propagates in a stable manner at the peel speed. The force required to continue cracking is monitored as a function of crack position and time. A drawback of the adhesion testing methods is that failure happens suddenly and can occur at the interface or within one of the layers, meaning that it is not always adhesion which is measured.

3.3. Other considerations

Interdiffusion of the layers should be considered. If the two adjacent layers are miscible, drug and/or polymer of one layer can diffuse into the other layer. It is most likely to happen using a single manifold die because the melt streams have more time to interact. In order to prevent delamination of the co-extruded structure, the shrinkage of the polymers also needs to be taken into account. Delamination occurs when the shrinkage of both layers differs

too much. Considering for example a co-extruded tube consisting of two concentric layers. If the shrinkage percentage of the inner layer is more than that of the outer layer, a gap will form between the two layers. If the outer layer is brittle and shrinks more than the inner layer it might burst or in case the outer layer is stretchable, it might tighten around the inner layers and a delamination-free structure may be achieved [27].

Given that carriers used in co-extruded dosage forms need to be thermoplastic and meet the regulatory requirements (GRAS, GMP and EHS) and taking into account the extra considerations (viscosity, adhesion, miscibility, shrinkage) for combination of polymers, it is obvious that polymer selection for co-extrusion is not always straightforward. There is a need for new polymers to improve the polymer variety in order to facilitate the choice of polymers in a co-extruded dosage form.

4. Pharmaceutical Applications

The development of fixed-dose combinations is becoming increasingly important from a public health perspective. Not only do they improve patient adherence, they can also have a better efficacy, a reduced incidence of adverse effects and/or less development of resistance (in the case of antimicrobials). Additionally there can be economical benefits such as lower manufacturing costs and simpler logistics of distribution. Such “polypills” are being used in the treatment of e.g. cardiovascular disease, diabetes, hyperlipidemia, HIV, tuberculosis and malaria. An innovative way to produce fixed-dose combinations is via hot-melt co-extrusion. Depending on the type and concentration of the carriers used in the different layers, fixed-dose combination products with different release rate of both drugs can be designed. A well-known application is the combination of a beta-blocker and a diuretic for the treatment of

cardiovascular disease [28]. Furthermore, co-extruded dosage forms offer the opportunity to modulate the release profile of a specific drug by incorporating the same drug in layers formulated with different carriers. This way, it is possible to develop controlled release formulations with a fast onset of action. Co-extrusion further allows to formulate incompatible drugs in different layers, enabling their simultaneous administration. A well-known example of incompatible drugs which are concurrently used is isoniazid and rifampicin for the treatment of tuberculosis.

Despite the versatility of co-extrusion as manufacturing technique for pharmaceutical dosage forms, only a few applications exist to date. Table 1 gives an overview of the current pharmaceutical applications of hot-melt co-extrusion. Until now only two of these co-extruded dosage forms are commercially available i.e. Nuvaring® and Implanon®. Nuvaring® (MSD) is a contraceptive intravaginal ring that releases etonogestrel and ethinyl estradiol over a period of 21 days. Implanon® (Schering-Plough) is a non-biodegradable flexible rod that contains etonogestrel and provides contraceptive efficacy during a period of 3 years [29]. Both dosage forms consist of a core (composed of ethylene vinylacetate copolymers) containing the drug(s), surrounded by an outer layer (also composed of ethylene vinylacetate copolymers) that regulates drug release.

Table 1. Overview and composition of pharmaceutical products manufactured via hot-melt co-extrusion.

Dosage form	Layer 1		Layer 2		Ref.
	Drug	Carrier	Drug	Carrier	
Oral	theophylline	soy protein isolate	-	soy protein isolate	[14]
	theophylline/ acetaminophen	polyethylene glycol	theophylline/ acetaminophen/ no drug	stearic acid	[15]
	theophylline	polyethylene glycol	theophylline	microcrystalline wax	[1]
	metoprolol tartrate	ethylcellulose	hydrochlorothiazide	polyethylene oxide	[16]
	troglitazone	povidone	-	ethylcellulose	[30]
	CI-1017	povidone	-	Eudragit® RS PO	[30]
	perindopril tert-butylamine salt	Eudragit® E 100	-	Eudragit® RL PO	[31]
	naltrexone HCl	Eudragit® RS PO	-	Eudragit® RS PO	[32]
Implant	etonogestrel	ethylene vinyl acetate (28% vinyl acetate)	-	ethylene vinyl acetate (14% vinyl acetate)	[13]
	flucinolone acetonide	polycaprolactone/ polyvinyl acetate	-	poly(lactic-co-glycolic acid)/ ethylene vinyl acetate	[33]
	macrocyclic lactone	ethylene vinyl acetate (28% vinyl acetate)	-	ethylene vinyl acetate (28% vinyl acetate)	[34]
Vaginal ring	etonogestrel + ethinyl estradiol	ethylene vinyl acetate (28% vinyl acetate)	-	ethylene vinyl acetate (9% vinyl acetate)	[35]

Co-extrusion is gaining importance in the production of oral drug products. So far, there are no co-extruded dosage forms for oral use on the market, but several research studies have already been done in this field. Quintavalle et al. characterized hot melt co-extruded cylindrical systems for controlled drug delivery. The sustained release profile was obtained by extruding two concentric theophylline-loaded matrices: an inner hydrophilic polyethylene glycol-based matrix combined with an outer lipophilic layer, mainly consisting of microcrystalline wax. A screening of several devices, differing in dimensions and relative proportions of inner and outer part was performed based on the in vitro drug release. The release mechanisms were studied with the use of a mathematical model [1, 15]. Vaz et al. produced double-layer delivery devices based on soy protein derived materials via co-injection moulding. Layer thickness uniformity was influenced by the viscosity ratio between core and coat materials. Through adequate material selection and the optimization of the processing conditions an accurate control of the relative thickness of the layers of the device was possible. The preliminary data demonstrated the potential of these systems to achieve a controlled drug delivery. [14]. A recent study by Vynckier et al. [16] described the successful preparation of fixed-dose combination mini-matrices with metoprolol tartrate embedded in a matrix core offering a range of controlled release profiles and hydrochlorothiazide incorporated in an immediate release coat. The influence of adjusting the concentration of polyethylene oxide as a hydrophilic component or changing the drug load in the plasticized ethylcellulose matrix was studied.

5. View to the future

Today's drug development challenges have tremendously increased. Over the last years the economy has played a role in many pharmaceutical products to be sidelined. Pharmaceutical production processes need to gain efficiency and versatility while new drug substances are more difficult to process because their bioavailability is often poor. Enhancing bioavailability of poorly water soluble drugs and moving from batch toward continuous processing are ever increasing topics in academia and pharmaceutical companies. As hot-melt (co-)extrusion allows the continuous production of a variety of dosage forms while offering the possibility to enhance the solubility of poorly water soluble drugs, this drug formulation technique provides the perfect answer to some of today's biggest challenges.

Hot-melt (co)-extrusion is a very promising innovative method to produce drug delivery systems. Co-extrusion provides manufacturers with a process that increases throughput, reduces manufacturing costs and supplies versatility for dosage forms. Furthermore, this technique presents great potential for the continuous production of fixed-dose combination products which are gaining importance in pharmaceutical industry.

However, the amount of marketed (co-)extruded drug products is still small. To our opinion the major barriers to the implementation of co-extrusion in the pharmaceutical industry are the conservative attitude of the pharmaceutical companies (the fear to change), the significant investment initially required and the lack of process knowledge. Other impediments are the limited number of thermoplastic polymers available and the elaborate method to predict a suitable carrier for a specific drug. The traditional approach used in carrier selection involves the manufacturing and characterization of numerous candidate formulations. The cost and time constraint of this empirical approach makes it unattractive.

Regardless of these hurdles, hot-melt extrusion has already achieved a strong place in the pharmaceutical industry and its use is steadily increasing. Successful products have been marketed (e.g. Kaletra® and Norvir®, Abbott Laboratories, USA) and many others are in the pipeline. Moreover an increasing number of formulations are being investigated within academia and pharmaceutical companies. Rapid screening tools are being developed to shorten the empirical screening time and thus reduce the corresponding costs. Process engineers and formulation scientists are cooperating in order to enhance the technology. New thermoplastic polymers are being designed, specifically for HME applications (e.g. Soluplus®, BASF, Germany). These facts prove that HME will become commonplace within the pharmaceutical industry in the near future. A logical next step would be the breakthrough for co-extrusion. For companies that have already invested in HME equipment, it would only be a small step towards co-extrusion. A limited extra investment cost would broaden the scope of dosage forms that can be manufactured. In conclusion, hot-melt co-extrusion is a versatile manufacturing technique for drug delivery systems and it will most likely face an exciting future within the pharmaceutical industry.

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CHAPTER 1

Physico-chemical polymer characterization for co-extrusion

1. Introduction

Proper material selection is critical in order to produce high quality co-extruded dosage forms. Some of the basic requirements for polymers used in hot-melt co-extrusion are that the polymers must exhibit thermoplastic characteristics (soften easily inside the barrel of the extruder and solidify quickly after exiting the die) and that they must possess a certain degree of thermal stability. Extrudability of a polymer is mainly determined by its glass transition (T_g) or melting temperature (T_m) and its melt viscosity. As a general rule of thumb, an extrusion process is run at a temperature of 10 or 50 °C above T_m or T_g, respectively [1]. Accordingly, polymers exhibiting a high T_g or T_m require a higher processing temperature increasing the risk of drug degradation during hot-melt extrusion. Moreover, polymers with a high molecular weight exhibit high melt viscosity and are difficult to extrude. Other relevant characteristics are a low hygroscopicity in order to ensure the stability of the formulation (e.g. prevent the risk of recrystallization of solubilized drugs) and no toxicity since relatively large amounts of polymer will be administered. Besides these basic requirements, some pharmaceutical aspects and technical considerations need to be taken into account. Pharmaceutical aspects include e.g. the drug release characteristics as hydrophilic polymers tend to release drugs in an immediate release manner, while hydrophobic polymers are expected to provide sustained drug release. Technical considerations include that co-extruded polymers need to have similar extrusion temperature and melt viscosity while adequate adhesion between the layers is also essential.

Accordingly preliminary polymer characterization is indispensable. This chapter focuses on the polymer characteristics relevant for hot-melt co-extrusion. These include solubility, hygroscopicity, toxicity, thermal stability, melt viscosity and extrudability. As adhesion, interdiffusion and delamination depend on specific polymer combinations as well as on the model drugs embedded, these properties are not considered in this chapter.

2. Materials and methods

2.1. Materials

The polymers tested were: Ethocel® std 10 (ethylcellulose, DOW Chemical Company, Midland, USA), Eudragit® E and RS PO (Evonik, Darmstadt, Germany), Kollidon® 30, VA and SR (BASF, Ludwigshafen, Germany), Sentry™ Polyox® WSR N10 (polyethylene oxide (MW: 100,000 g/mol), Colorcon, Dartford Kent, United Kingdom), Soluplus® (BASF, Ludwigshafen, Germany) and CAPA® 6506 (polycaprolactone (MW: 50,000 g/mol), Perstorp, Warrington, United Kingdom).

2.1.1. Ethylcellulose (Ethocel®)

Ethylcellulose (Fig. 1), an ethylether of cellulose, is a long-chain polymer of ß-anhydroglucose units. The number of monomeric units can vary to provide a wide variety of molecular weights. Viscosity increases with increasing chain length. It is a nonionic, non-hygroscopic, physiologically inert polymer that is practically insoluble in water. Ethylcellulose is widely used in oral and topical pharmaceutical formulations. Its main use in oral formulations is as a hydrophobic coating agent or matrix former to modify drug release, to improve the stability of a formulation (e.g. inhibit oxidation) and for taste masking. Ethylcellulose is GRAS listed and included in the FDA (Food and Drug Administration) inactive ingredients guide [2]. In our study, Ethocel® std 10 with an ethoxyl content of 48.0-49.5% w/w and a respective viscosity of 9-11 mPa.s (5% solution (w/v) in 80:20 toluene:ethanol, measured at 25°C) is applied as sustained-release agent.

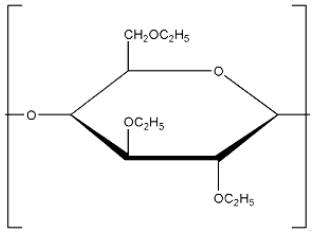

Figure 1: Chemical structure of ethylcellulose.

2.1.2. Polymethacrylates (Eudragit® E and RS PO)

Polymethacrylate polymers are primarily used as coating agents for oral capsule and tablet formulations. Depending on the type of polymer used, films with different solubility characteristics can be produced. Polymethacrylates are also used in direct-compression, as binders in wet-granulation processes and as matrix formers in oral formulations. They are included in the FDA inactive ingredients guide [2].

Eudragit® E PO (Fig. 2) is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate in a ratio of 2:1:1. The polymer has a weight average molar mass of approximately 47,000 g/mol. Eudragit® E PO is soluble in gastric fluid and acidic solutions up to pH 5 and swellable/permeable above pH 5.0. In our study, it is applied as immediate-release agent.

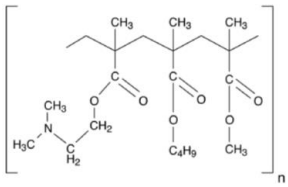

Figure 2: Chemical structure of Eudragit® E PO.

Eudragit® RS PO (Fig. 3) is a cationic copolymer based on ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride (1:2:0.1), with an average molecular weight of approximately 32,000 g/mol. Eudragit® RS PO is water-insoluble, but water-permeable with a pH-independent permeability which makes it suitable for the formulation of sustained-release dosage forms. Due to their cationic properties, Eudragit® E and RS PO can only be used in combination with nonionic and cationic drugs.

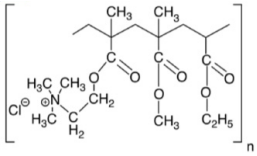

Figure 3: Chemical structure of Eudragit® RS PO.

2.1.3. Polyvinylpyrrolidone (Kollidon®) and copolymers (Kollidon® VA 64 and SR)

Polyvinylpyrrolidone, also known as povidone, is a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups (Fig. 4). Different degrees of polymerization result in polymers with various molecular weights. Kollidon® 30 has a molecular weight of 50,000 g/mol. Povidone has been widely used in solid dosage forms as tablet binder, drug carrier and coating agent. It is a very hygroscopic polymer that can absorb significant amounts of moisture even at low relative humidity. Polyvinylpyrrolidone is readily water soluble, therefore it is intended to be used for immediate release formulations [2, 3].

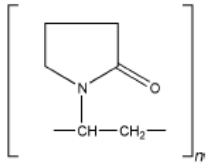

Figure 4: Chemical structure of Kollidon® 30.

Copovidone (Kollidon® VA 64, Fig. 5) is an amorphous copolymer manufactured from vinylpyrrolidone and vinyl acetate monomers. The average molecular weight of the polyvinylpyrrolidone and the polyvinyl acetate part is about 450,000 and 50,000 g/mol, respectively. Vinylpyrrolidone is a hydrophilic and water-soluble monomer whereas the vinyl acetate monomer is lipophilic and water-insoluble. The monomer ratio (6:4) is balanced in a way that the polymer is still freely soluble. Thus the release profile of formulations composed of this polymer is mostly instant release. Copovidone is used in the pharmaceutical industry as a tablet binder, coating agent or matrix former. It is less hygroscopic than PVP [2, 3].

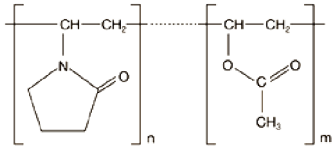

Figure 5: Chemical structure of Kollidon® VA 64 and SR.

Kollidon® SR is a spray-formulated mixture of polyvinylpyrrolidone and polyvinyl acetate in a ratio of 2:8. Due to the large amount of the water-insoluble vinyl acetate monomer, Kollidon® SR is water-insoluble and therefore used for sustained drug delivery.

Kollidon® SR contains no ionic groups and is therefore inert to drug substances. The sustained-release properties are unaffected by ions or salts. The water uptake is much less than that of povidone or copovidone [2, 3]. Polyvinylpyrrolidone and its copolymers are generally regarded as nontoxic and included in the FDA inactive ingredients guide.

2.1.4. Polyethylene oxide (Sentry™ Polyox®)

Polyethylene oxide (PEO) (Fig. 6) is a nonionic, water-soluble homopolymer of ethylene oxide. It is available in a broad range of molecular weights, i.e. from 100,000 up to 8,000,000 g/mol. Polyox® WSR N10 has a molecular weight of 100,000 g/mol. Low molecular weight PEO is suitable for immediate release formulations. High molecular weight PEO has been successfully applied in sustained-release dosage forms due to its swelling properties. As the swelling properties depend on the molecular weight, modification of the release profile is possible by choosing the appropriate PEO grade. PEO exhibits low hygroscopicity, resulting in a low moisture content < 1%. Polyethylene oxides are used as tablet binder in direct compression, in hot-melt produced dosage forms and in other drug delivery systems. They are included in the FDA inactive ingredients guide.

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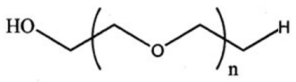

Figure 6: Chemical structure of polyethylene oxide.

2.1.5. Polyethylene glycol – polyvinyl caprolactam – polyvinyl acetate graft copolymer (Soluplus®)

Polyethylene glycol – polyvinyl caprolactam – polyvinyl acetate graft copolymer (Fig. 7) is a polymeric solubilizer with an amphiphilic chemical structure. The hydrophilic backbone of the polymer consists of polyethylene glycol (molecular weight 6,000 g/mol); the side chains consisting of vinyl acetate randomly copolymerized with vinyl caprolactam are lipophilic. Hence, Soluplus® forms micelles in aqueous solution above the critical micelle concentration (7.6 mg/l). The average molecular weight of Soluplus® is in the range of 90,000 to 140,000 g/mol. Soluplus® was designed to serve as a matrix for solid glassy solutions and to solubilize poorly water soluble drugs in aqueous media. According to BASF, Soluplus® has been tested over the full range of toxicological studies [3].

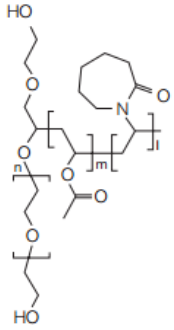

Figure 7: Chemical structure of polyethylene glycol–polyvinyl caprolactam–polyvinyl acetate grafted copolymer.

2.1.6. Polycaprolactone (CAPA®)

Polycaprolactone (Fig. 8) is a biodegradable, biocompatible polyester derived from ε-caprolactone. The number average molecular weight can vary from 3,000 to 80,000 g/mol. CAPA® 6506 is a high molecular weight (50,000 g/mol) linear polyester. Due to its hydrophobic character and a high permeability to many drugs, polycaprolactone is suitable for controlled drug delivery. It has been approved by the FDA in specific applications used in the human body as e.g. drug delivery device, suture or adhesion barrier.

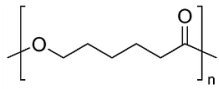

Figure 8: Chemical structure of polycaprolactone.

2.2. Thermogravimetric analysis (TGA)

A thermogravimetric analyser (Hi-res TGA 2950, TA instruments, Leatherhead, UK) was employed to investigate the thermal stability of the pure polymers. Samples (±15 mg) were equilibrated at 50 °C and heated to 500 °C at a heating rate of 10 °C/min while recording the weight loss.

2.3. Differential scanning calorimetry

Glass transition temperature (T_g) and/or melting point (T_m) of pure components were analyzed by differential scanning calorimetry (DSC) using a Q2000 DSC (TA Instruments, Leatherhead, UK). The system was equipped with a refrigerated cooling system. Samples (±10 mg) were run in hermetically sealed aluminum pans. Depending on the samples and the determined parameters, the experimental method consisted of a single heating cycle (heating rate of 10 °C/min) or a three-phase analysis with consecutive heating, cooling and heating cycles. All results were analyzed using the TA Instruments Universal Analysis 2000 software.

2.4. Melt flow index determination

The basic property measured by the melt flow test was the melt viscosity of the polymer at a particular shear stress (related to the applied load) and temperature. Melt flow index (MFI) was determined by means of a MPX 62.92 melt flow indexer (Göttfert, Germany) according the ISO 1133 standard (Fig.9). A die with a diameter of 2.095 mm was used. Different loads (1.20, 2.16, 3.80, 5, 10, 12.5, 15 and 21.6 kg) were applied (corresponding to shear stresses of 11148, 20066, 35302, 46450, 92900, 116125, 139350 and 200664 Pa). Polymers were manually fed into a barrel and after manual compression of the material to remove air, the powder mixture was preheated for 360 seconds. The amount of polymer extruded in 10 min was measured, expressed in units of cm^3/10 min. This value (the MFI) was then converted to shear rate (s^{-1}) and melt viscosity (Pa.s). Measurements were performed at the lowest possible temperature allowing flow through the die channel and at higher temperatures if applicable.

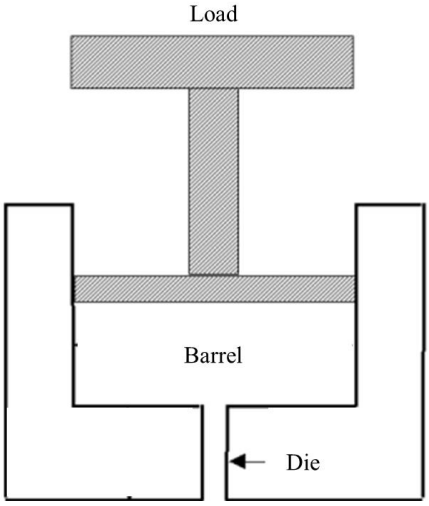

Figure 9: Schematic of a melt flow indexer.

2.5. Hot-melt extrusion

All thermoplastic polymers were hot-melt extruded using a Prism Eurolab 16 co-rotating, fully intermeshing twin screw extruder (ThermoFisher Scientific, Germany). The extrusion temperature varied according to the polymer, but all five heating segments of the extruder were set at the same temperature. The appropriate extrusion temperature was defined as the lowest temperature at which the extruder torque was below 80% motor load. A strand die with a diameter of 3 mm was mounted at the end of the extruder. The machine was equipped with a gravimetric Brabender powder feeder (Duisburg, Germany). The screw speed and feed rate were kept constant at 60 rpm and 250 g/h.

3. Results

3.1. Thermal analysis

As polymers must be thermally stable at least at the extrusion temperature employed, thermal decomposition was studied using thermogravimetric analysis. Glass transition and melting temperatures of the polymers were determined with DSC. The DSC and TGA results are summarized in Fig. 10. Following polymers were pure amorphous as they exhibited no melting, but one (or more) glass transition temperature(s): Ethocel® std 10, Eudragit® E and RS PO, Kollidon® 30, VA and SR and Soluplus®. The presence of both a glass transition and a melting temperature for Polyox® WSR N10 and CAPA® 6506 indicated they were semi-crystalline polymers.

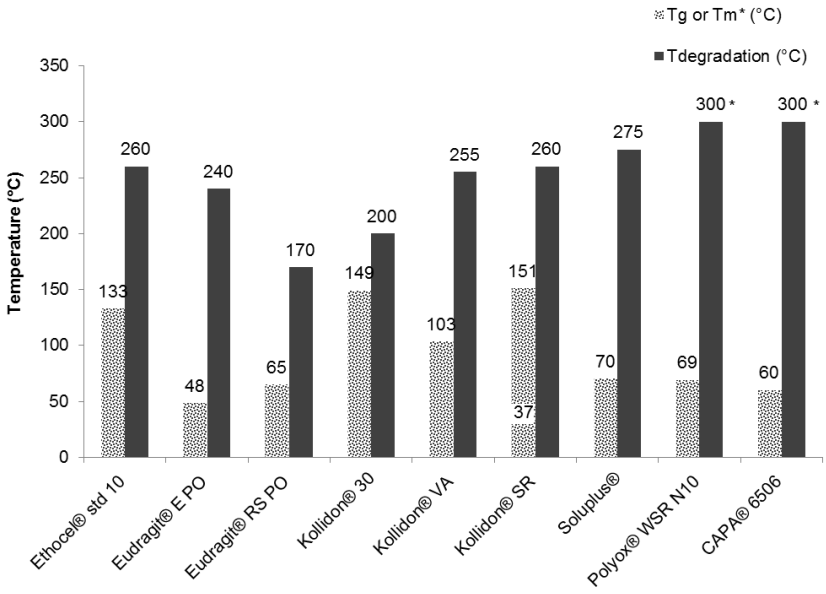

Figure 10. Comparison of T_g or T_m (by DSC) with degradation temperature (by TGA) of pure polymers.

As mentioned in the introduction, it is estimated that thermoplastic polymers can be extruded at a temperature of 10 or 50 °C above their T_m or T_g, respectively [1]. Thus, the difference between T_m + 10 °C or T_g + 50 °C and the degradation temperature serves as a first indication of the extrusion temperature range. Within the extrusion temperature range, extrusion can be performed from a process and polymer stability point of view. Kollidon® 30 showed a glass transition and degradation temperature around 149 and 200 °C, respectively. The small difference between the T_g and decomposition temperature limits its application as pure polymer for HME. Kollidon® SR showed two glass transitions at 37 and 151 °C, respectively. Although pure Kollidon® SR showed no decomposition on TGA below 260 °C, estimation of the extrusion range was difficult due the existence of two T_g's. For all other polymers the estimated extrusion temperature ranges were relatively broad (≥50 °C): Ethocel® std 10 (183-260 °C), Eudragit® E PO (98-240 °C), Eudragit® RS PO (115-170 °C), Kollidon® VA (153-255 °C), Soluplus® (120-275 °C), Polyox® WSR N10 (79-300 °C), CAPA® 6506 (70-300 °C).

Besides the width of the extrusion temperature range, the lower limit is also important. In pharmaceutical HME applications, it is advisable not to exceed a process temperature of 150 °C, in order to guarantee the stability of the active pharmaceutical ingredient. In this manner, materials with a high T_g/T_m can only be extruded within a small temperature range irrespective of their degradation temperature. In spite of the broad extrusion temperature range of Ethocel® std 10, in pharmaceutical applications the use of a plasticizer is mandatory (due to its high Tg). On the contrary, high thermal stability combined with a relative low T_g/T_m, provides a broad (estimated) range for pharmaceutical extrusion of Eudragit® E PO (98-150 °C), Eudragit® RS PO (115-150 °C) and Soluplus® (120-150 °C), Polyox® WSR N10 (79-150 °C), CAPA® 6506 (70-150 °C). Besides, the low T_m of Polyox® WSR N10 and

CAPA® 6506 allows extrusion at low temperature which makes them suitable carriers for thermolabile drugs.

3.2. Melt viscosity

Besides the glass transition and the melting temperature, melt viscosity is another crucial factor determining extrudability. Polymer melt viscosity should be low enough to enable flow through the extrusion channel. At the same time it should be high enough to avoid problems during downstream processing. The measurement of MFI is a convenient method for estimating the flow behavior of polymer melts. Because of its simplicity and the relatively low cost of the equipment, it is widely used for polymer processing control. It provides information about the ease of processing of polymers at different temperatures and shear rates. Accordingly, MFI measurements can be helpful in predicting the appropriate extrusion temperature. Besides, viscosity matching is indispensable for co-extrusion with a single manifold die as viscosity mismatch can cause interfacial instability and non-uniformity of the layer thickness.

The influence of shear and temperature on the melt viscosity of the polymers is shown in Fig. 11. Melt viscosity is plotted versus shear rate for temperatures within the process temperature range of the pure polymers. Of all tested polymers, CAPA® 6506 required the lowest temperature (80 °C). Polyox® WSR N10 was processable from 120 °C, followed by the polymethacrylate polymers (130-150 °C), Soluplus® (140-150 °C), Ethocel® Std 10 (160 °C) and Kollidon® 30 (190 °C). All polymers demonstrated shear thinning behavior which means that the viscosity reduces as a function of increasing shear stress. The influence of shear rate on melt viscosity was the biggest for Ethocel® Std 10 and Polyox® WSR N10 and the smallest for CAPA® 6506. Furthermore, all tested polymers showed a decrease in melt

viscosity with increasing temperature. In terms of viscosity, the polymethacrylates were more sensitive to temperature changes than all other tested polymers.

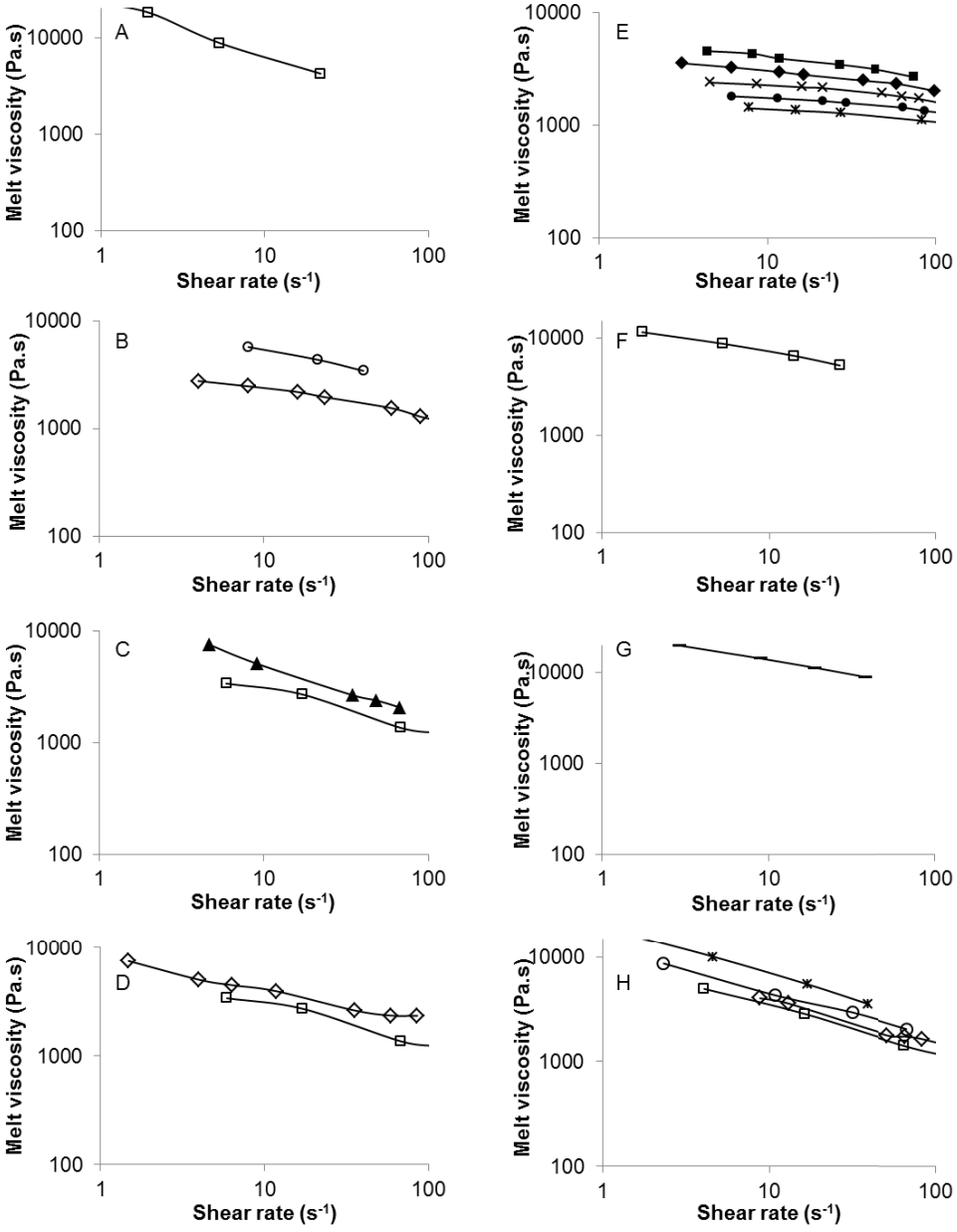

Figure 11. Melt viscosity of pure polymers as a function of shear rate at different temperatures: (■) 80 °C, (♦) 90 °C, (×) 100 °C, (●) 110 °C, (∗) 120 °C, (○) 130 °C, (◊) 140 °C, (□) 150 °C, (▲) 160 °C, (—) 190 °C. A: Ethocel® std 10, B: Eudragit® E PO, C: Kollidon®

VA (low) and Kollidon® SR (high), D: Soluplus®, E: CAPA® 6506, F: Eudragit® RS PO, G: Kollidon® 30 and H: Polyox® WSR N10.

3.3. Extrusion temperature of pure polymers

As mentioned in the general introduction, a successful co-extrusion process requires that the polymer melts can be processed at similar temperatures because they need to flow through the co-extrusion die under the same temperature conditions. Therefore, the pure polymers (without plasticizer) were hot-melt extruded and evaluated for processability. The extrudability was determined by various factors such as T_g or T_m, the melt viscosity, the power consumption of the extruder and the die pressure. The minimum extrusion temperature (Table 1) was defined as the lowest temperature at which the extruder torque and die pressure were below 80% motor load and 100 bar, respectively.

Table 1. Glass transition, melting and minimum extrusion temperature of pure polymers.

	T_g (°C)	T_m (°C)	**Minimum extrusion temperature (°C)**
Ethocel® std 10	133	-	-
Eudragit® E PO	48	-	130
Eudragit® RS PO	65	-	-
Kollidon® 30	149	-	-
Kollidon® VA	103	-	160
Kollidon® SR	37 & 151	-	140
Soluplus®	70	-	140
Polyox® WSR N10	-	69	75
CAPA® 6506	-	60	70

The semi-crystalline polymers CAPA® 6506 and Polyox® WSR N10 were already processable at a temperature of 70 and 75 °C, respectively. Extrusion at higher temperatures (120 °C) was also possible, still yielding adequate viscosity. With respect to CAPA® 6506, these results were in agreement with the MFI results. For Polyox® WSR N10 on the other hand, the minimum temperature required during the MFI measurements was not representative for the minimum extrusion temperature. This was explained by the additional shear in the extruder originating from the screws, taking into account the fact that the viscosity of Polyox® WSR N10 is strongly affected by shear. For the processing of pure Eudragit® E PO a temperature of at least 130 °C was required, irrespective of its low T_g (48 °C). Pure Soluplus® and Kollidon® SR were extrudable at 140 °C, whereas Kollidon® VA required 160 °C. Despite its relatively low Tg (65 °C), extrusion of Eudragit® RS PO without plasticizer was impossible. The temperature required to extrude the pure polymer approached the degradation temperature (170 °C) of the polymer. Because of their high T_g (section 3.1) and viscosity (section 3.2), extrusion of Ethocel® Std 10 and Kollidon® 30 will also require plasticization.

4. Conclusions

Taking into account the T_g/T_m, the minimum extrusion temperature, the degradation temperature and the melt viscosity CAPA® 6506, Polyox® WSR N10 and Eudragit® E PO demonstrated good suitability for pharmaceutical hot-melt extrusion. Pure Soluplus® and Kollidon® SR also showed good extrudability, but within a narrow temperature range. Extrusion of Eudragit® RS PO without any plasticizer was not possible because the required temperature approached the degradation temperature of the polymer. Ethocel® std 10 and

Kollidon® 30 will require a plasticizer because of their high T_g, melt viscosity and a too small difference between T_g and degradation temperature in case of Kollidon® 30.

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CHAPTER 2

Co-extrusion as manufacturing technique for fixed-dose combination mini-matrices

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1. Introduction

Multiparticulates are less dependent on gastric emptying rate, have a lower tendency for local irritation and have a reduced risk of dose dumping compared to monolithic dosage forms [1]. The greatest advantage of multiparticulate systems is the ease of dose adjustment without any formulation or process change. Because the dose can be adjusted by increasing or decreasing the number of individual particles in the dosage form, the surface area and consequently the drug release profile are not affected. This reduces the extra time and cost used for bioequivalence studies [2]. In addition, the use of fixed-dose combination (FDC) dosage forms is likely to increase in the future because they improve patient adherence [3]. A well-known application is the combination of a beta-blocker and a diuretic for the treatment of cardiovascular disease [4]. The aim of the present study was to evaluate the potential of co-extrusion as manufacturing technique for the production of multiparticulate FDC dosage forms for oral application. Therefore, in this study hydrochlorothiazide (HCT, a diuretic) and metoprolol tartrate (MPT, a beta-blocker) were incorporated as immediate and sustained release model drugs, respectively. Via proper selection of polymers, a core/coat dosage form was developed via co-extrusion, the core providing sustained drug release (SR) and the coat immediate drug release (IR).

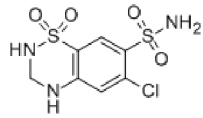
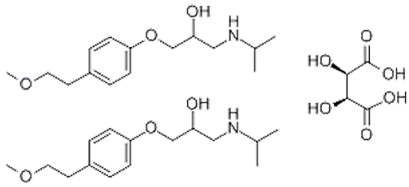
2. Materials and methods

2.1. Materials

The polymers tested were: Soluplus® (BASF, Ludwigshafen, Germany), Eudragit® E and RS PO (Evonik, Darmstadt, Germany), Kollidon® VA and SR (BASF, Ludwigshafen, Germany), Ethocel® std 10 (ethylcellulose, DOW Chemical Company, Midland, USA),

SentryTM Polyox® WSR N10 (polyethylene oxide (PEO) (MW: 100,000 g/mol), Colorcon, Dartford Kent, United Kingdom), polyethylene glycol (PEG (MW: 4,000 g/mol), Fagron, Waregem, Belgium) and CAPA® 6506 (polycaprolactone (MW: 50,000 g/mol), Perstorp, Warrington, United Kingdom). Colloidal silicium dioxide (Fagron, Waregem, Belgium) was added to CAPA® to improve the flow properties. Pluronic® F68 (PLUR), triethyl citrate (TEC) and dibutyl sebacate (DBS) (Sigma-Aldrich, Bornem, Belgium) were used as plasticizers. Hydrochlorothiazide (HCT) (UTAG, Amsterdam, the Netherlands) and metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain) were incorporated as immediate release and sustained release model drugs, respectively. Their relevant physico-chemical properties are listed in Table 1. All other chemicals were of analytical grade.

Table 1. Physico-chemical properties of hydrochlorothiazide and metoprolol tartrate.

Properties		**Structural formula**
Name	hydrochlorothiazide	
Melting point	274 °C	
Degradation temperature	290 °C [5]	
Solubility in water	very slightly soluble [6]	
pKa	7.9; 9.2 [7]	
Name	metoprolol tartrate	
Melting point	124 °C	
Degradation temperature	160 °C [8]	
Solubility in water	very soluble [6]	
pKa	9.6	

2.1.1. Pluronic® F68

PLUR is a nonionic polyoxyethylene–polyoxypropylene copolymer used in pharmaceutical formulations as emulsifying or solubilizing agent. The polyoxyethylene segment (80%) is hydrophilic while the polyoxypropylene segment (20%; MW: 1,800 g/mol) is hydrophobic. PLUR occurs as white, waxy, free-flowing granules with a melting point of 52–57 °C. It is included in the FDA inactive ingredients guide.

2.1.2. Triethyl citrate

TEC is a water-soluble plasticizer prepared by esterification of citric acid and ethanol. It is a clear, oily and practically colourless liquid with a boiling point of 155 °C. TEC is used in the pharmaceutical industry as plasticizer for polymeric coating of capsules, tablets, beads and granules. It is GRAS listed and included in the FDA inactive ingredients guide.

2.1.3. Dibutyl sebacate

DBS is a dibutyl ester of sebacic acid. It is present as an oily, water-insoluble colourless liquid with a boiling point of 344-349 °C. DBS is used in oral pharmaceutical formulations as plasticizer for film coatings and in controlled-release tablets. It is included in the FDA inactive ingredients guide.

2.2. Polymer selection

For the selection procedure several thermoplastic polymers were hot-melt extruded and evaluated for processability, macroscopic properties (surface smoothness, die swell) and in vitro drug release. Polymers were mixed with different amounts of drug (2.5-30% HCT; 10-50% MPT) and hot-melt extruded using a Prism Eurolab 16 co-rotating, fully intermeshing twin screw extruder (ThermoFisher Scientific, Germany). The extrusion temperature varied according to the polymer, but all five heating segments of the extruder were set at the same temperature. The appropriate extrusion temperature was defined as the lowest temperature at which the extruder torque was below 80% motor load. A strand die with a diameter of 3 mm was mounted at the end of the extruder. The machine was equipped with a gravimetric Brabender powder feeder (Duisburg, Germany). The screw speed and feed rate were kept constant at 60 rpm and 250 g/h.

2.3. Production of co-extrudates

Polymer and drug were premixed in a tumbling mixer (Turbula® T2A, W.A. Bachofen, Basel, Switzerland) for 30 min. Co-extrusion was performed using two Prism Eurolab 16 co-rotating, fully intermeshing twin screw extruders (ThermoFisher Scientific, Germany) having a length-to-diameter ratio of 25/1. The two pairs of co-rotating screws each consisted of three mixing sections and a densification zone (the geometry of the screws is illustrated in Fig. 1).

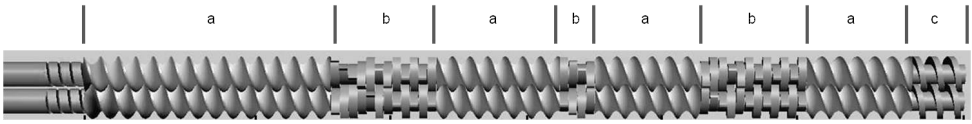


Figure 1. Configuration of the intermeshing co-rotating screws. Standard screw configuration with three kneading blocks: transport zone (a), mixing zone (b) and densification zone (c).

A multimanifold co-extrusion die (Guill, West Warwick, USA) was connected to both extruders (Fig. 2). In the die, the two melts were combined to form two concentric layers, a core and a coat. All five heating segments of both extruders as well as the co-extrusion die were heated to 70 °C. Both premixes were fed into the corresponding extruders by two Brabender Flexwall® (loss-in-weight) powder feeders (Duisburg, Germany) at a feed rate of 150 g/h for the coat and 250 g/h for the core material. A screw speed of 60 rpm was used in both extruders. The die dimensions were 3 mm core diameter and 0.5 mm coat thickness, resulting in a total diameter of 4 mm. After cooling down to room temperature, the cylindrical co-extrudates were manually cut into mini-matrices of 2 mm length.

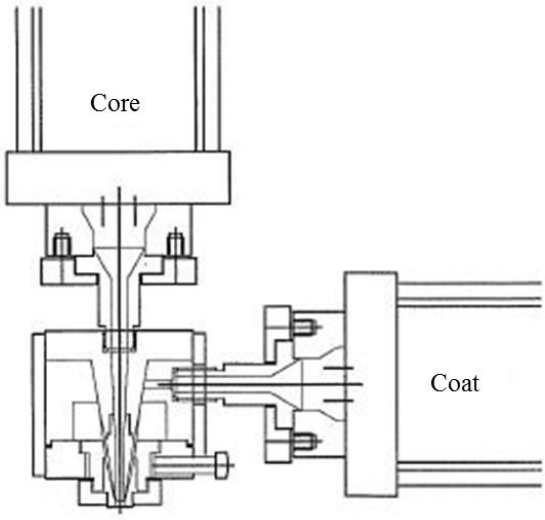


Figure 2. Co-extrusion die with cylindrical core and annular coat (reprinted with permission of Thermo Fisher Scientific®).

2.4. In vitro drug release

Dissolution studies were performed using USP apparatus 1 (baskets). The equipment consisted of a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, NJ, USA). The vessels were filled with 900 ml dissolution medium. The mini-matrices (six tablets of 2 mm length) were exposed to a 0.1 M solution of hydrochloric acid (pH=1) for 1 hour to mimic the pH of the stomach and were then transferred to 900 ml of demineralized water (pH=±7) for the next 23 hours to mimic the pH of the intestine. Sink conditions were maintained during the experiments. The bath temperature was kept constant at 37±0.5 °C. The rotational speed of the baskets was set to 100 rpm. Samples (5 ml) were withdrawn at 5, 10, 15, 20, 30, 45 and 60 minutes for HCT,

and at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24 hours for MPT. They were spectrophotometrically assessed for metoprolol tartrate and hydrochlorothiazide concentration at a wavelength of 222 nm and 272 nm, respectively, using a Perkin-Elmer Lambda 12 UV-VIS double beam spectrophotometer (Zaventem, Belgium). Since the drugs showed interference at their respective wavelengths the release of the MPT was determined using a placebo coat and vice versa.

2.5. Solid state characterization

2.5.1. Differential scanning calorimetry

Differential scanning calorimetry was used to study the crystallinity of the drug in the matrix. The thermal behavior of the individual components, physical mixtures and extrudates was evaluated using a Q2000 DSC (TA Instruments, Leatherhead, UK). The system was equipped with a refrigerated cooling system. Samples (5-10 mg) were accurately weighed and hermetically sealed in aluminum pans. They were cooled to -50 °C followed by heating to 150 °C at a linear heating rate of 10 °C/min.

2.5.2. Raman analysis

Raman spectroscopy was applied to detect changes in solid-state properties of the model drugs. Raman spectra of drug, polymer, physical mixtures and extrudates were collected with a Raman RXn1 spectrometer (Kaiser Optical Systems, Ann Arbor, USA) equipped with an air-cooled CCD detector. The laser wavelength was the 785 nm line from a

785 nm Invictus NIR diode laser. The spectra were recorded at a resolution of 4cm^{-1} and an exposure time of 10 s, using a laser power of 400 mW. Data collection and data transfer were automated using the HoloGRAMSTM data collection software, the HoloREACTTM reaction analysis and profiling software, the Matlab software (version 7.1, The MathWorks Inc., Natick, MA) and SIMCA-P^{+} (version 12.0.1.0, Umetrics, Umeå, Sweden) was used for data analysis . The analyzed spectral region was 0 – 1800 cm^{-1}, since this region contained all useful drug and polymer information.

2.5.3. X-ray diffraction

X-ray diffraction was performed to investigate the crystallinity of the drug in the mini-matrices. X-ray patterns of drug, polymer, physical mixtures, coat and core material of the co-extrudates were obtained using a D5000 Cu Kα Diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany). The angular range (2θ) varied from 10 to 60° (step width = 0.02°, counting time = 1 s/step).

2.6. SEM

Scanning electron microscopy was used to study the interface between both layers and to compare the surface of the mini-matrices before and after administration to dogs. Tablets were coated with platinum by means of a sputter coater (Auto Fine Coater, JFC-1300, Jeol, Tokyo, Japan). Photomicrographs were taken with a scanning electron microscope (Jeol JSM 5600 LV, Jeol, Tokyo, Japan).

2.7. Adhesion

The adhesion between core and coat was measured using a tensile tester (LF Plus, Lloyd Instruments, West Sussex, UK). The capacity of the load cell was 100 N. The experimental setup is shown in Fig. 3. The co-extrudates were cut into slices of 1 mm height prior to testing. The slices were placed on a holding device with a central opening of 3.3 mm. They were positioned in such a way that only the coat was supported by the device, while the core was placed over the central opening. Using a probe (diameter: 2 mm, preload: 1 N, extension rate: 100 mm/min), which applied a downward force on the core, the maximum force needed to separate the core from the coat was measured. The test was done in 20-fold.

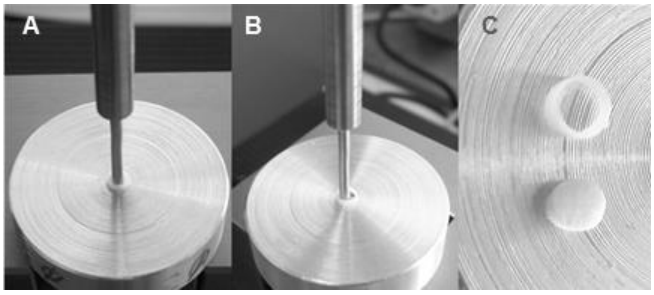


Figure 3. Experimental setup of the adhesion test: positioning the probe (above core) (A), applying a load (B), separation of core and coat (C).

2.8. In vivo study

2.8.1. Subjects and study design

A group of six male mixed-breed dogs (weight 23.5–39.0 kg) was used in this study. An oral dose of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide was administered

to the dogs, either as experimental co-extruded mini-matrices or as reference formulation (Zok-Zid®, Pfizer, Brussels, Belgium). The core of the co-extrudate was formulated with 45% MPT, 54% polycaprolactone and 1% colloidal silicium dioxide, while the coat contained 10% HCT, 45% PEO and 45% PEG.

The mini-matrices of the experimental formulation were filled in hard-gelatin capsules, whereas the reference formulation was given as a tablet. The formulations were administered in randomized order with a wash-out period of at least 1 week between sessions. On the experimental day the dogs were fasted for 12 h prior to the study period, although water was available. Before administration of a formulation, a blank blood sample was taken. The formulations were orally administered with 20 ml water. The blood samples were collected in dry heparinized tubes at fixed time points: 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after intake of the formulations. No food was administered to the dogs during the entire test period. Within 1 h after collection, blood was centrifuged for 10 min at 1500g. The plasma was separated and kept frozen at -20 °C until analysis.

2.8.2. Metoprolol tartrate and hydrochlorothiazide assay

Metoprolol tartrate and hydrochlorothiazide plasma concentrations were determined using two different HPLC methods. Since no interfering peaks of MPT and HCT were observed during the determination of HCT and MPT, respectively, the specificity of the methods was secured. For MPT, a validated HPLC-fluorescence method was used [9]. Plasma samples (300 µl) were thoroughly mixed with 20 µl bisoprolol (7.5 µg/ml bisoprolol in water, as internal standard) and 680 µl PBS. A solid phase extraction (SPE) procedure was used to extract metoprolol tartrate. The Oasis® HLB extraction cartridges (1 cc 30 mg)

(Waters, Etten-Leur, the Netherlands) were first conditioned by rinsing consecutively with methanol (1 ml), water (1 ml) and phosphate-buffered saline (PBS) (1 ml). Then, the prepared plasma samples were loaded on the columns and extracted using a 10-port vacuum manifold. In a next step, the columns were washed with water (1 ml) and the analytes were then eluted with methanol (1 ml). The eluates were evaporated to dryness under N_2. After reconstitution in 150 µl water, 20 µl was injected on the column. The metoprolol tartrate plasma concentrations were determined via a calibration curve. The HPLC equipment (Merck-Hitachi, Darmstadt, Germany) consisted of a solvent pump set at a constant flow rate of 1 ml/min, an autosampler, a LiChrospher® 100 CN (5 µm) column (250 x 4 mm) and precolumn (4 x 4 mm) and a fluorescence detector set at an excitation wavelength of 275 nm and emission wavelength of 300 nm. The mobile phase consisted of acetonitrile/sodium dihydrogen orthophosphate buffer (2 M)/water (4/0.5/95.5, v/v/v). The mixture was adjusted to pH 3.0 with phosphoric acid. An automatic integration system (software D-7000 Multi-Manager) was used to collect and process the signals.

Hydrochlorothiazide was determined using a validated HPLC-UV method [10]. The drug was extracted from the plasma samples by means of liquid-liquid extraction. Plasma samples (500 µl) were thoroughly mixed with 100 µl of internal standard solution (1.25 µg/ml hydroflumethiazide in water). After the addition of methyl tert.-butylether (5 ml), the samples were vortexed (2 min) and centrifugated (5 min at 1500g). 4.5 ml of the organic phase was removed into a new test tube and evaporated to dryness under N_2. After reconstitution of the residue in 200 µl of distilled water, 3 ml toluene was added. The mixture was further vortexed (2 min) and after 10 min of centrifugation (at 1500g), the toluene layer was removed. Once again 3 ml toluene was added and the extraction procedure was repeated. After removing the organic phase, the mixture was dried under a N_2-stream at 40 °C. After reconstitution in 200

µl of mobile phase, 100 µl of this solution was injected into the HPLC system. The HPLC equipment (Merck-Hitachi, Darmstadt, Germany) consisted of a solvent pump (set at a constant flow rate of 0.8 ml/min), an automatic injection system, a reversed-phase C-18 column (LiChrospher® 100 RP-18 (5 µm)) (250 x 4 mm) and precolumn (4 x 4 mm) (both conditioned at 40 °C) and a variable wavelength UV/VIS detector set to 272 nm. The mobile phase was composed of phosphate buffer pH 7/tetrahydrofurane/acetonitrile (85/10/5; v/v/v). An automatic integration system (software D-7000 Multi-Manager) was used for integration of the chromatographic peaks.

2.8.3. Data analysis

The peak plasma concentration (C_{max}), the extent of absorption (AUC_{0-12h}) and the time to reach C_{max} (T_{max}) were calculated. The relative bioavailability (F_{rel}, expressed in %) was calculated as the ratio of AUC_{0-12h} between a test formulation and the reference formulation. Data were statistically analysed using SPSS 17 (SPSS, Chicago, USA). To compare the effects of the different treatments, a paired samples t-test was performed with a significance level of $\alpha = 0.05$.

3. Results and discussion

A successful co-extrusion process requires that both polymer melts can be processed at similar temperatures because they need to flow through the co-extrusion die under the same temperature conditions. Pure polymers and polymer-drug mixtures (in different ratios) were hot-melt extruded and evaluated for processability and macroscopic properties (surface smoothness, die swell). The appropriate extrusion temperature range for each of the polymers

was established in order to investigate which polymers were combinable in terms of extrusion temperature. Several thermoplastic polymers were assessed for their utility in co-extrusion as immediate release coat (Soluplus®, Eudragit® E PO, Polyox® WSR N10 (PEO), Kollidon® VA) and sustained release core (CAPA® 6506, Eudragit® RS PO, Ethocel® std 10, Kollidon® SR). By adjusting the extrusion parameters all selected polymers were processable via hot-melt extrusion and yielded smooth extrudates, except for Kollidon® VA and SR. Extrusion around 160 and 140 °C of Kollidon® VA and SR, respectively, yielded extrudates with an irregular shape. Pure Soluplus® was extrudable in a temperature range between 140 and 180 °C, while the addition of 10% PLUR lowered the extrusion torque, which made it possible to lower the extrusion temperature to 110 °C. Extrudates with a drug load up to 5% were transparent, while the ones containing 10% HCT were slightly opaque. For the processing of pure Eudragit® E PO a temperature of at least 130 °C was required, but the addition of 5 and 10% of triethyl citrate lowered the extrusion temperature to 120 and 110 °C, respectively. Extrudates composed of only the polymer and triethyl citrate were transparent, whereas the ones containing HCT were all white. The minimal extrusion temperature for PEO was 75 °C, but extrusion at higher temperatures (130 °C) was also possible. At 75 °C, all PEO/HCT extrudates were brigthly yellow and transparent. Nevertheless, they became opaque after cooling down to room temperature due to the recrystallization of the PEO. The addition of 50% of PEG 4000 to PEO resulted in lower torque values. Polycaprolactone was already processable at a temperature of 70 °C without the use of any plasticizer, whereas the extrusion of Eudragit® RS PO without plasticizer was impossible. The temperature required to extrude pure Eudragit® RS PO approached the degradation temperature of the polymer (140-150 °C). Hence the addition of 10% triethyl citrate was required to reduce the extrusion temperature to 120 °C. Polycaprolactone yielded white extrudates at all tested MPT concentrations since the extrusion temperature was far below the melting point of MPT, whereas using Eudragit® RS

PO as a carrier the extrudates were all transparent. Extrusion of ethylcellulose also required a plasticizer. The addition of 20% dibutyl sebacate allowed extrusion at 120 °C. The obtained extrudates were not transparent. These above mentioned data showed that some polymers could be extruded at relatively low temperatures (polycaprolactone, PEO), while others required higher temperatures (Soluplus®, Eudragit® E & RS PO, ethylcellulose, PEO).

The polymers that yielded good quality extrudates were further tested for in vitro drug release. The dissolution profiles are shown in Fig. 4. The release of HCT from Eudragit® E PO was already complete in 30 minutes, whereas it took 1 hour for HCT to be released from PEO. In contact with the acidic dissolution medium, Eudragit® E PO became ionized and dissolved in the medium hereby releasing the drug. The solubility of PEO was pH independent and it took more time for this coat to dissolve. Nevertheless, the addition of 50% polyethylene glycol 4000 (PEG) to PEO resulted in a considerable increase in release rate (100% release in <30 min). HCT release from Soluplus® was incomplete after 1 h. Very low drug concentrations (2,5% HCT) were released relatively fast from Soluplus®, but with an increasing drug load (5% or more) the release rate dropped considerably (only 20% release after 1 h). Whereas the extrudates with 2,5% HCT had completely dissolved after 1 h, the ones with 5% HCT were swollen. Polycaprolactone and ethylcellulose provided sustained release of MPT. The extent of the release sustaining effect from these matrices depended on drug load: a lower drug concentration resulted in a slower release rate. Eudragit® RS showed a limited release retarding effect and it was impossible to sustain MPT release over 24 h with this polymer.

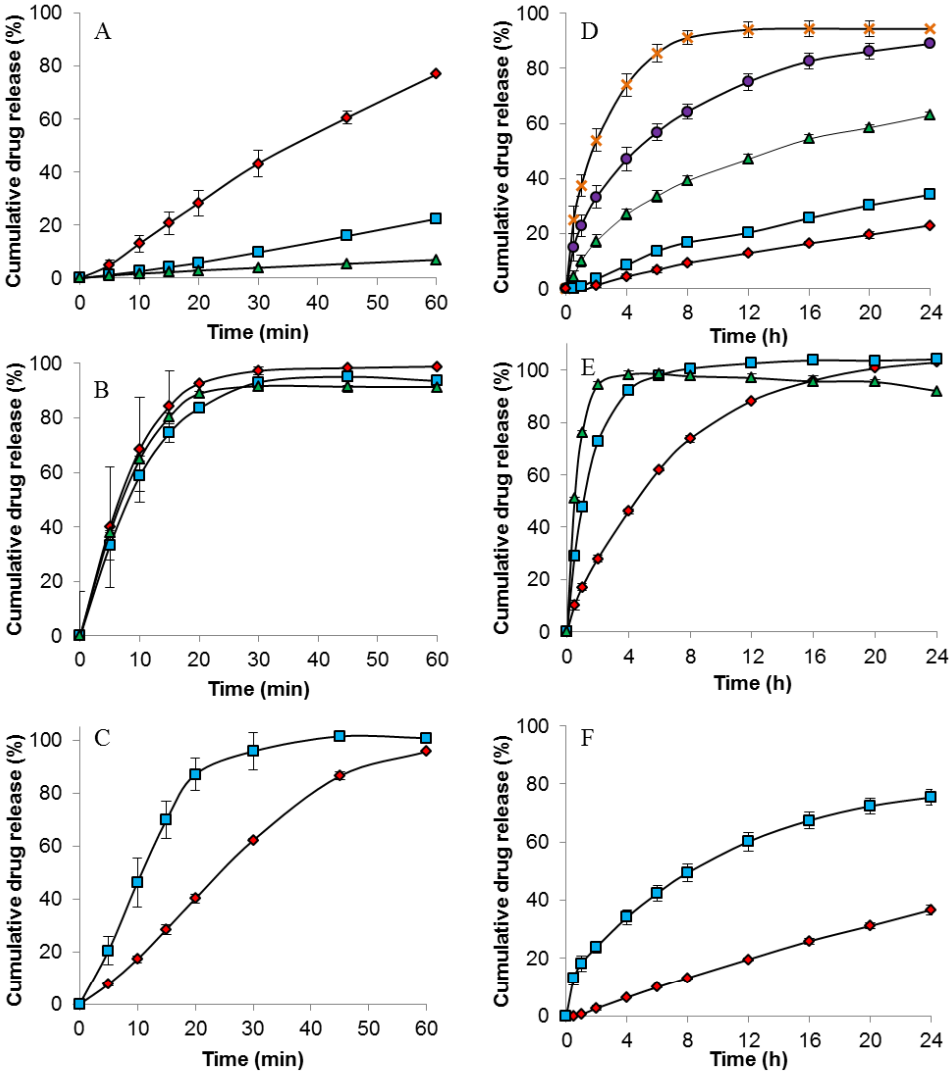


Figure 4. Influence of drug load on the release of HCT (A-C) and MPT (D-F) from different polymers after extrusion. Mean dissolution profiles (±S.D.) of formulations composed of A: Soluplus® and (♦) 2.5%, (■) 5%, (▲) 10% HCT; B: Eudragit® E PO and (♦) 10%, (■) 20%, (▲) 30% HCT; C: Polyox®, 10% HCT and (♦) 0%, (■) 50% PEG 4000; D: Polycaprolactone and (♦) 20%, (■) 30%, (▲) 35%, (●) 40%, (×) 50% MPT; E: Eudragit® RS PO and (♦) 10%, (■) 20%, (▲) 30% MPT; F: Ethylcellulose and (♦) 20%, (■) 30% MPT.

Taking into account the processability and the in vitro drug release data four polymers were selected: Eudragit® E PO and PEO (with 50% PEG) for immediate release, and polycaprolactone and ethylcellulose for sustained release. Based on the extrusion temperature data, two polymer combinations were considered for co-extrusion: ethylcellulose core with Eudragit® E PO coat (both extrudable around 120 °C) and polycaprolactone core with PEO coat (both extrudable around 70 °C). The polycaprolactone/PEO combination was finally selected for co-extrusion trials as these polymers could be processed at a low extrusion temperature (70 °C).

All co-extruded formulations consisted of a polycaprolactone-core and a PEO/PEG-coat but contained different drug concentrations of drug (10, 20, 30, 35, 40, 45, 50% MPT in the core and 10, 20, 30% HCT in the coat). Due to the poor flow properties of the polycaprolactone-MPT mixtures in the feeder 1% (w/w) colloidal silicium dioxide was added to the formulation. Polycaprolactone, a biodegradable polyester, possesses excellent thermoplastic properties and has a melting point of 58-60 °C. Formulations composed of unplasticized polycaprolactone were hot-melt extruded at temperatures between 70 and 80 °C. Below 70 °C, the melt viscosity was too high resulting in a high torque and an inadequate flow from the extruder, while above 80 °C thinner extrudates with a rough surface were obtained.

PEO (100,000 g/mol), a semi-crystalline non-ionic hydrophilic polymer which has previously been studied for hot-melt applications [11], has a melting point of 65-70 °C, whereas the lower molecular weight PEG (4,000 g/mol) exhibits a melting point of 50-58 °C. The ratio PEO/PEG in all coating formulations was 1/1. Preliminary studies indicated that at higher PEG content, the drug release rate increased while the extrudates tended to be more brittle. The addition of 50% (w/w) PEG resulted in a 100% drug release in less than 60 min

and good co-extrudate quality. The different formulations were easily processed at an extrusion temperature of 70 °C. The layer thickness was uniform, as confirmed with a marking gauge. No surface defects were detected and the extrudates having a smooth surface were cut into high quality mini-tablets.

After extrusion, the core and coat of the co-extrudates were physico-chemically characterized. Since pure metoprolol tartrate is crystalline, its Raman spectrum contained narrow, well defined peaks. No significant peak broadening was observed for the core compared to the pure drug, indicating crystalline MPT in the core of the co-extrudates (Fig. 5). The X-ray diffractogram of MPT showed distinct crystalline peaks at 2θ of 19.4 and 23.1 and a series of smaller peaks at 10.6, 15.8, 20.4 and 24.0 (Fig. 6). Those peaks were also present in the diffractogram of the core, confirming the crystalline state of MPT. The DSC thermogram of MPT (Fig. 7) showed a melting peak at 124.25 °C, the enthalpy of fusion indicated that the entire drug fraction remained crystalline. According to literature [12], the amorphous content of polycaprolactone remains relatively unchanged after hot-melt extrusion regardless of cooling rate. A higher amorphous content typically results in higher drug solubility, as drug molecules are soluble in the amorphous regions of the polymer. In this case, the extrusion process did not cause a considerable decrease in crystalline fraction of polycaprolactone as indicated by the enthalpy of fusion (Fig. 7).

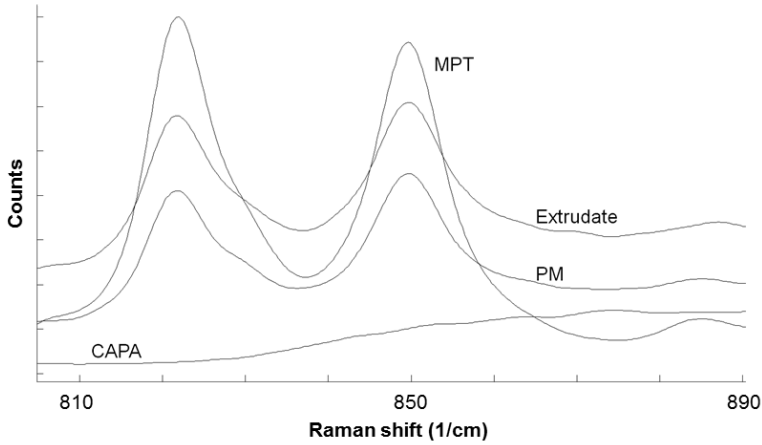


Figure 5. Raman spectra of MPT, polycaprolactone (CAPA), core of co-extruded tablet composed of 40/1/59% MPT/CSD/polycaprolactone, physical mixture (PM).

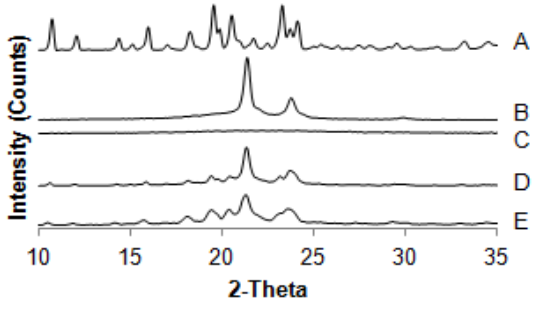


Figure 6. X-ray diffraction pattern of (A) MPT, (B) polycaprolactone, (C) colloidal silicium dioxide, (D) physical mixture and (E) extrudate composed of 40/1/59% MPT/CSD/polycaprolactone.

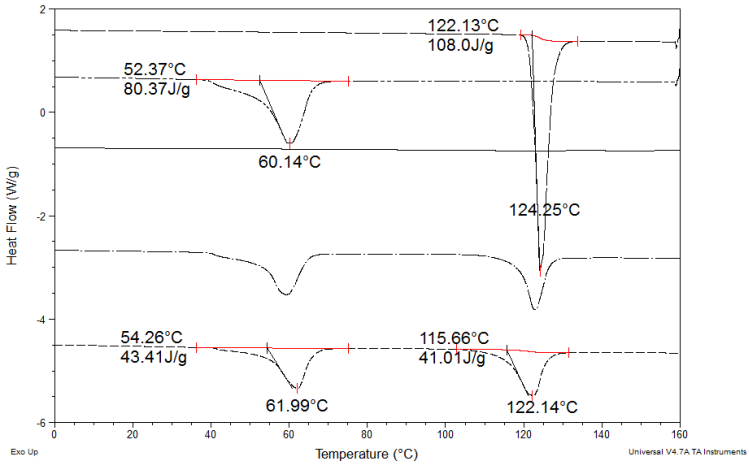


Figure 7. Differential scanning calorimetry profiles. From the top to the bottom: metoprolol tartrate, polycaprolactone, colloidal silicium dioxide, physical mixture and core of co-extruded tablet composed of 40/1/59% MPT/CSD/polycaprolactone.

The diffraction pattern of pure HCT revealed crystalline peaks which were also detected in the physical mixture (Fig. 8). The absence of these peaks in the diffractogram of the coat revealed that there were no drug crystals left in the coat of the co-extrudate. Since the melting point of HCT (274 °C) was never reached during the extrusion process, this indicated that HCT had dissolved in the PEO/PEG-matrix. These results were confirmed with Raman spectroscopy. Compared to the Raman spectrum of pure HCT, the HCT peaks in the extrudate were broader and flatter, demonstrating loss of crystallinity (Fig. 9). Other investigators already described the solubilization of drugs in PEO during extrusion [11, 13], which could be useful for solubility enhancement. After 12 months of storage at ambient conditions (25 °C), the Raman spectra, X-ray diffractograms and DSC thermograms remained unchanged.

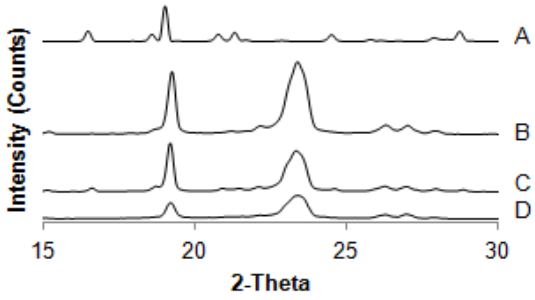


Figure 8. X-ray diffraction pattern of (A) HCT, (B) PEO/PEG (1/1), (C) physical mixture and (D) extrudate composed of 10/45/45% HCT/PEO/PEG.

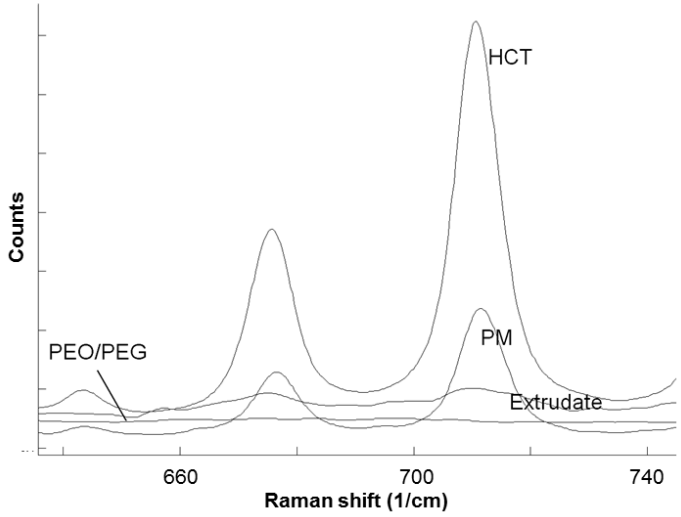


Figure 9. Raman spectra of HCT, PEO/PEG (1/1), physical mixture (PM) and extrudate composed of 10/45/45% HCT/PEO/PEG.

The SEM picture (Fig. 10A) clearly showed the two layers in the mini-tablets and indicated that core and coat were well attached to each other. The adhesion force between both layers was measured. For the formulation that contained 45% (w/w) MPT in the core and 10% (w/w) HCT in the coat the average force needed to separate core from coat was 10.5 ± 3.1 N.

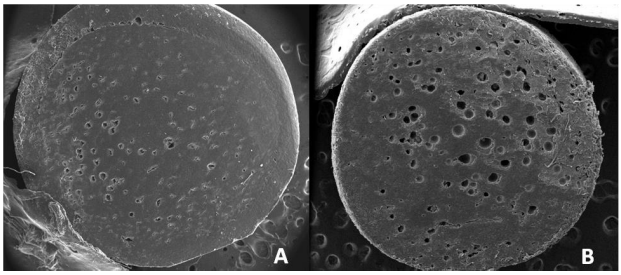


Figure 10. SEM images of co-extrudate with a core composed of 45/55% MPT/polycaprolactone and a coat composed of 10/45/45% HCT/PEO/PEG. (A) Immediately after production (magnification 60x), (B) After faecal recovery (70x).

Immediate and sustained drug release was observed from the coat and core respectively (Fig. 11 & 12). Fig. 11 shows the influence of drug load on the release of HCT from the coat. Formulations with drug loads up to 20% (w/w) provided a release of 100% in 30 min. Although HCT was completely dissolved in formulations with a drug load of 30% (w/w), a slower drug release was observed (100% released in 1 h) due to the slower dissolution of the coat compared to formulations containing a higher PEG/PEO fraction. The dissolution rate of MPT from the core is controlled by the drug/carrier ratio (Fig. 12): the release rate increased at higher MPT content in the core of the formulation. At higher MPT

concentration (45 and 50%) full drug release was observed after 24 h. There was no significant effect of the extrusion temperature on the release rate from the core when increasing the temperature from 70 to 80 °C. However, an extrusion temperature of 90 °C resulted in a significant faster release, which (after visual inspection) could be attributed to the smaller diameter (and as a consequence higher surface area) of these samples in comparison to the formulations extruded below 90 °C. The drug release characteristics of the coat were not influenced by the extrusion temperature. Based on the dissolution results, a formulation containing 45% MPT in the core and 10% HCT in the coat was selected for in vivo testing. The MPT/HCT ratio in this system was similar to the reference formulation (Zok-Zid®). After 12 months storage at ambient conditions the release profile of the experimental formulation remained unaltered. Considering also the solid state, this indicated that the formulation was stable for at least 12 months at ambient conditions.

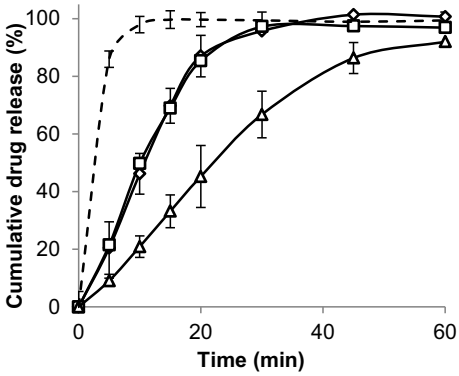


Figure 11. Influence of drug load on HCT release from the coat of co-extruded mini-matrices. The coat was composed of PEO/PEG (1/1) and variable HCT concentrations: (◊) 10%, (□) 20%, (Δ) 30%, (---) reference formulation (Zok-Zid®).

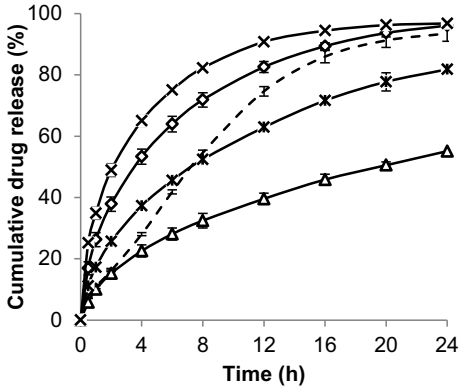


Figure 12. Influence of drug load on MPT release from the core of co-extruded mini-matrices. The core was composed of polycaprolactone and variable MPT concentrations: (Δ) 30%, (✳) 40%, (◊) 45%, (✕) 50%, (---) reference formulation (Zok-Zid®).

Fig. 13 shows the mean plasma concentration-time profiles after oral administration of 200 mg MPT and 25 mg HCT as experimental mini-matrices and Zok-Zid® (2 tablets). Although Zok-Zid® is administered as a tablet, in contact with fluids it immediately disintegrated into pellets, creating a multiparticulate system: hydroxypropyl cellulose-based pellets containing HCT and pellets composed of ethylcellulose and MPT. According to the dissolution data, both test and reference formulation provided immediate release (less than 30 min) of HCT and sustained MPT release over 24 h. However, the in vitro MPT release from the reference formulation was considerably slower, which was also reflected in the in vivo behaviour. The pharmacokinetic parameters of MPT and HCT are reported in Table 2.

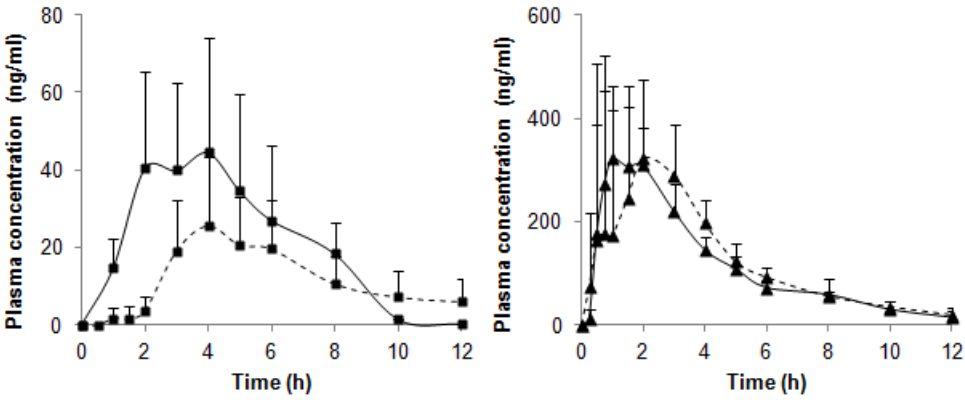


Figure 13. Mean MPT (■) and HCT (▲) plasma concentration-time profiles (± SD, n = 6) after oral administration of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide to dogs: Zok-Zid® (2 tablets) (dotted line), experimental co-extruded mini-matrices with a core consisting of 45% (w/w) MPT and a coat consisting of 10% (w/w) HCT (full line).

Table 2. Mean pharmacokinetic parameters (±S.D.) of MPT and HCT after oral administration of 200 mg metoprolol tartrate and 25 mg hydrochlorothiazide to dogs (n=6), as experimental co-extruded mini-matrices (with a core consisting of 45% (w/w) MPT and a coat consisting of 10% (w/w) HCT) or as reference formulation (Zok-Zid®).

	MPT			HCT		
	C_{max} (ng/ml)	T_{max} (h)	AUC (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)	AUC (ng.h/ml)
Exp	73.6 ± 46.9	2.8 ± 0.7	345.2 ± 257.9	371.6 ± 126.0	1.6 ± 0.5	1353.8 ± 320.3
Ref	23.5 ± 19.7	4.2 ± 1.2	117.1 ± 95.6	459.9 ± 227.0	2.5 ± 1.1	1479.3 ± 346.5

Fig. 14 represents the AUC values of each dog separately after administration of the experimental and the reference formulation. The bioavailability data of HCT (C_{max}, T_{max} & AUC) of both formulations were comparable, without a statistical significant difference between the test and reference formulations ($p > 0.05$). Although there was a trend that the MPT bioavailability of the test formulation for each dog was higher than the reference (Fig. 14A), the difference was statistically not significant. Besides that, the variability in AUC values for MPT was higher after administration of the experimental formulation than for the reference formulation. While the coat of the co-extrudates dissolved during gastro-intestinal passage, intact cores (which still contained 6.6 ± 0.4% of the initial MPT dose) were recovered from the faeces of the dogs. As no swelling or erosion was observed while the pore size increased (Fig. 10B), release from the caprolactone core was diffusion-controlled.

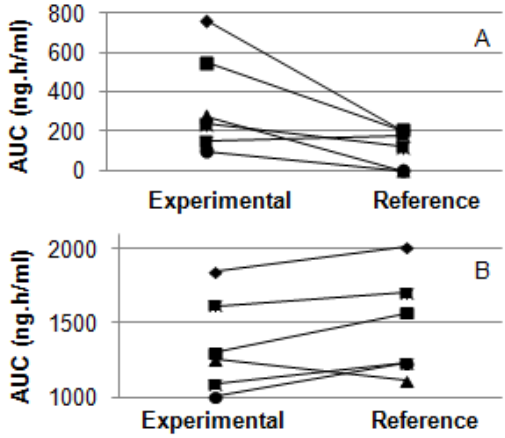


Figure 14. Comparison of AUC level of MPT (A) and HCT (B) after oral administration of experimental co-extruded and reference formulation to dogs.

4. Conclusions

This study showed that co-extrusion seems a promising technique to produce fixed-dose combination mini-matrices. A core/coat dosage form was developed, wherein the core and coat exhibited sustained and immediate release properties, using a combination of polycaprolactone (core) and PEO/PEG (coat). There was good adhesion between the two layers. The solid state characterization revealed that MPT maintained its crystalline form whereas HCT was molecularly dispersed in the coat of the co-extrudates. The differences in in vivo performance between a reference formulation and the test formulation were statistically not significant.

Acknowledgements

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CHAPTER 3

Co-extrusion as manufacturing technique for multilayer mini-matrices with dual drug release

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1. Introduction

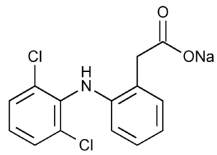
Extended release drug delivery systems improve the life quality of chronic and poly-medicated patients by reducing their daily intake of dosage forms, thereby improving patient compliance. Prolonged release dosage forms have a greater duration of action than conventional dosage forms, but the onset of action is often delayed. The aim of the present study was to design by means of co-extrusion a solid dosage form for oral application which provides dual release of a single drug: a layer with immediate drug release to ensure a fast onset of action, in combination with a sustained release layer to sustain the activity of the drug over a longer period. In this study, diclofenac sodium (DS) was incorporated as model drug in the co-extruded formulation. DS is a non-steroidal anti-inflammatory drug (NSAID) used in the long-term treatment of inflammation and painful conditions of rheumatic and non-rheumatic origin. It is sparingly soluble in water, rapidly absorbed in the gastrointestinal tract and exhibits a plasma half-life of about 1 to 2 h. Due to its biopharmaceutical and pharmacological properties, sustained release of DS is desirable. In addition, it has been shown that a non-enteric coated NSAID formulation has pharmacokinetic advantages (less variation in e.g. lag-time and time to peak plasma concentration) over an enteric coated formulation [1]. The aim of the present study was to design a core/coat dosage form via co-extrusion to obtain a dual release rate of DS, the inner core providing sustained drug release (SR) and the outer (non-enteric) coat immediate drug release (IR).

2. Materials and methods

2.1. Materials

The following polymers were used during the polymer screening experiments: Kollidon® VA and SR, Soluplus® (BASF, Ludwigshafen, Germany), Eudragit® E and RS PO (Evonik, Darmstadt, Germany), Ethocel® std 10 (ethylcellulose, DOW Chemical Company, Midland, USA), SentryTM Polyox® WSR N10 (polyethylene oxide, PEO 100,000 g/mol, Colorcon, Dartford Kent, United Kingdom), polyethylene glycol (PEG 4000 g/mol, Fagron, Waregem, Belgium) and CAPA® 6506 (polycaprolactone 50,000 g/mol, Perstorp, Warrington, United Kingdom). Dibutylsebacate (DBS), triethyl citrate (TEC) and Pluronic® F-68 (PLUR) (Sigma–Aldrich, Steinheim, Germany) were used as plasticizers for Ethocel® and Soluplus®, respectively. Colloidal silicon dioxide (Fagron, Waregem, Belgium) was added to CAPA® to improve the flow properties. Diclofenac sodium (DS, Fagron, Waregem, Belgium) was incorporated as model drug. Its relevant physico-chemical properties are listed in Table 1. All other chemicals were of analytical grade.

Table 1. Physico-chemical properties of diclofenac sodium.

Properties		**Structural formula**
Melting point	284 °C	
Degradation temperature	270-390 °C [2]	
Solubility in water	sparingly soluble [3]	
pKa	4	

2.2. Polymer selection

For the selection procedure several thermoplastic polymers were hot-melt extruded and evaluated for processability, macroscopic properties (visual inspection of surface, die swell quantification using marking gauge) and in vitro drug release. Polymers were mixed with different amounts (10-60%) of DS and hot-melt extruded using a co-rotating, fully intermeshing twin screw extruder (Prism Eurolab 16, ThermoFisher Scientific, Germany). The extrusion temperature varied according to the polymer, but all five heating segments of the extruder were set at the same temperature, except for the first heating zone which was set at 70 °C to avoid sticking of the powder in the feed section. A strand die with a diameter of 3 mm was mounted at the end of the extruder. The machine was equipped with a gravimetric powder feeder (Brabender, Duisburg, Germany). The screw speed and feed rate were kept constant at 60 rpm and 150 g/h.

2.3. Production of co-extrudates

Polymer and drug were premixed in a tumbling mixer (Turbula® T2A, W.A. Bachofen, Basel, Switzerland) for 20 min. Co-extrusion was performed using two co-rotating, fully intermeshing twin screw extruders (Prism Eurolab 16, ThermoFisher Scientific, Germany) having a length-to-diameter ratio of 25/1. The two pairs of co-rotating screws each consisted of three mixing sections and a densification zone. A multimanifold co-extrusion die (Guill, West Warwick, USA) was connected to both extruders. In the die, the two melts were combined to form two concentric layers, a core and a coat. Table 2 shows the composition of the co-extruded formulations as well as the extrusion conditions used for each formulation. Formulation 1 (F_1) was composed of an ethylcellulose-core in combination with a Soluplus®-

coat. Formulations 2 to 12 (F_2-F_{12}) consisted of a polycaprolactone-core and a PEO/PEG-coat loaded with different DS concentrations. Formulations 2 to 4 (F_2-F_4) were used in the in vivo study, whereas formulations 5 to 12 (F_5-F_{12}) were used to investigate the influence of drug load and extrusion temperature on core/coat adhesion. All five heating segments of both extruders as well as the die were set at the same temperature, except for the first heating zone which was set at 70 °C to avoid sticking of the powder in the feed section. The premixes were fed into the extruders using loss-in-weight powder feeders (Brabender Flexwall®, Duisburg, Germany). The die dimensions varied (core diameter: 2/3 mm; coat thickness: 0.5/1 mm) (Fig. 1b) though the total die diameter was 4 mm. After cooling down to room temperature, the cylindrical co-extrudates were manually cut into mini-matrices of 2 mm length.

Table 2. Composition and extrusion parameters of co-extruded formulations.

	DS concentration (%)		**T_{extr} (°C)**	**Feed rate (g/h)**		**Screw speed (rpm)**		**Die dimensions (mm)**		**DS ratio core:coat**
	core	**coat**		**core**	**coat**	**core**	**coat**	**core**	**coat**	
F_1	60	25	140	200	200	60	60	3	0.5	70:30
F_2	50	22.5	95	150	150	60	60	3	0.5	70:30
F_3	50	50	95	200	150	60	60	3	0.5	57:43
F_4	50	50	120	200	600	80	80	2	1	25:75
F_5	0	0	70	200	150	60	60	3	0.5	-
F_6	0	0	95	200	150	60	60	3	0.5	-
F_7	0	0	120	200	150	60	60	3	0.5	-
F_8	30	30	70	200	150	60	60	3	0.5	57:43
F_9	30	30	95	200	150	60	60	3	0.5	57:43
F_{10}	30	30	120	200	150	60	60	3	0.5	57:43
F_{11}	50	50	95	200	150	60	60	3	0.5	57:43
F_{12}	50	50	120	200	150	60	60	3	0.5	57:43

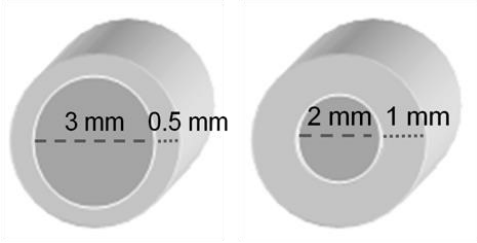


Figure 1b. Different dimensions of co-extrusion die.

2.4. X-ray diffraction

X-ray diffraction was performed to investigate the crystallinity of the drug in the mini-matrices. X-ray patterns of drug, polymer, physical mixtures, coat and core material of the co-extrudates were obtained using a D5000 Cu Kα Diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany). The angular range (2θ) varied from 10° to 60° (step width = 0.02°, counting time = 1 s/step).

2.5. Differential scanning calorimetry

Differential scanning calorimetry was used to study the crystallinity of DS in the formulation. The thermal behavior of the individual components, physical mixtures and extrudates was evaluated using a Q2000 DSC (TA Instruments, Leatherhead, UK). The system was equipped with a refrigerated cooling system. Samples (5-10 mg) were accurately weighed and hermetically sealed in aluminum pans. They were cooled to 0 °C followed by heating to 300 °C at a linear heating rate of 10 °C/min.

2.6. Adhesion

The adhesion between core and coat was measured using a tensile tester (LF Plus, Lloyd Instruments, West Sussex, UK). The capacity of the load cell was 100 N. The co-extrudates were cut into slices of 1 mm height prior to testing. The slices were placed on a holding device with a central opening of 3.3 mm. They were positioned in such a way that only the coat was supported by the device, while the core was placed over the central opening. Using a probe (diameter: 2 mm, preload: 1 N, extension rate: 100 mm/min), which applied a downward force on the core, the maximum force needed to separate the core from the coat was measured. The test was done in 20-fold.

2.7. SEM

Scanning electron microscopy was used to study the interface between both layers. Co-extrudates were sliced in order to visualize the cross section. Besides coat and core were separated using a tensile tester (see section 2.6) and the interfacial contact surfaces of core and coat were investigated. Samples were coated with platinum by means of a sputter coater (Auto Fine Coater, JFC-1300, Jeol, Tokyo, Japan). Photomicrographs were taken with a scanning electron microscope (Jeol JSM 5600 LV, Jeol, Tokyo, Japan).

2.8. In vitro drug release

Dissolution studies were performed using USP apparatus 1 (baskets). The equipment consisted of a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, NJ, USA). The vessels were filled with 900 ml dissolution

medium. Distilled water (900 ml) was used as dissolution medium. Sink conditions were maintained during the experiments. The bath temperature was kept constant at 37 ± 0.5 °C. The rotational speed of the baskets was set to 100 rpm. Samples (5 ml) were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min for the coat and at 0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24 h for the core. They were analyzed spectrophotometrically for DS at 276 nm by means of a Perkin-Elmer Lambda 12 UV-VIS double beam spectrophotometer (Zaventem, Belgium).

2.9. In vivo study

A group of six male mixed-breed dogs (weight 23.5–39.0 kg) was used in this study. An oral dose of 100 mg diclofenac sodium was administered to the dogs, either as experimental co-extruded mini-matrices or as reference formulation. Three experimental formulations (F_2, F_3 and F_4, which differed in DS content in the core and coat, Table 2) were selected for the in vivo study. Motifene® (Daiichi-Sankyo) was chosen as a multiparticulate reference formulation.

The mini-matrices of the experimental formulations and the Motifene® pellets were filled in hard-gelatin capsules. The formulations were administered in randomized order with a wash-out period of at least 1 week between sessions. On the experimental day the dogs were fasted for 12 h prior to the study period, although water was available. Before administration of a formulation, a blank blood sample was taken. The formulations were orally administered with 20 ml water. The blood samples were collected in dry heparinized tubes at fixed time points: 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after intake of the formulations. No food was administered to the dogs during the entire test period. Within 1 h after collection, blood

was centrifuged for 10 min at 1500g. The plasma was separated and kept frozen at -20 °C until analysis.

The determination of diclofenac plasma concentrations was based on a validated HPLC-fluorescence method [4]. Plasma samples (500 µl) were thoroughly mixed with 50 µl flurbiprofen (50 µg/ml flurbiprofen in methanol, as internal standard) and 450 µl phosphoric acid (1 M). A solid phase extraction (SPE) procedure was used to extract diclofenac. The Oasis® HLB extraction cartridges (1 cc 30 mg) (Waters, Etten-Leur, the Netherlands) were first conditioned by rinsing consecutively with methanol (1 ml) and water (1 ml). Then, the prepared plasma samples were loaded onto the extraction cartridges. A wash step was performed using 1 ml of 5% aqueous methanol and the samples were eluted using 1 ml of methanol. The eluates were evaporated to dryness under N_2. The residue was reconstituted in 150 µl of mobile phase and 100 µl was injected on the column. The diclofenac plasma concentrations were determined via a calibration curve. The HPLC equipment (Merck-Hitachi, Darmstadt, Germany) consisted of a solvent pump (set at a constant flow rate of 1 ml/min), an automatic injection system, a reversed-phase C-18 column (LiChrospher® 100 RP-18 (5 µm)) (250 x 4 mm) and precolumn (4 x 4 mm) and a UV detector set to 280 nm. The mobile phase was composed of methanol/water (adjusted to pH 3.3 with H3PO4) (63/37; v/v). An automatic integration system (software D-7000 Multi-Manager) was used for integration of the chromatographic peaks.

The peak plasma concentrations (C_{max1}, C_{max2}), the extent of absorption ($AUC_{0\text{-}12h}$) and the time to reach C_{max} (T_{max1}, T_{max2}) were calculated. Data were statistically analyzed using SPSS 17 (SPSS, Chicago, USA). The effect of the formulation on the bioavailability was assessed by repeated-measures ANOVA (univariate analysis). To compare the effects of the

different treatments, a multiple comparison among pairs of means was performed using a Bonferroni post-hoc test with a significance level of $\alpha = 0.05$.

3. Results and discussion

3.1. Polymer selection

As co-extruded dosage forms offer a lot of opportunities for oral applications via the proper selection of the polymers used in the different layers, the aim of this work was to design a formulation providing dual release of diclofenac sodium. To select the polymers incorporated in the immediate and sustained release layer, the same strategy was used as during the development of FDC mini-matrices via co-extrusion [5], i.e. for each layer the polymers were selected by performing conventional hot-melt extrusion experiments, prior to initiating co-extrusion trials. Several thermoplastic polymers that have been successfully used in hot-melt extrusion were assessed for their application in co-extrusion as immediate release coat (Soluplus®, Eudragit® E PO, Polyox® WSR N10 (PEO), Kollidon® VA) and sustained release core (CAPA® 6506, Eudragit® RS PO, Ethocel® std 10, Kollidon® SR). These polymers were mixed in different ratios with DS, hot-melt extruded and evaluated for processability and macroscopic properties (surface smoothness, die swell).

All polymers were processable via hot-melt extrusion and smooth extrudates were obtained, except for the Kollidon® polymers which yielded extrudates with an irregular surface. According to [5], extrusion of pure Soluplus® required high temperatures (140-180 °C), while the addition of PLUR improved the ease of processing of this polymer. Mixtures of Soluplus®/PLUR (ratio: 9/1) containing up to 30% DS were extruded at 130 °C with an acceptable torque (50-70% motor load). Unplasticized mixtures of Eudragit® E PO and up to

20% DS could be extruded at 140 °C, but higher drug concentrations resulted in too high torque values (>80% motor load). The addition of PEG 4000 to PEO/DS mixtures improved processing by lowering the extruder torque and die pressure. The advantage of the addition of PEG to a PEO-containing formulation was already shown in a previous study [5], the incorporation of PEG 4000 lowered the torque during extrusion, a PEG/PEO ratio of 1/1 yielding the best results. These PEO/PEG/DS mixtures were extruded at 70 °C, resulting in low torque values (<50% motor load). Polycaprolactone (loaded with maximum 50% DS) was processable at a temperature of 70 °C without the addition of a plasticizer. However, the addition of 1% colloidal silicon dioxide was required to improve the flow properties in the feeder. Mixtures of Eudragit® RS PO/triethyl citrate (9/1) with up to 30% DS were extruded at 130 °C. Dibutyl sebacate (20% (w/p)) was used as a plasticizer for ethylcellulose. Plasticized mixtures containing up to 60% DS were extruded at 140 °C. No significant die swell was observed for the tested polymers.

The polymers that yielded good quality extrudates were further tested for in vitro drug release. The dissolution profiles are shown in Fig. 2. Two polymers (PEO/PEG (1/1) and Soluplus®) provided immediate drug release, the DS release from these matrices was complete in 30 min. Varying the drug load from 10 to 30% DS in these polymers, did not affect the release rate. DS release from extrudates formulated with Eudragit® E PO was incomplete after 1 h dissolution testing in water as well as in 0.1 N HCl. Since Eudragit® E PO is only soluble in acidic media, the matrix remained intact in water which prevented immediate drug release. In contrast, in an acidic medium the polymer dissolved, but due to low solubility of DS at low pH the released drug crystals did not dissolve. Hence, Eudragit® E PO was not a proper carrier for the coat of co-extrudates containing DS. Two polymers provided sustained release of DS: polycaprolactone and ethylcellulose. The dissolution

profiles showed that increasing the DS concentration enhanced the release rate. A drug load of 60% DS in ethylcellulose and 50% DS in polycaprolactone resulted in ±100% release after 24 h. It was not possible to sustain the release of DS using Eudragit® RS as - after an initial burst release - the release leveled off, resulting in an incomplete DS release after 24 h. This is probably due to the drug load in these formulations which is below the percolation threshold, whereby drug particles entrapped in the water-insoluble matrix are not accessible for the dissolution liquid.

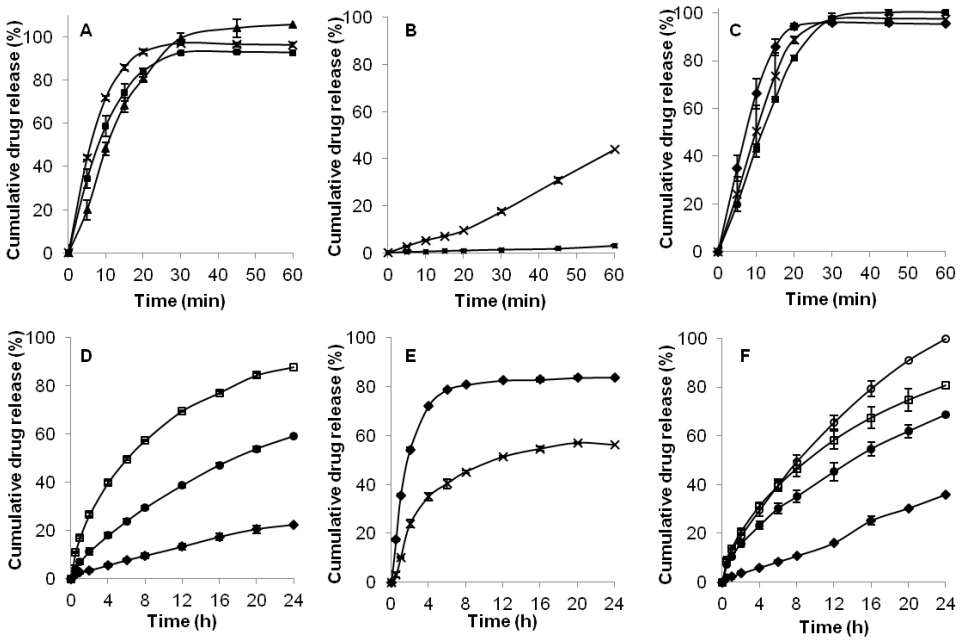


Figure 2. Influence of drug load on the release of DS from different polymers after extrusion. Mean dissolution profiles (±S.D.) of formulations composed of (A) Soluplus®/PLUR (9/1), (B) Eudragit® E PO, (C) PEO/PEG (1/1), (D) Polycaprolactone, (E) Eudragit® RS PO/TEC (9/1), (F) Ethylcellulose/DBS (8/2) and (■) 10%, (×) 20%, (▲) 25% DS, (♦) 30% DS, (●) 40% DS, (□) 50% DS, (○) 60% DS.

During the polymer screening four polymers were identified as useful for co-extrusion in terms of processability and in vitro drug release: Soluplus® and PEO (with 50% PEG) provided immediate release, while DS release from polycaprolactone and ethylcellulose was sustained over a 24 h period. Taking into account their respective extrusion temperatures, two polymer combinations were selected for co-extrusion trials: ethylcellulose (core) combined with Soluplus® (coat), and polycaprolactone (core) with polyethylene oxide (coat). The polycaprolactone/PEO combination could be processed at a lower extrusion temperature (70 °C), vs. 140 °C for ethylcellulose/Soluplus®. Previous work by the authors [5] already demonstrated the success of the combination of the polycaprolactone/PEO combination as sustained release core and immediate release coat in co-extrusion.

3.2. Production and characterization of co-extrudates

All formulations complied for content uniformity. The thickness of the coat and core was uniform, as confirmed with marking gauge. Co-extruded formulations with a core composed of ethylcellulose/DBS (4/1) and a coat consisting of Soluplus®/PLUR (9/1) were processed at a temperature of 140 °C. The maximum drug load (MDL) in ethylcellulose at this temperature was approximately 60% DS, resulting in a torque value of 65% motor load and a die pressure of 19 bar. The MDL in the coat (Soluplus®) was limited to 25% DS, giving rise to a torque value of 70% motor load and a die pressure of 33 bar. Above these values, the extruder torque was too high and the extrudates had a rough surface. Possibly MDL can be increased by processing at a higher extrusion temperature, but as this increases the risk of drug degradation, higher extrusion temperatures were not explored in this study. Extrusion of formulations with a core composed of polycaprolactone and a coat consisting of PEO/PEG (1/1) was performed at 70, 95 and 120 °C. The MDL at each temperature was determined,

also taking into account the dimensions of the die. Using a die with a core diameter of 3 mm and a coat thickness of 0.5 mm, the MDL in the core/coat system was 40%/30%, 50%/50% and 60%/50% at an extrusion temperature of 70, 95 and 120 °C, respectively. The corresponding torque values were 80/40%, 75/30%, 60/25% and the observed melt pressure was 50/75, 30/50, 15/40 bar. Using a die with a core diameter of 2 mm surrounded by a coat of 1 mm thickness, the MDL in core/coat at 70 °C, 95 °C and 120 °C was 10%/20%, 40%/40% and 50%/50%, respectively. The corresponding torque values were 85/40%, 75/35%, 60/35% and the observed melt pressure was 90/80, 60/80, 60/65 bar. The MDL in the core (processed at a specific extrusion temperature) was lower using a die with a core-diameter of 2 mm compared to a 3 mm diameter, since the cross sectional area decreased by more than half (7 mm^2 to 3.1 mm^2) leading to higher die pressures. On the contrary, the MDL in the coat was higher using a die with a coat-thickness of 0.5 mm compared to a 1 mm thickness given that although the cross sectional area increased (5.6 mm^2 to 9.5 mm^2) a higher feed rate (600 g/h, vs. 150 g/h) was required to manufacture the co-extrudates, resulting in a higher die pressure at lower drug concentrations.

All co-extruded formulations were characterized by XRD directly after preparation (Fig. 3 and 4). The X-ray patterns of the formulation composed of ethylcellulose (core) and Soluplus® (coat) exhibited crystalline peaks corresponding to DS with an intensity comparable to those in the physical mixtures, indicating that most of the drug had maintained its crystalline state in the co-extrudates. However DSC (data not shown) revealed that a limited amount of DS (±10%) was solubilized in Soluplus® during extrusion, which could compromise the long term stability of the coat of this co-extruded formulation due to recrystallization. Yet no recrystallization was observed during 12 months storage at room temperature. The co-extruded formulations composed of polycaprolactone (core) and

PEO/PEG (coat) contained crystalline DS. These results were confirmed with DSC (data not shown).

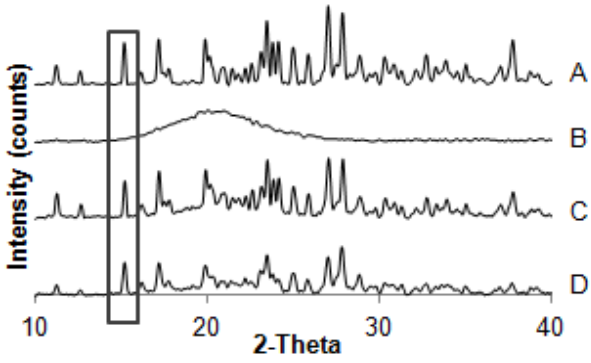


Figure 3a. X-ray diffraction pattern of (A) DS, (B) ethylcellulose/DBS (4/1), (C) physical mixture and (D) core of co-extrudate composed of 60/32/8% DS/ethylcellulose/DBS.

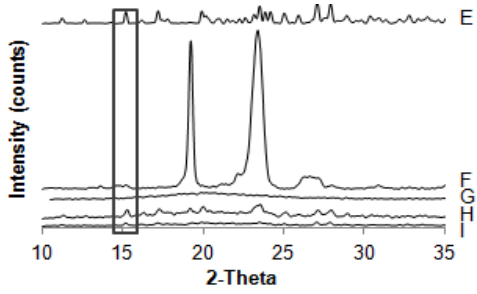


Figure 3b. X-ray diffraction pattern of (E) DS, (F) PLUR, (G) Soluplus®, (H) physical mixture and (I) coat of co-extrudate composed of 25/67.5/7.5% DS/Soluplus®/PLUR.

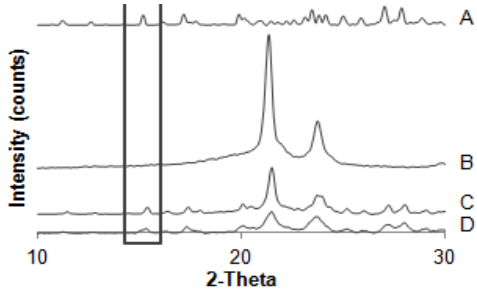


Figure 4a. X-ray diffraction pattern of (A) DS, (B) polycaprolactone, (C) physical mixture and (D) core of co-extrudate composed of 60/40% DS/polycaprolactone.

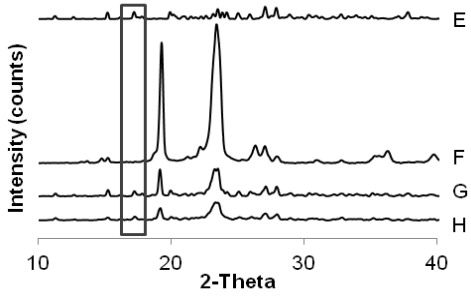


Figure 4b. X-ray diffraction pattern of (E) DS, (F) PEO/PEG (1:1), (G) physical mixture and (H) coat of co-extrudate composed of 22.5/38.75/38.75% HCT/PEO/PEG.

The adhesion force between core and coat in the co-extruded formulations was measured. For the formulation composed of an ethylcellulose core and a Soluplus® coat (F_1) no accurate values could be obtained, as the coat tended to fracture before of its separation from the core. Nonetheless, there seemed to be good adhesion as no delamination could be observed. The adhesion force of formulations composed of polycaprolactone (core), PEO/PEG (coat) and different DS concentrations extruded at different temperatures (F_5-F_{12},

Table 2) was measured to investigate the influence of drug load and extrusion temperature on core/coat adhesion (Table 3). The adhesion force increased with increasing extrusion temperature (except for the formulation without DS extruded at 95 and 120 °C) as this allowed more polymer entanglement at the interface. Although polycaprolactone and polyethylene oxide are immiscible [6] adhesion between these two polymers is possible, mainly caused by entanglements at the interphase and to a lesser extent by van der Waals or hydrogen-bonding interactions. As the extrusion temperature increased, the width of the interface between core and coat decreased (Fig. 5a) and the adhesion force increased, possibly attributed to an increased number of entanglements at higher temperature [7]. Unexpectedly we found that adhesion force was also influenced by drug load. There was almost no adhesion between the two pure polymer layers (without DS), while a significantly higher adhesion force was noticed for the formulations containing 30 and 50% of drug, irrespective of the extrusion temperature. Since the drug was mainly present in its crystalline form, it was unlikely that the improved adhesion was attributed to chemical interactions. Microscopic inspection (Fig. 5b) of the formulations with different drug loads (0, 30 and 50% DS) extruded at the same temperature (120 °C) revealed that with increasing drug load the surface of core and coat became rougher, which was probably resulted in the enhanced adhesion. Roughening of surfaces can improve adhesion through mechanical interlocking or by increasing the physical area of contact, thus enabling more interfacial interactions [8].

Table 3. Mean adhesion force in N (±S.D.) between core and coat in function of drug load (0%, 30%, 50%) and extrusion temperature (70, 95, 120 °C).

	70 °C	**95 °C**	**120 °C**
0% DS	$0.6 \pm 0.7^{a'}$	$5.2 \pm 2.3^{b'}$	$3.4 \pm 2.2^{c'}$
30% DS	$14.7 \pm 5.8^{a''}$	$25.1 \pm 5.3^{b''}$	$30.6 \pm 7.8^{b''}$
50% DS	---	$30.1 \pm 5.4^{b''}$	$39.3 \pm 7.1^{c''}$

^{a,b,c} means in the same row with different superscript are different at the 0.05 level of significance. $^{'}$ $^{''}$ means in the same column with different superscript are different at the 0.05 level of significance.

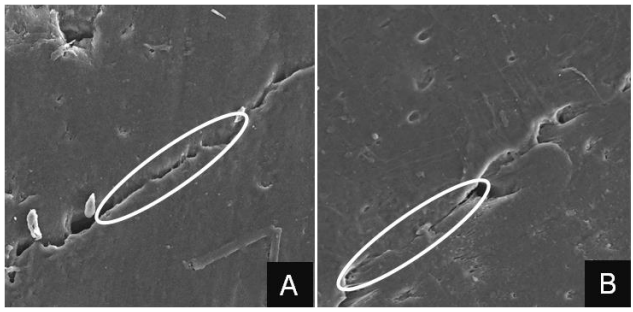


Figure 5a. SEM images of the coat/core interface of co-extruded formulations composed of polycaprolactone (core), PEO/PEG (ratio: 1/1) (coat) extruded at (A) 95 °C and (B) 120 °C (magnification 500x).

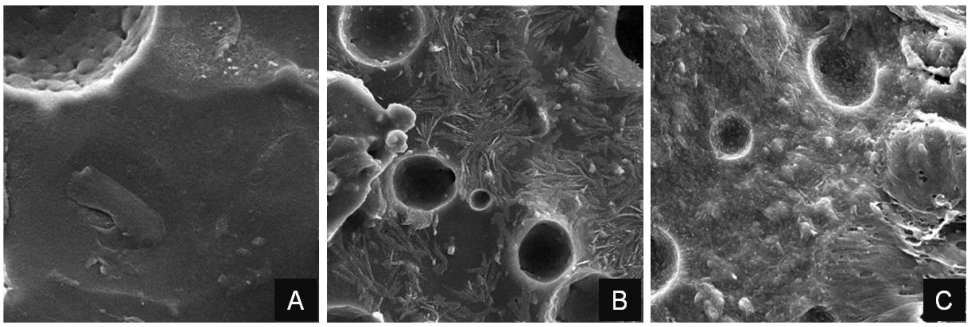


Figure 5b. SEM images of the core (at coat/core interface) of co-extruded formulations composed of polycaprolactone (core), PEO/PEG (ratio: 1/1) (coat) and a DS concentration of (A) 0%, (B) 30%, (C) 50% (magnification 1000x).

The in vitro release profiles of four experimental formulations (F1-F4) and the reference formulation are shown in Fig. 6. The coat of all experimental co-extruded formulations rapidly dissolved (±20 min) in the dissolution medium, through which the DS release from the core was hardly obstructed. All formulations showed an initial burst release (39, 37, 63 and 84% DS released in 1 h from F_1, F_2, F_3 and F_4), followed by a sustained DS release. The initial burst was mainly caused by the immediate release of the entire drug fraction in the coat, plus a small fraction already released from the core. The remaining DS fraction was sustained released from the core. Full drug release was observed after 24 h for all experimental formulations. After 12 months storage at room temperature, all dissolution profiles were identical.

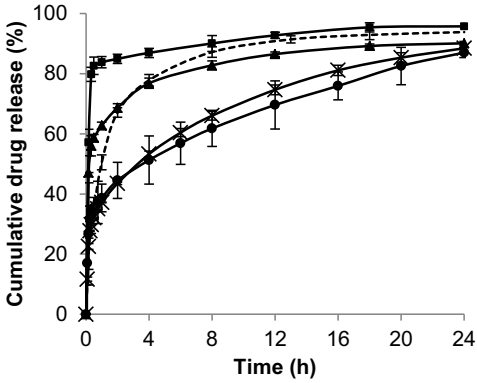


Figure 6. Mean dissolution profile (±S.D.) (n = 3) of experimental formulations (●) F_1, (X) F_2, (▲) F_3, (■) F_4 and (---) Motifene®.

3.3. Bioavailability

Fig. 7 shows the mean plasma concentration-time profiles after oral administration of 100 mg DS as experimental mini-matrices (F_2-F_4) and Motifene®. The Motifene® capsules contain 33% IR pellets (Eudragit® L) and 67% SR pellets (Eudragit® RS and RL). According to the dissolution data (Fig. 6), all test formulations as well as the reference formulation provided dual DS release: immediate drug release from the coat and sustained release over 24h from the core. The differences in in vitro release between formulations F_2-F_4 were caused by a variable DS ratio in the core/coat combination and were also reflected in the in vivo behavior: formulations with a higher DS ratio in coat/core resulted in higher initial plasma concentrations (Fig. 7). The pharmacokinetic parameters are reported in Table 4. In order to examine the contribution of the coat and the core separately, C_{max} and T_{max} are reported for the initial part as well as for the latter part of the bioavailability curve.

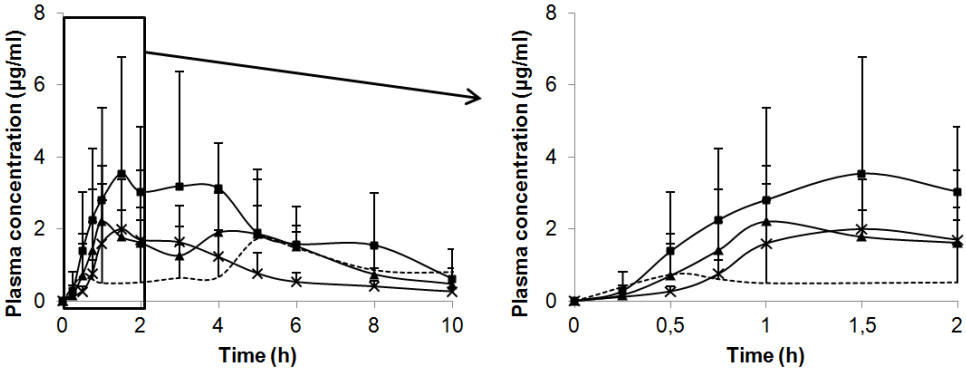


Figure 7. Mean DS plasma concentration-time profiles (± SD, n = 6) after oral administration of 100 mg diclofenac sodium to dogs as experimental formulation composed of a polycaprolactone core and a PEO/PEG (ratio 1/1) coat (F_2-F_4) or as reference formulation: (X) F_2 (coat: 30 mg DS; core: 70 mg DS), (▲) F_3 (coat: 43 mg DS; core: 57 mg DS), (■) F_4 (coat: 75 mg DS; core: 25 mg DS), (- - -) Motifene® (IR pellets: 33 mg DS; SR pellets: 67 mg DS).

Table 4. Mean pharmacokinetic parameters (±S.D.) after oral administration of 100 mg diclofenac sodium to dogs as F_2, F_3, F_4 or as reference formulation (Motifene®).

	C_{max1} (µg/ml)	C_{max2} (µg/ml)	T_{max1} (h)	T_{max2} (h)	AUC (µg.h/ml)
F_2	2.2 ± 1.3	2.4 ± 0.7	1.7 ± 0.3	2.75 ± 0.9[a]	9.2 ± 2.3[a]
F_3	2.4 ± 1.4	2.3 ± 1.3	1.5 ± 0.4	4.8 ± 1.0	12.8 ± 1.5[a]
F_4	5.4 ± 3.7	4.1 ± 2.9	1.5 ± 0.9	3.8 ± 0.4	20.4 ± 3.1[b]
Motifene®	0.9 ± 0.5	2.1 ± 1.6	2.4 ± 1.8	5.5 ± 1.4[b]	10.9 ± 5.6[a]

[a,b] means in the same column with different superscript are different at the 0.05 level of significance.

Oral administration of formulation F_4 resulted in a significantly higher AUC value compared to formulations F_2, F_3 and the reference formulation. Fig. 8 represents the AUC values of each dog separately after administration of formulations F_2-F_4 and the reference formulation. The variability in AUC values was higher after administration of the reference formulation than for all test formulations. This was probably due to the fact that the IR Motifene® pellets contained Eudragit® L, which only started to dissolve above pH 5. As mentioned in the introduction, enteric coated formulations show more variation in lag-time and time to peak plasma concentration [1]. Although only F_4 was significantly different from the other formulations, the AUC values tended to increase at higher DS concentration in the coat. The higher bioavailability of F_4 correlated well with the faster drug release rate in vitro. Diclofenac sodium, as a class II drug in the Biopharmaceutical Classification System with a high permeability and low solubility, is known to be absorbed well throughout the intestinal tract. However, the main site for the absorption of DS is considered to be the small intestine. For less soluble drugs, the drug release rate is influenced by the water content in the GI tract. Due to the low water content and GI motility in the colon, the drug dissolution and as a consequence the DS absorption in the colon is limited. The lower fraction of F_2, F_3 and the reference formulation absorbed in dogs in comparison to F_4 probably resulted from the incomplete drug release of DS in the upper GI tract owing to the short small intestine transit time and the low drug release in the colon because of its low solubility [9]. The dominant role of the upper GI tract in DS absorption was also demonstrated by the fact that F_2, F_3 and the reference formulation yielded comparable AUC numbers. Although between 2 and 24 h the dissolution profiles of F_3 and reference were uniquely different from F_2, during the first 2 h the release from the reference was intermediate to F_2 and F_3.

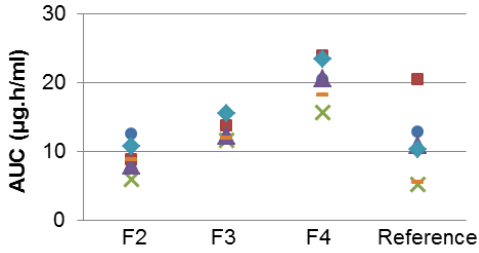


Figure 8. Comparison of AUC level of DS after oral administration of experimental co-extruded (F_2, F_3 and F_4) and reference formulation (Motifene®) to dogs.

No significant differences were found in C_{max1}, C_{max2} and T_{max1} values between all experimental formulations and the reference formulation ($p > 0.05$). *Cave*: statistics were influenced by the fact that 2 dogs showed limited drug absorption. T_{max2} of F_2 was significantly lower than that of the reference formulation ($p < 0.05$), whereas no significant differences with the other formulations were seen ($p > 0.05$). The distinction between F_2 and the reference was probably due to the difference in drug release rate. Initially DS was released fast from both formulations, however the rate of DS release from formulation F_2 already dropped after 2 h while for the reference formulation it stayed high until 4 h after administration.

4. Conclusions

Co-extrusion proved to be a promising technique to produce in a single step multilayer mini-matrices with dual drug release. Core/coat dosage forms were developed using two

different polymer combinations (ethylcellulose/Soluplus® and polycaprolactone/PEO). Co-extruded formulations composed of polycaprolactone (core) and PEO/PEG (coat) were preferable because they allowed extrusion at a lower temperature and they provided better mechanical properties. Furthermore, the adhesion force between the two layers depended on extrusion temperature and drug load. By varying the DS ratio in coat and core, the in vitro and in vivo drug release could be controlled, demonstrating the flexibility of the dosage form.

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CHAPTER 4

Co-extruded solid solutions as immediate release fixed-dose combinations

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**Both authors equally contributed*

1. Introduction

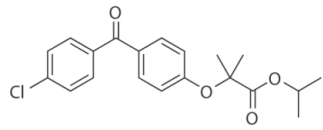
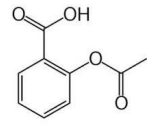
Hot-melt extrusion (HME) shows numerous benefits over traditional methods including the continuity of the production process, environmental advantages due to elimination of solvents and the possibility of improving drug solubility. The latter has drawn attention because large numbers of new chemical entities under development exhibit very poor solubility and bioavailability. Formulation of solid solutions via HME can be an efficient approach in the delivery of poorly water-soluble drugs. Co-extrusion is gaining importance for the production of oral drug products as combination therapy is becoming increasingly important as fixed-dose combination (FDC) products offer therapeutic (improved patient adherence) and economic (lower manufacturing costs) benefits. Such "polypills" are being used in the treatment of e.g. cardiovascular disease, diabetes, hyperlipidemia, HIV, tuberculosis and malaria. In this study acetylsalicylic acid (ASA, an anticoagulant) and fenofibrate (FF, a lipid regulating drug) were incorporated as hydrophilic and hydrophobic model drugs, respectively. While ASA is slightly soluble in water and has relatively high oral bioavailability, FF is poorly water-soluble and has a low bioavailability after oral administration. Due to their biopharmaceutical and pharmacological properties, immediate release of both drugs is required. The aim of this study is to design a core/coat dosage form suitable for co-extrusion, whereby the core and coat formulation provide immediate drug release (IR) of both drugs (ASA and FF). Several research groups have already investigated the feasibility of HME to produce immediate release FF dosage forms. Kollidon® VA 64 [1, 2], Eudragit® E PO [2], Soluplus® [3] and blends of PVPVA 64, HPMC and Soluplus® [4] were reported.

2. Materials and methods

2.1. Materials

The following polymers were used during the polymer selection procedure: Eudragit® E PO (Evonik, Darmstadt, Germany), Sentry™ Polyox® WSR N10 (polyethylene oxide, PEO 100,000 g/mol, Colorcon, Dartford Kent, United Kingdom), Soluplus®, Kollidon® VA 64, PF 12 and 30 (BASF, Ludwigshafen, Germany). Polyethylene glycol (PEG 4000 g/mol, Fagron, Waregem, Belgium) and Pluronic® F-68 (PLUR, Sigma–Aldrich, Steinheim, Germany) were used as plasticizers. Fenofibrate (FF, Roig-Farma, Barcelona, Spain) and acetylsalicylic acid (ASA, Utag, Amsterdam, The Netherlands) were incorporated as hydrophobic and hydrophilic model drug, respectively. . Their relevant physico-chemical properties are listed in Table 1. All other chemicals were of analytical grade.

Table 1. Physico-chemical properties of fenofibrate and acetylsalicylic acid.

Properties		**Structural formula**
Name	fenofibrate	
Melting point	81 °C	
Degradation temperature	>200 °C [5]	
Solubility in water	practically insoluble in water [6]	
Log P	5.24	
Name	acetylsalicylic acid	
Melting point	144 °C	
Degradation temperature	140 °C [7]	
Solubility in water	slightly soluble in water [6]	
pKa	3.5	
Log P	1.4	

2.2. Polymer selection

For the selection procedure several thermoplastic polymers were hot-melt extruded and evaluated for processability, macroscopic properties (visual inspection of surface, die swell quantification using marking gauge), salicylic acid content (ASA formulations) and in vitro drug release. Polymers/plasticizer were mixed (with mortar and pestle) with FF and ASA (concentration range: 20-40%, w/w) and hot-melt extruded using a co-rotating, fully intermeshing twin screw extruder (Prism Eurolab 16, ThermoFisher Scientific, Germany) having a length-to-diameter ratio of 25/1. The co-rotating screws consisted of three mixing sections and a densification zone. A co-extrusion die (Guill, West Warwick, USA) was connected at the end of the extruder. The extrusion temperature varied according to the polymer, but all five heating segments of the extruder were set at the same temperature, except for the first heating zone which was set at 70 °C to avoid sticking of the powder in the feed section. The premixes were fed (feed rate: 300 g/h) into the extruder using a loss-in-weight powder feeder (Brabender flexwall®, Duisburg, Germany). The screw speed was kept constant at 120 rpm and 180 rpm for extrusion of ASA and FF formulations, respectively. ASA formulations were extruded through the core orifice of the co-extrusion die, yielding extrudates with a diameter of 2 mm. FF formulations were extruded through the coat orifice (1mm coat thickness) yielding hollow cylindrical tubes with an outer and inner diameter of 4 and 2 mm, respectively. After cooling down to room temperature, the cylindrical extrudates were manually cut into mini-matrices of 2 mm length.

2.3. Production of co-extrudates

Polymer/plasticizer and drug were premixed in a tumbling mixer (Turbula® T2A, W.A. Bachofen, Basel, Switzerland) for 20 min. Co-extrusion was performed using two co-rotating, fully intermeshing twin screw extruders (Prism Eurolab 16, ThermoFisher Scientific, Germany). The multimanifold co-extrusion die (Guill, West Warwick, USA) was connected to both extruders. Both melts were combined in the die to form two concentric layers, a core and a coat. All five heating segments of both extruders were set at the same temperature, except for the first heating zone which was set at 70 °C to avoid sticking of the powder in the feed section. The premixes were fed into the corresponding extruders using loss-in-weight powder feeders (Brabender Flexwall®, Duisburg, Germany). The screw speed was kept constant at 120 rpm (core) and 180 rpm (coat). The co-extrusion die was designed with a core diameter of 2 mm and a coat thickness of 1 mm, resulting in a total die diameter of 4 mm. After cooling down to room temperature, the cylindrical co-extrudates were manually cut into mini-matrices of 2 mm length.

2.4. Determination of free salicylic acid

The salicylic acid (SA) content in the extrudates was assessed according to the USP 32 monograph for aspirin tablets.

2.5. In vitro drug release

Dissolution studies were performed using USP apparatus 1 (baskets). The equipment consisted of a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, NJ, USA). Acetate buffer pH 4.5 containing 0.05 M sodium lauryl

sulfate was used as dissolution medium [8, 9]. Sink conditions were maintained during the experiments. The temperature of the dissolution medium (900 ml) was kept constant at 37 ± 0.5 °C. The rotational speed of the baskets was set to 100 rpm. Samples (5 ml) were withdrawn at 5, 10, 15, 20, 30, 45, 60 (and 90) min.

ASA and FF concentrations were determined using a validated HPLC method. The HPLC equipment (Merck-Hitachi, Darmstadt, Germany) consisted of a gradient solvent pump set at a constant flow rate of 1 ml/min, an autosampler, a reversed-phase C-18 column (LiChrospher® 100 RP-18 (5 µm)) (250 x 4 mm) and guard column (4 x 4 mm) and a UV detector set at 285 nm. The injection volume was 20 µl. An automatic integration system (software D-7000 Multi-Manager) was used for peak integration. The mobile phase consisted of mixtures of buffer solution pH 2.9 [9] and methanol: initially using a 57:43-ratio (to elute ASA and SA, while FF was retained on the column). After 14.5 min the ratio of the mobile phase was rapidly changed to 10:90 (to elute the hydrophobic FF from the column), after 22.0 min the ratio between the aqueous and organic phase was again set at 57:43 and the column was equilibrated until 31.0 min prior to the following analysis.

2.6. X-ray diffraction

X-ray diffraction (XRD) was performed to investigate the crystallinity of the drugs in the mini-matrices. X-ray patterns of drug, polymer, physical mixtures and extrudates were obtained using a D5000 Cu Kα Diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany). The angular range (2θ) varied from 10° to 60° (step width = 0.02°, counting time = 1 s/step).

2.7. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to study the solid state properties of the extrudates. The thermal behavior of the individual components, physical mixtures and extrudates was evaluated using a Q2000 DSC (TA Instruments, Leatherhead, UK). The system was equipped with a refrigerated cooling system. Samples (5-10 mg) were accurately weighed and hermetically sealed in aluminum pans (TA Instruments, Leatherhead, UK).They were cooled to -70 °C, followed by heating to 170 °C at a linear heating rate of 10 °C/min.

2.8. Scanning electron microscopy

Scanning electron microscopy (SEM) was used to visualize the interface between both co-extruded layers. Samples were coated with platinum by means of a sputter coater (Auto Fine Coater, JFC-1300, Jeol, Tokyo, Japan). Photomicrographs were taken with a scanning electron microscope (Jeol JSM 5600 LV, Jeol, Tokyo, Japan).

2.9. Raman spectroscopy

The distribution of the different components in the coat and core of the co-extrudates was evaluated with Raman microscopic mapping using a Raman Rxn1 Microprobe (Kaiser Optical Systems Inc., Ann Arbor, MI, USA), equipped with an air-cooled CCD detector. The laser wavelength employed was 785 nm from a Invictus NIR diode laser (Kaiser Optical Systems Inc., Ann Arbor, MI, USA). All spectra were recorded with a resolution of 4 cm^{-1} and an exposure time of 7 s, using a laser power of 400 mW. Cross sections of co-extrudates were scanned by a 50× short working distance objective lens (spot size 10 µm) in point-by-point mapping mode

using a step size of 10 µm in both the x and y directions. The resulting images provide information about the distribution of different components in the co-extrudates. Data collection and data transfer were automated using the HoloGRAMS™ data collection software (version 2.3.5, Kaiser Optical Systems Inc., Ann Arbor, MI, USA). The analysis of the spectra was done using HoloMAP™ data analysis software (version 2.3.5, Kaiser Optical Systems Inc., Ann Arbor, MI, USA) and Matlab® software (version 7.1, The MathWorks Inc., Natick, MA, USA). All spectra were baseline corrected using the Pearsons method. To visualize the distribution of the drug within the co-extrudate, a specific peak of each drug was shown relatively to a specific peak of the polymer. In order to attribute specific Raman peaks in the spectra to the different components in the formulations, Raman spectra were collected from the pure components and the separate layers. All spectra were recorded with a resolution of 4 cm^{-1} and an exposure time of 10 s. Standard normal variate (SNV) pre-processing was applied on the collected spectra prior to analysis, to correct for the variation in path length/sampling distance between probe and sample.

2.10. Karl Fisher titration

The moisture content of the polymers and plasticizers at ambient conditions was determined by volumetric Karl Fischer titration using a V30 volumetric KF titrator (Mettler Toledo, USA). The experiments were performed in triplicate.

3. Results and discussion

3.1. Polymer selection

The aim of this work was to develop a formulation providing immediate release from a co-extruded dosage form, containing ASA as hydrophilic model drug and FF as hydrophobic model drug. Several thermoplastic polymers were therefore hot-melt extruded in combination with ASA and FF, and evaluated for processability (torque and die pressure), macroscopic properties (surface, transparency, consistency and die swell), ASA decomposition (via SA content determination) and in vitro drug release. Polymers that failed one criterion, i.e. were not processable below 140 °C with a torque value of <80% motor load and a die pressure of <100 bar, exhibited unfavorable macroscopic properties (irregular surface, sticky, irregular dimensions), contained >3% SA or did not release 80% of the drug in approximately 45 min, were rejected.

3.1.1. ASA

Five polymers (PEO, Eudragit® E PO, Soluplus®, Kollidon® VA 64 and Kollidon® PF 12) were tested during ASA-polymer screening. Table 2 presents the composition, extrusion temperature, SA content and in vitro drug release of the screened formulations. All polymers were processable via hot melt extrusion at the specified temperatures. All PEO/ASA extrudates (extruded at 75 °C) were smooth, slightly yellow and transparent. However, they became opaque after cooling down to room temperature as PEO recrystallized. Process monitoring revealed that the addition of PEG 4000 as a plasticizer resulted in lower die pressures and torque values. Unplasticized Eudragit® E PO/ASA mixtures had a minimum extrusion temperature of 140 °C. The incorporation of PEG 4000 improved processing by lowering the extruder torque and die

pressure. The addition of 25% PEG allowed extrusion at 120 °C. Eudragit® E PO/ASA extrudates were slightly yellow but transparent. They exhibited unfavorable macroscopic properties as they were very flexible and sticky. Extrusion of pure Soluplus® requires a temperature of 140 °C. Soluplus®/ASA mixtures were processable at a minimum temperature of 110 °C and good quality extrudates (smooth, clear, rigid, not sticky) were obtained, but with a slight pink discoloration. This discoloration was probably due to the formation of complexes between salicylic acid (ASA degradation) and free iron ions originating from the extrusion screws or barrel due to shear [10]. The addition of 1% sodium EDTA eliminated the pink discoloration, which supported our hypothesis. For the processing of Kollidon® VA 64/ASA extrudates a temperature of at least 130 °C was required. The extrudates were clear and smooth but the same pink discoloration as seen with Soluplus® appeared. Again, the problem was solved by adding 1% sodium EDTA. Kollidon® PF 12 was processable at a temperature of 110 °C. The quality of all Kollidon® PF 12/ASA extrudates was good (clear, rigid) and no discoloration was noticed. It was found in literature that Kollidon® forms complexes in solution with salicylic acid, which could be a possible explanation for the absence of the pink discoloration [11]. No significant die swell was observed for any of the tested polymers.

Table 2. Overview of polymer screening results for ASA.

Carrier	ASA (%)	T_{die} - $T_{extrusion}$* (°C)	SA content (%)	Complete release (min)
PEO (0-50 % PEG)	20	75 - 75	26.6 (± 0.17) -12.0 (± 0.23)	not tested***
Eudragit® E PO (0-25% PEG)	20	120 - 140-120	not tested**	not tested**
Soluplus®	20	95 - 110	4.7 (± 0.21)	not tested***
Kollidon® VA 64	20	105 - 130	2.4 (± 0.11)	20
Kollidon® PF 12	20	95 - 110	1.5 (± 0.16)	10

*: lowest extrusion temperature usable resulting in a torque value of <80% motor load and a pressure of <100 bar.
**: too sticky and highly flexible
***: SA content >3%

ASA undergoes thermal decomposition as is starts to decompose upon melting (140 °C) [7], while in the presence of water hydrolysis of ASA results in the formation of SA and acetic acid. Therefore the polymers that yielded good quality extrudates (PEO, Soluplus®, Kollidon® VA 64 and Kollidon® PF 12), were further tested for salicylic acid content (Table 2). The USP SA limits [8] for ASA tablets (≤0,3%) or coated ASA tablets (≤3%) were used as reference values, although solid dispersions do not comply with either dosage forms. For all PEO/ASA formulations a large amount of SA was formed during extrusion. It was found that the SA content decreased (26.6, 17.8, 12.0% SA) with increasing PEG concentration (0, 25, 50% PEG) and decreasing torque (60, 30, 15% motor load) and die pressure (55, 30, 13 bar). Breitenbach [12] stated that high shear forces can lead to a local temperature increase within the extrusion barrel. In addition, Breitenbach identified the residence time and die pressure as factors with a significant impact on the impurity profile. These findings support our hypothesis that the extruder torque and die pressure may play a role in ASA degradation during extrusion. The degree of decomposition in extrudates with Soluplus® as carrier was lower in comparison with PEO formulations, as it was possible to approach the USP limit of ≤3%. Nevertheless, the only two polymers that complied with the SA limit were Kollidon® VA 64 and Kollidon® PF 12, containing 2.4 and 1.5% SA respectively. Kollidon® VA 64 and Kollidon® PF 12, the polymers that complied with the criteria of processability and ASA stability, were tested for in vitro drug release. The ASA release from Kollidon® VA 64 was complete in 20 min, whereas the release from Kollidon® PF 12 was already complete in 10 min.

3.1.2. FF

Five polymers (PEO, Soluplus®, Eudragit® E PO, Kollidon® VA 64 and Kollidon® 30) were tested as FF carriers. Due to the plasticizing properties of FF, Kollidon® PF 12 (used during

ASA polymer screening) was replaced by Kollidon® 30 exhibiting a higher T_g (149 °C instead of 90 °C). Table 3 presents the composition, extrusion temperature and in vitro drug release of the screened formulations. All polymers were processable via hot-melt extrusion at the specified temperatures. Unplasticized PEO/FF mixtures had a minimum extrusion temperature of 100 °C as the die pressure exceeded 100 bar at lower process temperatures. PEO/PEG/FF mixtures could be extruded at 75 °C, although torque and die pressure increased at lower PEG concentration. Soluplus® (loaded with 20-30% FF) was processable at a temperature of 100 °C. Apparently, an increase in FF concentration (20-30% FF) improved the ease of processing by lowering the T_g (from 30.0 to 15.0 °C). FF melted during processing since the process temperature (100 °C) exceeded its melting point (80 °C). All Soluplus® extrudates exhibited a smooth surface. All extrudates up to 30% FF were transparent. Eudragit® E PO (loaded with 20% FF) was processable at a temperature of 120 °C without the addition of a plasticizer. Increasing FF concentrations improved the ease of processing by lowering the extruder torque and die pressure. Consequently the extrusion temperature of mixtures containing 30% and 40% FF was lowered to 110°C and 100°C, respectively. All Eudragit® E PO/FF extrudates were transparent when they emerged from the die. However, the extrudates had unfavorable properties as they were sticky and collapsed after cooling down to room temperature. Kollidon® VA 64/FF mixtures (20-40% FF) were processable between 100 and 130 °C. As observed for Soluplus® and Eudragit® E PO, the ease of processing enhanced at increasing FF loads. Clear extrudates with good quality (no die swell, thin, smooth, clear and rigid) were obtained. Kollidon® 30 loaded with 30% FF was extrudable at 150 °C. Increasing the drug load to 40% slightly enhanced the processability. However, the minimal extrusion temperature remained 150 °C as the die pressure increased sharply at lower temperature. All extrudates were clear during extrusion and remained clear after cooling down to room temperature. Good quality extrudates (no die swell, rigid, clear and a smooth surface) were obtained.

Table 3. Overview of polymer screening results for FF.

Carrier	FF (%)	T_{die}-$T_{extrusion}$ (°C)*	Complete release (min)
PEO (0-50 % PEG)	20	75 - 100-75	>60
Soluplus®	20-30	100 - 100	±60
Eudragit® E PO	20-40	100 - 120-100	not tested**
Kollidon® VA 64	20	105 - 130	20
	30-40	100 - 100	20
Kollidon® 30	30-40	125 - 150	20

*: lowest extrusion temperature usable resulting in a torque value of <80% motor load and a pressure of <100 bar.
**: too sticky and highly flexible

The polymers that yielded good quality extrudates were further tested for in vitro drug release (data not shown). The time required for complete FF release from the different formulations is shown in Table 3. FF release from PEO extrudates was incomplete after 1 h. Although the addition of PEG to PEO resulted in a considerable increase in release rate, the drug release rate remained too low. FF release from Soluplus® extrudates was nearly complete after 1 h. A higher drug load did not influence the release rate significantly. Although Soluplus® offers the particular advantage that precipitation and crystallization of drugs during dissolution is prevented as a result of its micellar character [13], the FF release rate was lower than expected. Hughey et al. described that Soluplus® tended to form a strong gel (in vitro) and that dissolution occurred through erosion of the matrix [14]. Recently, Soluplus® was also found to tailor (delay) the release of another hydrophilic drug (acetaminophen) [15]. Complete FF release from all formulations formulated with Kollidon® VA 64 and Kollidon® 30 was achieved within 20 min.

3.2. Co-extrusion

A successful co-extrusion process requires that both melts flow through the co-extrusion die under the same temperature conditions. Based on the polymer screening data, the following formulations were identified as potentially useful for co-extrusion: Soluplus®, Kollidon® VA 64 and Kollidon® 30 as FF carriers (coat) in combination with Kollidon® VA 64 or Kollidon® PF 12 as ASA carriers (core). The ASA:FF ratio in all formulations was 35:65, which complied with the ratio of 80 mg ASA and 145 mg FF (usual daily dose). As the coat had a total volume of ±19 mm^3 versus ±6 mm^3 for the core, FF was formulated in the coat. The content of ASA and FF in the co-extrudates was ensured by setting correct combinations of feed rate and drug load in both processes.

The combination of Kollidon® 30 as carrier for FF with Kollidon® VA 64 or Kollidon® PF 12 as carriers for ASA failed in terms of processability. Using the minimum possible die temperature for Kollidon® 30 (125 °C) the core formulations with Kollidon® VA 64 and Kollidon® PF 12 were too liquid as they left the die resulting in collapse during cooling down to room temperature. The co-extrusion trials showed that Kollidon® VA 64 and Kollidon® PF 12 as carrier for ASA were compatible with Kollidon® VA 64 and Soluplus® as carrier for FF in terms of extrusion temperature. The composition as well as the extrusion conditions used for each formulation are shown in Table 4. The core and coat of co-extrudate F_2 were processable at the same temperature (barrel: 130 °C, die: 105 °C). As the core and coat of F_1, F_3 and F_4 had different extrusion temperatures (cfr. polymer selection), temperature adjustments were required to enable the co-extrusion of these formulations. Nevertheless, all four formulations had good macroscopic properties as they were transparent and exhibited no die swell. Furthermore, both layers adhered firmly as no delamination was observed (Fig. 1).

Table 4. Composition and extrusion parameters of co-extruded formulations.

	Carrier		Drug concentration (%)		Extrusion temperature (°C)			Feed rate (g/h)	
	Core	Coat	Core (ASA)	Coat (FF)	Core	Coat	Die	Core	Coat
F_1	Kollidon® PF 12	Kollidon® VA 64	20	20	120	130	95	300	545
F_2	Kollidon® VA 64	Kollidon® VA 64	20	20	130	130	105	300	545
F_3	Kollidon® PF 12	Soluplus®	20	20	120	100	95	300	545
F_4	Kollidon® VA 64	Soluplus®	20	20	130	105	105	300	545

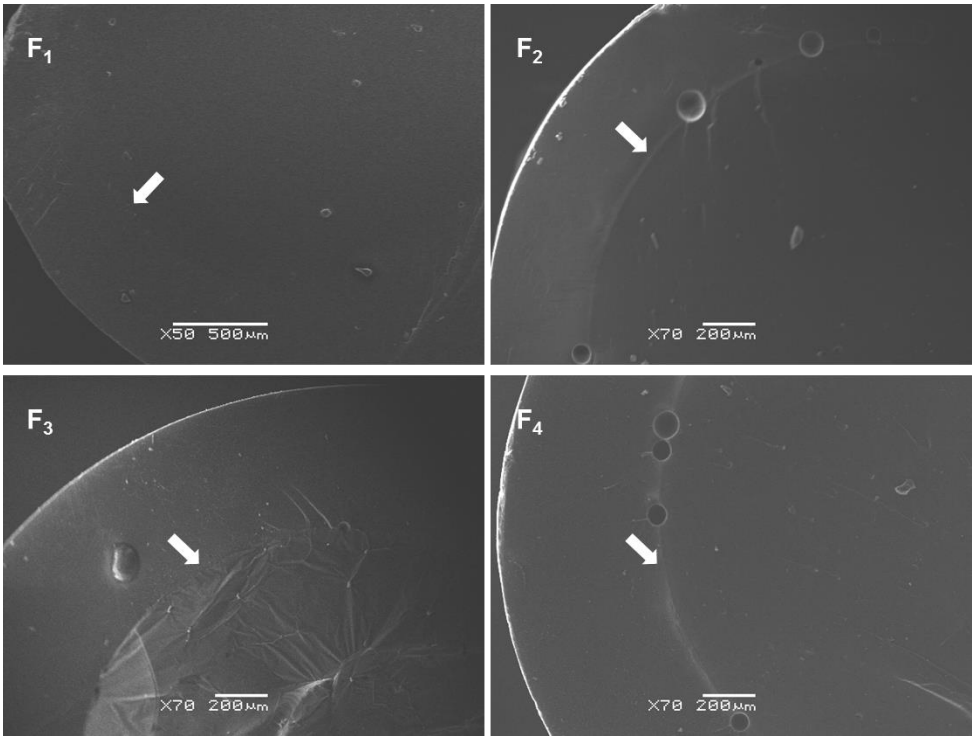


Figure 1. SEM images of co-extruded formulations (Table 4). Core/coat interface is marked by the white arrow.

In addition, the thickness of the coat and core was uniform, as confirmed with a marking gauge. After extrusion, the core and coat of the co-extrudates were physico-chemically characterized. The thermogram of all coat formulations revealed that there was no crystalline FF present in formulation F_1, F_2 (Fig. 2A), F_3 and F_4 (Fig. 2B). For all formulations, a single glass transition temperature (44.80 °C (F_1 and F_2), 32.73 °C (F_3 and F_4)) was detected, lying in between the individual glass transitions of FF (-21 °C) and Kollidon® VA 64 (101 °C) or Soluplus® (70 °C). This indicated the presence of a molecular dispersion. The DSC thermogram of ASA showed a melting peak at 144.18 °C (Fig. 3). This peak was absent in the thermogram of all core formulations, indicating the loss of crystallinity of ASA in the core of the co-extrudates. Since the melting point of ASA was never reached during the extrusion process, this indicated that ASA had dissolved in the matrices. A single glass transition temperature (30.15 °C (F_1 and F_3), 39.71 °C (F_2 and F_4)) was detected, lying in between the individual glass transitions of ASA (-30 °C) and Kollidon® PF 12 (90 °C) or Kollidon® VA 64 (101 °C). These results were confirmed with XRD (data not shown). The SA content in all core formulations 1.7 ± 0.12 for F_1 and F_3 and 2.3 ± 0.29 for F_2 and F_4 was in agreement with those found during the polymer screening tests (Table 2).

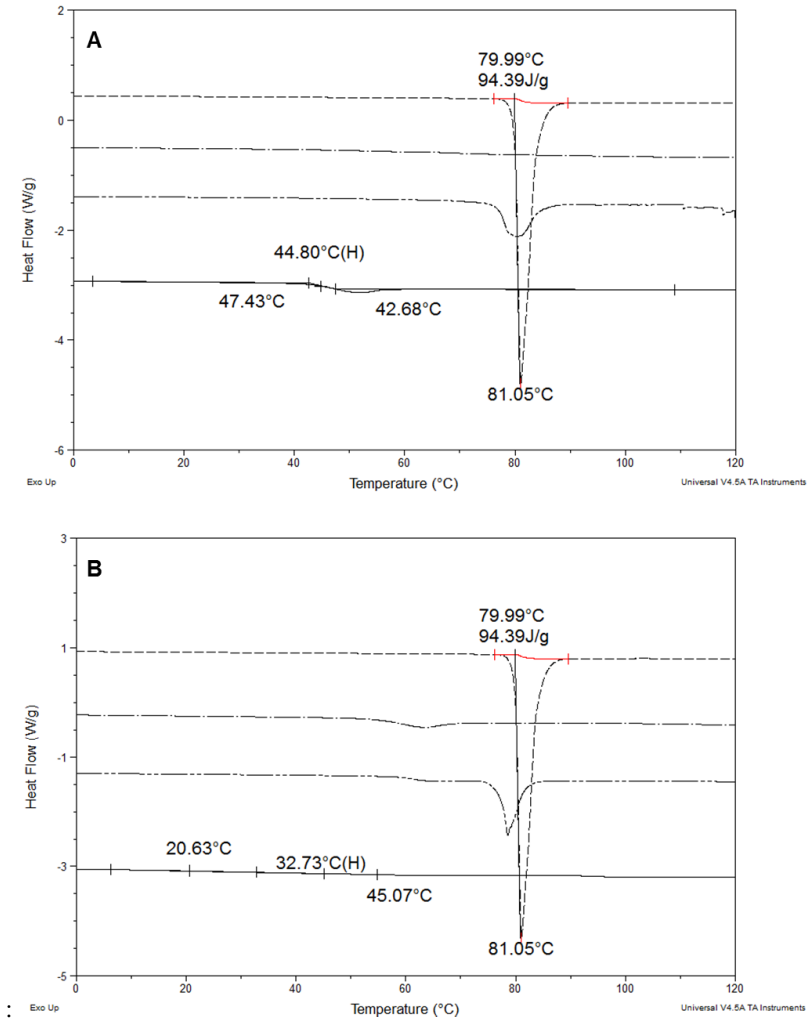


Figure 2. Solid state characterization (DSC) of coat of co-extrudated formulations: (A) 20% FF in Kollidon® VA 64 (F_1, F_2) and (B) 20% FF in Soluplus® (F_3 ,F_4). Within each figure from top to bottom: FF, carrier (Kollidon® VA 64 (A), Soluplus® (B)), physical mixture and extruded coat formulation.

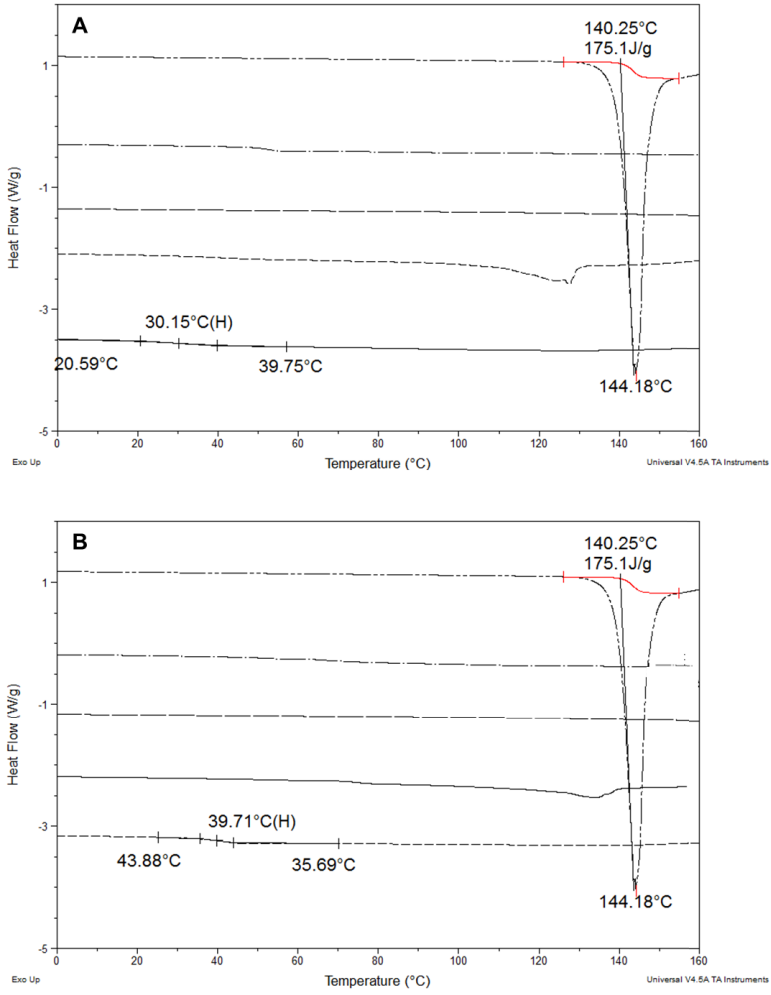


Figure 3. Solid state characterization (DSC) of core of co-extrudated formulations: (A) 20% ASA in Kollidon® PF 12 (F_1, F_3) and (B) 20% ASA in Kollidon® VA 64 (F_2 ,F_4). Within each figure from top to bottom: ASA, carrier (Kollidon® PF 12 (A), Kollidon® VA 64 (B)), physical mixture and extruded core formulation.

To evaluate the drug distribution in core and coat, Raman microscopic mapping was performed. The peak intensity of the Raman band of ASA in the 745-760 cm^{-1} region was monitored to map the ASA distribution in the core and to check if migration of ASA to the coat of the co-extrudates had occurred during co-extrusion. Likewise, the FF distribution in coat and core was mapped by monitoring the peak intensity of the Raman band of FF in the 760-778 cm^{-1} region. Fig. 4 shows the distribution of ASA throughout co-extruded formulation F_1. A red color corresponds to a high peak intensity, indicating a high ASA concentration, while a blue color corresponds to a low ASA concentration. The ASA band in the 745-760 cm^{-1} region showed an intense peak in the core. A very low peak intensity was found in the coat at the interface with the core (light blue), indicating very little migration of ASA to the coat. Comparing the Raman spectra of the light blue area with those of the individual drugs (Fig. 5), it was demonstrated that the light blue area contained both drugs. The FF band in the 760-778 cm^{-1} region showed an intense peak in the coat and not in the core. However, a low FF peak intensity was found in the core at the interface with the coat (yellow), indicating very little migration of FF in the core. Comparing the Raman spectra of the yellow area with those of the individual drugs (Fig. 5), it was demonstrated that the yellow area contains both drugs. The mapping results of all other formulations were similar (data not shown). Core and coat were clearly distinguished from one another, with a small region (10 μm) of intermigration in between.

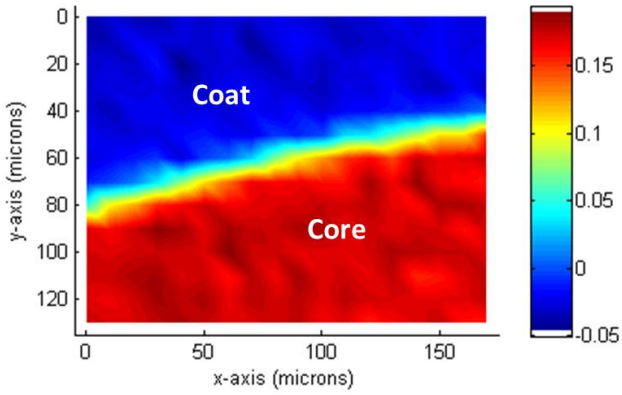


Figure 4. Raman mapping of ASA in co-extrudate F_1. A red color corresponds to a high peak intensity in the 745-760 cm^{-1} region, indicating the presence of ASA in the core. A blue color corresponds to a very low peak intensity, indicating the absence of ASA in the coat. A very low peak intensity was found in the coat at the interface with the core (light blue), indicating very little migration of ASA to the coat.

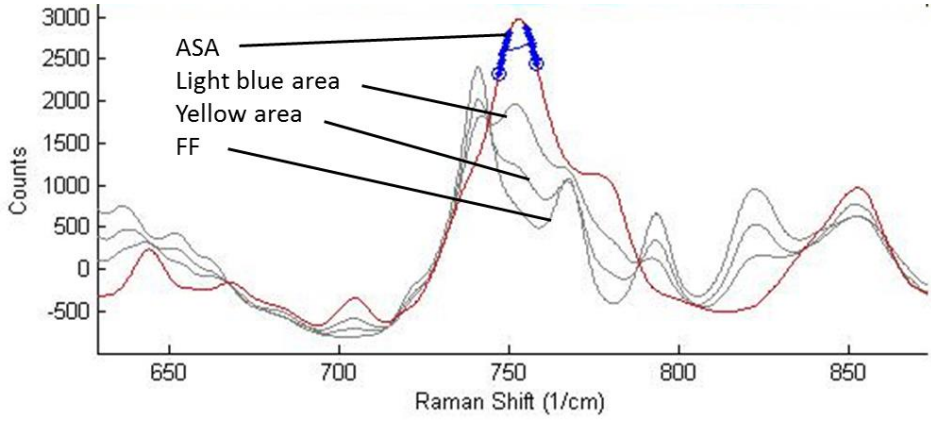


Figure 5. Selected region of the Raman spectra of FF, light blue area (Fig. 5), yellow area (Fig. 5), ASA.

The FF release from F_1, F_2, F_3 and F_4 was complete in 20, 30, 60 and 60 min, respectively (Fig. 6) and was not considered significantly different from the dissolution of the individual coat formulations during screening. Furthermore, the Kollidon® VA 64-based coat of F_1 and F_2 did not influence ASA release from the cores. ASA release from the Kollidon® VA 64 core (F_4) was clearly hindered by the Soluplus® coat. In comparison with the ASA release observed during the polymer screening (individual core), the ASA release rate from co-extrudate F_4 was significantly decreased (complete release after ± 60 min instead of 20 min). It was hypothesized that the Soluplus®-based coat partially covered the core surface during dissolution, thereby hindering ASA release.

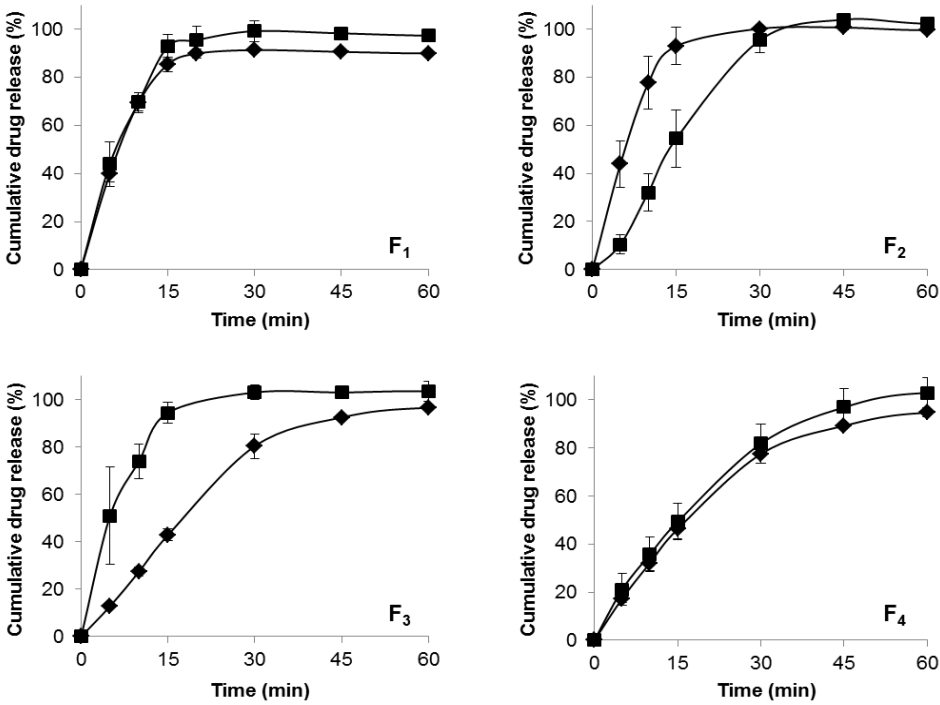


Figure 6. Mean FF (♦) and ASA (■) dissolution profiles (±S.D.) (n = 3) of co-extruded formulations (Table 4).

After 6 months of storage at ambient conditions (25 °C), all dissolution profiles were identical. The DSC thermograms of the coat (FF) remained unchanged, whereas a small ASA fraction (±1.5%) had recrystallized in the core of the co-extruded formulations. Furthermore, the SA concentration had increased significantly from 1.7 ± 0.12 (F_1 and F_3) and 2.3 ± 0.29 (F_2 and F_4) immediately after production to 7.4 ± 0.62 (F_1), 9.8 ± 0.74 (F_2), 9.7 ± 0.58 (F_3) and 11.0 ± 0.98 (F_4) after 6 months of storage. These results revealed that, although HME is often proposed as formulation technique for overcoming hydrolytic sensitivity, ASA was not stable in any of the co-extruded formulations.

4. Conclusions

This study identified co-extrusion as a promising technique to produce a multilayer FDC solid dosage form for oral application characterized by immediate release from both layers. Extrusion of ASA was challenging as in some carriers degradation to SA was observed, despite of the absence of water during thermal processing. However, core/coat dosage forms were successfully developed using four different polymer combinations: Kollidon® PF 12/Kollidon® VA 64, Kollidon® PF 12/Soluplus®, Kollidon® VA 64/Kollidon® VA 64 and Kollidon® VA 64/Soluplus®. All combinations showed good processability via co-extrusion, and the adhesion between core and coat was good. The solid state characterization revealed that both ASA and FF were molecularly dispersed in the co-extrudates. Raman mapping exposed very little intermigration of both drugs at the interface. 6 months of storage at ambient conditions revealed that ASA was not stable in any of the co-extruded formulations.

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CHAPTER 5

A critical reflection on co-extrusion

1. Introduction

Hot-melt extrusion (HME) and co-extrusion are valuable and versatile processing techniques for drug delivery systems with an exciting future within the pharmaceutical industry because they can be operated as continuous processes. In previous chapters (2 and 3) it was demonstrated that co-extrusion offers the extra opportunity (over HME) to combine different polymers in a co-extruded dosage form, through which drugs can be released with different release rates.

In chapter 4 it was shown that co-extrusion is also a suitable method for the production of fixed-dose combinations with both layers providing immediate release. Yet it can be questioned if in that case it is required to formulate the drugs in different layers. After all, in comparison to conventional HME, co-extrusion involves additional technical considerations (similar extrusion temperatures of the melts, melt viscosity matching and adhesion between the layers). The aim of the present study was to examine if co-extrusion offered an added value over conventional HME. Therefore, in this study the components of co-extruded formulations (developed in chapter 4) were blended and extruded. The processability, drug release, SA content and solid state characteristics of the blends were compared to those of the corresponding co-extrudates.

2. Materials and methods

2.1. Materials

The following polymers were used: Soluplus®, Kollidon® VA 64 and PF 12 (BASF, Ludwigshafen, Germany). Fenofibrate (FF, Roig-Farma, Barcelona, Spain) and acetylsalicylic

acid (ASA, Utag, Amsterdam, The Netherlands) were incorporated as hydrophobic and hydrophilic model drug, respectively. All other chemicals were of analytical grade.

2.2. Production of co-extrudates

Polymer and drug were premixed in a tumbling mixer (Turbula® T2A, W.A. Bachofen, Basel, Switzerland) for 20 min. Co-extrusion was performed using two co-rotating, fully intermeshing twin screw extruders (Prism Eurolab 16, ThermoFisher Scientific, Germany). The multimanifold co-extrusion die (Guill, West Warwick, USA) was connected to both extruders. Both melts were combined in the die to form two concentric layers, a core and a coat. Table 1 shows the composition of the co-extruded formulations as well as the extrusion conditions used for each formulation. All five heating segments of both extruders were set at the same temperature, except for the first heating zone which was set at 70 °C to avoid sticking of the powder in the feed section. The premixes were fed into the corresponding extruders using loss-in-weight powder feeders (Brabender Flexwall®, Duisburg, Germany). The screw speed was kept constant at 120 rpm (core) and 180 rpm (coat). The co-extrusion die was designed with a core diameter of 2 mm and a coat thickness of 1 mm, resulting in a total die diameter of 4 mm. After cooling down to room temperature, the cylindrical co-extrudates were manually cut into mini-matrices of 2 mm length.

Table 1. Composition and extrusion parameters of co-extruded formulations.

	Carrier		Drug concentration (%)		Extrusion temperature (°C)			Feed rate (g/h)	
	Core	Coat	Core (ASA)	Coat (FF)	Core	Coat	Die	Core	Coat
F_1	Kollidon® PF 12	Kollidon® VA 64	20	20	120	130	95	300	545
F_2	Kollidon® VA 64	Kollidon® VA 64	20	20	130	130	105	300	545
F_3	Kollidon® PF 12	Soluplus®	20	20	120	100	95	300	545
F_4	Kollidon® VA 64	Soluplus®	20	20	130	105	105	300	545

2.3. Production of extrudates

The components of formulations F_1-F_4 were blended and extruded. Besides, mixtures composed of both drugs and a single carrier were also extruded. The extrudates were evaluated for processability, macroscopic properties (visual inspection of surface, die swell quantification using marking gauge), salicylic acid content (ASA formulations) and in vitro drug release. The mixtures were hot-melt extruded using a co-rotating, fully intermeshing twin screw extruder (Prism Eurolab 16, ThermoFisher Scientific, Germany) having a length-to-diameter ratio of 25/1. The co-rotating screws consisted of three mixing sections and a densification zone. A strand die with a diameter of 4 mm was mounted at the end of the extruder. The extrusion temperature varied according to the formulation, but all five heating segments of the extruder were set at the same temperature, except for the first heating zone which was set at 70 °C to avoid sticking of the powder in the feed section. The premixes were fed into the extruder using a loss-in-weight powder feeder (Brabender flexwall®, Duisburg, Germany). The feed rate and screw speed were kept constant at 600 g/h and 180 rpm, respectively. After cooling down to room temperature, the cylindrical extrudates were manually cut into mini-matrices of 2 mm length. The dimensions of the resulting extrudates

were 4 x 2 mm. The composition and extrusion temperature of the hot-melt extruded formulations are shown in Table 2.

Table 2. Composition and extrusion temperature of hot-melt extruded formulations.

	Composition (%)					Extrusion temperature (°C)	
	ASA	FF	Kollidon® PF 12	Kollidon® VA 64	Soluplus®	Barrel	Die
F_1,	7.1	12.9	28.4	51.6	-	130	95
F_2,	7.1	12.9	-	80	-	130	105
F_3,	7.1	12.9	28.4	-	51.6	120	95
F_4,	7.1	12.9	-	28.4	51.6	130	105
F_5	7.1	12.9	80	-	-	120	95
F_6	7.1	12.9	-	-	80	105	105

2.4. Determination of free salicylic acid

The salicylic acid (SA) content in the extrudates was assessed according to the USP 32 monograph for Aspirin tablets.

2.5. In vitro drug release

Dissolution studies were performed using USP apparatus 1 (baskets). The equipment consisted of a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (VanKel Industries, NJ, USA). Acetate buffer pH 4.5 containing 0.05 M sodium lauryl sulfate was used as dissolution medium. Sink conditions were maintained during the experiments. The temperature of the dissolution medium (900 ml) was kept constant at 37 ±

0.5 °C. The rotational speed of the baskets was set to 100 rpm. Samples (5 ml) were withdrawn at 5, 10, 15, 20, 30, 45, 60 (and 90) min.

ASA and FF concentration were determined using a validated HPLC method. The HPLC equipment (Merck-Hitachi, Darmstadt, Germany) consisted of a gradient solvent pump set at a constant flow rate of 1 ml/min, an autosampler, a reversed-phase C-18 column (LiChrospher® 100 RP-18 (5 μm)) (250 x 4 mm) and guard column (4 x 4 mm) and a UV detector set at 285 nm. The injection volume was 20 μl. An automatic integration system (software D-7000 Multi-Manager) was used for peak integration. The mobile phase consisted of mixtures of buffer solution pH 2.9 (prepared by dissolving 136 mg of monobasic potassium phosphate in 1000 mL of distilled water and adjusting the pH with dilute phosphoric acid to 2.9 ± 0.05 [1] and methanol: initially using a 57:43-ratio (to elute ASA and SA, while FF was retained on the column), after 14.5 min the ratio of the mobile phase was rapidly changed to 10:90 90% methanol (to elute the hydrophobic FF from the column), after 22.0 min the ratio between the aqueous and organic phase was again set at 57:43 and the column was equilibrated until 31.0 min prior to the following analysis.

2.6. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to study the solid state properties of the extrudates. The thermal behavior of the individual components, physical mixtures and extrudates was evaluated using a Q2000 DSC (TA Instruments, Leatherhead, UK). The system was equipped with a refrigerated cooling system. Samples (5-10 mg) were accurately weighed and hermetically sealed in aluminum pans (TA Instruments, Leatherhead, UK).They were cooled to -70 °C, followed by heating to 170 °C at a linear heating rate of 10 °C/min.

3. Results and discussion

In order to examine if co-extrusion offered an added value over HME the processability, drug release, SA content and solid state characteristics of the blends were compared to those of the corresponding co-extrudates. Extrudates composed of both drugs and a single carrier were also characterized. All mixtures were processable via hot-melt extrusion at the specified temperatures (Table 2). The resulting extrudates were rigid and exhibited a smooth surface. One formulation ($F_{4'}$) showed significant die swell (6 mm). Fig. 1 shows the FF release from the extruded blends in comparison with the corresponding co-extrudates. In general, the FF release rate from the blend extrudates was lower compared to the co-extruded formulations (similarity factor <50). Full FF release was observed within 20, 30, 60 and 60 min for F_1, F_2, F_3, F_4 and after 30, 45, >60 and >60 min for $F_{1'}$, $F_{2'}$, $F_{3'}$, $F_{4'}$, respectively. The difference in FF release was most pronounced for formulations $F_{3'}$ and $F_{4'}$, which both contained Soluplus®. Apparently, the use of a combination of Soluplus® and a Kollidon® polymer hindered the matrix disintegration, whereby the FF release was delayed (which was in agreement with the visual observation). The difference between F_2 and $F_{2'}$ could be explained by the difference in diffusion depth. For formulations F_1 and $F_{1'}$, the difference in FF release was small.

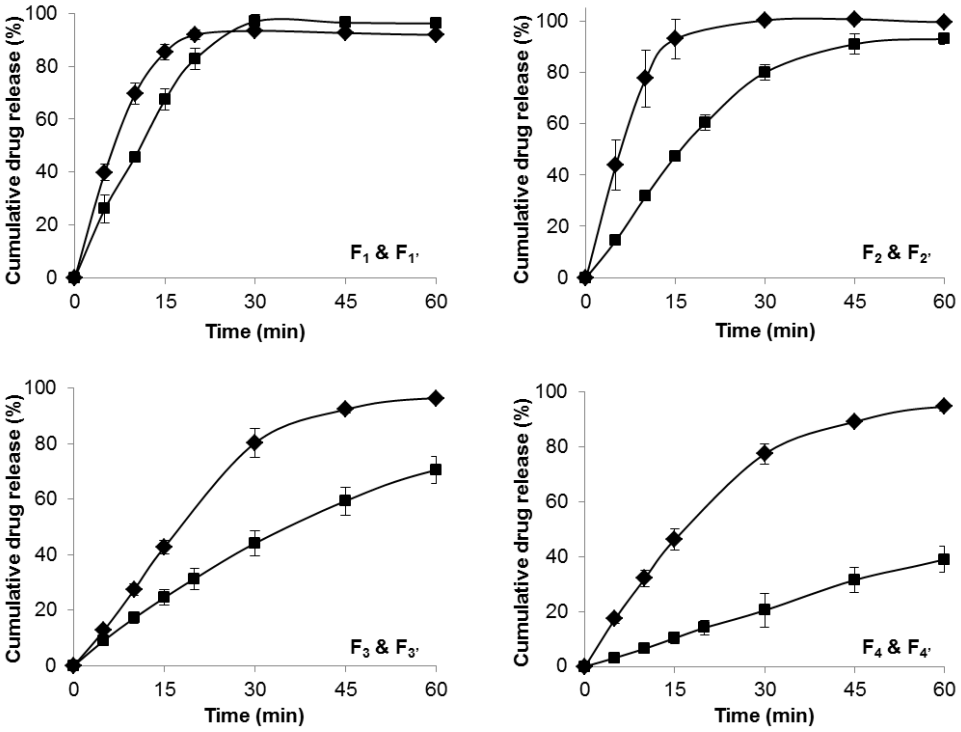

Figure 1: Comparison of FF release from (♦) coat of co-extrudates and (■) blend extrudates: F_1 and F_1', F_2 and F_2', F_3 and F_3', F_4 and F_4'.

The ASA release from the extruded blends in comparison to the corresponding co-extrudates is represented in Fig. 2. Whereas there was a small difference in release between F_1' and F_1 (similarity factor <50), the release of F_2' equaled that of F_2 (similarity factor >50). The remarkably lower ASA release rate from F_3' and F_4' in comparison to their corresponding co-extrudates could again be explained by the presence of Soluplus®. A supplementary dissolution test of a formulation composed of 20% ASA (molecularly dispersed) in Soluplus® demonstrated that Soluplus® improved the ASA release rate (100% release after 60 min) to a lower extent than the Kollidon® polymers (100% release after 10-20 min). Furthermore, as

also described for the FF release, the combination of Soluplus® and a Kollidon® polymer resulted in a slower matrix disintegration, whereby the ASA release rate was lowered in comparison with matrices composed of one of the polymers.

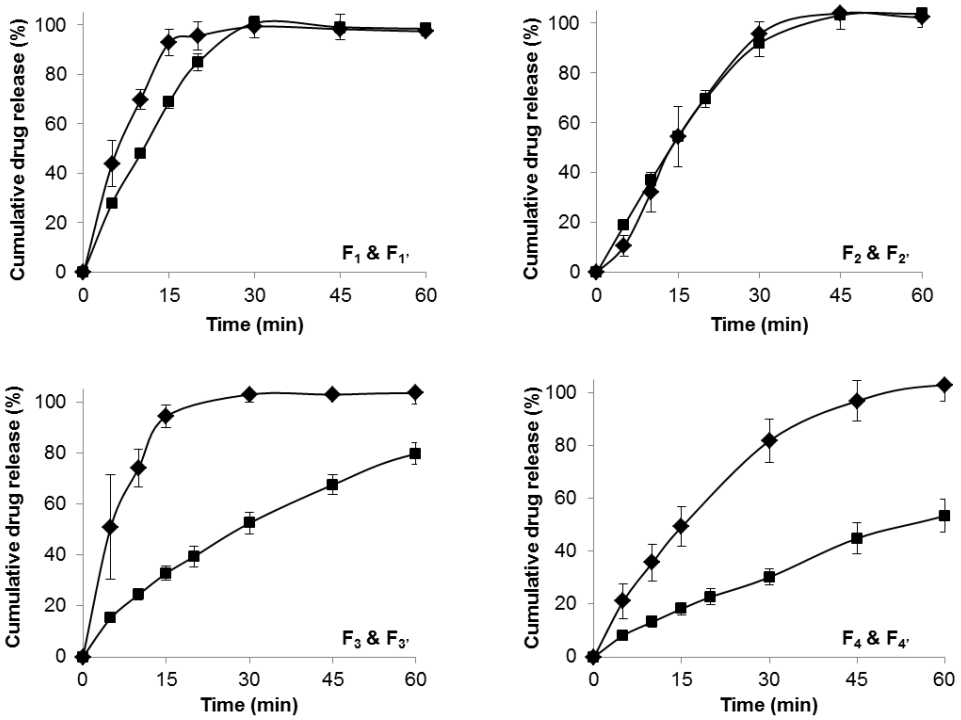

Figure 2: Comparison of ASA release from (♦) core of co-extrudates and (■) blend extrudates: F_1 and F_1', F_2 and F_2', F_3 and F_3', F_4 and F_4'.

The dissolution profiles of formulations F_5 and F_6 are shown in Fig. 3. The ASA and FF release from Kollidon® PF 12 (F_5) was already complete in 15 min. The release rate exceeded those of all co-extruded formulations (F_1-F_4). ASA and FF release from Soluplus® (F_6) was incomplete after 1 h. During previous studies it was already demonstrated that

despite its micellar character, Soluplus® does not always enhance drug release. Whereas diclofenac sodium release from Soluplus® matrices was complete in 30 min (chapter 3), hydrochlorothiazide release was incomplete after 1 h (chapter 2) and FF release rate (chapter 4) was lower than expected. A recent study revealed that Soluplus® can be used to delay the release of water soluble drugs as well as being used as solubilizer in case of poorly water soluble drugs [2].

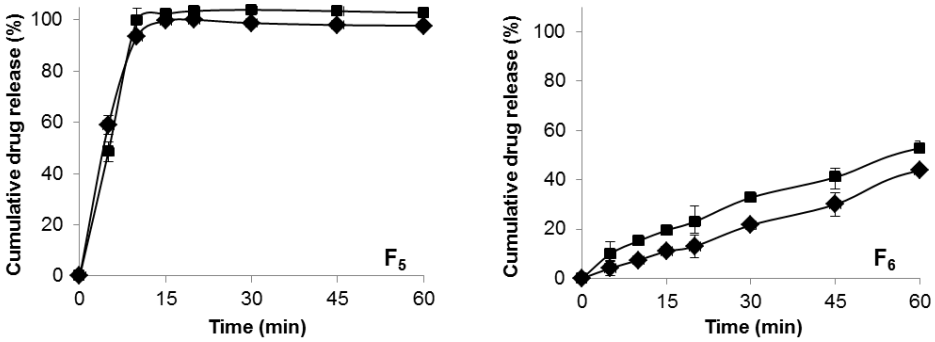

Figure 3: Mean FF (♦) and ASA (■) dissolution profiles (±S.D.) (n = 3) of blend extrudates F_5 and F_6.

The SA content of the blend extrudates were respectively 1.03 (± 0.13), 0.72 (± 0.08), 1.08 (± 0.11) and 1.81 (± 0.15)% for $F_{1'}$, $F_{2'}$, $F_{3'}$ and $F_{4'}$, while in the core of the respective co-extrudates 1.7 (± 0.12) (F_1 and F_3) and 2.3 (± 0.29) (F_2 and F_4) % SA was found. Comparison of the SA content in blend versus co-extruded formulations pointed out that the conventional hot-melt extrusion process was slightly favorable in terms of ASA stability. This could be explained by the higher shear forces (higher torque, higher die pressure, smaller die)

to which ASA was exposed during co-extrusion in comparison to HME (Table 3). The SA concentration of F_5 and F_6 was 1.34 (± 0.21) and 0.77 (± 0.10), respectively.

Table 3. Comparison of the extruder torque and die pressure between core of co-extruded formulation and blend formulation.

	Torque (% motor load)	Die pressure (bar)
F_1	80	25
$F_{1'}$	65	1
F_2	80	40
$F_{2'}$	70	1
F_3	80	25
$F_{3'}$	40	1
F_4	80	40
$F_{4'}$	55	1

The solid state of the blend extrudates ($F_{1'}$-$F_{4'}$) and F_5 and F_6 was characterized using DSC. As described in chapter 4 no drug crystals were detected in any co-extruded formulation. DSC exposed a crystalline ASA fraction of 22.1, 37.9, 42.1 and 16.9% in $F_{1'}$, $F_{2'}$, $F_{4'}$ and F_5. As an example, the solid state comparison between co-extruded formulation F_2 and blend formulation F_2' is shown in Fig. 4. These intermediate forms containing both crystalline and amorphous drug are undesirable from a stability point of view as there is a higher risk for the amorphous fraction to recrystallize.

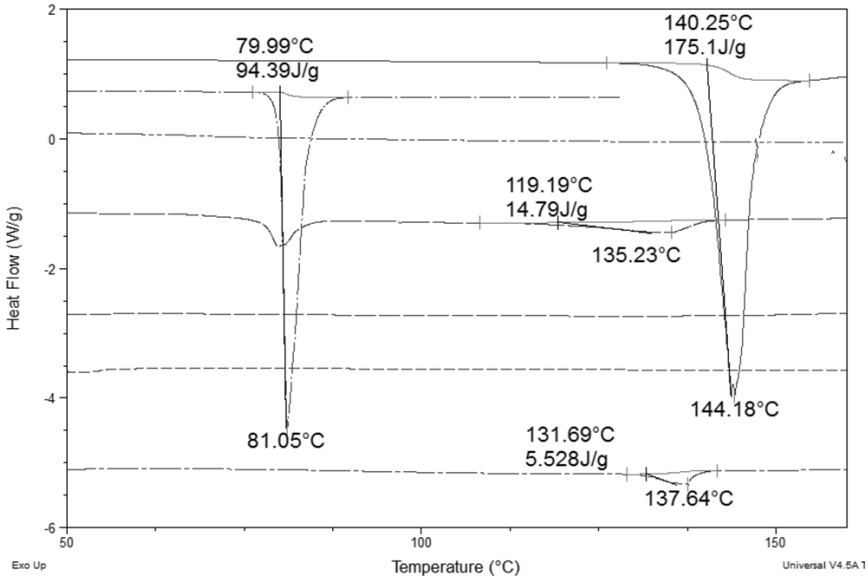

Figure 4: Solid state comparison between co-extruded formulation F_2 and blend formulation F_2'. From top to bottom: ASA, FF, Kollidon® VA 64, physical mixture of F_2', core of co-extruded formulation F_2, coat of co-extruded formulation F_2, extrudate F_2'.

4. Conclusions

This study showed that fixed-dose combinations with immediate drug release can be produced via HME and that it will not always be mandatory to proceed to co-extrusion. Using Kollidon® PF 12 as a carrier, a hot-melt extruded formulation was developed providing immediate release of both drugs (within 15 min). The conventional hot-melt extrusion process was slightly favorable in terms of ASA stability (lower SA content).

Acknowledgements

BASF is acknowledged for generously supplying their polymers.

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GENERAL CONCLUSION

The overall aim of this project was to evaluate the potential of hot-melt co-extrusion for the production of multilayer oral dosage forms.

Hot-melt co-extrusion seemed a promising technique to produce in a single step fixed-dose combination (FDC) mini-matrices. A core/coat dosage form was developed, wherein the core and coat exhibited sustained and immediate release properties, using a combination of polycaprolactone (core) and PEO/PEG (coat). There was good adhesion between the two layers. The in vivo performance of the test formulation was not significantly different from that of a reference formulation.

Co-extrusion also proved to be a promising technique to produce multilayer mini-matrices with dual drug release. Core/coat dosage forms were developed using two different polymer combinations (ethylcellulose/Soluplus® and polycaprolactone/PEO). Co-extruded formulations composed of polycaprolactone (core) and PEO/PEG (coat) were preferable because they allowed extrusion at a lower temperature and they provided better mechanical properties. Furthermore, the adhesion force between the two layers depended on extrusion temperature and drug load. By varying the DS ratio in coat and core, the in vitro and in vivo drug release could be controlled, demonstrating the flexibility of the dosage form.

Furthermore, a multilayer FDC solid dosage form characterized by immediate release from both layers was developed via co-extrusion. Extrusion of ASA was challenging as in some carriers degradation to SA was observed, despite of the absence of water during thermal processing. However, core/coat dosage forms were successfully developed using four different polymer combinations: Kollidon® PF 12/Kollidon® VA 64, Kollidon® PF 12/Soluplus®, Kollidon® VA 64/Kollidon® VA 64 and Kollidon® VA 64/Soluplus®. All combinations showed good processability via co-extrusion, and the adhesion between core and coat was good. Very little intermigration of both drugs was exposed at the interface.

The final part of this study showed that fixed-dose combinations with immediate drug release can be produced via HME and that it will not always be mandatory to proceed to co-extrusion. Using Kollidon® PF 12 as a carrier, a hot-melt extruded formulation was developed providing immediate release of both drugs (within 15 min). The conventional hot-melt extrusion process was slightly favorable in terms of ASA stability (lower SA content).

Overall, this research project has shown that hot-melt co-extrusion is a promising and versatile technique to produce in a single step multilayer oral solid dosage forms. Nevertheless, an extension of this project is essential to fully investigate the potential of co-extrusion applications for oral drug delivery, such as the combination of two sustained release layers in a co-extruded dosage form. Other aspects that are worthwhile exploring are: (1) combining more than two different layers with different drugs; (2) producing different shapes of co-extruded formulations, e.g. multilayer sheets instead of concentric core/coat systems; (3) formulating non-compatible drugs into different layers and investigating the (in)compatibility at the interface; (4) exploring the use of enteric coating polymers and their compatibility with immediate/sustained release polymers; (5) synthetizing “tailor made” polymers for co-extrusion that exhibit the desired properties in terms of processability, drug release profile, adhesion, etc.

SUMMARY

Despite more than half a century of experience in the plastics and food industry, hot-melt co-extrusion is a relatively new technology in the pharmaceutical industry. Recently, it has been promoted as an innovative continuous technology providing great potential for the production of drug delivery systems. Except from an implant (Implanon®) and a vaginal ring (Nuvaring®), there are no co-extruded dosage forms on the market so far. Therefore, the aim of this work was to evaluate the potential of co-extrusion for the production of oral solid dosage forms. Polymers were characterized and on the basis thereof combined into multilayer dosage forms offering immediate release, controlled release or a combination hereof. Using different model drugs parameters such as processability, in vitro drug release and solid state characteristics were evaluated. Additionally, a stability and in vivo study were performed for some selected formulations.

Chapter 1 described the polymer characteristics relevant for hot-melt co-extrusion. Several polymers were screened on the basis of their thermal behavior (glass transition (T_g)/melting temperature (T_m), thermal stability), melt flow index and processability via hot-melt extrusion. Taking into account the T_g/T_m, the minimum extrusion temperature, the degradation temperature and the melt viscosity CAPA® 6506, Polyox® WSR N10 and Eudragit® E PO demonstrated good suitability for pharmaceutical hot-melt extrusion. Pure Soluplus® and Kollidon® SR also showed good extrudability, but within a narrow temperature range. Extrusion of Eudragit® RS PO without any plasticizer was not possible because the required temperature approached the degradation temperature of the polymer. Ethocel® std 10 and Kollidon® 30 will require a plasticizer because of their high T_g, melt viscosity and a too small difference between T_g and degradation temperature in case of Kollidon® 30.

Chapter 2 evaluated hot-melt co-extrusion as manufacturing technique for multilayer (core/coat) dosage forms, the core providing sustained drug release and the coat immediate drug release. In this study polymers were selected which can be combined in a co-extruded

dosage form. Several thermoplastic polymers were hot-melt extruded and evaluated for processability and macroscopic properties (surface smoothness, die swell). Metoprolol tartrate (MPT) and hydrochlorothiazide (HCT) were incorporated as sustained and immediate release model drugs, respectively. Based on the polymer screening experiments a combination of polycaprolactone (core) and polyethylene oxide (coat) was selected for co-extrusion trials, taking into account their drug release profiles and extrusion temperature (70 °C). This combination (containing 10% HCT in the coat and 45% MPT in the core) was successfully co-extruded (diameter core: 3 mm/thickness coat: 0.5 mm). Adhesion between the two polymer layers was good. HCT release from the coat was complete within 30 min, while MPT release was sustained over 24 h (55%, 70%, 85% and 100% after 4, 8, 12 and 24 h, respectively). DSC, XRD and Raman spectroscopy revealed that MPT remained crystalline during extrusion, whereas HCT was dissolved in the polyethylene oxide matrix. The in vivo study revealed no significant differences between the experimental formulation and the reference formulation (Zok-Zid® tablet). Fixed-dose combination mini-matrices with good in vitro and in vivo performance were successfully developed by means of co-extrusion, using a combination of polycaprolactone and polyethylene oxide.

Chapter 3 assessed hot-melt co-extrusion for the development of a multilayered dosage form characterized by a dual release profile of the same drug. Co-extrudates consisted of two concentric polymer matrices: a core having a lipophilic character and a coat with a hydrophilic character. Diclofenac sodium (DS) was incorporated as model drug in both layers. Several polymers were screened on the basis of their processability via hot-melt extrusion (HME) and in vitro drug release. Polymer combinations with suitable properties (i.e., similar extrusion temperature, appropriate drug release profile) were processed via co-extrusion. (Co-) extruded samples were characterized in terms of solid state (XRD, SEM), in vitro drug release, core/coat adhesion, and bioavailability. Based on the polymer screening, two polymer

combinations were selected for co-extrusion: ethylcellulose (core) combined with Soluplus® (coat) and polycaprolactone (core) with PEO (coat). These combinations were successfully co-extruded. XRD revealed that DS remained crystalline during extrusion in ethylcellulose, Soluplus®, polycaprolactone, and PEO. The polycaprolactone/PEO combination could be processed at a lower temperature (70 °C), vs. 140 °C for ethylcellulose/Soluplus®. The maximum drug load in core and coat depended on the extrusion temperature and the die dimensions, while adhesion between core and coat was mainly determined by the drug load and by the extrusion temperature. In vitro drug release from the co-extruded formulations was reflected in the in vivo behavior: formulations with a higher DS content in the coat (i.e., faster drug release) resulted in higher C_{max} and higher AUC values. Multilayer dosage form with dual drug release were successfully developed by means of co-extrusion.

Chapter 4 evaluated the use of hot-melt co-extrusion for the production of a multilayer fixed-dose combination solid dosage form for oral application characterized by immediate release for both layers, the layers containing different drugs with different water-solubility. In this study polymers were selected which can be combined in a co-extruded dosage form. Several polymers were screened on the basis of their processability via hot-melt extrusion, macroscopic properties, ASA decomposition and in vitro drug release. Acetylsalicylic acid (ASA) and fenofibrate (FF) were incorporated as hydrophilic and hydrophobic model drugs, respectively. Based on the polymer screening experiments Kollidon® PF 12 and Kollidon® VA 64 were identified as useful ASA carriers (core), while Soluplus®, Kollidon® VA 64 and Kollidon® 30 were applicable as FF carriers (coat). The combination of Kollidon® 30 (coat) with Kollidon® PF 12 or Kollidon® VA 64 (core) failed in terms of processability via co-extrusion. All other combinations (containing 20% ASA in the core and 20% FF in the coat) were successfully co-extruded (diameter core: 2 mm / thickness coat: 1 mm). All formulations showed good adhesion between core and coat. ASA release

from the core was complete within 15-30 min (Kollidon® PF 12) or 30-60 min (Kollidon® VA 64), while FF release was complete within 20-30 min (Kollidon® VA 64) or 60 min (Soluplus®). DSC and XRD revealed that both drugs were molecularly dispersed in the carriers. Raman mapping exposed very little intermigration of both drugs at the interface. Fixed-dose combinations with good in vitro performance were successfully developed by means of co-extrusion, both layers providing immediate release.

Chapter 5 investigated if co-extrusion offered an added value over hot-melt extrusion. Components of co-extruded formulations were blended (in the same ratio as in the co-extruded formulations) and extruded. The processability, drug release and solid state characteristics of the blends were compared to those of the corresponding co-extrudates. Extrudates composed of both drugs and a single carrier were also characterized. Using Kollidon® PF 12 as a carrier, a hot-melt extruded formulation was developed providing immediate release of both drugs (within 15 min). The conventional hot-melt extrusion process was slightly favorable in terms of ASA stability (lower SA content). This study showed that fixed-dose combinations with immediate drug release can be produced via HME and that it will not always be mandatory to proceed to co-extrusion.

It can be concluded that hot-melt co-extrusion is a promising and versatile technique to produce – in a single step – multilayer oral solid dosage forms.

SAMENVATTING

Ondanks meer dan een halve eeuw ervaring in de plastic- en voedingsindustrie, is 'hot-melt' co-extrusie een relatief nieuwe technologie in de farmaceutische industrie. Co-extrusie werd recentelijk naar voren gebracht als een innovatieve techniek met veel potentieel voor de productie van geneesmiddeltoedieningssystemen. Met uitzondering van een implantaat (Implanon®) en een vaginale ring (Nuvaring®), zijn er tot op heden geen geco-extrudeerde doseringsvormen op de markt. Bijgevolg was het doel van dit werk om het potentieel van co-extrusie voor de productie van orale vaste doseringsvormen te evalueren. Polymeren werden gekarakteriseerd en op basis daarvan gecombineerd in meerlagige doseringsvormen met onmiddellijke of vertraagde vrijstelling of een combinatie van beide. Gebruik makend van verschillende modelgeneesmiddelen werden parameters zoals verwerkbaarheid, in vitro geneesmiddelvrijstelling en vaste toestand karakteristieken geëvalueerd. Bovendien werd een stabiliteits- en een in vivo studie uitgevoerd voor enkele geselecteerde formulaties.

Hoofdstuk 1 beschreef de polymeerkarakteristieken, die relevant zijn voor 'hot-melt' co-extrusie. Verschillende polymeren werden gescreend op basis van hun thermische eigenschappen (glastransitietemperatuur (T_g)/smeltpunt (T_m), thermische stabiliteit), 'melt flow' index en verwerkbaarheid via 'hot-melt' extrusie (HME). Gezien hun T_g/T_m, minimale extrusietemperatuur, degradatietemperatuur en smeltviscositeit bleken CAPA® 6506, Polyox® WSR N10 en Eudragit® E PO geschikte polymeren voor farmaceutische HME. Zuiver Soluplus® en Kollidon® SR waren ook vlot extrudeerbaar, echter binnen een nauw temperatuurgebied. Puur Eudragit® RS PO (zonder weekmaker) was niet extrudeerbaar aangezien de temperatuur die hiervoor vereist was de degradatietemperatuur van het polymeer benaderde. Ethocel® std 10 en Kollidon® 30 zullen een weekmaker vereisen omwille van hun hoge T_g, smeltviscosititeit en door een te klein verschil tussen T_g en degradatietemperatuur in het geval van Kollidon® 30.

Hoofdstuk 2 evalueerde 'hot-melt' co-extrusie als productietechniek voor meerlagige (kern/omhulsel) doseringsvormen, waarin de kern zorgde voor een vertraagde en het omhulsel voor een onmiddellijke geneesmiddelvrijstelling. In deze studie werden polymeren geselecteerd die gecombineerd kunnen worden in een geco-extrudeerde doseringsvorm. Verschillende thermoplastische polymeren werden 'hot-melt' geëxtrudeerd en geëvalueerd op verwerkbaarheid en macroscopische eigenschappen (gladheid van het oppervlak, zwelling van het extrudaat). Metoprolol tartraat (MPT) en hydrochloorthiazide (HCT) werden geïncorporeerd als modelgeneesmiddelen voor respectievelijk vertraagde en onmiddellijke vrijstelling. Op basis van de resultaten van de polymeerscreening werd een combinatie van polycaprolacton (kern) en polyethyleenoxide (omhulsel) weerhouden voor co-extrusie experimenten, rekening houdende met hun geneesmiddelvrijstellingsprofiel en extrusietemperatuur (70 °C). Deze combinatie (bevattende 10% HCT in het omhulsel en 45% MPT in de kern) werd met succes geco-extrudeerd (diameter kern: 3 mm/dikte omhulsel: 0,5 mm). De adhesie tussen de twee polymeerlagen was goed. HCT was binnen 30 min volledig vanuit het omhulsel vrijgesteld, terwijl MPT over een periode van 24 uur werd vrijgesteld (55%, 70%, 85% en 100% na respectievelijk 4, 8, 12 en 24 u). Dynamische differentiecalorimetrie (DSC), X-straal diffractie (XRD) en Raman spectroscopie onthulden dat MPT kristallijn bleef gedurende extrusie, terwijl HCT opgelost was in de polyethyleenoxide matrix. De in vivo studie kon geen significante verschillen aan het licht brengen tussen de experimentele formulatie en de referentieformulatie (Zok-Zid® tablet). 'Fixed-dose combination' (FDC) mini-matrices met goede in vitro en in vivo eigenschappen werden met succes ontwikkeld door middel van co-extrusie, gebruik makend van een combinatie van polycaprolacton en polyethyleenoxide.

Hoofdstuk 3 ging na of 'hot-melt' co-extrusie toeliet meerlagige doseringsvormen gekarakteriseerd door een tweeledige vrijstelling van eenzelfde geneesmiddel, te ontwikkelen. De co-extrudaten bestonden uit twee concentrische polymeermatrices: een kern met een lipofiel en een omhulsel met een hydrofiel karakter. Natrium diclofenac (DS) werd geïncorporeerd als modelgeneesmiddel in beide lagen. Verschillende polymeren werden gescreend op basis van hun verwerkbaarheid via HME en in vitro geneesmiddelvrijstelling. Polymeercombinaties met geschikte eigenschappen (d.i. gelijkaardige extrusietemperatuur, geschikt geneesmiddelvrijstellingsprofiel) werden geco-extrudeerd. Ge(co-)extrudeerde stalen werden gekarakteriseerd in termen van vaste toestand karakteristieken (XRD, SEM), in vitro geneesmiddelvrijstelling, adhesie tussen kern en omhulsel en biologische beschikbaarheid. Gebaseerd op de polymeerscreening werden twee polymeercombinaties geselecteerd voor co-extrusie: ethylcellulose (kern) in combinatie met Soluplus® (omhulsel) en polycaprolacton (kern) met polyethyleenoxide (omhulsel). Deze combinaties werden succesvol geco-extrudeerd. XRD toonde aan dat DS kristallijn bleef gedurende extrusie in ethylcellulose, Soluplus®, polycaprolacton en polyethyleenoxide. De polycaprolacton/polyethyleenoxide combinatie kon verwerkt worden bij een lagere temperatuur (70 °C), t.o.v. 140 °C voor ethylcellulose/Soluplus®. De maximaal mogelijke geneesmiddelbelading in kern en omhulsel hing af van de extrusietemperatuur en matrijsafmetingen, terwijl de adhesie tussen kern en omhulsel voornamelijk bepaald werd door geneesmiddelbelading en extrusietemperatuur. De in vitro geneesmiddelvrijstelling vanuit de geco-extrudeerde formulaties werd weerspiegeld in hun in vivo gedrag: formulaties met een hoger DS gehalte in het omhulsel (d.i. snellere vrijstelling) resulteerden in een hogere C_{max} en hogere AUC waarden. Meerlagige doseringsvormen met tweeledige geneesmiddelvrijstelling werden met succes ontwikkeld m.b.v. co-extrusie.

Hoofdstuk 4 evalueerde het gebruik van 'hot-melt' co-extrusie voor de productie van een meerlagige FDC doseringsvorm, gekarakteriseerd door een onmiddellijke vrijstelling vanuit beide lagen en waarin de lagen geneesmiddelen met verschillende oplosbaarheden bevatten. In deze studie werden polymeren geselecteerd die gecombineerd kunnen worden in een geco-extrudeerde doseringsvorm. Verschillende polymeren werden gescreend op basis van hun verwerkbaarheid via HME, macroscopische eigenschappen, acetylsalicylzuur (ASA) afbraak en in vitro geneesmiddelvrijstelling. ASA en fenofibraat (FF) werden geïncorporeerd als respectievelijk hydrofiel en hydrofoob modelgeneesmiddel. Op basis van de polymeerscreening werden Kollidon® PF 12 en Kollidon® VA 64 geïdentificeerd als bruikbare ASA dragers (kern), terwijl Soluplus®, Kollidon® VA 64 en Kollidon® 30 geschikt waren als FF dragers (omhulsel). Kollidon® 30 (omhulsel) kon niet met Kollidon® PF 12 of Kollidon® VA 64 (kern) gecombineerd worden via co-extrusie. Alle andere combinaties (bevattende 20% ASA in de kern en 20% FF in het omhulsel) werden succesvol geco-extrudeerd (diameter kern: 2 mm/dikte omhulsel: 1 mm). Alle formulaties vertoonden goede adhesie tussen kern en omhulsel. De ASA vrijstelling vanuit de kern was compleet binnen 15-30 min (Kollidon® PF 12) of 30-60 min (Kollidon® VA 64), terwijl dat voor FF na 20-30 min (Kollidon® VA 64) of 60 min (Soluplus®) was. DSC en XRD onthulden dat beide geneesmiddelen moleculair gedispergeerd waren in de dragers. Raman mapping toonde zeer weinig intermigratie van beide geneesmiddelen ter hoogte van het grensvlak aan. FDC's met goede in vitro vrijstelling werden ontwikkeld d.m.v. co-extrusie, waarin beide lagen een onmiddellijke vrijstelling garandeerden.

Hoofdstuk 5 onderzocht of co-extrusie een meerwaarde bood t.o.v. HME. De componenten van geco-extrudeerde formulaties werden gemengd (in dezelfde verhouding als in de co-extrudaten) en geëxtrudeerd. De verwerkbaarheid, geneesmiddelvrijstelling en vaste toestand karakteristieken van de mengextrudaten werden vergeleken met deze van de

overeenkomstige co-extrudaten. Extrudaten waarbij beide geneesmiddelen in één enkele drager waren ingebed, werden ook gekarakteriseerd. Gebruik makend van Kollidon® PF 12 als drager werd een formulatie ontwikkeld via 'hot-melt' extrusie waaruit beide geneesmiddelen onmiddellijk (binnen 15 min) werden vrijgesteld. Het conventionele HME proces genoot een lichte voorkeur in termen van ASA stabiliteit. Deze studie toonde aan dat FDC's met onmiddellijke geneesmiddelvrijstelling aangemaakt kunnen worden via HME en dat het niet steeds nodig zal zijn om, voor deze toepassing, over te gaan tot co-extrusie.

Er kan besloten worden dat 'hot-melt' co-extrusie een veelbelovende en veelzijdige techniek is om – in één enkele stap – meerlagige orale vaste doseervormen te produceren.

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2008 – 2009	Pharmacist internship
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PUBLICATIONS IN PEER REVIEWED JOURNALS

Co-extruded solid solutions as immediate release fixed-dose combinations;
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POSTER PRESENTATIONS

Hot-melt co-extrusion as manufacturing technique for multilayer mini-matrices with dual drug release;
L. Dierickx, C. Vervaet, J.P. Remon;
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Scientific Afternoon, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium, May 2011.

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Co-extrusion as manufacturing technique for fixed-dose combination mini-tablets;
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8th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Istanbul, Turkey, March 2012.

ATTENDED COURSES, CONFERENCES AND WORKSHOPS

Leadership Foundation course - Ghent University, Ghent, Belgium, November 2011.

Differential scanning calorimetry training course - TA Instruments, Ghent, Belgium, June 2010.

Modulated differential scanning calorimetry training course - TA Instruments, Ghent, Belgium, June 2010.

IWPCPS-12 - assa international, Lille, France, June 2010.

Pharmaceutical hot-melt extrusion workshop - Coperion GmbH, Stuttgart ,Germany, April 2010.

Course: Design of Experiments, Ghent, Belgium, January 2010.

2nd APV Hot-melt extrusion workshop and its use in manufacturing of pharmaceutical dosage forms, Ludwigshafen, Germany, December 2009.