Ghent University

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NON-CONVENTIONAL POLYMERS AS MATRIX EXCIPIENTS FOR HOT MELT EXTRUDED ORAL-RELEASE FORMULATIONS

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

^{1}H-NMR	^{1}H-Nuclear Magnetic Resonance
AIBN	Azoisobutyronitrile
API	Active Pharmaceutical Ingredient
ATR	Attenuated total reflectance
BSA	Bovine serum albumin
CEL	Celecoxib
DAD	Diode Array Detector
DMAEMA	Dimethylaminoethylmethacrylate
DMF	Deuterated Dimethylformamide
Dyph	Diprophylline
EC	Ethylcellulose
ENG	Etonorgestrel
EudrE	Eudragit® E
EudrE-Q	Quaternized Eudragit® E
EVA	Ethylene Vinylacetate
FBT	Fenofibrate
FTIR	Fourier-transform infrared
HME	Hot Melt Extrusion
HPC	Hydroxypropyl Cellulose
HPMC	Hydroxylpropyl Methyl Cellulose
HS	Hard Segment
HSM	Hot Stage Microscopy
IBP	Ibuprofen
IM	Injection Molding
iso-BMA	Isobornylmethacrylate
IUD	Intrauterine Device
IVR	Intravaginal Rings
LCST	Lower Critical Solution Temperature
MCR	Multivariate Curve Resolution
MDI	4,4'-Methylene Diphenyl Diisocyanate
MDSC	Modulated Differential Scanning Calorimetry
MMA	Methylmethacrylate
MPT	Metoprolol Tartrate
n-BMA	n-Butylmethacrylate
PCL	Polycaprolactone
PDI	Polydispersity Index
PEG	Polyethylene Glycol
PEO	Polyethyleneoxide
PEtOx	Poly(2-ethyl-2-oxazolin)e

PLGA	Poly D,L-Lactic-co-Glycolic Acid
PVA	Polyvinylacetate
PVP	Polyvinylpyrrolidone
PVPVA	Polyvinylpyrrolidone/Vinyl Acetate
R&D	Research & Development
RID	Refractive Index Detector
SCFA	Shortchain Fatty Acids
SDS	Sodium Dodecyl Sulfate
SEC	Size Exclusion Chromatography
SEM	Scanning Electron Microscopy
SHIME	Simulator of the Human Intestinal Microbial Ecosystem
SR	Sustained Release
SS	Soft Segments
t-BMA	tert-Butylmethacrylate
Tg	Glass Transition Temperature
TGA	Thermogravimetric Analysis
Th	Theophylline
Tm	Melting point Temperature
TPUR	Thermoplastic Polyurethanes
TPR	Tamper Resistant Formulation
XRD	X-ray Diffraction

OUTLINE AND AIMS

Hot melt extrusion (HME) is an established process that has been used for almost a century. The combination with injection molding (IM) enables the processing of materials with high dimensional precision. These techniques rely on obtaining a homogeneous system by converting raw materials into a product of uniform shape via a substantial energy input, provided by elevated temperature, high shear force, and pressure. HME and IM are widely used for a plethora of applications as they allow the continuous processing (replacing traditional batch processing), as well as the implementation of process analytical technology to understand and control the manufacturing process. In the pharmaceutical field, on the other hand, research valorization has been disappointing.

The objective of this doctoral thesis was, therefore, to evaluate the use of several non-conventional polymers as matrix excipients for hot melt extruded oral-release formulations. Expanding the range of polymers currently used for HME/IM could potentially solve the problems associated with the current formulations: pH dependent release profiles, stability issues, and low drug loaded dosage forms. Also, formulations containing 3 components (active pharmaceutical ingredient (API), polymer and other additional excipient) have been extensively described in literature. If the characteristics of an extrudate containing API and polymer does not meet the requirements, a third component (plasticizer, drug release modifier, swelling agent, etc.) is often added to improve the formulation its performance. This doctoral thesis has the intention to emphasize the importance of the polymer. Try to ‘keep it

simple'. The focus should first be on the polymer rather than on the addition of a third component. To this end, the process of HME could be simplified as a combination of 2 components requires less quality control, process control and decreases the complexity of formulation characterization. Overall, this doctoral thesis accentuates the need for a more rational design of polymer matrix excipients for drug formulation via HME and IM.

The objectives of this study were:

1. To create a pH independent immediate release formulation via the modification of a conventional polymer: polymethacrylates

2. To alter the polymer composition of a conventional polymer to increase a formulation's mechanical unstabiliy: polymethacrylates

3. To evaluate the use of a new non-conventional polymer as immediate and/or sustained release matrix excipient: polyoxazolines

4. To evaluate the use of a new non-conventional polymer to produce high drug loaded sustained release formulations: polyurethanes

INTRODUCTION

Hot-melt extrusion and injection molding:

a critical review

Introduction

Hot melt extrusion (HME) is an established process that has been used for almost a century. It was introduced in the plastics manufacturing industry, quickly followed by the food processing industry as it allows the continuous manufacturing of a wide variety of forms and shapes at a low cost. Over the last three decades, the pharmaceutical industry also started to recognize the potential of HME with a boost in HME-related research and patents [1], as a consequence. HME is defined as a process that transforms raw materials into a homogeneous melt (the extrudate) under controlled conditions, such as temperature, feed rate, screw speed and pressure.

The basic extrusion set-up (Figure 1) consists of three parts: a feeding device, a temperature-controlled barrel containing one or two screws (co-rotating or counter-rotating) and a die to shape the extrudate in a final form. The function of the feeding device is to transport the raw materials, most likely a powder blend containing API, thermoplastic polymer and other additional excipients, into the barrel under controlled conditions. The barrel, heated to the desired temperature, provides the energy needed for the powder blend to melt, while the screws in the barrel are responsible for the kneading, mixing and transportation of the blend towards the die. The friction generated by the rotating screws provides additional energy input to transform the powder blend into a homogeneous extrudate. The die, located at the end of the extrusion barrel, shapes the extrudate into a distinct form, which is then subjected to further downstream processing.

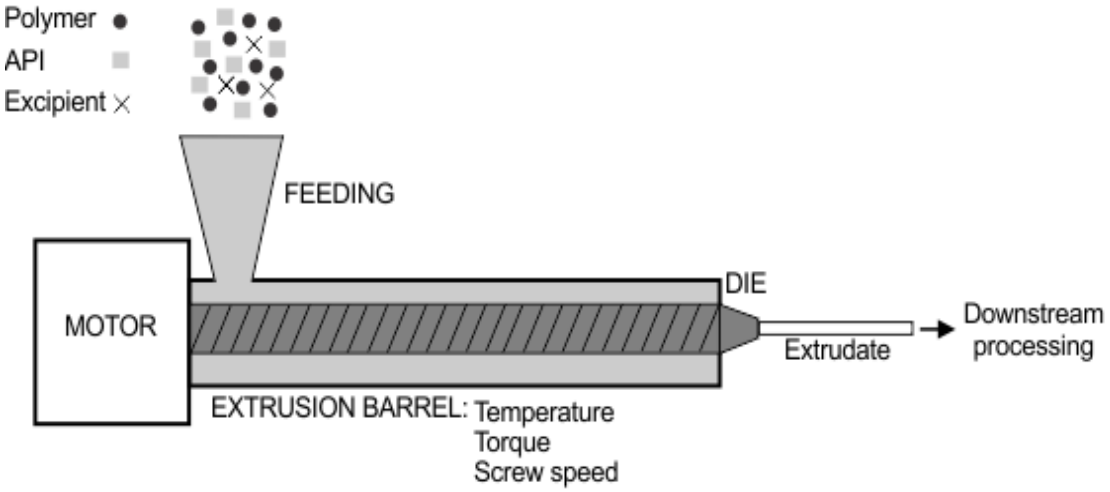


Figure 1. Hot melt extrusion equipment

Several downstream processing devices are available to transform the homogeneous extrudate into its final product form: (a) the extrudates can be cooled on conveying rolls [2]; (b) cutting the extrudates into small pellets can be done via a pelletizer (fast spinning short knives) immediately at the die exit (die-face pelletizing) or after cooling (strand pelletizing) [3]; (c) forcing the extrudates through chilled rolls (chill rolling) results in the continuous manufacturing of films; (d) calendering using chilled rolls with tablet-shaped cavities allows the continuous shaping of the extrudates into tablets [4]; (e) grinding of the hot melt extrudates yields a powder which can be filled into capsules or compressed into tablets; (f) shaping the extrudates into a final product form via injection molding.

Injection molding (IM) is one of the most versatile downstream processing techniques available. It allows the production of complex final product forms with high dimensional precision. IM has three basic components: the injection unit, the mold and the clamping system. The injection unit prepares the homogeneous melt to be transferred to the mold, while the clamping system is responsible for the opening and closing of the mold. The molten material is transferred by means of a pressure-controlled injection step into a closed and

shape-specific mold cavity, basically duplicating the cavity of the mold. Maintaining the injected material under pressure for a specified time (post-pressure) is necessary to prevent back flow of the melt and to compensate for the decrease in volume during hardening of the melt. Upon complete solidification, the final drug product is obtained by opening the mold. The mold basically consists of a sprue, a runner and a cavity. The sprue is the opening, located at the beginning of the mold that is responsible for an appropriate connection between the die of the HME device and the runner of the mold. The runner is the transport channel of the mold. Hence, the molten material flows through the die, sprue and runner in order to reach the mold cavity. Variations in final drug product form can be easily obtained by varying the complexity or the shape of the mold cavity. Molds can consist of a single cavity or multiple cavities to increase the production capacity. In multiple cavity molds, each cavity can be identical (mass production) or can be unique with special selected geometries. This range of design considerations and possibilities endorses the versatility of the injection molding technique.

The first injection molding device was build and patented in 1872 by John Wesley Hyatt [5]. It consisted of a needle-like plunger that injected plastic through a heated cylinder into a mold. About seventy years later (1946), the first screw injection molding machine was created by James Watson Hendry, introducing a more precise and controlled injection step, thereby increasing the quality of the produced products. Although injection molding found its origin in the plastic processing industry (nowadays consuming approximately 32 wt.% of all plastics [6]), the pharmaceutical industry has recently become interested in IM as a versatile processing technology.

HME in combination with IM offers several advantages compared to conventional pharmaceutical production processes: a) it is a solvent-free process, avoiding time-consuming drying steps, residual solvent issues and possible solvent-mediated drug degradation; b) as the materials only encounter shear forces, it allows the processing of brittle materials; c) the extensive mixing in the barrel enables the production of final products with a precise, and homogeneously dispersed, drug content; d) it is a low-cost operation as it is not a labor-intensive process and almost no post-production work is required as the product is finished upon ejection; e) high production output rates are possible using multi-cavity molds; f) product design flexibility by manufacturing molds with various shapes; g) it is a continuous process which offers distinct advantages over batch processes in terms of reduced development time, reduction of material waste, less product variability and improved product quality. During HME, the drug becomes homogeneously dispersed at a molecular level in the carrier (often a thermoplastic polymer). This offers several advantages from a formulation perspective: increased bioavailability of poorly soluble drugs; enhancement of the dissolution rate; inhibition of the recrystallization of an amorphous API; taste masking of API's; possibilities for controlled or targeted drug release.

Limitations of the HME and IM process are mostly related to stability issues. During extrusion, all components of the formulation must be thermally stable at the selected processing temperature. Due to local friction and shear forces induced by the rotating screws, the temperature inside the barrel can become higher than the set temperature, leading to possible drug and polymer degradation. The temperature and torque of each barrel segment should, therefore, be accurately monitored. The state (crystalline, amorphous) of the drug or of other excipients in the formulation form can have a profound impact on the processability

and stability of the final product. The API, for instance, can lower the glass transition temperature (Tg) of the polymer, thereby decreasing the processing temperature and increasing the processability. Or the melting of the API can prevent the hardening of the polymer matrix. These changes in physicochemical characteristics are difficult to predict upfront and have to be experimentally determined. Moreover, it is for the operator not straightforward to change a parameter if product defects are detected. For instance, if degradation in the final formulation occurs due to a too high processing temperature, this could be resolved by lowering the processing temperature. However, this increases the polymer viscosity and the resulting higher shear forces can locally increase the temperature, thus enhancing the risk of product degradation. Possible solutions for lowering the processing temperature without increasing the shear forces include the lowering of Tg via the addition of a plasticizer [7-8], compressed gas [9], CO_2 [10-11] or by using API's with a plasticizing effect on the polymer [12-13]. A final limitation of the HME and IM process is the high initial equipment investment.

Marketed applications

Currently, hot melt extrusion and injection molding have been applied for numerous applications: dental equipment [14], capsules [15], vaginal rings [16], tissue-engineered scaffolds [17], (biodegradable) implants [18], stents [19], taste masking purposes [20], films for transdermal or transmucosal delivery [21], solid dispersions [22], etc. In literature, an extensive number of reviews have been published representing HME as a robust manufacturing method with an enormous potential. It is, therefore, not the aim of this introduction to provide a complete literature review about HME/IM and its use as a processing technique in research & development (R&D). Examples of commercially available

formulations manufactured via HME and/or IM are listed below as these processing techniques are the focal point of this research project.

Manufacturing

The FlexTab™ technology is an interesting example to demonstrate the potential of HME/IM. Pharmaceutical companies are continuously looking for ways to improve the patient compliance and to create new combination therapies to boost their revenues. To this end, new capsule designs are needed to meet their increasing demands (e.g. delivering of two liquids in one dose, multicompartimented capsules to incorporate a drug in powder form and in a liquid form, etc.). The traditional capsule manufacturing technique (dip-molding) is currently not capable of meeting those demands. The FlexTab™ technology, on the other hand, allows the manufacturing of new complex and multicompartimented capsules as IM as processing technique offers the dimensional precision needed in the design of these new capsules.

The Egalet®system [15] was developed to create a sustained release formulation. As erosion and dissolution of the polymer matrix increases the formulation's surface area, thereby hampering the sustained release characteristics, the Egalet® system is based on the development of a product with a constant surface area. It consists of a two-step IM process. The first step involves the molding of a non-degradable polymer into an open-ended tube in which, in a second step, the formulation is injected (Figure 2). As the formulation is surrounded by a non-degradable polymer, the drug is released via erosion from the open ends (i.e. constant surface area), thereby controlling the drug release. Covering both open ends with polymeric plugs resulted in a delayed release system (the Egalet® Chrono technology). Before

drug is released from the core of the tablet, the end-plugs, containing polymeric carriers with pre-determined dissolution rates, must dissolve.

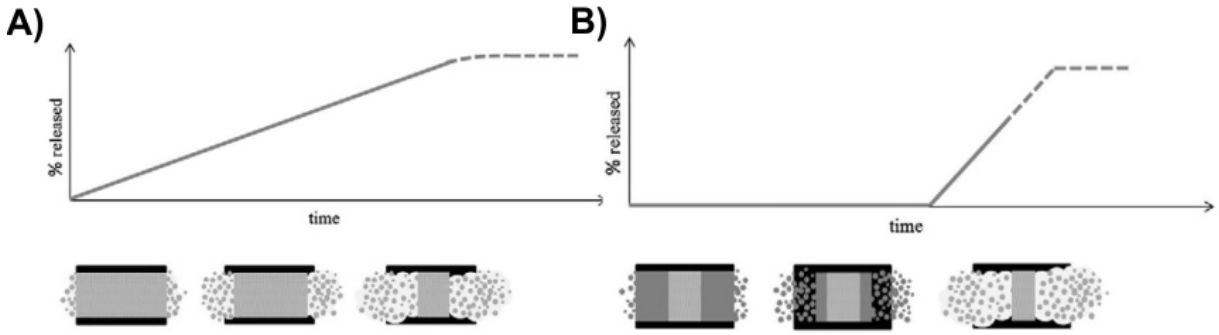


Figure 2. The Egalet® release technology (A) and the Egalet chrono delayed release system (B); Obtained from ref [15]

The Intac® technology is a tamper-resistant formulation technology (TRF) developed by Grünenthal. Using this technology should prevent the misuse and abuse of medication, which is a raising concern of public health. Abusers seek to achieve a "high" from prescription medication, by crushing the pills, followed by snorting, smoking or injecting the new altered formulation (e.g. sustained release formulation with opioids) [23]. The combination of HME as processing technique and (very) high molecular weight polyethylene oxide as matrix polymers, allow them to create TRF-formulations, thereby preventing the abuse. Nucynta® (Janssen), for example, was developed as an opioid, sustained release, and tamper resistant formulation [24].

Intravaginal rings

Several intravaginal rings (IVR) such as FemRing®/Estring® and Progering®/Fertiring® for hormone replacement therapy and contraception, respectively, were manufactured via HME and/or IM. They are commonly made of silicone (poly(dimethylsiloxane)) due to its

low toxicity, high thermal stability and physiological inertness. As the production process involves the curing of the silicones in the mold at high temperatures (around 150°C) and often a post-curing (at 200°C), several other raw materials such as thermoplastic polyurethanes (TPUR) [25] and polyethylene vinylacetate (EVA) [26-27] are evaluated as alternatives. NuvaRing® [26, 28], for example, is a novel contraceptive vaginal ring, manufactured with 2 different EVA-polymers via HME. The ring consists of a core of EVA-polymer (with 28% vinylacetate content) containing both contraceptive APIs (ethinyl estradiol and etonorgestrel) surrounded by a coat of drug-free EVA-polymer (with a 9% vinylacetate content). The polymer with the lower vinylacetate content in the coat is responsible for the sustained release profiles over a period of 3 weeks as the drug first must diffuse through this low permeable EVA coat [29]. (Figure 3).

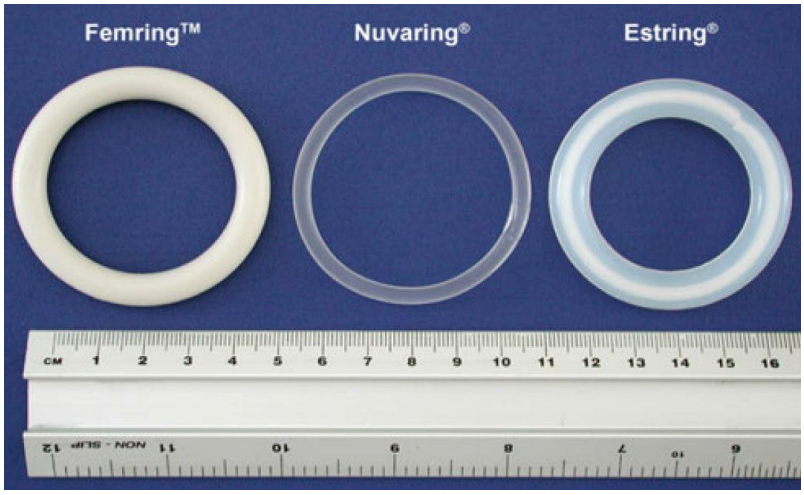


Figure 3. Commercially available IVRs for hormone replacement therapy (Femring® and Estring®) or contraception (Nuvaring®). Obtained from ref. [26]

Ocular, dental and subcutaneous implants

Lacrisert® was the first hot melt-extruded pharmaceutical product, launched by Merck (now MSD) in 1981. It is a drug-free, translucent, rod-shaped, water soluble ophthalmic insert made of hydroxypropyl cellulose (HPC). The polymer lubricates and protects the eye from

dryness by stabilizing the precorneal tear film and prolonging the tear film breakup time [30]. HME was chosen as a processing technique as it allows the formation of rods with a specific shape (to fit into the eye) in a continuous manner at low cost.

Ozurdex® is a sterile, single-use system intended to deliver a biodegradable implant containing dexamethasone to treat macular oedema [31]. The formulation was initially developed as a solid, tablet-shaped implant that was surgically inserted in the posterior segment of the eye. Manufacturing via HME allowed the production of a precisely controlled filament, which could be inserted in the eye using a thin needle-shaped applicator. A combination of poly D,L-lactic-co-glycolic acid (PLGA) polymers was selected to deliver dexamethasone in a sustained manner, while ensuring a mechanical strength suitable for use in the applicator [31]. Upon production, the implant was sterilized via gamma irradiation, in compliance with the European Pharmacopeia requirements.

Zoladex® is a small implant designed to be subcutaneously injected to release goserelin acetate (a decapeptide analogue of lutinizing hormone releasing hormone) over 1 or 3 months, depending on the drug loading [32]. During processing, peptide and PLGA are co-dissolved in acetic anhydride as a solvent and subsequently freeze-dried to remove the solvent. Afterwards, the mixture is hot-melt extruded into an implant, sterilized and packaged. These marketed PLGA-products are only partially made via extrusion as it is used as a tool to shape the product into its final form, not as a process to mix and homogenize the raw materials.

Progestasert® is a T-shaped intrauterine device (IUD) developed to release a hormone directly into the uterus to prevent pregnancy over a 1 year period. In order to compensate for a too fast release, the hormone was suspended in a hydrophilic liquid in which the active ingredient is insoluble, mixed with a poly dimethylsiloxane matrix and upon cross-linking extruded in the specific T-shaped form [33-34].

Implanon® is a single rod implant, similar to a matchstick, containing sufficient etonorgestrel (ENG) to inhibit ovulation for up to 3 years [35]. It is inserted under the skin of a woman's upper arm, releasing its ENG content in a sustained manner. Comparable to Nuvaring®, it consists of a drug-loaded EVA-core (with a 28% vinylacetate content) surrounded by a low permeable EVA coat (with a 15% vinylacetate content). Implanon® and Nuvaring® highlight the capability of EVA polymers to control drug release and their essential characteristics (ease of manufacturing, flexibility, non-toxic) for HME/IM applications [36-37]. However, a currently unresolved issue with EVA polymers is a commercial source of medical grade approved materials (e.g. Celanese polymers). Litigation issues and related costs are negatively influencing the new supply agreements with a lack of medical-approved raw materials which hinder further developments [26]. The research of incorporating microbicides in IVRs composed of EVA polymers, for instance, has a huge potential but is hindered due to these regulatory constraints.

Oral delivery applications

In terms of drug delivery, oral drug administration still remains the route of choice for the majority of applications due to its high patient compliance. To manufacture oral dosage forms HME/IM has received considerable attention to incorporate drugs in polymer matrices. Basically, the drug is homogeneously mixed with the molten polymer during thermal

processing, which upon cooling results in a formulation with distinct characteristics: (a) the drug can be released in a sustained manner as the polymer acts as a release retardant; (b) the drug is protected from external influences (e.g. alcohol, enzymes); (c) taste masking of the drug; (d) higher drug solubility/bioavailability. Especially the latter has received considerable attention

as a means to manufacture solid dispersions via HME/IM in order to improve the dissolution of new chemical entities when poor solubility is the rate limiting step for its *in vivo* application.

The classification of solid dispersions, first introduced by Chiou and Riegelman [22], include simple eutectic mixtures, amorphous precipitations, glass suspensions and (glassy) solid solutions (Table 1). An eutectic mixture is a two-phase system where two components cocrystallize at the eutectic temperature, which is lower than the melting temperatures of both individual components. Glass suspensions and amorphous precipitations are two-phase systems were the crystalline and amorphous API is dispersed in an amorphous and crystalline/amorphous carrier, respectively. Miscibility between drug and polymer, on the other hand, leads to the formation of solid solutions and glassy solid solutions, i.e. homogeneous one-phase systems where the drug is molecularly dispersed in a crystalline and amorphous matrix, respectively. To obtain a homogeneous one-phase system, a certain degree of drug/carrier miscibility and kinetic stabilization is required [38]. The latter referring to the immobilization of an amorphous drug in a highly viscous matrix (i.e. when the difference between storage temperature and glass transition temperature (Tg) of the formulation is higher than 50°C). The idea behind the creation of the different types of solid dispersions is derived from the Noyes-Whitney equation [39]:

$$\frac{dC}{dt} = \frac{DA(Cs - C)}{V\,h}$$

which defines the rate of dissolution (dC/dt) as a function of diffusion coefficient (D), surface area (A), the maximum concentration of the compound in the dissolution medium (saturated solution, Cs), the concentration of the compound in the dissolution medium (C), the volume of the medium (V) and the diffusion layer height (h). Dispersing crystalline API in a crystalline or amorphous matrix increases the surface area which positively influences the dissolution rate. Transferring the drug into its amorphous state maximizes the surface area, but also excludes the breakage of the crystal lattice of the drug which is often a dissolution rate limiting step.

Table 1. Types of solid dispersions. Obtained from [40-42]

	Eutectic mixture	**Glass Suspension**	**Amorphous precipitation**		**Glassy solid solution**	**Solid solution**
PHASES	2	2	2	2	1	1
DRUG	crystalline	crystalline	amorphous	amorphous	molecularly dispersed	molecularly dispersed
CARRIER	crystalline	amorphous	crystalline	amorphous	amorphous	crystalline

The first directly shaped HME solid dispersion on the market was Verapamil® SR-E, created by Abbott Laboratories as an alcohol-resistant dosage form [43-44]. As a controlled-release formulation contains a significantly higher amount of API relative to its immediate release counterpart, failure of the controlled release system could lead to critical, and even life-threatening, situations due to the sudden exposure to high drug concentrations (dose dumping effect). Therefore, in order to improve the safety profile of a sustained release formulation, resistance to the dose dumping effect caused by alcohol is advised. Processing a verapamil.HCl formulation via HME allowed to disperse the API in a HPMC/HPC polymer

melt, thereby protecting the formulation from the concomitant intake of alcohol (shielding effect). To this end, Roth et. al. [43] compared the influence of ethanol on the *in vitro* release rate of Verapamil® SR-E with three commercially available Verapamil SR formulations processed via direct compression. The results indicated that the melt extrusion formulation was resistant to the solubilizing effects of ethanol in a medium containing up to 40% ethanol.

The development of Kaletra® illustrates the potential of HME as processing technique to increase the solubility and bioavailability of an API. Abbott Laboratories was facing difficulties to achieve adequate plasma concentrations when lopinavir and ritonavir were processed via conventional processing techniques (direct compression into tablets or filling into capsules). Although soft gelatin capsules, wherein both API's were dissolved, improved bioavailability of these drugs, patient compliance for this formulation was low as it required storage at low temperature and the intake of up to 6 capsules/day, concomitant with food. HME, on the other hand, enabled the production of a solid solution as both API's completely dissolved in a polyvinylpyrrolidone/polyvinylacetate (PVP/PVA) matrix during processing. HME allowed the production of a formulation, which was stable at room temperature, with a reduction of the daily tablet intake, less influenced by the patient's food intake and with higher plasma levels. A similar approach was used for the development of Norvir®, designing a solid dispersion of ritonavir in a PVP/PVA matrix which can be stored at room temperature.

Abbott Laboratories also developed a fast-onset ibuprofen (IBP) formulation via HME [45], where IBP was formulated in a readily soluble dosage form. Thermal processing of IBP in combination with PVP induced molecular interactions between both substances, which solubilized (i.e. molecularly dispersed) IBP in the PVP matrix. As a result IBP release depended on the disintegration time of the formulation and the dissolution of the polymer,

which provided a fast onset of drug release and a pH-independent release profile [44-45]. Upon extrusion, the extrudate was conveyed to a calendering device, shaped into granules, milled, mixed with other ingredients and finally compressed into a tablet.

Rezulin® was also successfully melt extruded into a solid dispersion containing troglitazone as an antidiabetic drug, but this formulations was withdrawn from the market because of safety concerns of the drug (liver toxicity) [46].

Table 2. Overview of commercially available formulations that are manufactured via hot-melt extrusion.

Product	Company	API	Indication	Polymer	Application	Reason for HME/IM?
Femring®	Warner Chilcott	Estradiol acetate	Hormone replacement	Silicone	Vaginal	Specific shape + SR
Estring®	Pfizer	Estradiol acetate	Hormone replacement	Silicone	Vaginal	Specific shape + SR
Progering® **Fertiring®**	Silesia Laboratories	Progesteron	Contraception	Silicone	Vaginal	Specific shape + SR
Nuvaring®	MSD	Estradiol Etonorgestrel	Contraception	EVA (28%) EVA (9%)	Vaginal	Specific shape + SR
Implanon®	MSD	Etonorgestrel	Contraception	EVA (28%) EVA (15%)	Subdermal	Specific shape + SR
Progestasert®	Alza Corporation	Progesteron	Contraception	Silicone EVA	Intra Uterine Device	Specific shape + SR
Lacrisert®	MSD	/	Dry eye	HPC	Ophthalmic insert	Specific shape + SR
Orzurdex®	Allergan	Dexametha-sone	Macular edema	PLGA	Biodegr. implant	Specific shape + SR

Zoladex®	AstraZeneca	Goserelin acetate	Prostate cancer	PLGA	Biodegr. implant	Specific shape + SR
Norvir®	Abbott Laboratories	Ritonavir	HIV	PVP/PVA	Oral	increase in bioavailability
Kaletra®	Abbott Laboratories	Lopinavir Ritonavir	HIV	PVP/PVA	Oral	increase in bioavailability
Isoptin® SR-E	Abbott Laboratories	Verapamil	Hypertension	HPMC HPC	Oral	resistant to dose dumping
Ibuprofen meltlets ®	Abbott Laboratories	Ibuprofen	Pain	PVP	Oral	fast onset
Rezulin®	Withdrawn	Troglitazone	Diabetic	PVP	Oral	increase in bioavailability

EVA: ethylene vinyl acetate (% vinyl acetate content); HP(M)C: hydroxyl propyl (methyl) cellulose; PLGA: poly D,L-lactide-co-glycolide acid; PVP(VA): polyvinyl pyrrolidone (vinyl acetate); SR: sustained release

The commercially available pharmaceutical dosage forms which are (partially) manufactured via HME/IM are listed in table 2. Despite the benefits of HME/IM as processing technique, the large number of research papers and several high quality reviews [1, 41, 47-49], only a limited number of HME/IM-processed products have reached the commercial market. Especially, the manufacturing of oral drug formulations has been limited. And even if HME/IM is included in the manufacturing process it is often combined with other techniques to finalize the dosage form (e.g. via direct compression).

A variety of problems have been limiting the commercial applications of solid dispersions, the low availability of manufacturing equipment being a first reason. Pharmaceutical companies are currently not convinced that it is worthwhile making the

significant investments required to install HME/IM equipment in their facilities as solid dispersions can also be manufactured via other techniques which are widely available (e.g. spray-drying) . A possibility to limit these high investment costs is to omit IM in the early stages of development. Analyzing the performance of a solid dispersion does not require the transformation into its final specific shape, the characterization can be done on the hot melt extrudates. A second limiting factor for the low number of commercially available HME/IM products has been the formulation's stability [49]. A molecularly dispersed drug can be subjected to drug diffusion (drug mobility) leading to non-homogeneous distribution (amorphous drug clusters). This thermodynamically unstable amorphous drug can nucleate to (partially) crystalline drug particles. Several underlying forces are influencing this crystallization process. To this moment, there is still a lack of fundamental understanding with respect to the chemistry behind these underlying forces [50]. Stability issues can also occur upon dissolution. Some excipients (e.g. PEG) or polymers have been able of stabilizing the supersaturated drug state, while others fail. The underlying reasons are, again, not fully understood. Third, the process of HME still remains a 'black box'. A physical mixture API/polymer is fed to the extruder, where thermal energy and shear forces (rotational screws) transform the material into a homogeneous extrudate. But how the polymer/API mixture is interacting or behaving inside the polymer barrel is largely unknown; characterization mainly depends on off-line instruments. Recent process analytical tools (e.g. near infrared and raman spectroscopy) are currently addressing this issue, also providing a quality built into the products rather than testing it off-line [51-52]. To this end, there has been a narrow range to select the proper parameters from a formulation point of view. Processing at, for instance, 100°C could lead to the formation of a glassy solid solution, where the drug is molecularly dispersed in the amorphous carrier, while processing at 90°C could yield an amorphous

precipitation, a 2-phase system where the amorphous drug is dispersed in the amorphous carrier. Similar, a rotational screw speed of 100rpm instead of 60rpm can have significant consequences on the type of solid dispersion formed. Only a small shift in processing parameters can have major consequences on the batch quality. Moreover, these small molecular changes (glassy solid solution or amorphous precipitation) are difficult to distingue during characterization [53]. A final limiting factor for the low number of commercially available HME/IM products has been the formulation's drug load. Elevated drug loads are difficult to achieve. Most drug-carrier systems are only partially miscible, resulting in phase separation and the formation of unstable amorphous drug clusters at elevated drug loads [54-55]. It is, therefore, important to choose an ideal polymer/API combination. A tool to estimate the solubility of the API in the polymer is proposed by the Hansen solubility parameters [56]. Small differences in solubility parameters are, most likely, equal to high miscibility between API and polymer. Similar, the sustained release (SR) formulations have been limited in drug load, either linked to processing issues during the HME process, or due to a significant burst release when less polymeric matrix former is incorporated in the formulation. Quinten et. al. [57], for instance, described that drug load in an acrylic polymer matrix was limited to 30% when processed via HME/IM, drug release from these matrices occurred in a first order manner via a combination of swelling and diffusion

Polymers

To date, a variety of polymers have been evaluated as excipient for the production of immediate or sustained release formulations via HME. Examples of polymers used for this purpose are listed with their respective chemical structure in table 3 and 4. The polymers need to fulfil several criteria in order to allow processing via HME: thermoplastic, thermostable,

chemically stable, pharmacologically inactive and non-toxic. Thermoplastic polymers are a class of polymers which exhibit softening and elasticity at a temperature above its glass transition temperature (Tg). Upon cooling, the polymer returns to its original hardened state, regaining its structural strength with a smooth surface finish as a result. Generally, a thermoplastic polymer consists of non-crosslinked polymer chains, often with high molecular weights. During processing, it is advisable to use low viscosity grade thermoplastic polymers [58] as the combination of a high processing temperature and the mechanical shear stress during HME/IM could damage the polymer. Especially during the injection step into the mold, the materials are exposed to more stress. The choice of the type of thermoplastic polymer is critical as its properties determine the processing conditions, the release mechanism, the type of solid dispersion, etc.

Controlled release formulations can be developed with a variety of polymers: ethylcellulose (EC) [59-61], hydroxypropyl (methyl) cellulose (HP(M)C) [62], ethylene vinyl acetate (EVA) [29, 63], polyvinyl acetate (PVA) [64], poly lactic (co-glycolic) acid (PL(G)A) [65-66], silicone [67], polycaprolactone (PCL) [68-69], polyoxazolines [70], polyanhydrides [71], methacrylate copolymers (Eudragit® RS/RL) [72-73], and even several lipid materials [74-76]. Using one of these polymers results in matrix or reservoir systems [77-78]. In matrix systems, the drug is homogeneously distributed in a polymer matrix. Drug release occurs via diffusion through pores, swelling of the matrix and/or polymer erosion. The cumulative release of an API from a matrix formulation is generally first order (i.e. release rate is in function of the drug concentration available at that time) [27]. As drug fraction at the surface of the system is released faster than the drug in the inner core, due to the smaller diffusion distance, an initial burst release is likely to occur. Two types of matrix devices exist, depending on the concentration of the API in the polymer matrix. The API has a maximum

solubility in the polymer matrix (saturated concentration). If the formulation contains less API than the saturated concentration, the formulation is classified as a monolithic solution device. If an amount of API is not able to dissolve in the polymer matrix (API concentration > saturated concentration), the formulation is classified as a monolithic dispersion system. In reservoir systems, the drug is encapsulated in a core matrix, which is completely surrounded by a release-controlling polymer membrane. An initial burst release cannot occur as the drug release rate is controlled by the polymer membrane. However, reservoir systems are less reliable than matrix systems as rupture or damaging of this membrane causes dose dumping [79]. Generally, zero order release kinetics (i.e. a constant rate independent of the initial or existing concentration) are pursued from reservoir systems.

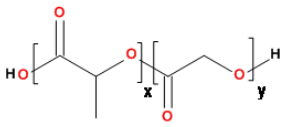
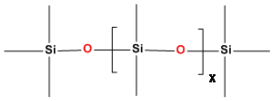
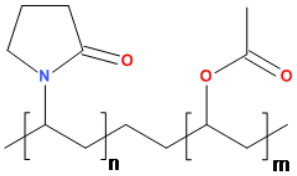
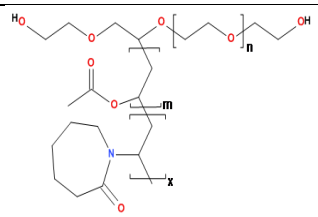
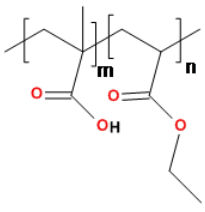
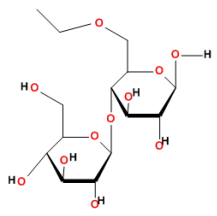
A wide range of mechanisms can control the drug release rate from a dosage form: delayed dissolution, diffusion controlled and solvent flow controlled. Polymers synthesized to delay the drug dissolution aim to protect the drug from the aqueous environment using a reservoir or matrix system where a polymer coating or a polymer matrix dissolves, degrades or erodes at a slower rate than the respective drug. In diffusion-controlled mechanisms, the polymer acts as an insoluble polymer matrix through which the drug molecules must diffuse. The percolation theory states that a minimal drug load is needed to generate sufficient pores and diffusional channels throughout the insoluble matrix to allow dissolution and release of the entire drug content (percolation threshold). Polymers that form a hydrogel upon contact with the dissolution medium (e.g. xanthan gum or polyethyleneoxide, PEO) are also able of controlling the drug release [80]. The viscous gel hinders the API's mobility and diffusion via its entangled polymer structure. The solvent flow mechanism utilizes the osmotic potential gradient across a semi-permeable membrane to release the drug from the delivery device. The

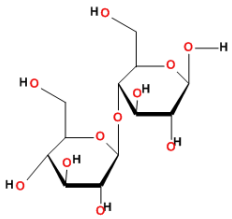
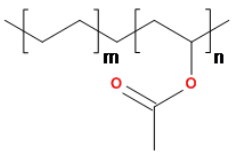
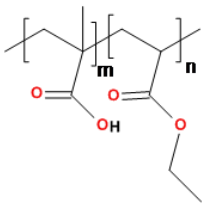
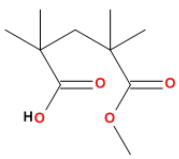
flow rate of the dissolved drug from the dosage form is determined by the pore diameter of the semi-permeable membrane or by the osmotic gradient (which depends on the drug load). Polymers used in controlled release applications can also be classified as either biodegradable or non-biodegradable. Biodegradable matrices (e.g. thermoplastic starch, polylactic acid) are able to degrade in an aqueous environment via hydrolytic- or enzymatic-induced polymer chain scission. They often are synthesized as a combination of two or more polymers (copolymer) which allows the formulation scientist to alter the degradation rate by varying the distinct polymer ratios [81]. Wu et. al., for instance, determined a higher biodegradation rate for PLGA containing a higher glycolic acid moiety. Ester bond hydrolysis was considered as responsible for its biodegradability.

Immediate release systems can be developed via a variation of polymers: low molecular weight polyethylene oxide (PEO) [82-83], starch [84], hydroxypropyl (methyl) cellulose (HP(M)C, Klucel®) [85], polyvinylpyrrolidone (PVP, Kollidon®) [86], vinylpyrrolidone/vinylacetate copolymer (Kollidon® VA) [87-88], methacrylate polymer (Eudragit® E) [53, 89], and a copolymer of PEG6000/vinylcaprolactam/vinyl acetate (Soluplus®) [58, 90]. An important factor determining the release rate is the state of the drug in the polymer matrix, which can be crystalline, amorphous or dissolved. As breaking of the crystal lattice during dissolution is often a rate-limiting step, drug particles in the amorphous or dissolved state are preferred for immediate release formulations. Critical with these formulations is their stability. Due to the substantial energy uptake during the HME/IM process, followed by a fast cooling of the melt, the amorphous drug is kinetically trapped resulting in a blend far from its thermodynamic equilibrium. Several methods have been proposed to decrease the rate of the recrystallization and, hence, increase the stability. One of them is the use of a polymer with a high glass transition temperature (Tg) providing lower

molecular mobility to the drug in the viscous polymer matrix, resulting in an increased physical and kinetic stability [38]. This approach, however, is not always successful as recent studies evidenced the existence of β-mobility, besides the known α-mobility. The latter referring to slow movement on a large length scale, similar to those involved in viscous flow, while β-mobility is related to fast motions on the length scale of local molecular motions such as rotations of side chains. A high β-mobility can cause API recrystallization, even at temperatures below the polymer glass transition temperature [91]. A second, and far more important, issue towards stabilization is the molecular interaction between polymer and API (miscibility). Addition of a miscible polymer may reduce the tendency of the drug to recrystallize by increasing the energy barrier since prior to recrystallization the drug must break its interaction with the polymer. If the drug load is lower than the saturated solubility, the solid dispersion is unsaturated with no thermodynamic driving force to recrystallize (i.e. drug is solubilized). An API solubilized in the polymer matrix becomes an intrinsical part of the matrix, thus influencing its wettability, viscoelastic properties and release characteristics. A thermodynamically unstable formulation occurs when the drug load is exceeding the saturated solubility. Therefore, drug-polymer miscibility is an important aspect of the formulation design. However, drug solubility in the polymer matrix is usually low [92], often resulting in solid dispersions that do not meet the dose requirements. Many studies indicate that strong drug-polymer interactions may even help to minimize thermal degradation of heat sensitive drugs, and also to prevent drug precipitation during dissolution by maintaining the supersaturation state of the drug [93-94].

Table 3. Overview of important polymers used to process sustained release formulations via HME

Polymer	Chemical name	Chemical structure	Comment	Ref.
PLGA	Copolymer of poly lactic and poly glycolic acid		• Biodegradable polymer • Used in implants • Tg, crystallinity and biodegradation can be varied by altering the lactic and glycolic acid molar ratio	[66, 95]
Silicone polydimethyl	Polydimethyl-siloxaan (pDMS)		• Used for production of vaginal rings • Very flexible, often used in cosmetics and food industry (anti-foaming agent)	[27, 96]
Kollidon® SR	Spray dried mixture of PVP and poly vinyl acetate (PVA)		• Molar ratio PVP/PVA 20/80 • The soluble part, PVP, can dissolve and leach out, resulting in porous PVA matrices • Requires high extrusion temperatures (140-180°C)	[51, 97]
Soluplus®	Copolymer of PEG, vinyl-caprolactam and vinylacetate		• Can solubilize a wide range API's • Amphiphilic structure: micelle formation with APIs • Amorphous polymer, low Tg • Broad temperature range for extrusion (120-200°C)	[58, 90]
Kollicoat® MAE	Copolymer of methacrylic acid and ethylacrylate		• Molar ratio 50/50 • Anionic: intended to be used as an enteric matrix, drug mainly released in the intestine • Targetting duodenum	[98-99]
EC: Ethylcelulose	Polysaccharide		• Good rheological properties, cohesiveness • Needs a plasticizer for extrusion • Often used as coating agent • Specific properties possible depending on the degree of ethoxyl substitution	[100-101]

MCC: Microcrystalline cellulose	Polysaccharide		• Good rheological properties, cohesiveness • Often used in extrusion-spheronization	[102-103]
Klucel®	Hydroxypropyl cellulose (HPC)	Similar to MCC, with H partially substituted by $CH_2CH(OH)CH_3$	• Thickening and swelling upon contact with water (depends on degree of substitution) • Flexible without the need of plasticizer	[85]
Hypromellose®	Hydroxypropyl methyl cellulose (HPMC)	Similar to MCC, with H partially substituted by CH_3 or $CH_2CH(OH)CH_3$	• Thickening and swelling upon contact with water (depends on degree of substitution) • Flexible without the need of plasticizer • Acidic groups can be added to create enteric coating formulations (e.g. succinic and acetic acid for HPMC-AS)	[104-106]
EVA	Poly ethylene vinylacetate		• Drug permeability can be tailored by varying the ratio of vinyl acetate • Non-conventional polymer for oral drug release • Used in vaginal ring formulation (Nuvaring®)	[63, 107]
Eudragit® L 100-55	Copolymer of methacrylic acid and ethyl acrylate		• Soluble above pH>5.5 • Requires plasticizer for extrusion • Anionic: used as enteric coating, can be used to form polycomplex matrices • Targetting duodenum	[108-109]
Eudragit ® L	Copolymer of methacrylic acid and methyl methacrylic acid		• Soluble above pH> 6 • Anionic: used as enteric coating, can be used to form polycomplex matrices. Targetting jejunum	[110-112]

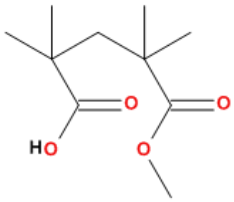
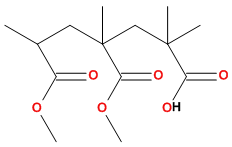
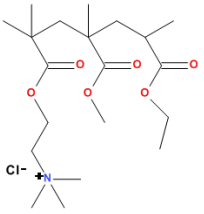
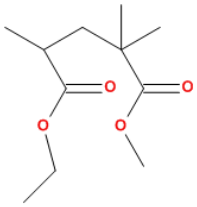
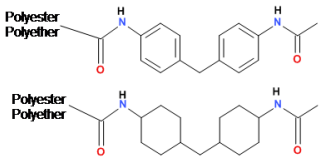
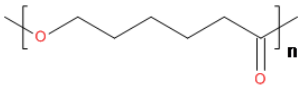
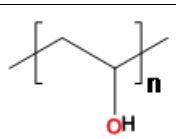
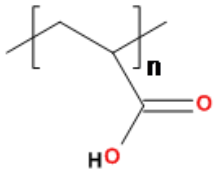
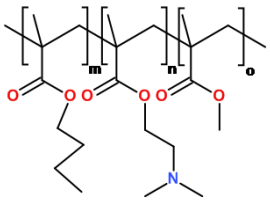
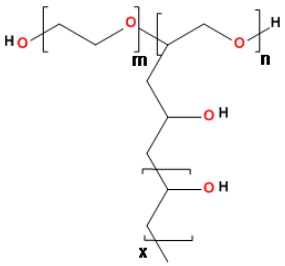
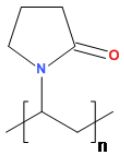
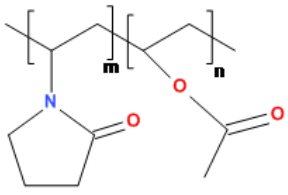
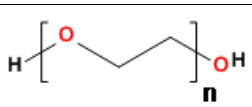
Eudragit® S	Copolymer of methacrylic acid and methyl methacrylate		• Soluble above pH> 7 • Anionic: used as enteric coating, can be used to form polycomplex matrices • Targetting ileum and colon	[112-114]
Eudragit® FS	Eudragit S + methyl acrylate		• Similar characteristics as Eudragit S • More flexible (lower glass transition temperature)	[115]
Eudragit ® RS Eudragit ® RL	Copolymer of ethyl acrylate, methyl metha-crylate, dimethyl-aminoethyl methacrylate		• Sustained release characteristics dependent on the number of cationic groups • Dimethylaminoethyl methacrylate with quaternary ammonium groups to induce hydrophilicity/porosity in the polymer structure	[72-73, 116-118]
Eudragit ® NE	Copolymer of ethyl acrylate and methyl methacrylate		• Insoluble • Neutral polymer: swells independent of pH	[119-120]
Polyurethanes based on polyesters or polyethers	Polyesters or polyethers linked together via a urethane (NCO) group:	 Note: Other variants of soft segments and hard segments are also possible.	• Superior physical strength • High flexural endurance • Ease of processability • Allow high drug loading	[121-122]
Polycaprolactone	Polyester		• Biodegradable • Very broad temperature range for extrusion, highly flexible • Often used for bone tissue engineering	[123-125]

Table 4. Overview of polymers used to process immediate release formulations via HME

Polymer	Chemical name	Chemical structure	Comment	Ref.
PVOH	Poly-vinylalcohol		• Formed by hydrolyzing poly vinylacetate • Requires high extrusion temperatures • Drug release can be tailored depending on the amount of hydroxyl groups	[126-127]
Carbopol	Polyacrylic acid		• Various types available dependent on the degree of crosslinking • Becomes tacky upon wetting	[128-129]
Eudragit® E	Copolymer of methyl-, dimethyl-aminoethyl-, and n-butyl methacrylate		• Soluble above pH> 1 • Targetting stomach: becomes protonated at low pH values • Ammoniumgroup of the polymer is important for molecular interaction	[53, 89, 130]
Kollicoat® IR	Copolymer of PEG and PVA		• Semi-crystalline • Excellent water solubility: can be used as pore-forming agent • Difficult to extrude (Tg 45°C, Tm 208°C) • Emulsion stabilizer	[131-132]
Kollidon® (Povidone)	Polyvinyl pyrrolidone (PVP)		• Range of Mw available • Very hygroscopic, amorphous • Used in coatings, binding agent • Often used to stabilize the supersaturated state of API's	[86, 133]
Kollidon® VA 64 (Copovidone)	Copolymer of PVP and Polyvinylacetate (PVA)		• Molar ratio PVP/PVA 60/40 • Less hydroscopic as PVP • Broad temperature range for extrusion	[88, 134]

PEO	Polyethyleneoxide		• Available in variety of Mw • Often used as pore-forming agent • Often used to stabilize the supersaturated state of API's • Easily extrudable at low temperatures	[135-136]

Conclusion

HME and IM have been identified as promising manufacturing techniques for the production of formulations as they offer distinct advantages over standard pharmaceutical processing technologies: it is a solvent-free process, allows the processing of brittle and dusty materials, a reduction in labor forces during processing, high production rates are possible, enables the manufacturing of products with a high three-dimensional precision and it is a continuous process. Moreover, several types of solid dispersions can be manufactured, offering a solution for poorly water soluble drugs: 40% of all the new molecular entities have poor bioavailability due to a low aqueous solubility and this percentage is likely to increase as a result of high throughput screening and combinatorial chemistry. Despite these advantages and the extensive research that has been published, the number of marketed products manufactured via HME and/or IM as processing technique has been disappointing. The implementation of HME in the pharmaceutical industry is hindered by a number of barriers which are mainly linked to five key areas:

1) The limited availability of **manufacturing equipment** as HME/IM is not yet an established processing technology within the pharmaceutical industry.
2) **Stability issues**. Numerous studies have observed changes to the dissolution rate on storage as drug mobility during storage can induce recrystallisation.
3) **Drug load**. Stable glassy solid solutions occur when the drug is molecularly dispersed in the polymer matrix. As drug solubility in the polymer of choice is often low, this hinders the production of formulations with high drug loads, limiting their commercial use. Hence, it is important to select an ideal polymer/API combination.

4) **The availability of thermoplastic polymers.** The complex intellectual property landscape inhibits the development of new thermoplastic polymers for HME and IM. The approval of a new polymer as pharmaceutical excipient requires enormous investments, which limits the introduction of novel polymers.
5) The **mechanism of dissolution enhancement**. Some excipients (e.g. PEG) or polymers are able of stabilizing the supersaturated drug state, while others fail. The underlying reasons are not fully understood.

The key issues listed above are to a large extent related to the type of polymer used in the formulation. Although much research has been performed in terms of molecular interactions between API and polymer or the use of polymer combinations, little attention has been given to the molecular structure of the polymer itself. This is remarkable as the availability of novel excipients is important to foster the innovation in (oral) drug delivery. The formulation challenges of today cannot be solved with yesterday's excipients. It is, therefore, important that several research groups start to focus on the design and synthesis of new polymer excipients. A research collaboration between the polymer chemistry and the formulation departments could lead to a more profound understanding of the polymer/API interactions and miscibility. This knowledge could then be used to create new polymer excipients from a bottom-up approach, instead of the top-down method used today. As example: if formulation scientists want to increase the bioavailability of a drug, the current protocol is to screen several polymer excipients on the market. Despite the fact that the highest drug solubility in available polymers is limited to e.g. 15wt.%, the formulation scientist will select the best-performing polymer excipient (top-down method), thus limiting the drug load in the formulation and future commercial applications. In contrast, approaching this issue from a bottom-up manner could result in a superior formulation in terms of drug

load: e.g. an in-depth investigation of the polymer structure indicated that the best-performing polymer consist of 2 alternating monomers in a 50/50 ratio. The first monomer being responsible for the molecular interaction, while the second monomer is essential for the processability (i.e. defining the thermoplastic behavior of the formulation). Synthesizing a new polymer with a monomer ratio of e.g. 75/25 increased the polymers' viscosity (while still in the viscosity window that allows processing via HME) and the available functional groups to interact with the drug, resulting in a polymer that is now able of solubilizing e.g. 30% drug. Hence, approaching the problem from bottom-up could result in custom-made formulations with beneficial characteristics for HME/IM applications. An interesting illustration of this concept was the launch of Soluplus® by BASF. This thermoplastic copolymer of PEG, vinylcaprolactam and vinylacetate was designed to provide solubilization capacity for poorly aqueous drugs. The amphiphilic character of the polymer allows the formation of micelles making it possible to encapsulate (and solubilize) a low aqueous soluble drugs. Moreover, the polymer was designed with a low Tg (70°C), facilitating its use during thermal processing.

Formulations containing 3 components (API, polymer and other additional excipient) have also been extensively described in literature. If the extrudate containing API and polymer does not meet the requirements, a third component (plasticizer, drug release modifier, etc.) is often added to improve the characteristics of the formulation. Despite the fact that the major fraction of the formulation is in most cases the polymer phase (often >50%), few research groups would consider modifications of the polymer to modify the behavior of the formulation and most will prefer to add an additional excipient to improve the formulation's characteristics.

The availability of novel polymeric excipients also depends on regulatory constraints departments. As there is currently no regulatory approval process specifically for excipients, novel excipients are not independently evaluated by the regulators. Information about the quality and safety of new excipients is only reviewed by the health authorities in the context of a new drug application [137]. The absence of such an independent approval process for new excipients causes a dilemma for both manufacturers and the users of these excipients. Formulation scientists, for instance, prefer to use only the best performing excipients in their formulation, yet at the same time they prefer excipients that are regulatory approved in order to avoid additional risks in the drug approval process. Manufacturers of novel excipients, on the other hand, promote the use of their polymers in new drug products, yet they only disclose their sensitive information (e.g. molecular structure, specific additives) in confidentiality. A direct communication with the health authorities would be beneficial, rather than communicating via the user of the excipient as an intermediate. In the end, a registration process of excipients that is independent of the drug product registration would be the best option for all parties involved. This could mitigate the risk of a delayed product registration when new excipients are used, which should positively affect the HME/IM-based product development [138].

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CHAPTER 1

The creation of a pH-independent immediate release polymethacrylate formulation via quaternization of the polymer or the addition of acids – An observational study

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Introduction

Hot melt extrusion (HME) combined with injection molding (IM) is a versatile manufacturing technique which has generated significant interest in the pharmaceutical field based on the possibilities offered by this technique. It enables the production of tablets independent of the powders compactibility. A homogeneous system can be created via a substantial energy input, provided by elevated temperature, high shear force and pressure. Different polymers are used as matrix drug delivery systems, wherein the drug is uniformly dispersed or dissolved (providing immediate or sustained drug release depending on the polymer properties). A well established drug delivery matrix which can be used for HME/IM applications is a methacrylate terpolymer based on n-butylmethacrylate (n-BMA), dimethylaminoethylmethacrylate (DMAEMA) and methylmethacrylate (MMA) in a 1/2/1.5-ratio (Eudragit® E PO) [42, 53, 89, 139-141]. It allows the development of stable glassy solid solutions, i.e. homogeneous one-phase systems with the drug molecularly dispersed in the matrix, ensuring immediate drug release [53, 89]. However, the pH-dependent solubility of Eudragit E (i.e. insoluble at high pH, soluble at low pH) could possibly cause bioavailability problems when dealing with elderly [142-143], upon food intake [144] or diseases that tend to raise the stomach pH [145-146].

In vitro dissolution studies of nimodipine, for instance, in a medium containing 0.1N hydrochloric acid and 0.05% (w/v) sodium dodecyl sulfate (SDS) showed that a solid dispersion with EudrE dissolved significantly faster than formulations with polyvinylpyrrolidone/vinyl acetate copolymer (PVPVA) and hydroxypropyl methylcellulose (HPMC) as polymer excipient. *In vivo* studies in male beagle dogs, on the other hand, revealed the fastest release for the formulation containing PVPVA as polymer excipient, followed by EudrE and HPMC [147]. This difference between *in vitro* and *in vivo* behavior

could be due to the gastro-intestinal (GI) motility of a beagle dog which is among the fastest of all laboratory animal (fast stomach clearance), to the limited volume of gastric fluids (± 400mL) and most importantly to the gastric pH of the dogs which can reach pH 5 [144]. EudrE is also used as coating material for pH-controlled drug release in the treatment of inflammatory bowel disease [148]. Lag times of drug release for EudrE-coated formulations were determined at 10min, 50min and 33h in media with pH values of 2, 5 and 6.8, respectively. The pH-dependent release profile of Eudragit E is due to its dimethylaminoethyl methacrylate (DMAEMA) moiety which becomes protonated at low pH values. Moreover, as shown in previous work [53], the DMAEMA units are crucial with respect to API/polymer interaction (which are essential to create glassy solid solutions) and drug release characteristics.

This research focuses on the development of a pH-independent Eudragit E-based formulation, using 2 approaches to achieve pH-independent ibuprofen release from an Eudragit E matrix processed via HME/IM: 1. chemical modification of the Eudragit polymer structure by quaternization of the amine function; 2. creation of a low pH micro-environment during dissolution via the addition of dicarboxylic acids (succinic, glutaric and adipic acid).

Experimental Section

Materials

Ibuprofen 25 (IBP), with a melting endotherm at 76°C and a Tg of -42°C, was purchased from Abbott (Ludwigshafen, Germany). Eudragit® E PO (EudrE), a methacrylate terpolymer based on n-butylmethacrylate (n-BMA), dimethylaminoethylmethacrylate

(DMAEMA) and methylmethacrylate (MMA) in a 1/2/1.5-ratio, was supplied by Evonik (Darmstadt, Germany). Diethylether and acetic acid were purchased by Biosolve (Valkenswaard, Netherland), hydrochloric acid from VWR International (Leuven, Belgium). Iodomethane, silver nitrate and dicarboxylic acids (succinic, glutaric and adipic acid) were purchased from Sigma-Aldrich (St-Louis, USA) (Table 1).

Table 1: Chemical characteristics of dicarboxylic acids. (Characteristics obtained from PubChem)

Dicarboxylic acid	COOH -R- COOH	pKa_1	pKa_2	T_m (°C)	Solubility in H_2O (g/L) at 25°C	logP
Succinic	CH_2CH_2	4.2	5.6	184	60	-0.59
Glutaric	$(CH_2)_3$	4.3	5.4	95	430	-0.29
Adipic	$(CH_2)_4$	4.4	5.4	152	24	0.08

Quaternization of Eudragit® E PO

Eudragit® E PO (20g) was dissolved in 200mL methanol (final concentration: 100mg/mL), followed by the addition of 0.41, 1.02, 2.03 and 3.05mL iodomethane (methylating agent) to synthesize polymethacrylates with a quaternization degree of 10, 25, 50 and 75%, respectively. The reaction (addition of methylgroup to the polymer structure) was allowed to proceed for 2h at room temperature, followed by precipitation of the polymer via the addition of diethylether (1/20, v/v). Consequently, the iodide counter ion of the quaternary amine was replaced by chloride via dialysis (using a cellulose dialysis membrane with a Mw cut-off of 14 kDa, Mw of EudrE ± 18 kDa) for 2 days against a 60g/L aqueous sodium chloride solution, which was refreshed multiple times. The removal of iodide ions was

verified via the addition of a silver nitrate solution as described in previous research [149]. Finally, the quaternized Eudragit® E polymer (EudrE-Q) was isolated as a dry powder by lyophilization (average yield: 70%).

^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR) Spectroscopy

Polymer composition and degree of quaternization was determined through ^{1}H-NMR spectroscopy on a Varian Mercury 300 NMR Spectrometer (Vernon Hills, Illinois, USA). Samples were dissolved in deuterated methanol. ^{1}H-NMR (300 MHz, CD_3OD) δ = 4.12 (br, $COOC\underline{H}_2CH_2N(CH_3)_2$), 3.64 ($COOC\underline{H}_3$), 2.68 (br, $COOCH_2C\underline{H}_2N(CH_3)_2$), 2.35 (br, $COOCH_2CH_2N(C\underline{H}_3)_2$), 2.21-1.75 (br, $C\underline{H}_2$ backbone), 1.45 (br, $COOC(C\underline{H}_3)_3$, 1.30-0.8 (br, $C\underline{H}_3$). The degree of quaternization was verified according to Obermeier et al. [149].

Determination of pKa

A polymer sample (200mg) was dissolved in 5mL 0.1M HCl solution, followed by the addition of 45mL demineralized water. While continuously measuring the pH, small amounts of 0.1M NaOH were added to the polymer solution up to pH 12. Consequently, the pKa was determined as a minimum of the first derivative of the titration cruve.

Thermal analysis

Thermogravimetric analysis (TGA 2950, TA instruments, Leatherhead, UK) was used to investigate the thermal stability of the polymers. The samples were equilibrated at 30°C and heated (10°C/min) to 500°C under an N_2 atmosphere.

Tg and melting point (T_m) of pure components, physical mixtures (homogenized using mortar and pestle) and injection molded tablets were analyzed by modulated differential scanning calorimetry (MDSC Q2000, TA Instruments, Leatherhead, UK) using a heating rate of 2°C/min. The modulation period and amplitude were set at 1min and ±0.318°C,

respectively. Dry nitrogen at a flow rate of 50ml/min was used to purge the MDSC cell. A heating/cool/heat cycle was run between -70 and 120°C. All results were analyzed using the TA Instruments Universal Analysis 2000 software. Samples (± 5mg) were run in Tzero pans (TA Instruments, Zellik, Belgium). MDSC heat capacity calibration was done via small sapphire disks, placed in a Tzero pan.

X-ray diffraction (XRD)

The crystallinity of the samples was determined via X-ray diffraction using a D5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 kV and a current of 40 mA in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

Production of injection molded tablets

Physical mixtures of IBP and polymer (30/70, wt.%) were extruded at 90°C using a co-rotating twin-screw extruder at 90rpm (Haake MiniLab II Micro Compounder, Thermo Electron, Karslruhe, Germany). Biconvex tablets (mass: 349 ± 2.1mg; diameter: 10mm; height: 5mm) were produced via injection molding (Haake MiniJet System, Thermo Electron). The injection pressure was 800bar during 10s, in combination with a post-pressure of 400bar for 5s. Formulations containing dicarboxylic acids were processed via HME/IM at a constant drug load (30%), but varying ratios of Eudragit E to dicarboxylic acid: 60/10, 55/15 and 50/20 (wt.%).

***In vitro* drug release**

Drug release from the injection molded tablets was determined using the paddle method on a VK 7010 dissolution system (VanKel Industies, New Jersey, USA) with a paddle speed of 100rpm. Hydrochloric acid (pH 1), citric buffer (pH 3 and 5) and phosphate buffer

(pH7) were used as dissolution media (900mL) at 37 ± 0.5°C. Samples were withdrawn at 5, 10, 15, 20, 30, 45 and 60min, and spectrophotometrically analyzed for API concentration at 221nm.

Results and Discussion

Ibuprofen (IBP) is a weak acid with a pKa of 4.4. The carboxylic group in the chemical structure is responsible for its pH-dependent solubility. At pH 7, IBP is completely dissolved after 15 min, whereas, the release at pH 5, 3 and 1 is limited to 57, 40 and 29%, respectively, after 60min of dissolution testing. The tertiairy amine function in the chemical structure of Eudragit® E (EudrE) causes its pH-dependent release profiles. In contrast to IBP, a higher pH reduces the dissolution rate of EudrE. It was therefore appropriate to combine both components (IBP and EudrE) in one formulation.

The processing of an EudrE mixture containing 30wt.% ibuprofen (IBP) via hot melt extrusion (HME), followed by injection molding (IM) yielded a transparent formulation, classified as a glassy solid solution. Thermal analysis revealed a single Tg, located between the Tg values of the individual components, indicating complete miscibility and compatibility between drug and polymer. Spectroscopic analysis indicated that electrostatic interactions between the ammonium group of the polymer and the carboxyl group of IBP (i.e. salt formulation) were responsible for the solubilization of IBP [cf. chapter 2] [53]. EudrE is a fast dissolving polymer in acidic media (pH 1 and 3) due to the hydratation of the dimethylamino groups that are fully protonated at this lower pH range, yet it is insoluble in media with a pH above 5. Chemical modification of the tertiary ammonium group of the polymer to its quaternized form should allow to determine the minimum amount of positive charges needed to eliminate this pH-dependent effect, quaternisation of 10, 25, 50 and 75% were tested.

All polymer samples were analyzed via ^{1}H-nuclear magnetic resonance spectroscopy to verify the degree of quaternization. Figure 1 illustrates that the decrease of the signal of the tertiary ammonium group R-N$(CH_3)_2$ at ~2.7 ppm is correlated with larger signals of the quaternary ammonium group R-N$^{+}(CH_3)_3$ at ~3.15 ppm. The deviation between the theoretical calculated and experimental degree of quaternization was 5, 7, 5 and 8% (higher experimental value) for EudrE-Q10, -Q25, -Q50 and -Q75, respectively. As the objective was to determine the relative influence of the degree of quaternization on drug release, these differences were regarded as negligible.

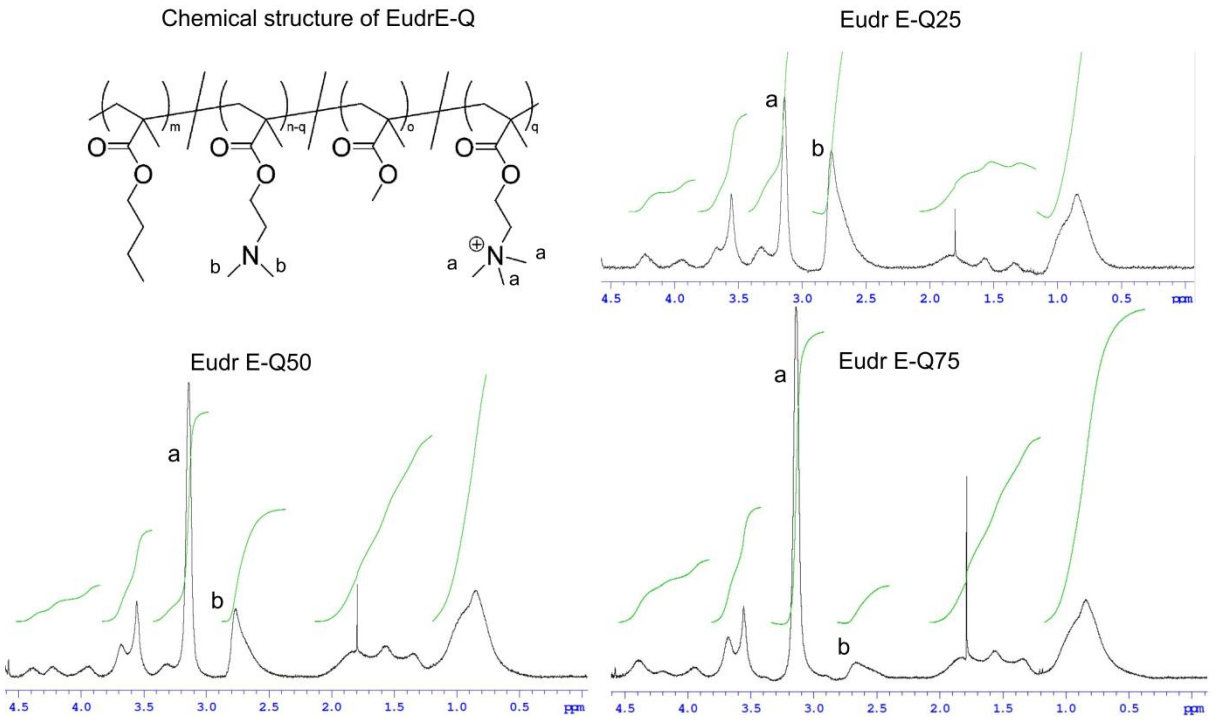

Figure 1. ^{1}H-NMR (300 MHz, CD_3OD) of EudrE-Quaternized (EudrE-Q) to verify the degree of quaternization via integration of the signals a and b, representing the signals of the quaternary and tertiary ammonium groups, respectively.

Second, it was determined whether quaternized Eudragit® E (q-EudrE) samples were suitable as polymers to solubilize ibuprofen (IBP) upon processing via hot melt extrusion (HME) and injection molding (IM). As the quaternization of EudrE did not significantly alter the polymers' glass transition temperature (maximum deviation of 3°C) and a similar drug load (30wt.%) was used, the processing conditions were chosen similar to the EudrE/IBP 70/30 mixture [53]. All processed formulations with quaternized EudrE (EudrE-Q) as carrier were transparent with smooth surfaces. Figure 2 illustrates their dissolution behavior in function of pH. At pH 1, all formulations had similar release characteristics. At pH 3, the protonation rate of the tertiary ammonium group of EudrE is reduced, resulting in a slower hydratation of the polymer and a lower IBP release rate compared to pH 1. In contrast, all quaternized EudrE (EudrE-Q) formulations were not affected by this lower acidic character of the dissolution medium. As a positive charge is intrinsically present in the chemically modified polymers, the lag phase for polymer protonation and hydratation is avoided, yielding faster release profiles for EudrE-Q formulations. At pH 5, no IBP was released from the EudrE formulation, while the EudrE-Q10 formulation resulted in a release of 40% after 1h. At pH 5, not all ammonium groups of the polymer are protonated by the solvent based on their pKa value of 6.1, resulting in insufficient or no release from the EudrE-Q10- and EudrE- formulations, respectively. Eudr-Q25, -Q50 and -Q75 formulations, on the other hand, still resulted in fast IBP release profiles as they already carried sufficient positive charges (due to the high degree of quaternization) and do not rely on protonation by the solvent to obtain fast drug release. At pH 7, release from all formulations (EudrE as well as EudrE-Q grades) was slow, indicating that at this pH even a high degree of quaternisation could not ensure fast hydration of the chemically modified polymethacrylate. Possibly, the formation of a complex between the positively charged polymer and the negatively charged IBP also contributed to

the incomplete release under these conditions [150-151]. Overall, *in vitro* dissolution experiments revealed that a minimum of 25% of quaternization was sufficient to partially (up to pH 5) eliminate the pH-dependent effect of the EudrE/IBP formulation.

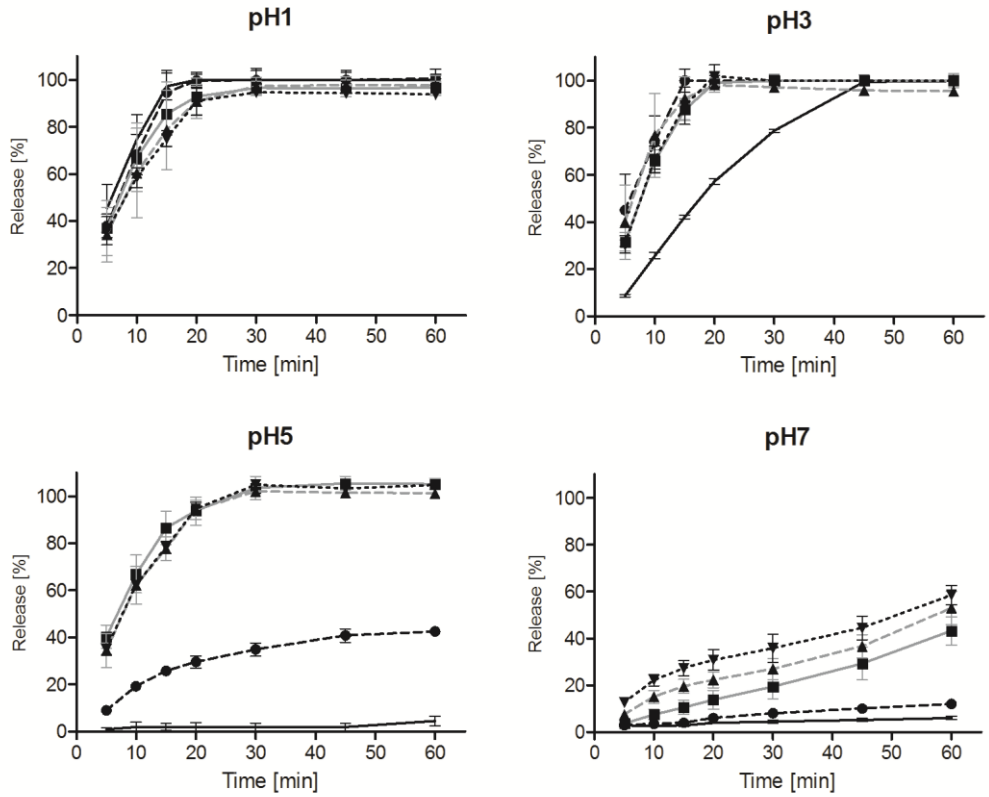

Figure 2. Release characteristics at different pH-values (1, 3, 5 and 7) of formulations containing 30wt.% ibuprofen and different polymethacrylate carriers: EudrE (no symbol), EudrE-Q10 (●), EudrE-Q25 (■), EudrE-Q50 (▲), EudrE-Q75 (▼).

As glassy solid solutions are inherently thermodynamically metastable, recrystallization is inevitable. However, a previous study indicated that the tertiary ammonium group of the polymer is of high importance as an interaction with the carboxylgroup of IBP (i.e. salt formation) stabilizes the glassy solid solution for at least 6 months of storage at 25°C and 60% relative humidity [53]. Performing a stability study in similar conditions revealed the recrystallization of IBP in all formulations containing

quaternized EudrE polymers (EudrE-Q) upon 3 months of storage, irrespective of the amount of quaternization. The transparent formulations became opaque, an IBP melting endotherm was observed via thermal analysis and XRD-spectra evidenced clear signs of crystallinity (data not shown). Hence, quaternization of EudrE, even at a low percentage (i.e. 10%), limits the interactions between drug and polymers, and reduces the stability of IBP solid solutions upon storage. Possibly the positive charges of EudrE-Q polymers are obstructing the ability of IBP to release its hydrogen atom, limiting the possibility for electrostatic interaction with the polymer which is essential for the stabilization of molecularly dispersed ibuprofen in an Eudragit E matrix. It is also possible that EudrE-Q polymers, obtained after quaternization in methanol, precipitation in diethylether, dialysis and lyophilization, still contained some residual solvents. These can alter the molecular mobility of IBP and increase its tendency to recrystallize.

As protonation of EudrE is responsible for the fast hydratation/dissolution of the polymer and as this protonation is evidently reduced at higher pH values, a second approach to achieve pH-independent release was to create a low pH micro-environment around the tablet during dissolution via the addition of acids to the HME/IM processed formulations. High concentrations of acids in the diffusion layer during dissolution could lower the pH, leading to accelerate protonation of EudrE and enhance the drug release rate. To this end, several dicarboxylic acids (succinic, glutaric and adipic acid) were added to the formulation (Table 1).

The addition of dicarboxylic acids to the IBP/EudrE 30/70 mixture did not influence the formulation's ability to form transparent tablets. Dissolution experiments illustrated that the addition of dicarboyxlic acids did not alter IBP release in a pH 1 and 3 medium (data not shown), as the dimethyl amino groups of EudrE are already fully protonated. Moreover, the

ability of dicarboxylic acids to release hydrogen atoms is lower at this pH given pKa values of succinic, glutaric and adipic acid of 4.2, 4.3 and 4.4, respectively. At pH 5, IBP release was significantly improved (Figure 3) upon the addition of dicarboxylic acids, as the low pH environment in the diffusion layer around the tablet enhances IBP release rate. This improvement was concentration driven as higher concentrations of dicarboxylic acids induced faster drug release. IBP release depended also on the type of dicarboxylic acid: the fastest release was observed in combination with succinic acid, while adipic acid had less impact. This could be related to the polarity of the dicarboxylic acids, as succinic acid was the most polar compound (log P -0.59, vs. -0.29 and 0.08 for glutaric and adipic acid, respectively) (Table 1).

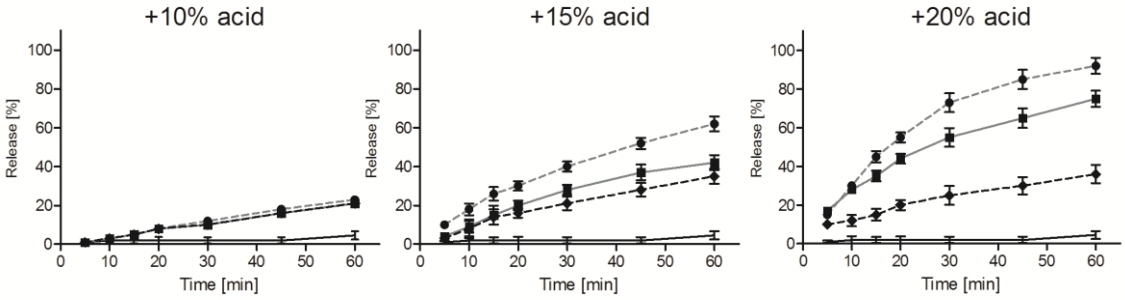

Figure 3. Release profiles of IBP/EudrE 30/70 mixtures (no symbol) at pH 5 with the addition of 10, 15 and 20% of adipic (♦), glutaric (■) and succinic acid (●), respectively.

The importance of low pH in the diffusion layer was illustrated by the addition of 20% disodium succinate to the formulation: IBP release was limited to 10% after 60 min, vs. 92% in combination with 20% succinic acid (cf: a solution containing 0.1N of succinic acid and disodium succinate has a pH value of 2.7 and 7, respectively).

Figure 4 illustrates the formulation's stability at room temperature. The glassy solid solution tablets containing dicarboxylic acids were mechanical unstable (unable to maintain their structure). Two underlying reasons were identified: 1. The plasticizing effect of IBP on EudrE [53]. Increasing the dicarboxylic acid concentration also increased the IBP/EudrE ratio thereby inducing more molecular mobility; and 2. The molecular mobility of the dicarboxylic acids. Figure 4 and Table 2 illustrates that the formulation's mechanical stability was dependent on the length of the dicarboxylic acid (stability of formulation with succinic > glutaric > adipic). It is known from previous research [53] that the change of a t-butyl group in the polymer structure to a n-butyl group increases the molecular mobility of the polymer as a result of an increase in free volume and a less denser polymer structure. As adipic acid had the highest amount of carbons between its 2 carboxylic groups, the polymer's free volume and its molecular mobility were increased to a higher extent compared to succinic and glutaric acid containing formulations, resulting in a lower mechanical stability (Table 2).

Table 2. Tablet diameter upon 1 month of storage at 25°C, 60% relative humidity of EudrE/IBP 70/30 with the addition of 10, 15 and 20% of dicarboxylic acid, respectively.

Dicarboxylic acid	**IBP/EudrE/Acid**			
	30/70/0	**30/60/10**	**30/55/15**	**30/50/20**
Succinic	10.0mm	10.2mm	10.4mm	11.9mm
Glutaric	10.0mm	10.4mm	11.1mm	13.8mm
Adipic	10.0mm	10.4mm	11.4	14.2mm

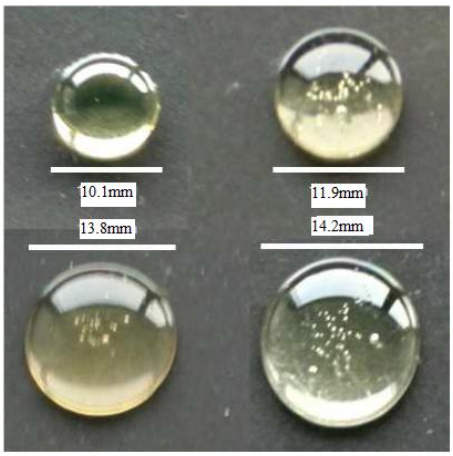

Figure 4. Tablet diameter upon 1 month of storage at 25°C, 60% relative humidity of EudrE/IBP 70/30 (upper left) with the addition of 20% succinic acid (upper right), glutaric acid (lower left) and adipic acid (lower right), respectively.

Conclusion

A pH-independent immediate release polymethacrylate formulation was created via a chemical modification of the polymer (i.e. quaternisation of amine function) and via the addition of dicarboxylic acids (succinic, glutaric and adipic acid). The presence of a positively charged polymer and the low pH micro-environment during dissolution allowed the release of IBP independent of the solvent pH (up to pH 5). However, the quaternization of the polymer induced stability issues (recrystallization of API) and the formulations containing dicarboxylic acids were classified as mechanically unstable. Hence, further research is needed to obtain a pH-independent immediate release formulation containing EudrE and IBP.

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CHAPTER 2

Structural Modifications of Polymethacrylates: Impact on Thermal Behavior and Release Characteristics of Glassy Solid Solutions

Parts of this chapter were submitted for publication in:

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Introduction

Hot melt extrusion (HME) has attracted increasing attention as novel drug formulation strategy to produce solid solutions with enhanced oral bioavailability of dissolution-limited drugs [1, 41, 47-48, 152-154]. Moreover, the combination with injection molding (IM) enables the processing of materials with high dimensional precision [155-156]. This technique relies on obtaining a homogeneous system via a substantial energy input, provided by elevated temperature, high shear force and pressure during HME and IM. The development of glassy solid solutions, i.e. homogeneous one-phase systems with the drug molecularly dispersed in the matrix, is challenging in particular, as such formulations are inherently metastable [157-160]. Due to the substantial energy uptake during the HME/IM-process, followed by a fast cooling of the melt, the obtained glassy solid solution is kinetically trapped resulting in a blend far from its thermodynamic equilibrium.

Several methods have been proposed to decrease the rate of recrystallization and, hence, increase the stability of solid solutions. These methods are often based on molecular interactions between the active pharmaceutical ingredient (API) and the polymer. For instance, Eudragit E PO (EudrE; an n-butyl-, dimethylaminoethyl-, methylmethacrylate-terpolymer) was used as antinucleant agent in ibuprofen containing transdermal polydimethylsiloxane patches [161]. Interactions on a molecular level inhibited drug mobility inside the matrix and reduced recrystallization. An antiplasticizing effect by combining two polymers is also proposed as a stabilizing factor by several authors [162-164]. The use of a polymer with a high glass transition temperature (T_g) provides lower molecular mobility of the drug in a polymer/drug system at room temperature, maintaining the drug in its metastable amorphous state. Sufficient miscibility of the drug in the polymer matrix [165] and the absence of clusters are crucial conditions for this approach. Six et al.[162], for instance,

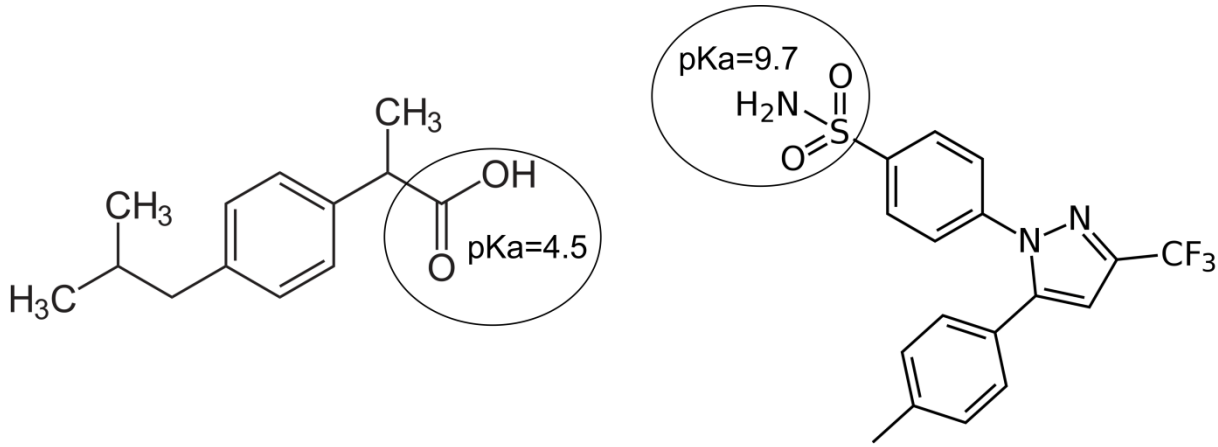
combined Eudragit E PO with PVP-VA64 in order to increase the physico-chemical drug stability in a hot melt extruded polymer matrix. Although much research has been performed in terms of molecular interactions between API and polymer or the use of polymer combinations, little attention has been given to the molecular structure of the polymer itself.

In this paper, we report the synthesis of several novel polymethacrylate analogues of Eudragit E PO, with the aim to increase the Tg of the polymers, allowing better processing of drugs into glassy solid solutions, based on increased mechanical stability, via HME and IM. Ibuprofen (IBP, a non-traditional plasticizer) was selected as model drug since it challenges the polymethacrylates to a higher extent [13, 117, 166-167]. The second API used in this study was celecoxib (CEL). Eudragit E PO (EudrE) was chosen as carrier to produce glassy solid solutions.

Experimental Section

Materials

Ibuprofen 25 (IBP; figure 1, left), with a melting endotherm at 76°C and a Tg of -42°C, was purchased from Abbott (Ludwigshafen, Germany). Celecoxib (CEL; figure 1, right), with a melting endotherm of 162°C and a Tg of 58°C, was purchased from Utag (Amsterdam, The Netherlands). Eudragit® E PO, a methacrylate terpolymer based on n-butylmethacrylate (n-BMA), dimethylaminoethylmethacrylate (DMAEMA) and methylmethacrylate (MMA) in a 1/2/1.5-ratio, was supplied by Evonik (Darmstadt, Germany).



F**igure 1**. Chemical structure of ibuprofen (left) and celecoxib (right) with a pKa of 4.5 and 9.7, respectively.

Polymer synthesis

The different monomers tert-butylmethacrylate (t-BMA), DMAEMA, MMA, and isobornylmethacrylate (iso-BMA; Sigma Aldrich, St-Louis, USA) were purified to remove the inhibitor via filtration over aluminium oxide (Acros Organics, New Jersey, USA) and subsequently degassed via N_2 bubbling. Free radical polymerization of these monomers in varying ratios (Table 1) was carried out in toluene (Biosolve, Valkenswaard, the Netherlands) under a nitrogen atmosphere at 70°C for 24h using azoisobutyronitrile (AIBN, Sigma Aldrich, St-Louis, USA) as initiator. The resulting polymethacrylates were subsequently precipitated (3 times) from toluene in hexane (Biosolve, Valkenswaard, the Netherlands), dried for 48h at 40°C and vacuum dried at 55°C for 48h.

Size exclusion chromatography (SEC)

SEC measurements were performed in an Agilent 1260-series equipped with a 1260 ISO-pump, a 1260 Diode Array Detector (DAD), a 1260 Refractive Index Detector (RID), and a PSS Gram30 column in series with a PSS Gram1000 column inside a 1260 Thermostated Column Compartment at 50°C. The used solvent was DMA containing 50mM

of LiCl (flow rate of 1 mL min^{-1}). The molar masses were calculated against polymethyl methacrylate standards.

^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR) Spectroscopy

Polymer composition was determined through ^{1}H-NMR spectroscopy on a Varian Mercury 300 NMR Spectrometer (Vernon Hills, Illinois, USA). Samples were dissolved in deuterated methanol. ^{1}H-NMR (300 MHz, CD_3OD) δ = 4.12 (br, $COOC\underline{H_2}CH_2N(CH_3)_2$), 3.64 ($COOC\underline{H_3}$), 2.68 (br, $COOCH_2C\underline{H_2}N(CH_3)_2$), 2.35 (br, $COOCH_2CH_2N(C\underline{H_3})_2$), 2.21-1.75 (br, $C\underline{H_2}$ backbone), 1.45 (br, $COOC(C\underline{H_3})_3$, 1.30-0.8 (br, $C\underline{H_3}$). More apolar samples were dissolved in deuterated chloroform. ^{1}H-NMR (300 MHz, $CDCl_3$) δ=4.34 (br, $COO\underline{CH}C_9H_{16}$), δ=4.08 (br, $COO\underline{CH_2}CH_2N(CH_3)_2$), δ=3.60 ($COO\underline{CH_3}$), δ=2.59 (br, $COOCH_2\underline{CH_2}N(CH_3)_2$), δ=2.31 (br, $COOCH_2CH_2N(\underline{CH_3})_2$), 2.11-1.65 (br, $C\underline{H_2}$ backbone), δ=1.41 (br, $COOC(\underline{CH_3})_3$), 1.30-0.7 (br, $C\underline{H_3}$).

Thermal analysis

Thermogravimetric analysis (TGA 2950, TA instruments, Leatherhead, UK) was used to investigate the thermal stability of the polymers. The samples were equilibrated at 30°C and heated (10°C/min) to 500°C under an N_2 atmosphere.

The Tg and melting point (T_m) of pure components, physical mixtures (homogenized using mortar and pestle) and injection molded tablets were analyzed by modulated differential scanning calorimetry (MDSC Q2000, TA Instruments, Leatherhead, UK) using a heating rate of 2°C/min. The modulation period and amplitude were set at 1min and ±0.318°C, respectively. Dry nitrogen at a flow rate of 50ml/min was used to purge the MDSC cell. A heating/cool/heat cycle was run between -70°C and 120°C. All results were analyzed using the TA Instruments Universal Analysis 2000 software. Samples (± 5mg) were run in Tzero

pans (TA Instruments, Zellik, Belgium). MDSC heat capacity calibration was done via small sapphire disks, placed in a Tzero pan. The thermoanalytical investigations in terms of interaction were surveyed in the first heating cycle by analyzing the melting enthalpy, Tmelt-max (i.e. inflection point of melting endotherm) and Tmelt-onset (i.e. start of melting endotherm).

Hot stage microscopy (HSM)

Polarized light microscopy images were recorded on a Leica DM2500P microscope equipped with a 10x objective and a DFC 425 CCD camera. Polymer samples were subjected to controlled heating using a Linkham THHS 600 heating stage.

X-ray diffraction (XRD)

The crystallinity of the samples was determined via X-ray diffraction using a D5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 kV and current of 40 mA in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

Fourier-transform infrared (FTIR) spectroscopy

Attenuated total reflectance (ATR) FTIR spectroscopy was used to evaluate the solid-state of the injection molded tablets. Spectra were collected from the pure amorphous components (after melting and quenching in liquid nitrogen), the physical mixtures and the injected molded tablets. The ATR-FTIR spectra were collected with a Bruker Vertex 70 FT-IR spectrometer, equipped with a DTGS detector and a PIKE accessory, equipped with a diamond ATR crystal (4 cm^{-1} resolution, 32 scans).

Production of injection molded tablets

Physical mixtures, homogenized using mortar and pestle, of drug (IBP, CEL) and polymer (with a drug content varying from 30 to 50 wt.%) were extruded at 100-120°C using a co-rotating twin-screw extruder at 100rpm (Haake MiniLab II Micro Compounder, Thermo Electron, Karslruhe, Germany). Biconvex tablets (diameter: 10mm/height: 5mm) were produced via injection molding (Haake MiniJet System, Thermo Electron). The injection pressure was 800bar during 10s, in combination with a post-pressure of 400bar for 5s.

***In vitro* drug release**

Drug release from the injection molded tablets was determined using the paddle method on a VK 7010 dissolution system (VanKel Industies, New Jersey, USA) with a paddle speed of 100rpm. Hydrochloric acid (pH 1) and citric/phosphate buffers (pH 3 and pH 5) were used as dissolution media (900mL) at 37 ± 0.5°C. Samples were withdrawn at 5, 10, 15, 20, 30, 45 and 60min and spectrophotometrically analyzed for API concentration at 221 and 250nm for IBP and CEL, respectively.

Results and Discussion

Polymer synthesis and characterization

The synthesis of novel polymethacrylates for the manufacturing of immediate release tablets via hot melt extrusion (HME) and injection molding (IM) was performed aiming to ensure good mechanical and physical stability of these dosage forms via high Tg polymethacrylates. The starting point for this study was the commercially available Eudragit E PO, a n-BMA/DMAEMA/MMA terpolymer with monomer molar percentages of 22/45/33 as determined by ^{1}H-NMR spectroscopy. Based on this monomer composition we synthesized novel polymethacrylate analogues via free radical polymerization, the yield of all synthesis procedures was about 70%. Compared to the commercial Eudragit E PO we first replaced the n-BMA group by t-butylmethacrylate (t-BMA, Figure 2). Substituting the flexible n-butyl side chains with the more compact t-butyl side chains should result in a reduced free volume and a denser polymer structure, promoting interpolymer interactions as is evident from the higher Tg of poly(t-BMA) (Tg = 107 ^{o}C) in comparison to poly(n-BMA) (Tg = 20 ^{o}C). MDSC indeed demonstrated that changing the n-BMA groups to t-BMA yielded a Tg increase of 14.8°C to a value of 64,7 ^{o}C (Table 1; thermograms in supporting information). In a next step, we investigated the influence of the cationic DMAEMA repeating unit on the thermal behavior of the polymethacrylates and on the drug release properties of injected molded tablets. Lowering the DMAEMA content yielded polymers with a higher Tg, i.e Tg increased from 64.7±2.8°C to 80.8±2.2°C upon decreasing the DMAEMA content from 45 to 17% (Table 1; thermograms in supporting information), which is due to the low Tg of poly(DMAEMA) (Tg = 20 ^{o}C). Further decreasing the DMAEMA content was not an option as the DMAEMA group appeared to be critical for the polymer's dissolution behavior and its

interaction with API (see section Interactions and *in vitro* drug release). A third modification of the polymer structure was the incorporation of an isobornyl-group to the polymer structure, creating a quarterpolymer (i.e. consisting of 4 different monomers). Incorporation of isoBMA increased the rigidity of the polymer (Tg of poly(isoBMA) is 197 ^{o}C) as indicated by a Tg increase from 62.7 to 103.0°C for polymers with 5 and 50% iso-BMA, respectively (Table 1). These modifications identified two strategies to increase the Tg of polymethacrylates [168]. First, by decreasing the length of side groups (replacing n-butyl by t-butyl and lowering the DMAEMA-content), the free volume was reduced, increasing the probability of interpolymer interactions and yielding a higher Tg of the obtained polymers. Secondly, by incorporating a bulky side group (via the incorporation of an isobornyl repeating unit), the mobility of the polymer chain is reduced as steric hinderance reduces the rotation of the polymer backbone. This latter effect also plays a role when replacing the n-butyl side chains with t-butyl groups.

Table 1. Characteristics of the synthesized polymethacrylates: polymer composition (theoretical molar percentages vs. composition determined via ^{1}H-NMR spectroscopy), molecular weight (determined via SEC), and glass transition temperature (Tg, determined via MDSC).

Polymer	t-BMA/DMAEMA/MMA(%)[1]		Mn[2] (x 10^4)	Mw[3] (x 10^4)	PDI[4]	Tg ± SD (°C)
	Theoretical	determined by NMR				
A1	Eudragit E PO[5]	22/45/33[5]	1.75	4.48	2.56	49.9±0.6
A2	22/45/33	24/44/32	1.32	3.65	2.77	64.7±2.8
B1	36/36/27	39/34/36	1.45	3.86	2.66	70.5±2.0
B2	29/28/43	31/28/41	1.27	3.64	2.87	78.5±3.7
B3	33/17/50	36/15/49	1.24	3.60	2.90	80.8±2.2
	t-BMA/DMAEMA/MMA/isoBMA(%)[1]					
C0	25/50/25/0	22.6/48.5/28.9/0	1.32	3.65	2.77	62.7±1.2
C1	22.5/50/22.5/5	21.1/50.3/26.2/2.4	1.83	4.13	2.26	67.1±1.8
C2	17.5/50/17.5/15	18.6/53/18.1/10.3	2.13	4.78	2.24	75.3±1.5
C3	15/50/15/20	14.8/48.2/20.2/16.8	2.35	4.89	2.08	77.5±1.9
C4	12.5/50/12.5/25	12.5/51.5/16.1/19.9	2.36	5.09	2.16	84.7±1.7
C5	10/50/10/30	12.5/51.9/9.4/26.1	2.28	5.76	2.52	88.1±2.4
C6	5/50/5/40	5.4/55.3/5.5/34	2.43	6.42	2.64	91.1±1.3
C7	2.5/50/2.5/45	4.9/52.3/5.2/38	2.86	6.95	2.43	98.2±2.5
C8	0/50/0/50	0/53.9/0/46.1	3.21	6.27	1.95	103 ±2.2

(1) Molar percentages of tertbutylmethacrylate (t-BMA), dimethylaminoethylmethacrylate (DMAEMA), methylmethacryalte (MMA) and isobornylmethacrylate (isoBMA)
(2) Number average molecular weight
(3) Weight average molecular weight
(4) Polydispersity-index (Mw/Mn)
(5) This polymer contains n-butylmethacylate (n-BMA) instead of t-BMA

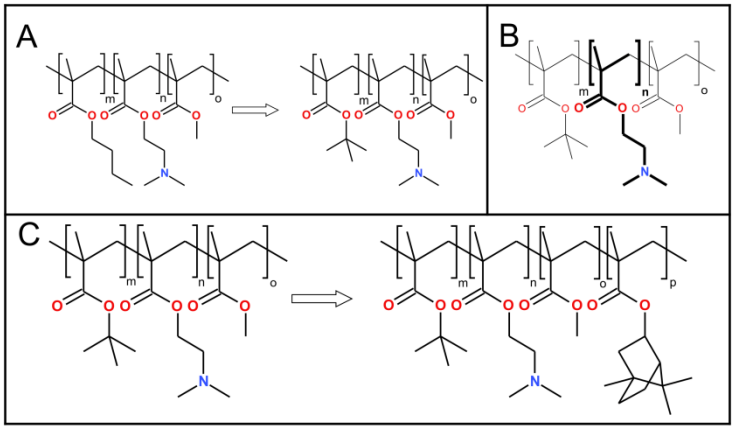


Figure 2. Overview of the different chemical modifications to the polymer structure: (A) replacement of n-BMA to t-BMA in n-BMA/DMAEMA/MMA terpolymers, (B) reducing the DMAEMA content (highlighted monomer) of t-BMA/DMAEMA/MMA and (C) incorporation of an isoBMA monomer.

The synthesized polymers were further characterized by ^{1}H-NMR spectroscopy and size exclusion chromatography (SEC, Table 1). The good correlation between the theoretical and experimental compositions of the different polymers indicated a robust polymer synthesis process. Small differences between experimental and theoretical values for the isobornyl group repeating units were attributed to the technical grade of the monomer solution. As the objective was to determine the relative influence of the isobornyl group on the drug release characteristics and thermal behavior, these small difference were regarded as negligible. Furthermore, the molecular weight and the polydispersity index (PDI) of the synthesized polymers were analyzed by SEC. Replacing the n-butyl groups with t-butyl groups and reducing the DMAEMA content (Figure 2, polymer A and B) did not affect the polymer Mw or Mn compared to Eudragit E PO. Incorporation of isobornyl repeating units (Figure 2, polymer C) increased the Mw from 1.32 to 3.21 and the Mn from 3.65 to 6.27 for the polymers with an isoBMA content of 0 and 50%, respectively. The molecular weight distributions of all the polymers investigated were comparable, as indicated by their similar

PDI values. It should be noted, however, that based on these characterization data it is not possible to exclude variations in microstructure (average block lengths) and the stereoregularity (tacticity) between different polymer chains that might result from differences in monomer reactivity.

Interactions between ibuprofen and the polymers

In a next series of experiments we evaluated the interactions between the different polymers and ibuprofen (IBP) using three different methods: thermal analysis via MDSC, hot stage microscopy (in combination with visual evaluation of injection molded tablets) and ATR- FTIR.

Thermal analysis provides four parameters to identify possible drug/polymer interactions: API melting enthalpy (% crystallinity), Tmelt-max and Tmelt-onset during the first heating cycle, and the presence of a single Tg during the second heating cycle [38, 169]. The melting enthalpy of IBP was found to be inversely correlated with the polymer's DMAEMA content (Figure 3, left). The percentage of crystallinity dropped from 40 to 11% for physical mixtures, homogenized using mortar and pestle, of IBP and polymer (in a 50/50 wt% ratio) with 17 and 50% DMAEMA, respectively. The lower crystallinity (observed during the first heating cycle) indicated that part of the API dissolved in the polymeric carrier during heating, whereby the DMAEMA group in the polymer structure is essential for interaction with the API. This was confirmed by Tmelt-onset (Figure 3, right) and Tmelt-max (data not shown) as the more intense interaction between API and carrier at higher DMAEMA content shifted these signals to a lower temperature. As more interactions occurred smaller IBP crystals are formed, being intrinsically less stable, which resulted in a broadened melting peak with a lower Tmelt-max and Tmelt-onset. It should be noted that these thermal investigations only provide a rough estimate of drug/polymer interactions as only directly

adjacent molecules are able to interact in the MDSC-cup (limited mobility). Figure 4 illustrates the importance of DMAEMA with respect to drug/polymer interactions by analyzing the difference between the theoretical (predicted via the Gordon-Taylor equation, supporting information for calculations) and experimental Tg. The experimental Tg values of polymers with a DMAEMA-content of 36 and 28% (B1 and B2) exhibited a positive deviation (of ca. 20°C for formulations with 50wt.% IBP) compared to the theoretical Tg values, which is indicative for molecular interactions between IBP and the polymer. However, at a DMAEMA-content of 17% (B3), there were insufficient DMAEMA units available to allow complete interaction with IBP, leading to similar experimental and theoretical Tg values. In this formulation, phase separation is likely to occur which increases the likelihood of recrystallization of this less-stabilized phase during storage. The positive deviation between experimental and theoretical Tg values was also detected for isoBMA-containing polymers (Figure 4, C1-3), indicating that the bulky isobornyl group is not hindering the ability of IBP to interact with DMAEMA.

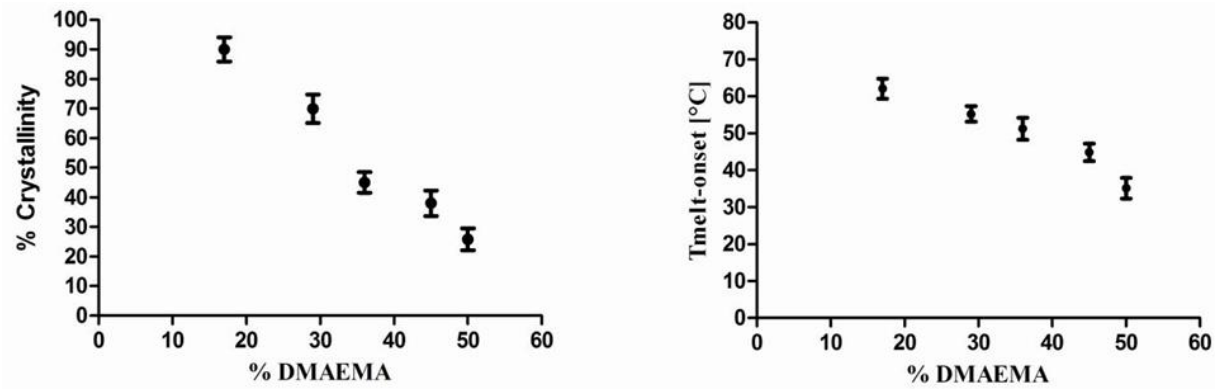


Figure 3. Percentage crystallinity (left) and Tmelt-onset (right) of physical mixtures of IBP in combination with polymethacrylates having a varying DMAEMA content. The IBP/polymer ratio in all formulation was 50/50 (wt.%). Thermal properties were measured during the first heating cycle.

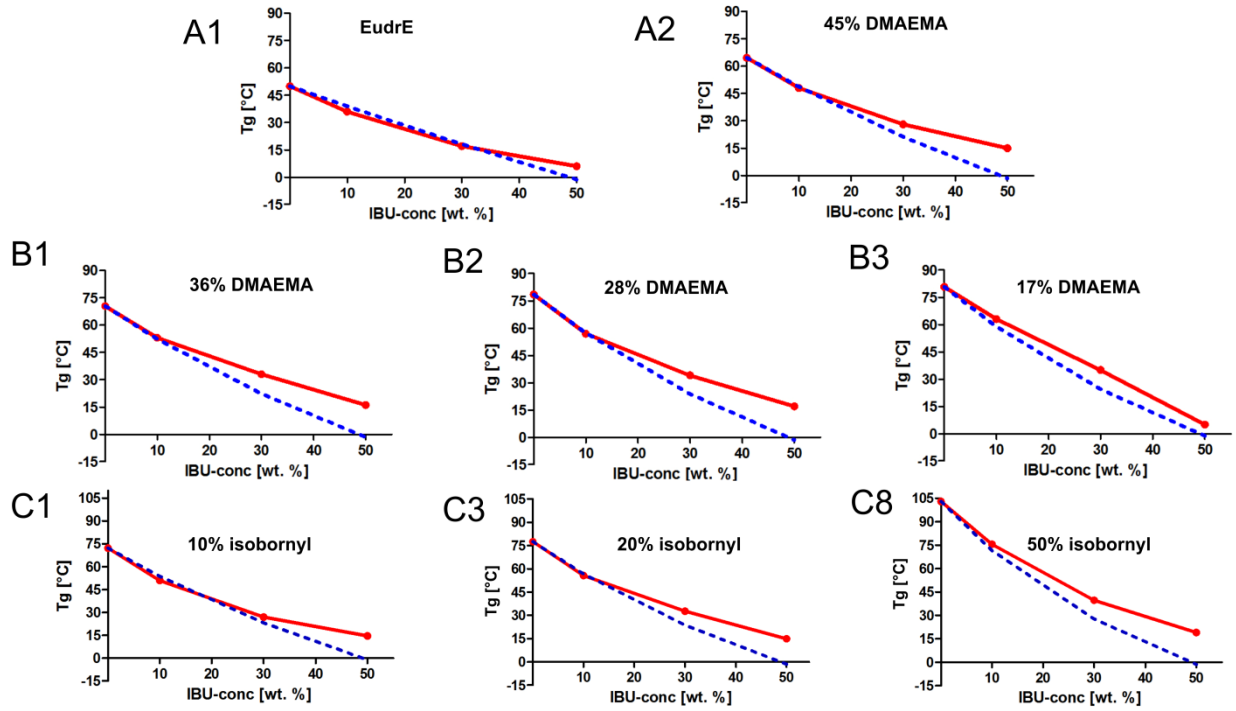


Figure 4. Comparison of the experimental (red ●) and theoretical (calculated using the Gordon-Taylor equation) Tg values (dotted blue line -) of formulations containing IBP and different polymethacrylate carriers: (A1) Eudragit E, (A2) polymethacrylate with n-butyl replaced by t-butyl, (B1-3) polymethacrylates with DMAEMA contents varying from 36% to 17%, (C1, C3, C8) polymethacrylates with isobornyl contents of 10, 20 and 50%, respectively. The IBP content in the formulations was varied from 0 to 50%.

The analysis of the second heating cycle revealed a single Tg, located between the Tg values of the individual components, which indicated complete miscibility and compatibility between drug and polymer. This was also confirmed by the presence of a single Tg when analyzing the first heating cycle of the injection molded tablets. The formation of transparent tablets after injection molding and visualization by hot stage microscopy (HSM) under polarized light (Figure 5) confirmed good miscibility between IBP and the polymethacrylates. On the left side of figure 5, the melting process of pure IBP is presented. IBP in combination with Eudragit E, polymer B1 (36% DMAEMA) and polymer B2 (28% DMAEMA) showed a similar melting behavior as compared to pure IBP. However, after cooling no recrystallization

of API was observed in drug/polymer mixtures (note that pure IBP crystallized immediately upon cooling, whereas the pictures of the polymer/drug formulations were taken after 2 days storage at ambient conditions).

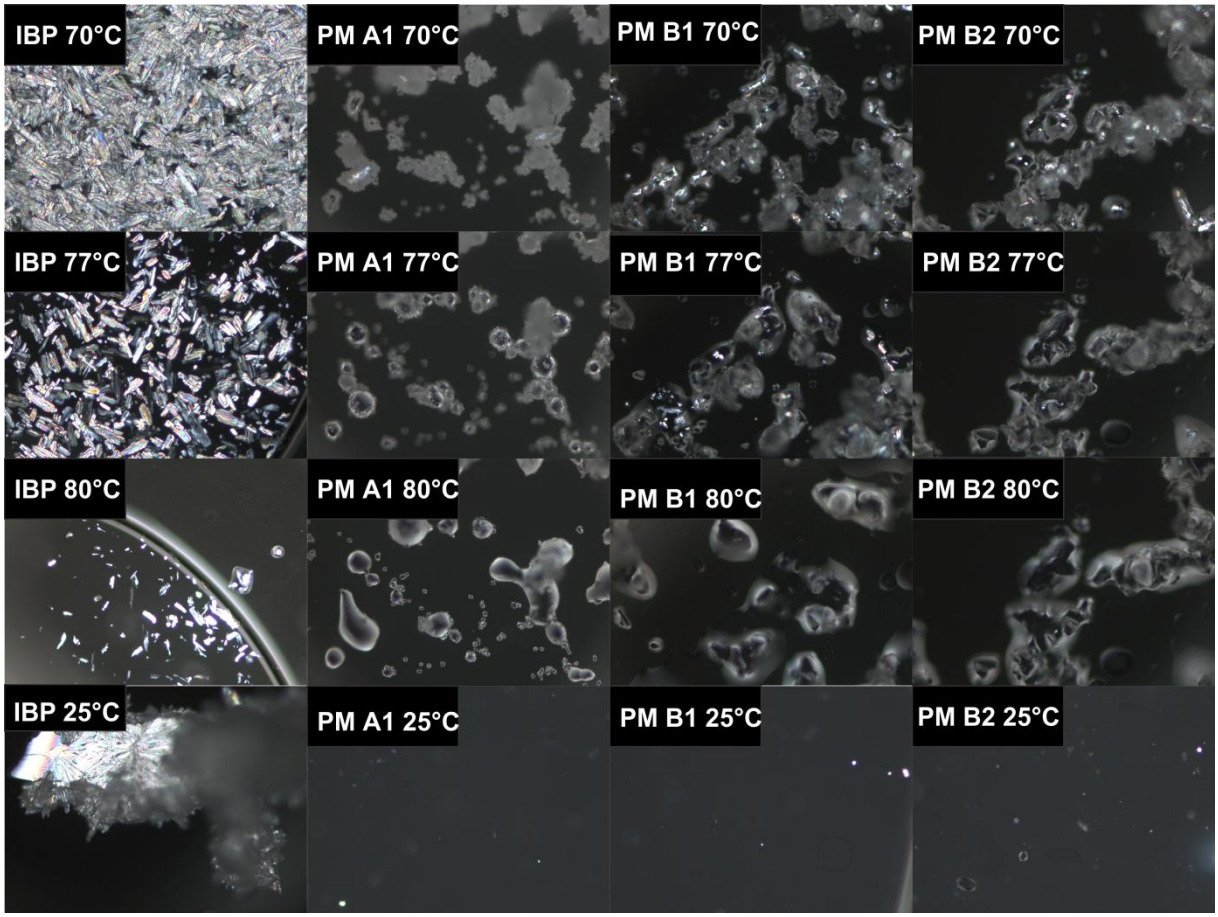


Figure 5. Hot stage microscopy under polarized light of IBP (left) and physical mixtures (PM) of IBP in combination with (A1) EudragitE, (B1) 36% DMAEMA polymer, (B2) 28% DMAEMA polymer. The IBP/polymer ratio in all formulation was 70/30 (wt.%).

Whereas thermal analysis and visual evaluation revealed attractive interactions and good miscibility between API and polymers, in this section we aimed to further identify the type of interactions occurring between IBP and the polymethacrylates via spectroscopic analysis. FTIR spectra of the injection molded tablets (IM-spectrum) were different from those of the physical mixture (PM-spectrum; which can be considered as the sum of the

spectra of the individual components) and the pure amorphous components (Figure 6). First, peak broadening occurred in the IM-spectrum, indicating interactions between the components and the presence of amorphous segments in the formulation. Second, a peak at 1565-1579 cm^{-1} was observed in the IM-spectrum which was absent in the PM-spectrum. This specific peak is characteristic for carboxylate groups, indicating that electrostatic interactions between the tertiary ammonium group of the polymer and the carboxyl group of IBP are occurring (i.e. salt formation) when a physical mixture of these components is processed by HME and injection molding. The 2770-2980cm^{-1} region, in which the symmetrial and asymmetrical C-H stretch vibrations of the tertiary ammonium group (methyl and methylene) appear, was not suitable for interpretation due to overlap with the C-H stretch vibrations of the aliphatic carbons of IBP (2850-2980cm^{-1}). Third, in formulations where the entire IBP load can interact with the polymer (i.e. when combined with polymethacrylates with a sufficient DMAEMA content), the fingerprint region (500-1430cm^{-1}) is completely dominated by the polymer. In contrast, the spectrum of formulation IBP-B3 (with 17% DMAEMA and a drug load of 50wt.% IBP, Figure 6) produced a fingerprint region which was the sum of the two spectra of the individual components. In addition, a broad peak (2500-3300cm^{-1}) is present in the IM-spectra, indicating intermolecular, H-bond based, IBP interactions (i.e. partial phase-separation of IBP, allowing dimerization and crystallization). Interestingly, these intermolecular IBP interactions are absent in formulation IBP-B2 (using a polymer with 28% DMAEMA content) for 30 and 50wt.% drug load (data not shown) and in formulation IBP-B3 (using a polymer with 17% DMAEMA) at a drug load of 30wt.% (Figure 6). This again confirmed that complete IBP-polymer interactions and the creation of a glassy solid solution is possible when a sufficient amount of DMAEMA is present in the formulation. The minimum amount of DMAEMA needed in the polymer to interact with 50wt.% IBP is

between 17 and 28% DMAEMA, which corresponds to a DMAEMA/IBP molar ratio between 0.25 and 0.45. The substitution of n-butyl by t-butyl groups and the incorporation of isobornyl repeating units does not influence these interactions.

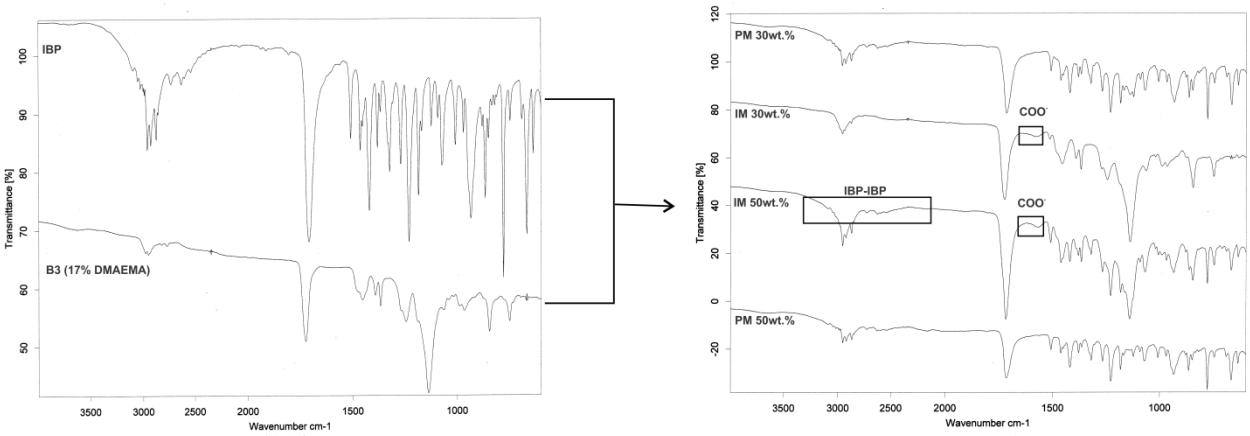


Figure 6. FTIR-spectra of (left) IBP and polymer B3 (with 17% DMAEMA content), and of (right) physical mixtures (PM) and injection molded tablets (IM) of IBP and polymer B3, at drug loads of 30 and 50wt.%.

Processability via extrusion and injection molding: mechanical stability

Formulations composed of EudrE/IBP in a 70/30 (wt.%) ratio were easily extruded and injection molded. However, at higher IBP concentration (50wt.%) solid non-sticking extrudates could not be obtained due to the plasticizing effect of IBP. As a consequence, tablets containing EudrE/IBP in a 50/50 (wt.%) ratio exhibited a high plasticity and were, due to a too low Tg, not sufficiently solid to maintain their structure. Figure 7 displays a stable and an unstable formulation after 1 week storage at room temperature. The mechanical stable tablet has a height and width of 5 and 10mm, respectively, while deformation of the highly plastic tablet after 1 week storage at room temperature resulted in a height and width of 3.5 and 12.5mm, respectively. Injection molding of the commercial EudrE grade was therefore considered impossible in combination with 50wt.% IBP. The extrusion of the other formulations (using the modified polymers A, B1-2, C) with 50wt.% IBP yielded non-sticking

extrudates which could be injection molded. These tablets retained their structure after processing as their Tg was sufficient to provide a solid mechanically stable matrix. These experiments indicated that by increasing the polymer's Tg, the processability improved as the novel polymethacrylates enabled the incorporation of 50wt.% IBP in the formulation. However, the processability also depended on the DMAEMA content as formulations containing polymer with 17% DMAEMA were mechanically unstable. DSC data indicated that the plasticizing effect of IBP on the 17% DMAEMA polymer (Figure 4, B3) was higher compared to the other polymethacrylates (Figure 4, B1-2), which can be ascribed to incomplete salt formation.

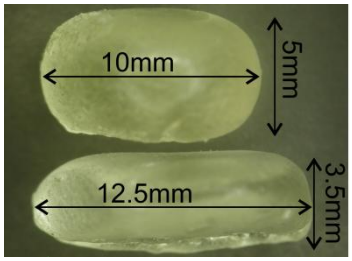


Figure 7. Cross section of injection molded tablets containing 50wt.% ibuprofen in combination with polymer B1 (top, 36% DMAEMA) and polymer B3 (bottom, 17% DMAEMA) as matrix.

In vitro drug release

The commercially available Eudragit E is a fast dissolving polymer up to a pH of 5 due to the hydratation of the dimethylamino groups that are fully protonated at this pH value. Although lowering the DMAEMA content decreased the amount of tertiary amines, it did not affect the erosion based release profiles at low pH (pH 1 and 3) for matrices formulated via polymers with DMAEMA contents varying from 45 to 28% (Figure 8). Interestingly, formulations containing 17% DMAEMA did not release IBP, indicating that the DMAEMA content is a crucial parameter with respect to immediate drug release and that a minimal

DMAEMA content is required to have sufficient charge density of the polymer to ensure sufficient hydrophilicity for fast dissolution at low pH values. This again highlights the importance of the DMAEMA repeating unit as it is not only essential to stabilize the solid solution via interaction with IBP, but also determines the release rate of the drug.

The addition of an isobornyl group to the polymer did not influence the release profile at pH 1 up to an isobornylmethacrylate content of 40% and at pH 3 up to 30% isobornyl-methacrylate content (Figure 8).

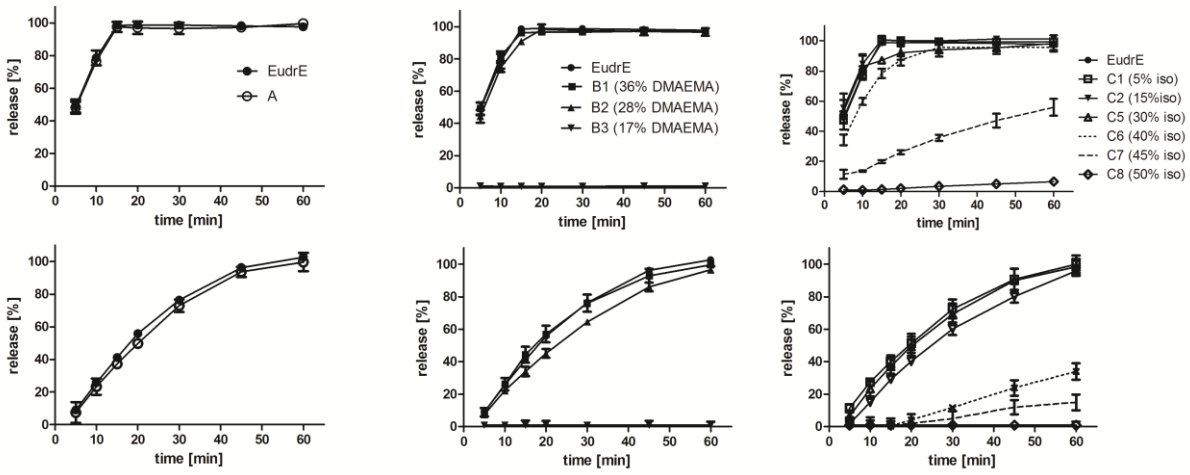


Figure 8. Release curves of IBP at pH 1 (top) and pH 3 (bottom) from formulations containing IBP (30%) and different polymethacrylate carriers: Eudragit E, (A) n-butyl replaced by t-butyl, (B) variable DMAEMA-content and (C) variable isobornyl content.

The release profiles of formulations with 30 and 50wt.% drug load were similar (data not shown) confirming the carrier-mediated release of glassy solid solutions. This observation leads to the assumption that, besides phase transformation of the drug from crystalline to amorphous, sufficient interactions are needed between drug and carrier in order to improve the drug release properties.

Stability

As glassy solid solutions are inherently thermodynamically metastable, recrystallization is inevitable. Previous studies revealed that a strategy for dealing with amorphous pharmaceutical formulations, in order to obtain a physically stable formulation, is storage at 50°C below the glass transition temperature of the formulation [9]. At this temperature, API mobility is negligible and API recrystallization is delayed. Therefore, the effect of IBP content on the thermal behavior of the formulations was analyzed. Figure 4 indicates the plasticizing effect of IBP on the polymethacrylates with varying DMAEMA content. It is obvious that the Tg increase in the chemically modified polymers was counteracted by the plasticizing effect of IBP, and that producing stable formulations (i.e. with a Tg 50°C above room temperature) was therefore not possible. However, no recrystallization was observed in the XRD patterns after 6 months storage of injection molded tablets with a 30wt.% IBP load at 25°C and 60% relative humidity (Figure 9). At a 50% drug load crystallinity was detected for the mixtures formulated with the polymer containing 17% DMAEMA, whereas the other formulations showed no signs of crystallinity. This again illustrated the importance of drug/polymer interactions for the stabilization of the injection-molded IBP/polymethacrylate mixtures, i.e. the IBP salt form does not readily diffuse through the glassy hydrophobic polymer matrix.

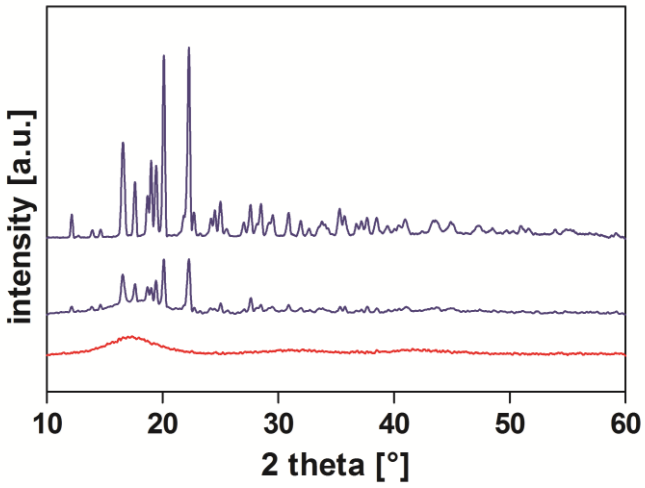


Figure 9. XRD-patterns of pure IBP powder (top), a physical mixture of IBP and EudrE (ratio: 30/70 wt.%) (blue) and an injection molded tablet (red) containing 30wt.% IBP with polymer B1 (36% DMAEMA) as matrix (red) after 6 months storage at 25°C and 60% relative humidity.

Evaluation of celecoxib as non-plasticizing API

In addition to IBP, celecoxib (CEL) was also combined with the polymethacrylates. This non-steroidal anti-inflammatory drug was chosen for several reasons. Similar to IBP, it is able to form a glassy solid solution with the polymethacrylates [89] and it has a low solubility in acidic media. In contrast to IBP (pKa 4.5 and Tg -42°C), CEL has a weak acidic character (pKa 9.7) and a higher Tg (58°C). Therefore, it was interesting to evaluate the possible differences with respect to thermal behavior, interactions and drug release properties.

When combined with the polymethacrylates a lower melting enthalpy, Tmelt-max and Tmelt-onset of CEL was detected in the first heating cycle, in combination with a single Tg, situated between the Tg values of the individual components, in the second heating cycle (data not shown). Similar to IBP/polymer mixtures, this was indicative for molecular interactions between CEL and polymethacrylate. The free electron pair of the DMAEMA moiety enables interaction with the hydrogen atom in the sulfonamide group of CEL. The

difference between the Tg's of the pure components is too low (Tg CEL=58°C, Tg EudrE=50°C) and taking the precision of DSC-data into account (± 5%), a significant interaction between CEL and the polymethacrylates cannot be identified via a deviation of Tg. Using IBP (Tg= - 42°C) as API this deviation was significant to identify the interaction. The formation of transparent tablets confirmed the miscibility between CEL and the polymethacrylates.

FTIR spectra of the injection molded tablets also evidenced molecular interactions between CEL and polymethacrylates (Figure 10). In comparison to spectra of physical mixtures and individual amorphous components, peak broadening was observed for the injection molded tablets, an indication of molecular interactions and the presence of amorphous CEL in the formulation. Second, the broad peak around 3100-3600 cm^{-1} (as compared to the two sharp ν_{N-H} stretch vibration absorptions of theCEL amino group around 3333 and 3327cm^{-1} for the physical mixtures and the small peak in the amorph component) is indicative of intermolecular hydrogen bonds in the formulation, most likely between the tertiary ammonium group of the polymer and the sulfonamide of CEL. The asymmetrical C-H stretch vibration of the tertiary ammonium group present at 2950cm^{-1} in the physical mixture is shifted to 2974cm^{-1}in the formulation (highlighted in Figure 10). Last, as the fingerprint region (500-1430cm^{-1}) of the physical mixtures (PM) and injection molded tablets (IM) show multiple differences in wavenumber as well as in intensity (not shown on Figure 10), it can be decided that CEL is completely dissolved in the polymer. FTIR analysis of the formulations containing IBP and CEL revealed the importance of the API's pKa towards the type of molecular interactions in the thermally processed formulations. Whereas electrostatic interactions (salt formation) were identified between the polymethacrylates and IBP (pKa 4.5), salt formation in combination with CEL was not possible due to its lower acidity (pKa

9.7) and molecular interactions were limited to the formation of hydrogen bonds.

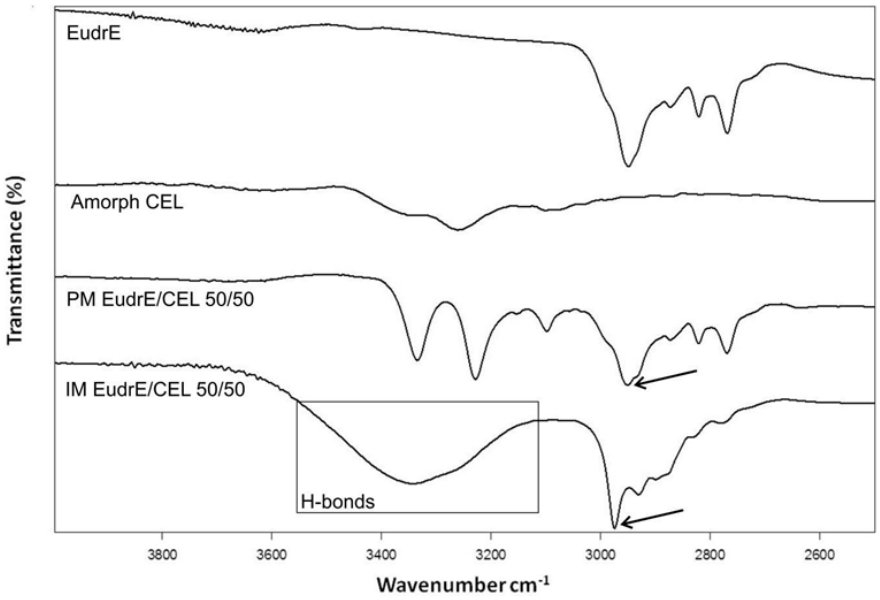


Figure 10. FTIR-spectra of CEL, Eudragit E, physical mixtures (PM) and injection molded tablets (IM) of CEL and Eudragit E, at a drug load of 50wt.%.

Stability studies were performed on formulations with 30 and 50% drug loads with EudrE as carrier. MDSC-results indicated partial recrystallization (about 10%) of celecoxib in a formulation with a 50% drug load. No recrystallization was observed in the 30% drug load formulation. The instability detected with the 50% formulation was assigned to the strength of interaction between API and polymer. The H-bond interaction detected between CEL and EudrE (Figure 10) is known to be weaker than the electrostatic interactions detected between IBP and EudrE. Furthermore, this difference in strength was also confirmed by the difference in API affinity for EudrE, estimated from the API melting enthalpy in the first MDSC heating cyclus of physical mixtures (API/polymer, 50/50): the percentage crystallinity (compared with their pure crystalline form) after processing in the EudrE matrix was about 38% and 72% for IBP and CEL, respectively

All formulations containing 30 and 50wt.% CEL drug loads were easily extruded and injection molded. Even at higher CEL concentrations solid non-sticking extrudates were obtained, due to the higher Tg of CEL. The formulations with EudrE and polymer B2 (28%DMAEMA) combined with 50wt.% CEL resulted in glassy solid solutions with a Tg of 62°C and 76°C, respectively. The release profiles of formulations with CEL and IBP as API were similar (data not shown). At pH 1 and 3, API release was 80% after 10 and 30min, respectively. This again confirmed the carrier-mediated release of glassy solid solutions.

Conclusion

The structural modification of polymethacrylates revealed that it is possible to alter the polymer Tg (thermal behavior) without changing the drug release characteristics and glassy solid solution forming properties. However, in order to produce mechanical and physical stable formulations, the API still has a large influence on the formulation's Tg. Nonetheless, careful attention should be given to a more rational design of new extrusion (and injection molding) polymers for specific drug formulations.

Acknowledgment

The authors acknowledge the Polymer Chemistry and Biomaterials group (UGent, Belgium) and the Laboratory of Medicinal Chemistry (UGent, Belgium) for their support with TGA and ^{1}H-NMR spectroscopy, respectively. BC acknowledges INTERREG IVA "2 Mers Seas Zeeën" IDEA cooperation programme for financial support. BGDG acknowledges the FWO-Flanders for a postdoctoral fellowship. RH and PA gratefully acknowledge Belspo in the frame of IAP network VII/FS2, initiated by the Belgian State Prime Minister's Office, for financial support.

Supporting information

Gordon-Taylor Equation: the experimental values of the glass transition temperature can be compared with the calculated theoretical values to evaluate the miscibility of drug and excipients following the Gordon-Taylor equation. This relationship states that if drug and polymer are miscible, the mixture will show a single Tg that ranges between the Tg of pure components and depends on the relative portion of each component:

$$Tg = \frac{Tg_1 w_1 + K Tg_2 w_2}{w_1 + K w_2}$$

For which Tg_1 and Tg_2 are the glass transition temperature of the ibuprofen and the polymer, respectively, w_1 and w_2 are the weight fractions of the ibuprofen and the polymer, and K is a constant that can be calculated using the Simha-Boyer rule:

$$K \cong \frac{\rho_1 Tg_1}{\rho_2 Tg_2}$$

With ρ_1 and ρ_2 the true densities of the respective ibuprofen and polymer as determined by means of helium pycnometry (AccuPyc 1330, Micromeritics Instruments, Norcross, USA). Since the Gordon-Taylor addresses the densities of amorphous components, the density of amorphous ibuprofen was estimated from the true density of teir respective crystalline counterpart, reduced by 5%.

MDSC-thermograms

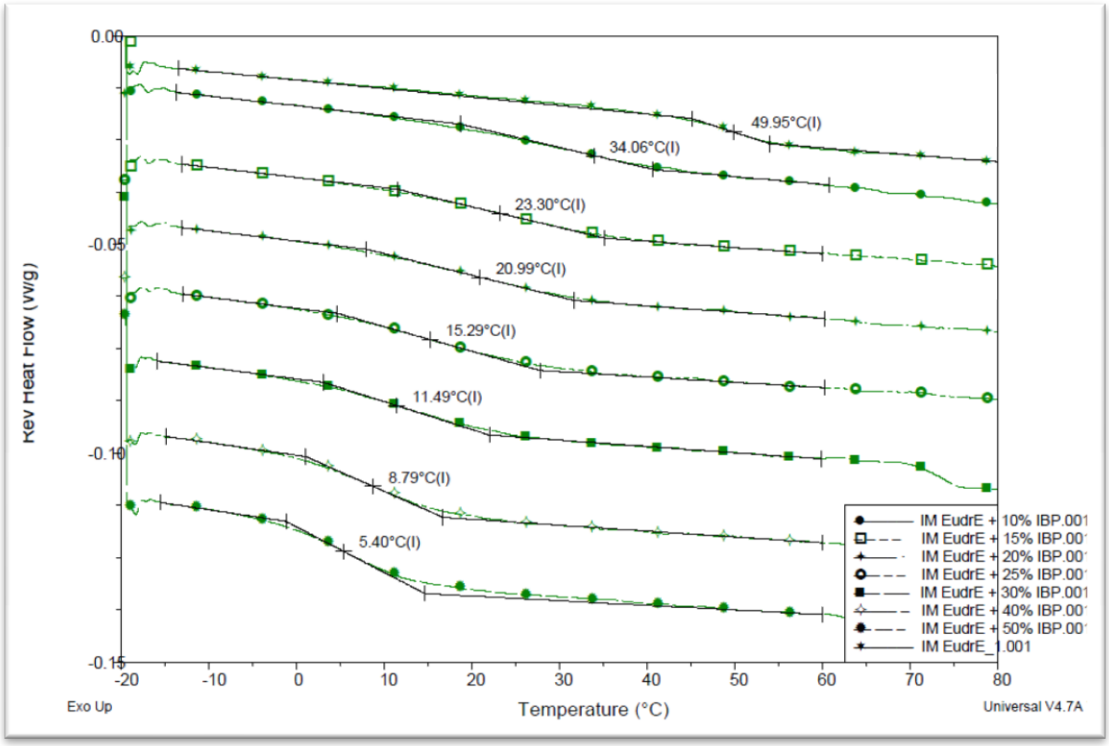


Figure S1. MDSC-thermograms (reversed heat flow) of injection molded tablets with EudrE/IBP at various ratios (wt.%) indicating the plasticizing effect of IBP on EudrE.

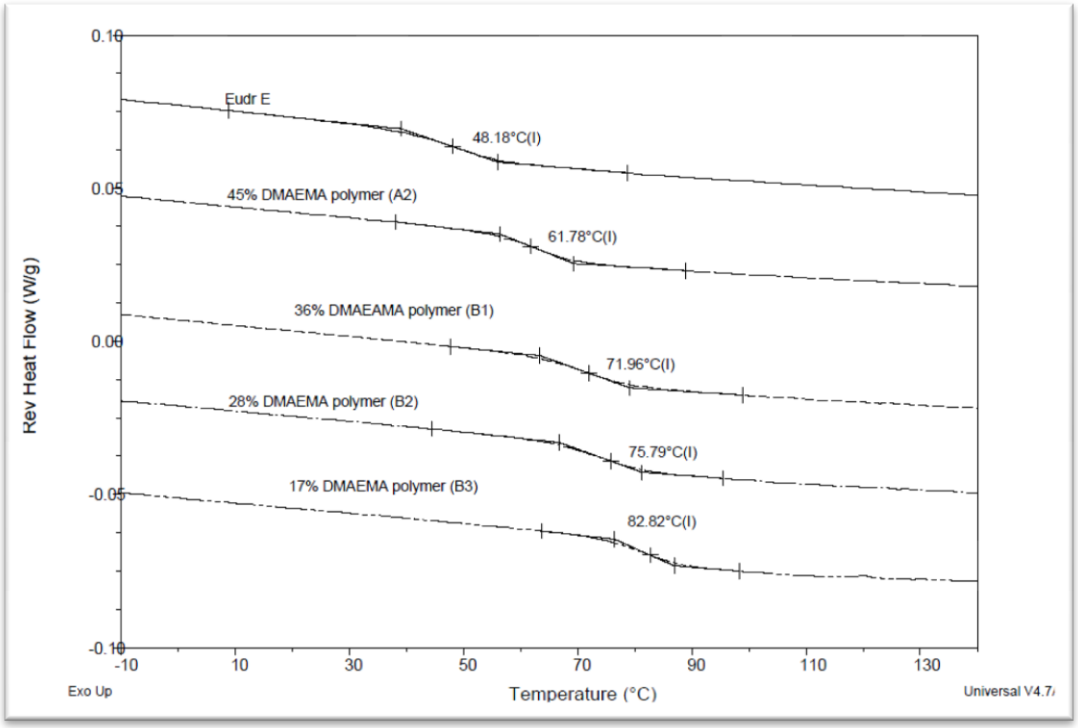


Figure S2. MDSC thermograms (reversed heat flow) demonstrating that changing the n-BMA groups to t-BMA (EudrE vs polymer A2) and lowering the DMAEMA content (polymer B1-3) yielded polymers with a higher Tg.

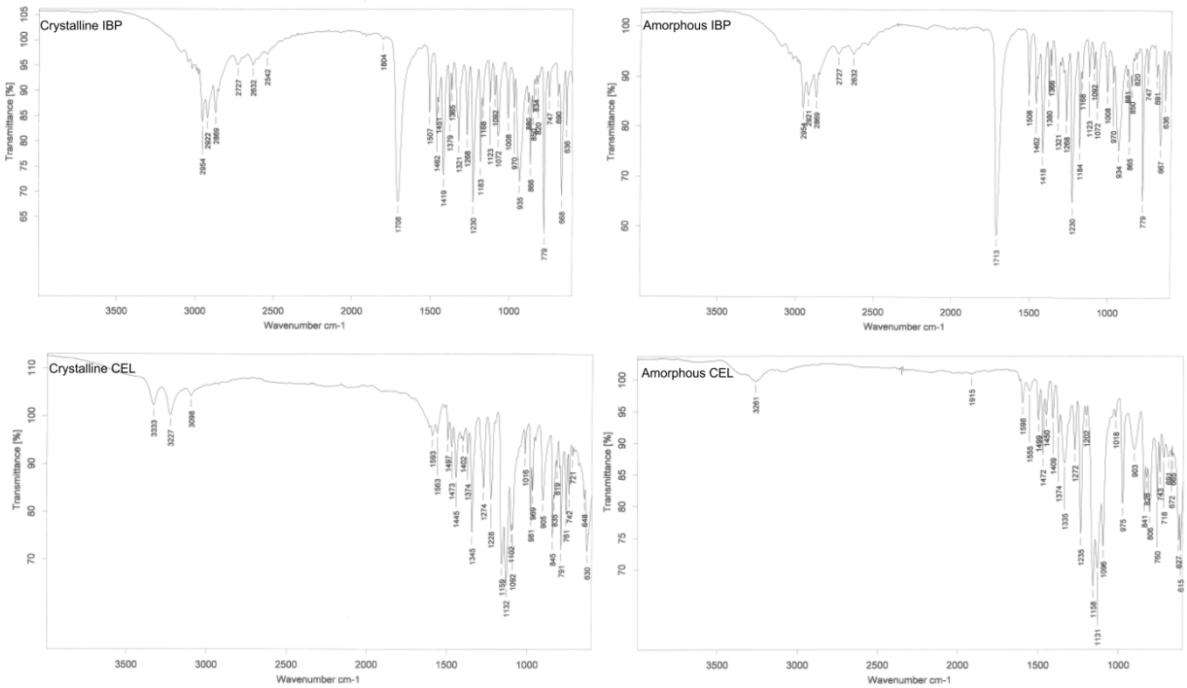


Figure S3. FTIR-spectra comparing both API's in crystalline (left) and amorphous form (right).

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CHAPTER 3

Poly(2-ethyl-2-oxazoline) as Matrix Excipient for Drug Formulation via Hot Melt Extrusion and Injection Molding

Parts of this chapter were submitted for publication in:

B. Claeys, A. Vervaeck, C. Vervaet, J.P. Remon, R. Hoogenboom, B.G. De Geest, Poly (2-ethyl-2-oxazoline) as Matrix Excipient for Drug Formulation by Hot Melt Extrusion and Injection Molding, Macromolecular Rapid Communications, 33 (2012) 1701-1707.

Introduction

Hot melt extrusion (HME) and injection molding (IM) are emerging as pharmaceutical processes for the formulation of drugs in polymeric matrices for controlled drug release. [170] In these processes heat and shear forces are applied to convert thermoplastic polymers mixed with drug into matrix tablets that can contain the drug in a dispersed (i.e. solid dispersion) or solubilised (i.e. solid solution) state. Both solid solutions and solid dispersions can offer enhanced drug dissolution, which is highly desired for poorly water-soluble drugs. On the other hand, by using polymers with different properties one can design either immediate release formulations or sustained drug formulations. Immediate release formulation produced via HME usually contain the amorphous drug dispersed in a hydrophilic carrier matrix of one or more polymers, such as polyethylene oxide (PEO), hydroxypropyl (methyl) cellulose (HP(M)C), vinylpyrrolidone/vinyl acetate copolymer (Kollidon® VA), polymethacrylates (Eudragit® E) and PEG6000/vinylcaprolactam/vinylacetate copolymer (Soluplus®). In case of a solid solution where the drug is molecularly dissolved in the matrix polymer, drug dissolution will be governed by the dissolution of the hydrophilic matrix polymer. Sustained release formulations aim to release drug over an extended period or at a specific time during treatment. This is in particular beneficial for drugs with short half-lifes and/or fast excretions. Controlled drug release is obtained by slow diffusion of the drug through a hydrophobic polymer matrix or by a slowly eroding polymer matrix, or by a combination of both. Typical polymers used for HME of sustained release formulations are ethylcellulose (EC), ethylene vinyl acetate (EVA), polyvinyl acetate (PVA), poly lactic (co-glycolic) acid (PL(G)A), polycaprolactone (PCL) and the methacrylate copolymers (Eudragit® RS/RL).

Despite the usefulness of these polymers there is still a need for generic polymeric excipients that allow formulation of a wide variety of drug molecules with different physicochemical behaviour, to produce immediate as well as sustained release formulations. Poly(2-alkyl-2-oxazoline)s are an interesting class of polymers for the preparation of tailored made polymers with well-defined structure. [171] A wide range of functionalities can easily be incorporated in the poly(2-alkyl-2-oxazoline) structure by both side chain and end group functionalization. Dissolution properties of these polymers can be altered by changing the chain length of the side groups. Poly(2-alkyl-2-oxazoline) with methyl and ethyl side-chains, as example, are fully water-soluble at ambient body temperature with a lower critical solution temperature (LCST) of 60°C for poly(2-ethyl-2-oxazoline) (PEtOx). Poly(2-alkyl-2-oxazoline) with propyl side chains, on the contrary, exhibits a LCST below physiological temperature (i.e. 37 °C). Moreover, the physicochemical properties of poly(2-alkyl-2-oxazoline)s can be widely tailored from amorphous materials with branched aliphatic side chains to semi-crystalline polymers with linear aliphatic side chains.

Previously we and others have reported on the biocompatibility of PEtOx, paving the road for their use as component in drug delivery systems. [172-174] So far polyoxazoline-based materials have been evaluated as protein-conjugates, [175] block copolymer micelles for encapsulation of low molecular weight hydrophobic drugs, [176] as well as for surface functionalization of materials intended for biomedical use. [177] However, up to our knowledge, polyoxazolines have not yet been used as excipient to formulate drugs into solid dosage forms for oral intake. An important issue in this regard, is the stability of PEtOx in the gastro-intestinal tract. PEtOx are prone to hydrolysis in acidic medium, resulting in the formation of ethylene imine

units that hold potential toxicity risks. [178] Recently we addressed this issue and revealed that 24 h at 0.1 M HCl (the acidic environment in the stomach) and 37 °C, results in negligible, i.e. less than 1 %, hydrolysis. [174] Moreover, we also assessed the influence of the extent of hydrolysis on cell viability and mucosal irritation. We observed that PEtOX with up to 25 % ethylene imine units did not significantly affect cell viability and did not induce mucosal irritation. These findings encouraged us to further explore the potential of PEtOx for drug delivery applications.

In this paper we evaluate PEtOx as pharmaceutical excipient to produce oral solid dosage forms for drug molecules with different water solubility. For this purpose, commercially available PEtOx with molecular weights of respectively 50, 200 and 500 kDa were formulated with metoprolol tartrate (MPT) and fenofibrate (FBT) as good and poorly water-soluble drugs, respectively. Hot melt extrusion (HME) coupled with injection molding (IM) was used as technique to produce these tablet formulations. [179]

Experimental section

Materials

Poly(2-ethyl-2-oxazoline) (PEtOx) with a molecular weight of respectively 50, 200 and 500 kDa was purchased from Sigma-Aldrich. Note that this material is not of pharmaceutical grade, however high purity grade PEtOx has become commercially available very recently under the tradename Aquazol HP from PCI, Inc. To reduce the particle size, the PEtOx was mechanically milled using a hammer mill, **Figure S1 (supporting information)** shows scanning electron microscopy images of the polymeric material before and after milling. **Figure 1A** shows the molecular structure of PEtOx. MPT (**Figure 1D**) was purchased from Esteve Quimica. FBT (**Figure 1E**) was purchased from Roig Farma.

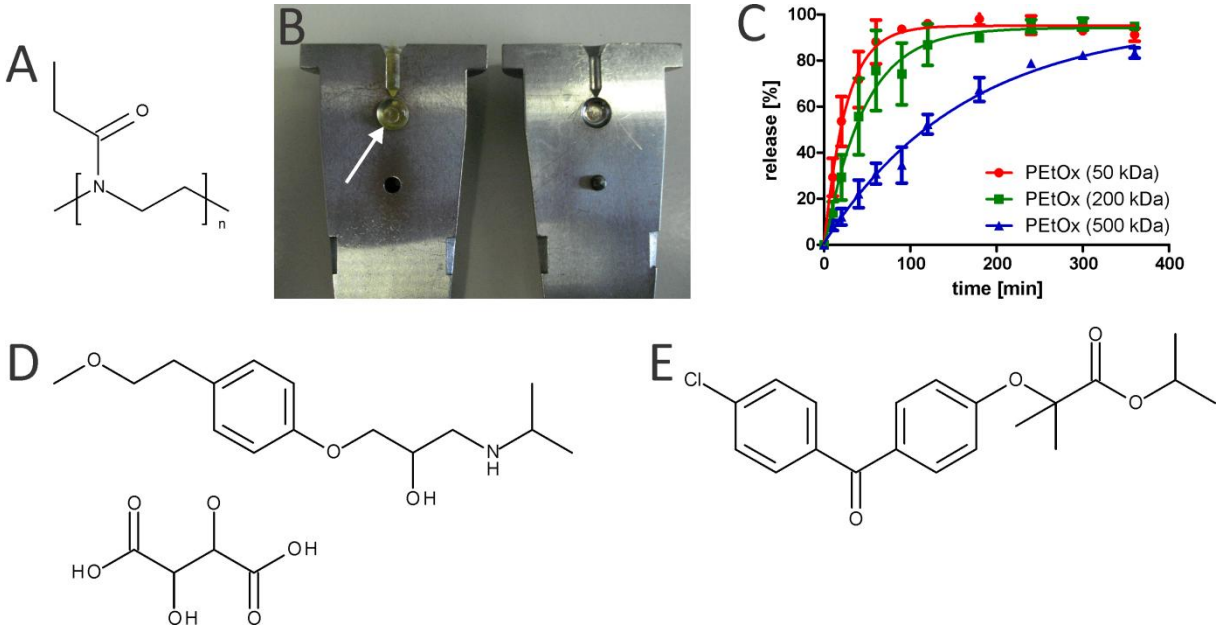

Figure 1. (A) Molecular structure of PEtOx. (B) Photograph of a HME/IM tablet after opening of the biconvex mold. The tablet is indicated with a white arrow. (C) Cumulative release curves showing the dissolution of pure PEtOx tablets, produced via HME/IM of PEtOx of different molecular weight. (D) Molecular structure of metoprolol tartrate. (E) Molecular structure of fenofibrate.

Hot melt extrusion and injection molding

Active pharmaceutical ingredient (API) and polymer were mixed with a mortar and pestle, and fed to a co-rotating twin-screw extruder at 100 rpm (Haake MiniLab II Micro Compounder, Thermo Electron). **Table 1** lists the respective process temperatures. These optimal extrusion settings were empirically selected in order to achieve an optimal torque value, melt flow and retention time. The homogeneous extruded blends are consequently collected in a reservoir and injection molded (Haake MiniJet System, Thermo Electron) with high dimensional precision to produce biconvex tablets (height = 5 mm/ diameter = 10 mm). **Figure 1B** shows a photograph of a PEtOx tablet in an opened mold. The injection pressure was 880 bar during 10 s, in combination with a post-pressure of 400 bar for 5 s. The temperature of the mold was set at 20 °C.

Scanning electron microscopy (SEM)

Samples were first sputtered with gold followed by imaging with a Quante FEG FEI scanning electron microscope operating at an acceleration voltage of 5 kV.

Hot stage microscopy

Optical microscopy images were recorded on a Leica DM2500P microscope equipped with a 10x objective, a 360FX CCD camera and a Linkham THMS600 heating stage.

X-ray diffraction (XRD

X-Ray diffraction was performed on a D5000 diffractometer (Siemens). Diffractograms were ontained with Cu Kα radiation (45 kV x 40 mA; λ = 1.54 Å) at a scanning speed of 25 °(2θ)/min and step size of 0.03 °(2θ).

Thermal analysis

The glass transition temperature (Tg) and melting point (Tm) of pure components, physical mixtures and injection molded tablets were analyzed by differential scanning calorimetry. (DSC Q2000, TA Instruments, Leatherhead, UK) Dry nitrogen at a flow rate of 50 ml/min was used to purge the DSC cell. Temperature heating/cool/heat cycle was run between -70 °C and 140 °C applying 10 °C/min heating and cooling ramps. All results (first cycle) were analyzed using the TA Instruments Universal Analysis 2000 software.

***In vitro* dissolution testing**

The release characteristics of the injection molded tablets were evaluated using the paddle method on a VK 7010 dissolution system (VanKel Industies, New Jersey, USA) with a paddle speed of 100rpm. Hydrochloric acid (pH 1) and phosphate buffer (pH 7) were used as dissolution media (900 mL) at 37 ± 0.5 °C. For *in vitro* dissolution testing of the poorly water-soluble FBT, sodium lauryl sulfate (0.5 %) was added to the medium to simulate sink conditions. Samples were withdrawn at regular time intervals and spectrophotometrically analyzed for API concentration at their specific wavelength of maximum absorbance. For FBT, MPT and PEtOx this wavelength was respectively 289, 274 and 203 nm.

Results and Discussion

First we assessed whether PEtOx is suitable as matrix polymer to produce tablets via hot melt extrusion (HME) followed by injection molding (IM). Therefore, an essential step is to mechanically mill the commercial PEtOx to reduce the particle size. This is required to allow, in a further part of this research, producing tablets with the drug homogeneously distributed within the polymer matrix and to avoid large discrepancies between inter-tablet drug loads. **Figure S1 (Supporting Information)**, shows scanning electron microscopy images of the POX before and after milling, clearly indicating a substantial size reduction below 1 mm of the polymeric material, needed to obtain a homogeneous drug:polymer mixture. Next we assessed the process conditions required for HME/IM of PEtOx. PEtOx has a Tg varying between 43 °C and 57 °C, dependent on its molecular weight. [180] We observed that applying a process temperature of 160 °C, which is sufficiently below the decomposition temperature of PEtOx (>300 °C; thus avoiding degradation), allowed obtaining transparent tablets with a smooth surface. Subsequently we assessed the dissolution behaviour of these tablets under conditions that are used to monitor *in vitro* dissolution of oral drug formulations. This means adding the PEtOx tablets to dissolution vessels containing 900 mL of 0.1 M HCl (to simulate the acidic conditions in the stomach) and set at 37 °C. Subsequently, liquid samples were withdrawn at regular time points and as PEtOx exhibits UV activity in the 200 nm region, PEtOx concentration could be determined by measuring the UV-VIS absorbance. **Figure 1B** shows the dissolution behaviour of the PEtOx tablets, indicating the dissolution time of the tablets is affected by the molecular weight of the PEtOx as might be expected from the increased chain entanglement density with longer chains. Furthermore, although PEtOx has high water-solubility it takes a considerable amount of time to

dissolve, i.e. 30 min, 60 min and 120 min for 50 % dissolution, for PEtOx with a molecular weight of respectively 50, 200 and 500 kDa. The reason for this slow dissolution is likely the high pressure applied during the HME/IM process, which results in a dense entangled polymer matrix with very low porosity. Note that lower pressures would lead to incomplete filling of the mold with the molten polymer/drug. These observations open the avenue to control drug release by varying the molecular weight of the PEtOx as well as the concentration of PEtOx in a PEtOx/drug formulation.

Next we investigated whether solid solutions could be formed between PEtOx and the two model APIs (i.e. MPT as good water-soluble API and FBT as poor water-soluble API). A solid solution is a molecular dispersion of the API in a polymer matrix, obtained by dissolving the API in a molten polymer phase, followed by cooling of the system to a solid state. Crucial in such process is the solubility of the drug molecules in the molten polymer phase required to suppress phase separation and drug crystallization. To assess this for our two model APIs we performed hot stage microscopy experiments. **Figure 2** shows the corresponding microscopy images. All rows start with an image recorded at a temperature of 70 °C where no melting of either drug or PEtOx is observed. The subsequent series of images start from the temperature at which melting or flowing occurs. **Figures 2A-B** indicate that MPT and FBT melt at respectively 125 °C and 85 °C while PEtOx started to flow at 125 °C. Although PEtOx is an amorphous polymer it is likely that plastic deformation can be induced during the extrusion process at considerably lower temperatures. When mixtures of PEtOx and respectively 25 wt% MPT (used in this study as good water-soluble model drug; **Figure 2D**) and 20 wt% FBT (used in this study as poorly water-soluble model drug; **Figure 2E**) are heated, it was observed that both

components were miscible. Moreover, upon cooling of the molten phase to a solid phase no recrystallization of either of the model drugs was observed.

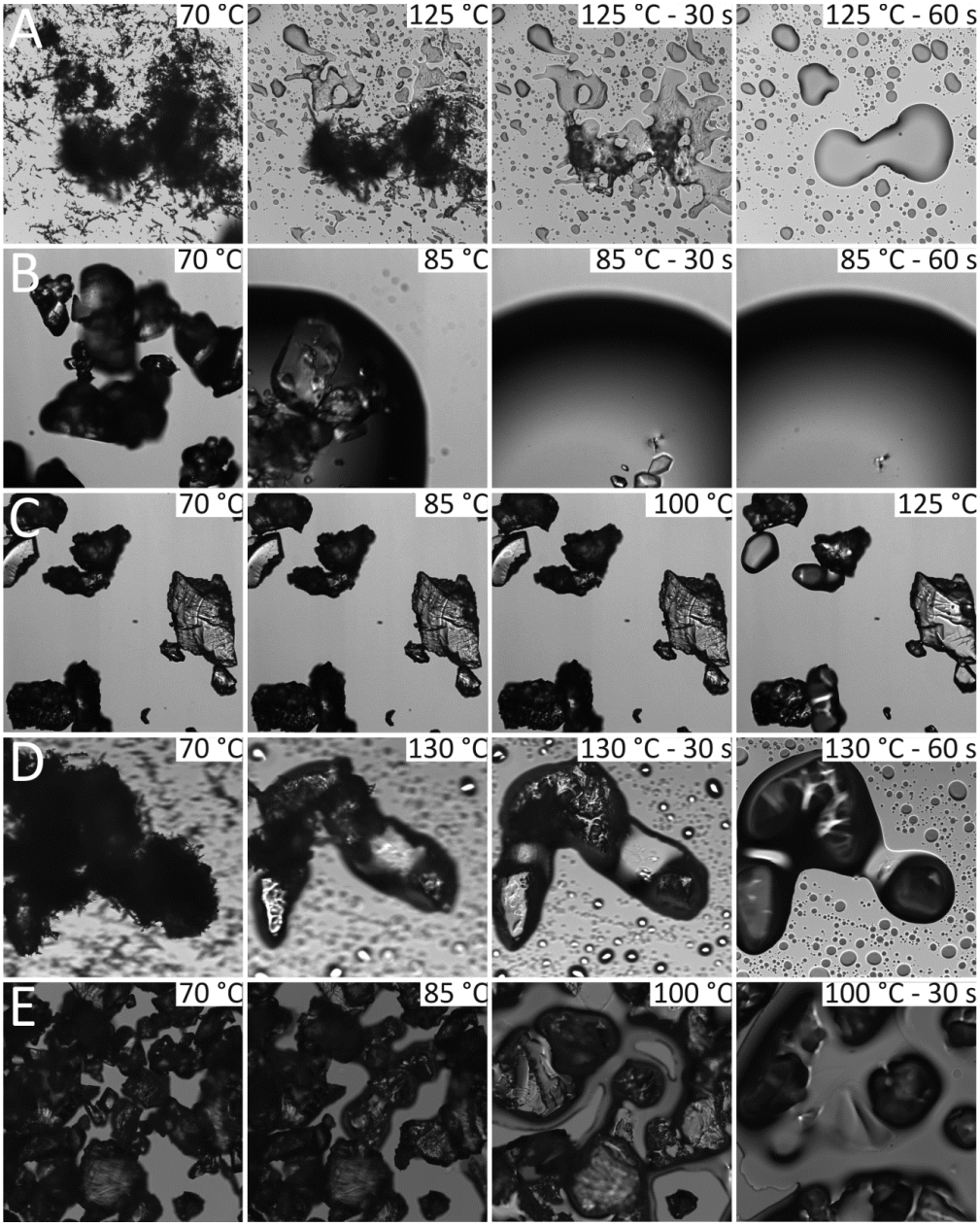

Figure 2. Optical microscopy images recorded on a hot stage set-up. Panels (A) and (B) represent respectively (A) metoprolol tartrate and (B) fenofibrate. These crystalline drugs readily melt when their melting point is reached. Panel (C) represents PEtOx (as representative example PEtOx was chosen with a molecular weight of 200 kDa). This polymer started to flow at a temperature of 125 °C. Panels (D) and (E) represents mixtures of PEtOx and respectively (D) metoprolol tartrate (25 wt%) and (E) fenofibrate (20 wt%). These mixtures form a solution with PEtOx upon heating above the melting point of the respective drug molecules.

Taken into account the above-described encouraging results, we prepared powder mixtures containing PEtOx with different molecular weight and respectively MPT and FBT that were fed to a twin screw extruder. The applied extrusion temperatures are listed in **Table 1**. We observed that a transparent molten phase was produced, indicating that elevated temperature combined with high shear forces during the extrusion process enables the production of homogenous molecularly dispersed polymer/API blends. This blend is consequently collected in a reservoir and injection molded with high dimensional precision to produce biconvex tablets.

Table 1. Process temperatures [°C] used to extrude the drug/PEtOx formulations. MPT refers to metoprolol tartrate while FBT refers to fenofibrate.

	PEtOx 50 kDa [°C]	**PEtOx 200 kDa [°C]**	**PEtOx 500 kDa [°C]**
25 wt.% MPT	120	120	140
50 wt.% MPT	120	130	145
20 wt.% FBT	115	115	120

In a first series of drug formulation experiments we used MPT as good water-soluble model API. MPT is a β1 blocker used in the treatment of hypertension and is on the market formulated as tablets. Drug payloads of 25 and 50 wt% were chosen and the obtained tablets were subjected to differential scanning calorimetry (DSC) (**Figure 3A**) analysis. The thermograms of the tablets clearly indicate the formation of a solid solution in which the MPT is molecularly dissolved within the polymer matrix. This is evidenced by the absence of a melting peak for metoprolol tartrate in the thermogram and the absence of the crystalline peaks in the diffractogram, whereas crystallinity is clearly observed for physical mixtures of the two components that were recorded as a control. In addition, one single Tg, situated between the Tg's of

both components separately, indicates good miscibility and the absence of pronounced phase separation. **Figure 3A** shows thermograms for crude metoprolol tartrate, PEtOx, the physical mixture and HME/IM tablets. These data correspond to PEtOX with an molecular weight of 200kDa, however identical observations were done for the other molecular weights. Furthermore, all tablets were fully transparent and no birefingance is observed by polarized light microscopy. However, after several weeks of storage, the tablets bearing 50 wt% MPT became opaque. X ray diffraction (XRD) analysis (**Figure 3B**) indicated recrystallisation of the drug molecules. By contrast the tablets containing 25 wt% MPT remained stable for several months and no recrystallisation could be observed. Again, identical observations were done, irrespective of the molecular weight of the PEtOx. **Figure 3B** shows the X-ray diffractograms of the tablets containing respectively 25 wt% and 50 wt% MPT after 4 weeks of storage.

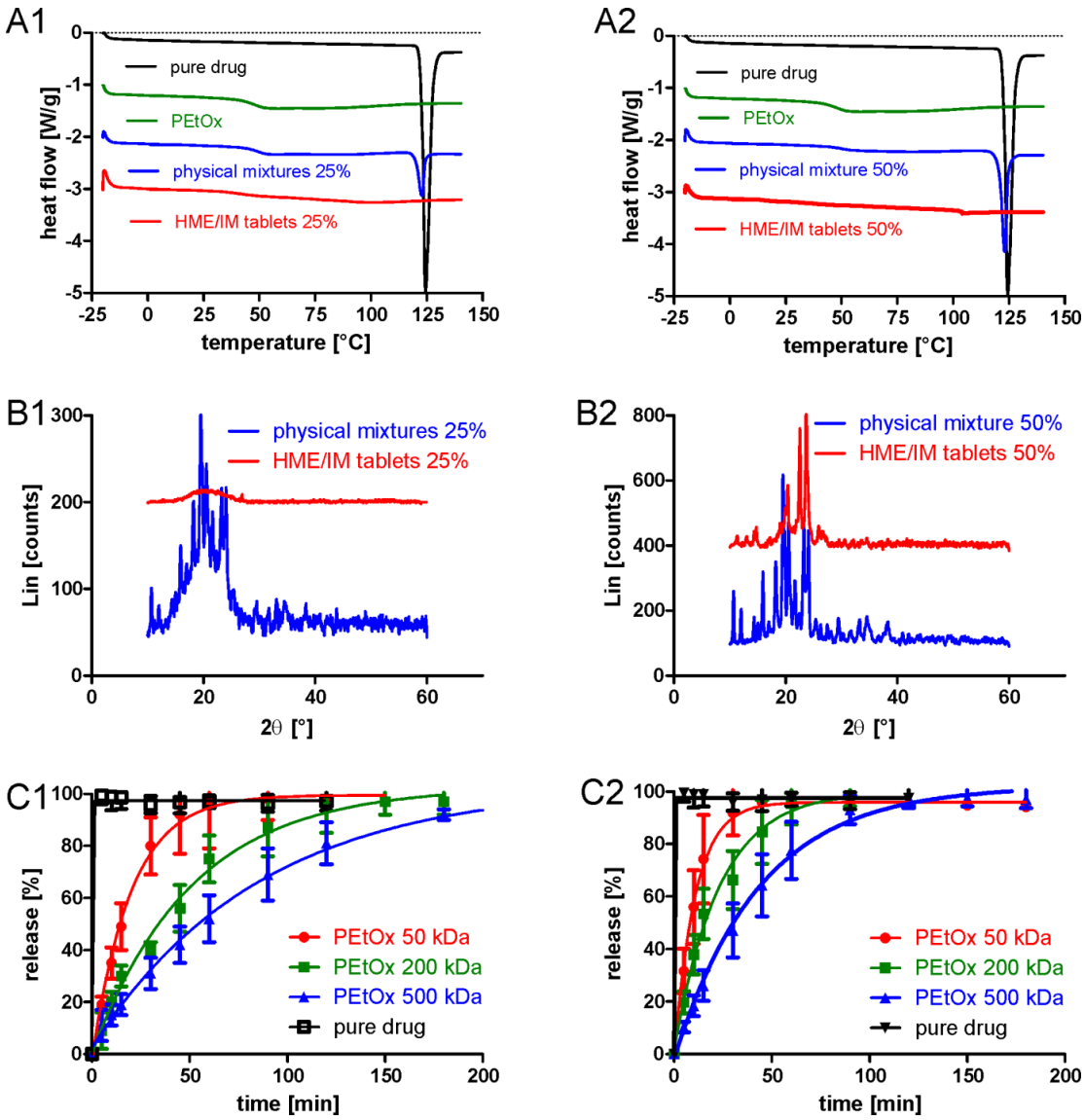

Figure 3. (A) Differential scanning calorimetry profiles recorded of metoprolol tartrate, PEtOx (200 kDa was chosen as representative example), a physical mixture of both drug and polymer and HME/IM tablets. Panels (A1) and (A2) represent respectively a 25 wt% and 50 wt% MPT:PEtOx ratio. (B) X-ray diffractograms recorded from physical mixtures and HME/IM tablets of PEtOx and metoprolol tartrate with a metroprolol content of respectively (B1) 25 wt% and (B2) 50 wt%. The tablets were stored for 4 weeks at ambient conditions prior to XRD analysis. (C) Cumulative release curves showing the dissolution of metoprolol tartrate from HME/IM PEtOx tablets using PEtOx of different molecular weight. In (C1) the drug load was 25 wt% while in (C2) the drug load was 50 wt%.

Subsequently the tablets were assessed for their *in vitro* release properties by putting them in dissolution vessels, at pH 1 and 37 °C to simulate the conditions in the stomach. **Figure S2 (Supporting Information)** shows the UV-VIS spectra of respectively PEtOx and MPT, showing that there is no interference from PEtOx when measuring at the secondary absorption maximum of MPT (i.e. 274 nm). The drug dissolution profiles are shown in **Figure 3C** along with the dissolution profile of pure MPT. These graphs show that whereas the pure drug immediately dissolves, sustained release is observed for metoprolol tartrate formulated in PEtOX HME/IM tablets. The fastest dissolution rate was observed for tablets containing 50 wt% metoprolol tartrate followed by the 25 % tablets. When looking at **Figure 1C**, pure PEtOx tablets exhibit an even slowed dissolution. This clearly demonstrates that higher loads of hydrophilic drug increases the dissolution rate. Additionally, in accordance to the dissolution profiles of the pure PEtOx tablets, a decrease in dissolution rate was observed with increasing molecular weight of the PEtOx. For many applications, a sustained release of up to 24h is desired, which is not achieved in the present study as complete release of MPT is reached after 3 hours. However, we anticipate that the release kinetics of good water-soluble drugs could further delayed by increasing the length of the alkyl-side chain of the oxazoline monomer. In previous studies the introduction of longer side chains >3 carbons atoms clearly indicated a more hydrophobic behaviour of the resulting polymer, [180] which could be beneficial for the production of sustained release formulations. Furthermore, longer monomer alkyl side result in a lower Tg of the polymer, which might facilitate processing via HME/IM.

In a next series of experiments we used FBT as poorly water-soluble model drug. Fenofibrate is used in the treatment of elevated cholesterol levels and is on the

market formulated as gelatin capsules filled with fenofibrate micro- or nanocrystals. Due to its poor water solubility we lowered the API content and produced HME/IM tablets containing 20 wt% FBT. DSC (**Figure 4A**) and XRD (**Figure 4B**) analysis on these tablets revealed the absence of crystallinity and thus the formation of a solid solution. **Figure 4** shows the representative data for 200 kDa PEtOx tablets containing 20 wt% FBT. These data are representative for all studied molecular weights of PEtOx. Moreover, storage over prolonged times did not alter the crystallographic state of the drug.

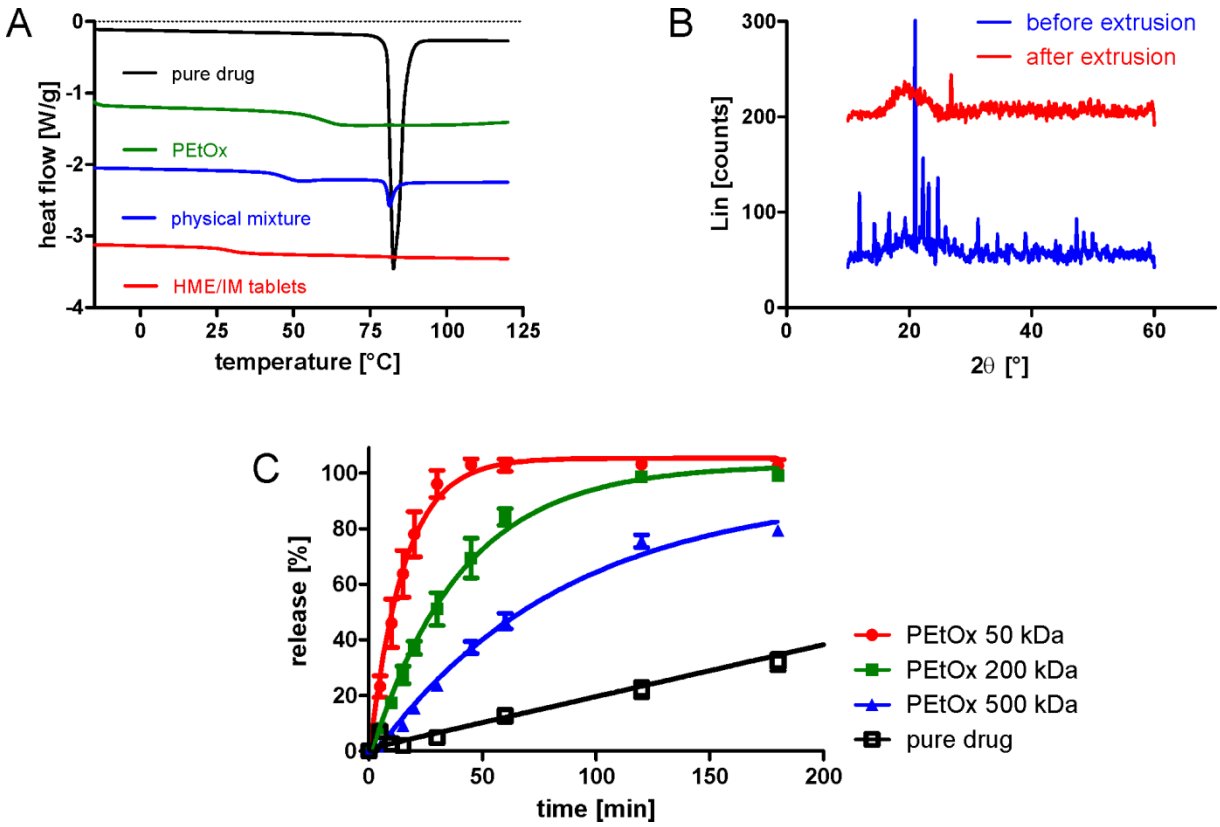

Figure 4. (A) Differential scanning calorimetry profiles recorded of fenofibrate, PEtOx (200 kDa was chosen as representative example), a physical mixture of both fenofibrate and PEtOx (20 wt% fenofibrate) and HME/IM tablets. (B) X-ray diffractogram of HME/IM PEtOx tablets containing 20 wt% fenofibrate. The molecular weight of the PEtOx was 200 kDa. (C) Cumulative release curves showing the dissolution of fenofibrate from HME/IM PEtOx tablets containing 20 wt% fenofibrate using PEtOx of different molecular weight.

For the dissolution experiments, sodium lauryl sulfate (SLS) was added as surfactant in order to enhance the dissolution of FBT according to the instructions of the European Pharmacopoeia. [181] Note that there is a physiological relevance for the addition of surfactant to the dissolution medium as the bile salts in the gastro intestinal tract also possess surface-active properties that will enhance the dissolution of poorly water-soluble drugs *in vivo*. Again, as shown in **Figure S2 (Supporting Information)**, interference from PEtOx is avoided when measuring at 289 nm. **Figure 4C** shows the dissolutions profiles of the tablets as well as pure FBT. Whereas pure FBT exhibits only slow and incomplete dissolution, formulation into PEtOX tablets via HME/IM greatly enhances the dissolution rate as well as the total availability. Most likely this is attributed to the formation of solid solutions of fenofibrate in a PEtOx matrix, which was evidenced by XRD and DSC, i.e. dissolution from a solid solution does not compete with crystal formation as is the case for pure FBT. Furthermore, also FBT formulated in PEtOx HME/IM tablets revealed a dissolution rate that was dependent on the molecular weight of the PEtOx.

Conclusions

In conclusion, we have demonstrated in this paper that PEtOx is a potentially interesting class of polymers to serve as matrix for controlled released formulations produced by hot melt extrusion followed by injection molding. We found that both good water-soluble as well as poorly water-soluble drug molecules could be solubilized within the polymeric matrix upon hot melt extrusion. Whereas formulation of a good water-soluble drug led to a slower dissolution and drug release profile, due to a slower dissolution rate of the polymeric matrix compared to the pure drug, a dramatic increase in dissolution rate was observed when a poorly water-soluble drug was formulated. Furthermore we also showed that the release rate could be tailored by varying the molecular weight of the PEtOx.

Despite that we showed the great promise of PEtOx for controlled release applications by HME/IM, there is still a long way to go before the first commercial tablets will enter the market. In depth studies have to be performed on toxicity of PEtOx, the influence of longer alkyl side chains or higher PEtOx MW on the release properties, elaborate stability studies and pharmaceutical grade PEtOx has to be developed on the way to FDA approval, which is currently only granted for usage as indirect food additive.

Acknowledgements

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Supporting Information

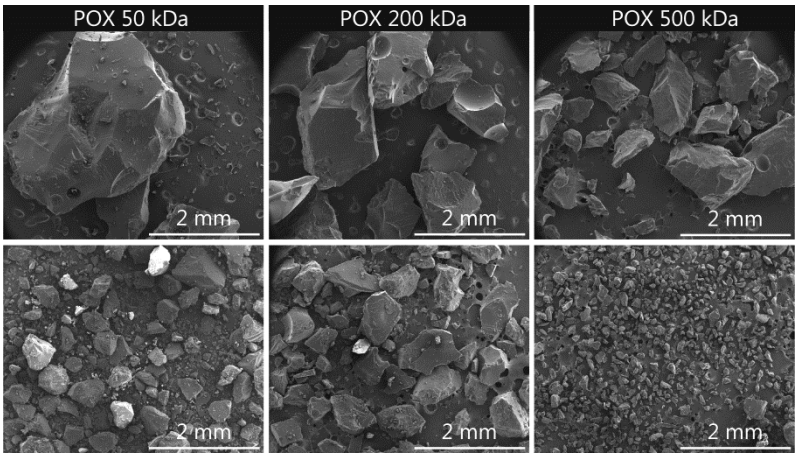


Figure S1. Scanning electron microscopy images of PEtOx of different molecular weight before (upper row) and after (lower row) milling.

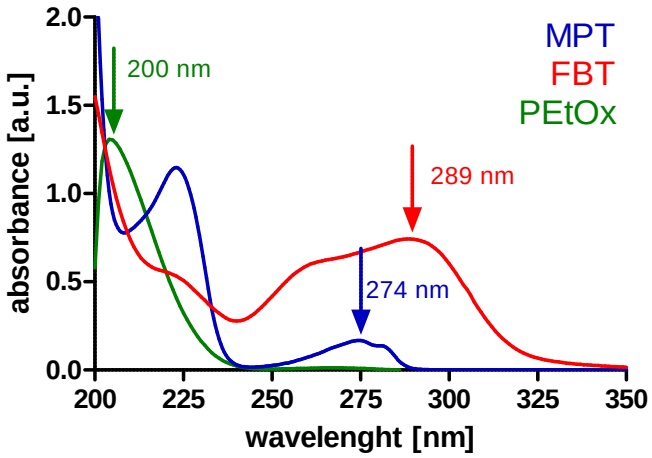


Figure S2. UV-VIS spectra recorded at the maximum concentration of the respective components in the dissolution vessel. The wavelengths that were chosen to calculate the concentration of the respective components are annotated with an arrow.

CHAPTER 4

Thermoplastic Polyurethanes for the Manufacturing of Highly Dosed Oral Sustained Release Matrices via Hot Melt Extrusion and Injection Molding

Parts of this chapter were submitted for publication in:

B. Claeys, A. Vervaeck, X.K.D. Hillewaere, S. Possemiers, L. Hansen, T. De Beer, J.P. Remon, C. Vervaet, Thermoplastic Polyurethanes for the Manufacturing of Highly Dosed Oral Sustained Release Matrices via Hot Melt Extrusion and Injection Molding, European Journal of Pharmaceutics and Biopharmaceutics, 90 (2015) 44-52.

Introduction

Sustaining drug release from a dosage form after oral administration offers distinct advantages to chronic and poly-medicated patients: maintaining drug levels in the therapeutic range, lower dosing frequency, less side effects; resulting in a better patient compliance. While sustained drug release can be achieved based on the design of the dosage form (reservoir systems vs. matrices) and/or the physicochemical properties of the polymeric materials incorporated in the formulation (diffusion controlled vs. delayed polymer dissolution), hot melt extrusion (HME) (possibly in combination with injection molding) has been evaluated to manufacture sustained-release matrices using various polymers: ethylcellulose (EC) [59-61], hydroxypropyl (methyl) cellulose (HP(M)C) [62], ethylene vinyl acetate (EVA) [29, 63], polyvinyl acetate (PVA) [64], poly lactic (co-glycolic) acid (PL(G)A) [65-66], silicone [67], polycaprolactone (PCL) [68-69], polyoxazolines [70], polyanhydrides [71], methacrylate copolymers (Eudragit® RS/RL) [72-73], and several lipid materials [74-76]. While sustained-release dosage forms have been successfully developed via HME using these polymers, a common drawback is that the drug load in these formulations is often low, either linked to processing issues during HME of formulations with a high drug load, or due to a significant burst release when less polymeric matrix former is incorporated in the formulation. Quinten et. al. [57], for instance, described that drug load in an acrylic polymermatrix was limited to 30% when processed via HME/IM, drug release from these matrices occurred in a first order manner via a combination of swelling and diffusion. Reitz et al. managed [182] to produce extrudates with 65wt.% diprophylline via solid lipid extrusion (with glycerol trimyristate as carrier) and identified the importance of drug particle size: although a larger drug particle size reduced the release rate and minimized the burst release, sustained release from these high dosed lipid matrices was limited (70% drug release after 1

and 3 h for small and large drug particle sizes, respectively). Another study [183] incorporated 30wt.% Dyph in Eudragit® S100 and Eudragit® L matrices, processed via HME at 160°C, and due to the complete dissolution of dyphylline in the matrix poor sustained release properties (>50% released within 2h in 1N HCl) were registered. It is well documented that a higher drug load enhanced the release rate from the matrix since more pores are created in the micro-capillary network of the insoluble matrix upon drug release, often combined with a burst release. To this end, the design of novel sustained release dosage forms using innovative polymeric materials with improved characteristics for controlled drug release is continuously under investigation.

Thermoplastic polyurethanes (TPUR) are inert, non-ionic, water-insoluble polymers that have been successfully used for many years as drug release controlling polymers in vaginal rings [16, 25, 184], stents [185], coatings [186] and implants [187]. Another important application of TPUR is in medical tubing as its superior mechanical properties (compared to polyvinyl chloride) allow the use of thinner walled tubes, even without a plasticizer [122]. The chemical structure of TPUR consists of alternating hard segments (HS) in a continuous phase of soft segments (SS) (Figure 1). Typically the SS phase is composed of a relatively long, flexible polyester or polyethers with a molecular weight of 1000-10.000g/mol. The HS can be composed of linear 4,4'-methylene diphenyl diisocyanate (MDI) or its hydrogenated form (HMDI), possibly linked to one another via a chain extender (often short chain diols). Thermodynamic incompatibility of both segments results to a certain degree of insolubility between HS and SS, yielding a microphase-separated (segmented) polymer. This generates a polymer with unique physicochemical characteristics: an elastomeric material with superior tensile strength, abrasion resistance, crack resistance, inherent lubricity and biocompatibility [188]. To this end, the HS contributes to the polymers' strength due to the formation of intermolecular hydrogen bonds between the urethane structures (NH-(C=O)-O) in each HS,

while the SS fraction with a low glass transition temperature (Tg) provides the polymers' elasticity [189]. TPUR are available in various molecular weights, different types (polyester, polyether) of SS, different SS lengths, and variable SS/HS ratios which makes them attractive candidates to alter drug release performances based on polymer composition.

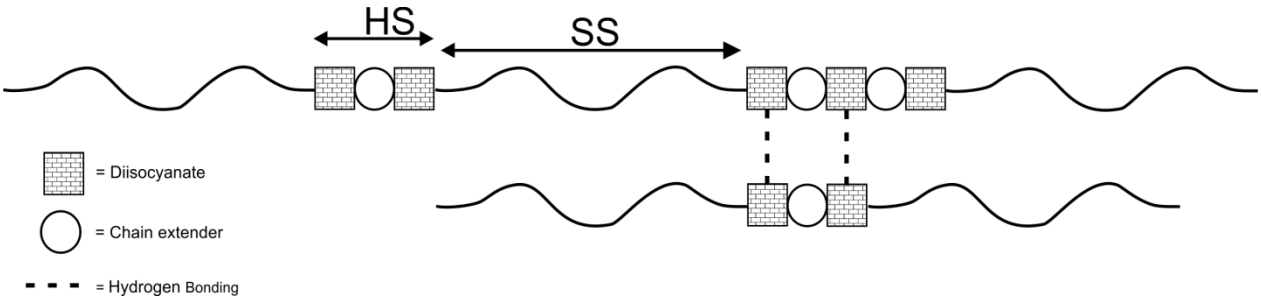


Figure 1. Schematic structure of thermoplastic polyurethanes

In this study, we evaluated thermoplastic polyurethanes (TPUR) as matrix excipients for oral sustained release purposes. The formulations were produced via hot-melt extrusion followed by injection molding and were consequently (physicochemically) characterized. Metoprolol tartrate (MPT), theophylline (Th) and diprophylline (Dyph) were embedded as model drugs in the TPUR matrices.

Experimental Section

Materials

Various grades of TPUR (Table 1) with varying composition of the hard and soft segments and with variable SS/HS ratio (Table 1) were obtained from Merquinsa (a Lubrizol company, Ohio, USA): the Pearlbond polyurethanes (P520, P522, P523, P539) were non-medical grades, while the Tecoflex types (T85A, T100A, T72D) were medical grades (Figure 2). Metoprolol tartrate (MPT) (Esteve Quimica, Barcelona, Spain), theophylline (Th) and diprophylline (Dyph, 7-(2,3-dihydroxypropyl)-theophylline) (Sigma Aldrich, Bornem,

Belgium) are embedded as model drugs in the TPUR matrices. Polyethylene glycol 4000 and Tween 80 were obtained from Fagron (Waregem, Belgium).

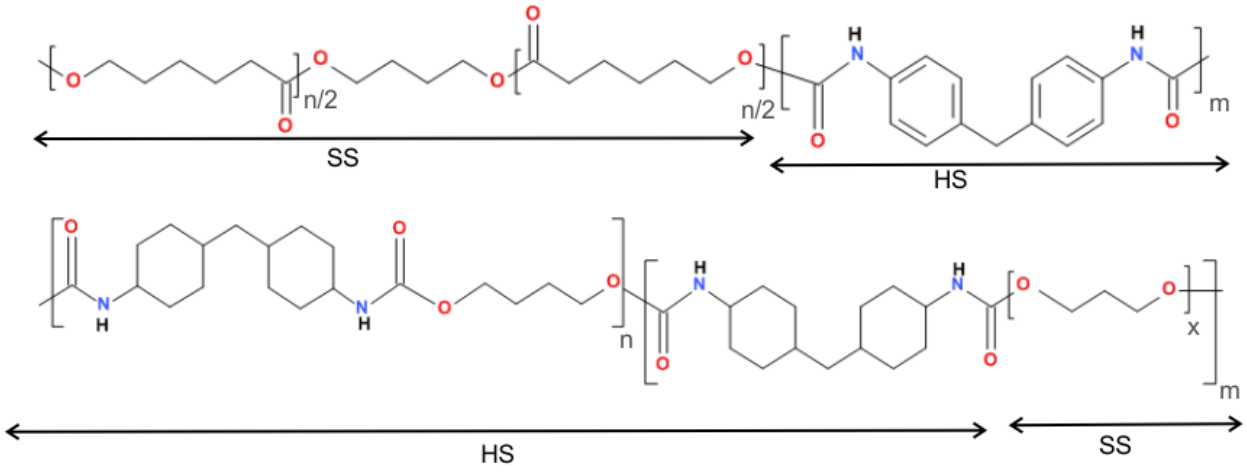


Figure 2. Chemical structure of the aromatic Pearlbond TPUR (top) and the aliphatic Tecoflex TPUR (bottom)

Size exclusion chromatography (SEC)

Size exclusion chromatography (SEC) was performed on a Waters instrument, equipped with 3 serial Polymer Standards Services columns (1 x GRAM Analytical 30 Å and 2 x GRAM Analytical 1000 Å, 10 µm particle size) at 35°C. Poly(methylmethacrylate) (PMMA) standards were used for calibration and dimethylacetamide (DMA), containing LiBr (0.42 g/mL) to increase polymer solubility, was used as solvent at a flow rate of 1 mL/min. 100 µL of a 10 mg/mL TPUR solution was injected onto the column. TPUR in the eluent was detected using a Waters 2414 refractive index detector. Molecular weights were determined using the Empower software (Waters, Zellik, Belgium).

Nuclear magnetic resonance (NMR)

NMR spectra were recorded on a Bruker AVANCE 300 spectrometer, using deuterated dimethylformamide (DMF) as solvent, to determine the polymer structure and SS/HS ratio. The spectra were analyzed with the ACD/Spec Manager software from ACD/Labs. ^{1}H-NMR (300 MHz, DMF-d7) of Pearlbond polymers: δ (ppm) = 1.37 (m, C*H*$_2$-CH$_2$-CH$_2$-O), 1.61 (m, CH$_2$-C*H*$_2$-CH$_2$-O), 2.33 (t, CH$_2$-CH$_2$-C*H*$_2$-(CO)), 3.86 (s, Ph-C*H*$_2$-Ph), 4.05 (t, CH$_2$-CH$_2$-C*H*$_2$-O), 7.17 (d, aromatic), 7.48 (d, aromatic), 9.45 (s, O(CO)N*H*). ^{1}H-NMR (300 MHz, DMF-d7) of Tecoflex polymers: δ (ppm) = 0.86 – 1.88 (br, C*H*$_2$ cyclic and C*H*$_2$-CH$_2$-O(CO)NH), 1.57 (br, C*H*$_2$ backbone pTHF), 3.39 (br, C*H*$_2$-O), 3.62 (br, O(CO)NH-C*H*), 3.98 (br, CH$_2$-C*H*$_2$-O(CO)NH), 6.71-7.03 (br, O(CO)N*H*).

Fourier-transform infrared spectroscopy

Attenuated total reflection Fourier-transform infrared (ATR FT-IR) spectroscopy was performed on the polymers before and after the SHIME-experiment in order to identify molecular changes. Spectra were recorded using a Nicolet iS5 ATR FT-IR spectrometer (Thermo Fisher Scientific). A diamond ATR crystal was pressed against the samples. Each spectrum was collected in the 4000 - 550 cm^{-1} range with a resolution of 2 cm^{-1} and averaged over 32 scans.

Thermal analysis

Thermogravimetric analysis (TGA 2950, TA instruments, Leatherhead, UK) was used to investigate the thermal stability of the polymers. The samples were equilibrated at 30°C and heated (10°C/min) to 500°C under an N_2 atmosphere.

The glass transition temperature (Tg) and melting point (T_m) of pure components, physical mixtures and injection molded tablets were analyzed in Tzero pans (TA instruments,

Zellik, Belgium) by modulated differential scanning calorimetry (MDSC Q2000, TA Instruments, Leatherhead, UK) using a heating rate of 2°C/min. The modulation period and amplitude were set at 1min and 0.318°C, respectively (heat-iso method). Dry nitrogen at a flow rate of 50mL/min was used to purge the MDSC cell. All results were analyzed using the TA Instruments Universal Analysis 2000 software. Samples (± 5mg) were run in Tzero pans (TA Instruments, Zellik, Belgium). MDSC heat capacity calibration was done via small sapphire disks, placed in a Tzero pan. Analysis of the thermal characteristics (T_m and T_g) was done via a heating/cool/heat run between -70°C and 75°C and between -70°C and 140°C for the physical mixtures with Pearlbond and Tecoflex polymers, respectively. The melting enthalpy (in the total heat flow signal), Tmelt-max (i.e. inflection point of melting endotherm) and Tmelt-onset (i.e. start of melting endotherm) were analyzed in the first heating cycle. Analysis of the glass transition temperature was done in the first and second heating cycle for injection molded tablets and physical mixtures, respectively. All results were analyzed using the TA Instruments Universal Analysis 2000 software.

Production of injection molded tablets

Physical mixtures, homogenized using mortar and pestle, of drug/polymer at a ratio of 50/50, 65/35 and 75/25 were extruded at 70°C for MPT-containing formulations, and at 140°C for Th- and Dyph-containing formulations using a lab-scale co-rotating twin-screw extruder at 100rpm (Haake MiniLab II Micro Compounder, Thermo Electron, Karlsruhe, Germany). The mixtures were manually fed into the extruder in order to avoid segregation due to differences in particle size between API (µm range) and TPUR (mm range). Immediately after HME, the thermoplastic melt was processed into biconvex tablets (diameter: 10mm/height: 5mm) via injection molding (Haake MiniJet System, Thermo Electron). The injection pressure was 800bar during 10s, in combination with a post-pressure

of 400bar for 5s. The temperature during injection molding was the same as during HME: 70 and 140°C for MPT-containing and Th- and Dyph-containing formulations, respectively.

Raman mapping

The homogeneity of the distribution of MPT in the tablets was evaluated by Raman microscopic mapping using a Raman Rxn1 Microprobe (Kaiser Optical Systems, Ann Arbor, MI, USA) equipped with an air-cooled CCD detector. The laser wavelength employed was a 785 nm from a Invictus NIR diode laser. The tablet surface was scanned by a 10x long working distance objective lens (spot size 50 μm) in area mapping mode using an exposure time of 4s and a step size of 50 μm in both the x (18 points) and y (13 points) direction (=234 spectra or 850 x 600μm per mapping segment). Six areas were analyzed in total. Data collection and data transfer were automated using HoloGRAMS™ data collection software (version 2.3.5, Kaiser Optical Systems), the HoloMAP™ data analysis software (version 2.3.5, Kaiser Optical Systems) and Matlab® software (version 7.1, The MathWorks, Natick, MA, USA). All spectra were reduced to 800-1500cm^{-1}, a spectral range which contains the fingerprint region of both components. The spectra were preprocessed using Pearson's method to perform a baseline correction and normalized.

The 234 Raman spectra collected per monitored area were each introduced into a data matrix (**D**), resulting in a Raman data matrix per area. Each **D** was analyzed using multivariate curve resolution (MCR). MCR aims to obtain a clear description of the contribution of each pure component in the area from the overall measured variation in **D**. Hence, all collected spectra in the area are considered as the result of the additive contribution of all pure components involved in the area. Therefore, MCR decomposes **D** into the contributions linked to each of the pure components in the system:

$$\mathbf{D = CS + E}$$

where **C** and **S** represent the concentration profiles and spectra, respectively. **E** is the error matrix, which is the residual variation of the dataset that is not related to any chemical contribution. Next, the working procedure of the resolution method started with the initial estimation of **C** and **S** and continued by optimizing iteratively the concentration and response profiles using the available information about the system. The introduction of this information was carried out through the implementation of constraints. Constraints are mathematical or chemical properties systematically fulfilled by the whole system or by some of its pure contributions. The constraint used for this study was the default assumption of non-negativity; that is, the data were decomposed as non-negative concentration times non-negative spectra [190].

Melt rheology

Melt rheology of TPUR was determined using an Anton Paar MCR301 (Oregon, USA) rheometer. The gap between plate spindle (diameter 25 mm) and plate was 1 mm. The strain amplitude and the angular frequency used were 1% and 10 rad/s, respectively. The Pearlbond and Tecoflex viscosities were measured at a temperature of 70 and 140°C, respectively.

Scanning electronic microscopy

IM tablets were sputtered with platinum using the JEOL JFC 1300 Auto Fine Coater (Jeol, Zaventem, Belgium). The samples were examined with a JEOL JSM 5600 LV scanning electron microscope (Jeol) at a magnification of 1000x.

He pycnometry

The tablet porosity was calculated based on the difference between the bulk and skeletal volume of the injection molded tablets. The skeletal volume of the tablets was measured (at different time points during dissolution experiments: 2, 4, 6, 8 and 24 h) via He pycnometry (AccuPyc 1330, Micromeritics, Norcross, USA). Prior to He pycnometry the tablets were dried for 2 days at 30°C. As no shrinkage or swelling of the injection molded tablets was observed immediately after injection molding nor after 24 h dissolution testing (verified by measuring tablet diameter and height using a digital slide caliper), the bulk volume of the tablets was determined from the dimensions of the mold. The tablet porosity (ε) was calculated based on the following equation:

$\varepsilon = [(\text{bulk volume} - \text{skeletal volume})/\text{bulk volume}] \times 100$

***In vitro* drug release**

Drug release from the injection molded tablets was determined using the paddle method on a VK 7010 dissolution system (VanKel Industries, New Jersey, USA) with a paddle speed of 100rpm. Distilled water was used as dissolution medium (900mL) at 37 ± 0.5°C. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h and spectrophotometrically analyzed for API concentration at 272nm for Th and 274nm for MPT and Dyph, respectively.

***In vivo* evaluation**

All procedures were performed in accordance with the guidelines and after approval by the Ethics Committee of the Faculty of Veterinary Medicine (Ghent University). To study the influence of MPT concentration, 2 formulations were administrated to 6 dogs: (a) formulation F1: IM tablets containing 65 % MPT and 35 % Pearlbond 539 (equivalent to

239mg MPT), (b) formulation F2 (reference): Slow-Lopresor® 200 Divitabs® (Sankyo, Louvain-la-Neuve, Belgium), a commercial sustained release formulation consisting of matrix tablets containing 200 mg MPT.

All formulations were administrated to 6 male mixed-breed dogs (10 – 13 kg) in a cross-over study with a wash-out period of at least 8 days. Since the size of the molded tablets was fixed, different MPT doses (239 and 200 mg for F1 and F2, respectively) were administered. The pharmacokinetic profiles were normalized as linear pharmacokinetics have been reported for MPT in a dose range between 50 and 400 mg [191]. The dogs were fasted 12 h prior to administration and 12 h after administration, although water was available ad libitum. Before administration, an intravenous cannula was placed in the lateral saphenous and a blank blood sample was collected. The formulations were administrated with 20 mL water, and blood samples were collected in dry heparinized tubes at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h after administration. The obtained blood samples were centrifuged at 1500g during 5 min. A validated HPLC method [192] with fluorescence detection was used for the determination of MPT in dog plasma. The peak plasma concentration (C_{max}) and the time needed to reach the highest plasma concentration (t_{max}) were determined. The controlled release characteristics of the formulations were evaluated by means of the $HVD_{t50\%Cmax}$ defined by the period during which the plasma concentration exceeds 50 % of C_{max} [193-194]. The intact tablets, collected in the faeces of the dogs, were analyzed for their remaining MPT concentration. These tablets were crushed using mortar and pestle, suspended in 100mL demi water for 24 h and the MPT concentration in the supernatant was spectrophotometrically analyzed at 274nm.

Simulator of the Human Intestinal Microbial Ecosystem (SHIME)

The stability of TPUR grades T85A and P523 upon oral ingestion was evaluated in the Simulator of the Human Intestinal Microbial Ecosystem (SHIME), developed by the Laboratory of Microbial Ecology and Technology, Ghent University, as described earlier [195]. In brief, both polymers (2 g/l) were added to a standardized nutritional medium and incubated under simulated stomach conditions for 90 min (37°C, aerophilic conditions). Next, an appropriate amount of bile salts and digestive enzymes was added to simulate small intestinal conditions, and the samples were further incubated for 150 min (37°C, microaerophilic conditions). Finally, a complex microbial community was taken from the ascending colon compartment of the SHIME and added to the setup. The samples were further incubated for a period of 48 h (37°C, anaerobic conditions). All experiments were performed in triplicate. As a control, the same experiment was performed in parallel, without addition of TPUR. Both polymers were isolated from the stomach, small intestinal and colon incubation medium, and the polymer's integrity and structure was analyzed by means of MDSC and FTIR. The potential breakdown of the polymer by the intestinal microflora was indirectly assessed. Changes in composition or activity of the microbial community in the test with TPUR as compared to the control were used as marker for interaction between TPUR and the intestinal microbiota. Changes in composition were assessed by selective plate counting for different bacterial groups, as described by Possemiers et al. [196]. Effects on microbial activity were evaluated by pH measurements and by quantification of the concentrations of shortchain fatty acids (SCFA) in the samples at the beginning and end of the colonic incubations, as described earlier [196].

Results and Discussion

Processability via extrusion and injection molding

Initially, the maximum drug load of the formulations that allowed processing via HME and IM was determined. Using Pearlbond and Tecoflex polymers as matrix formers, two distinct factors were negatively influencing the production of high drug load matrices: processing temperature and powder fraction in the formulation. If the processing temperature exceeded the API's melting point (T_m), HME processing became impossible at high drug loads as the matrix former was not able to absorb the large amount of molten API, resulting in a too liquid phase without the plasticity required for the HME process. In addition, a large powder fraction in a formulation also compromised HME processing below the API's T_m as the high percentage of crystalline API resulted in a too high torque during HME. Therefore, the TPUR fraction in the formulation must be sufficient to provide sufficient plasticity during thermal processing.

Thermal processing of Pearlbond polymers was possible at a temperature of 70°C. Polycaprolactone (PCL, $(C_6H_{10}O_2)_n$), the semi-crystalline polyester soft segment (SS) in Pearlbond, has a Tg of around -60°C and melts at 55°C [197]. The combination of hard segments (HS), intermolecular connected via H-bonds, and the molten SS provides the polymer with sufficient plasticity needed for the extrusion process. This low processing temperature enabled the production of high drug loaded formulations with all three API's: MPT, Dyph and Th (T_m of 120, 160 and 270°C, respectively). The maximum drug load was 65wt.% API using P523 and P539 as matrix formers, while only 50wt.% API could be combined with P520 and P522. This difference in processability was correlated with the lower SS/HS ratios of P520 and P522 (Table 1). A higher fraction of hard segment (HS), methylene diphenyl diisocyanate (MDI) in Pearlbond, hampers the movement of SS, which makes the

polymer more rigid and, hence, more difficult to process. Thermal analysis confirmed this increase in rigidity as the change in heat capacity (ΔCp) at the Tg of P539, P523 and P520 was inversely correlated to the SS/HS ratio (Figure 3): a higher fraction of HS in TPUR increased the energy needed to transform the polymer from its glass state to a rubbery phase, reducing the processability of P520. These findings were also confirmed by melt rheology experiments of the polymers, as higher melt viscosities were measured at 70°C for P520 and P522, respectively (Table 1). The polymer melt viscosity could be correlated with their extrusion processability as the API did not dissolve in the polymer melt during HME/IM processing: no loss of API crystallinity was detected in the IM tablets based on the melting enthalpy of an MPT/P539 formulation containing 50 and 65% drug, corresponding to 99 and 100% MPT crystallinity, respectively. Similar results were obtained when the other Pearlbond/drug combinations were processed (data not shown).

The formulations based on the medical grade polyether TPUR (Tecoflex) could only be processed via extrusion and injection molding at a temperature of 140°C. This higher energy input, required for the Tecoflex polymers to provide sufficient plasticity to the formulation, is most likely linked to their chemical structure consisting of hydrogenated MDI (HMDI) as HS with a shorter and thus more rigid poly-tetrahydrofuran (pTHF, $(C_4H_8O)_n$) as SS [198]. They also contain a chain extender, most likely a butanediol, which increases the HS length, a significantly lower SS/HS ratio (Table 1) and a higher polymer melt viscosity. The higher processing temperature, however, excluded MPT from Tecoflex-based formulations as its melting point (T_m: 120°C) was below the process temperature, yielding a liquid mixture without the (thermo)plasticity required for HME. Using T85A and T100A as matrix former, formulations were produced up to an API content of 65wt.%, while even a drug load of 75wt.% was possible in combination with T72D. Processing of Dyph/Tecoflex mixtures at high drug load via HME and IM was facilitated by the partial loss of Dyph

crystallinity during HME: at a drug load of 65 wt%. in T72D and T100A matrices 63 and 70%, respectively, of crystalline Dyph was recovered in the IM tablets.

An additional advantage of TPUR is its inherent lubricity [188]. Previous studies considering the injection molding technique used a silicon-based anti-sticking spray to facilitate the release of the solidified tablets from the mold [60, 199] or had problems with the brittleness of their formulations [53, 70]. Using TPUR as matrix former, no sticking to the mold was observed, nor brittleness of the matrix after cooling.

Table 1. Physico-chemical characteristics of poly-ester (Pearlbond) and poly-ether (Tecoflex) thermoplastic polyurethanes (TPUR).

TPUR grade	**HS**	**SS**	**SS/HS[(1)]**	**Mw (g/mol)**	**Tm (°C)**	**Tg (°C)**	**Melt ŋ (Pa.s)[(2)]**	**Max. drug load allowing HME (wt.%)**
P522	MDI[(3)]	PCL[(5)]	100	72 000	55	-60	12 000	50
P520	MDI[(3)]	PCL[(5)]	100	72 000	55	-62	8 000	50
P523	MDI[(3)]	PCL[(5)]	140	78 150	55	-60	1 500	65
P539	MDI[(3)]	PCL[(5)]	150	67 500	56	-60	700	65
T85A	HMDI[(4)]	pTHF[(6)]	15	82 000	77	-26	7 000	65
T100A	HMDI[(4)]	pTHF[(6)]	5	89 000	64	10	12 100	65
T72D	HMDI[(4)]	pTHF[(6)]	3.5	59 000	53	/	20 000	75

[(1)] determined via ^{1}H-NMR; [(2)] determined at 70 and 140°C for Pearlbond and Tecoflex grades, respectively; [(3)] methylene diphenyl diisocyanate; [(4)] Hydrogenated methylene diphenyl diisocyanate; [(5)] polycaprolactone; [(6)] polytetrahydrofuran

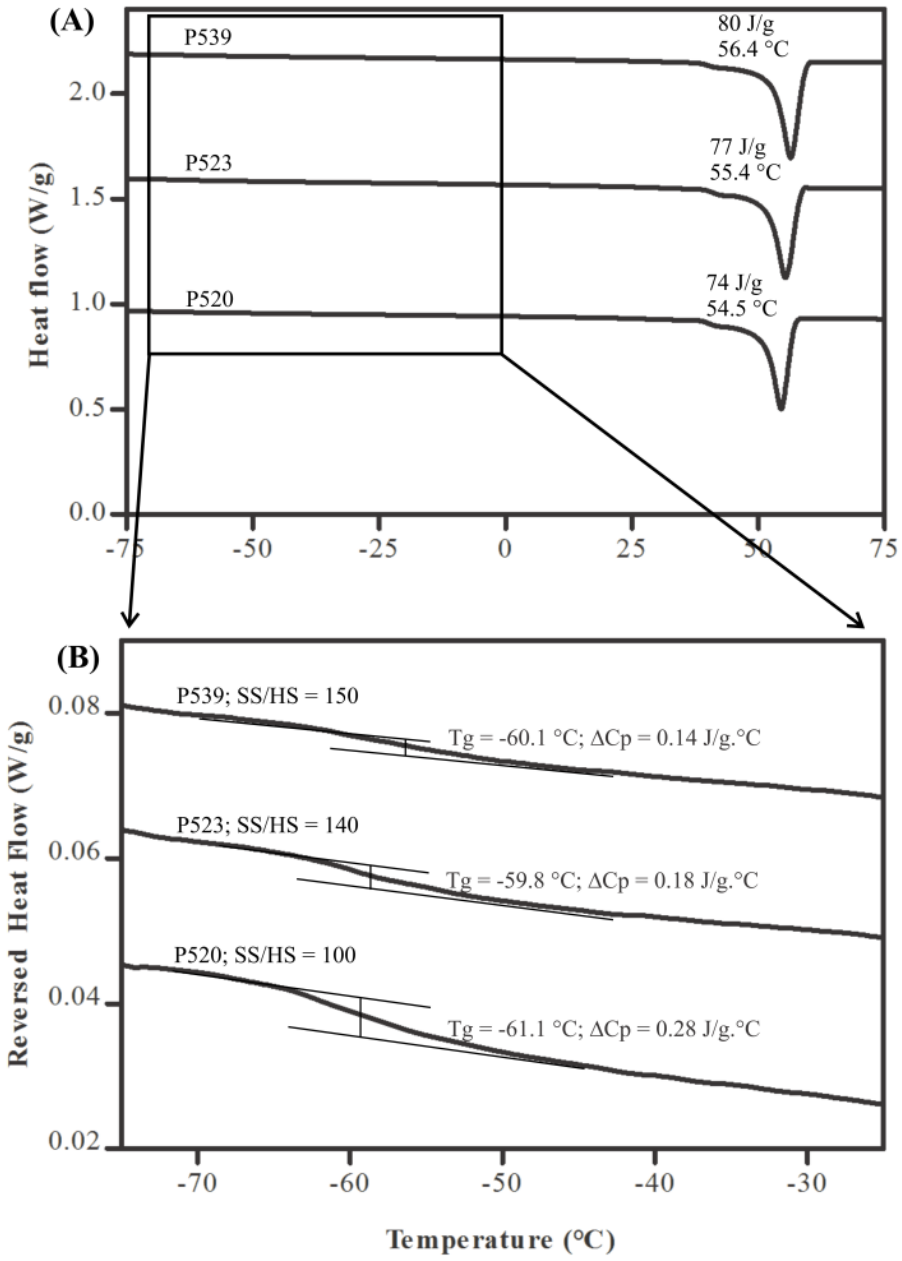


Figure 3. Thermal analysis: (A) MDSC thermograms of Pearlbond TPUR grades with different SS/HS ratios ; (B) detailed MDSC thermograms identifying Tg and ΔCp.

In-vitro drug release

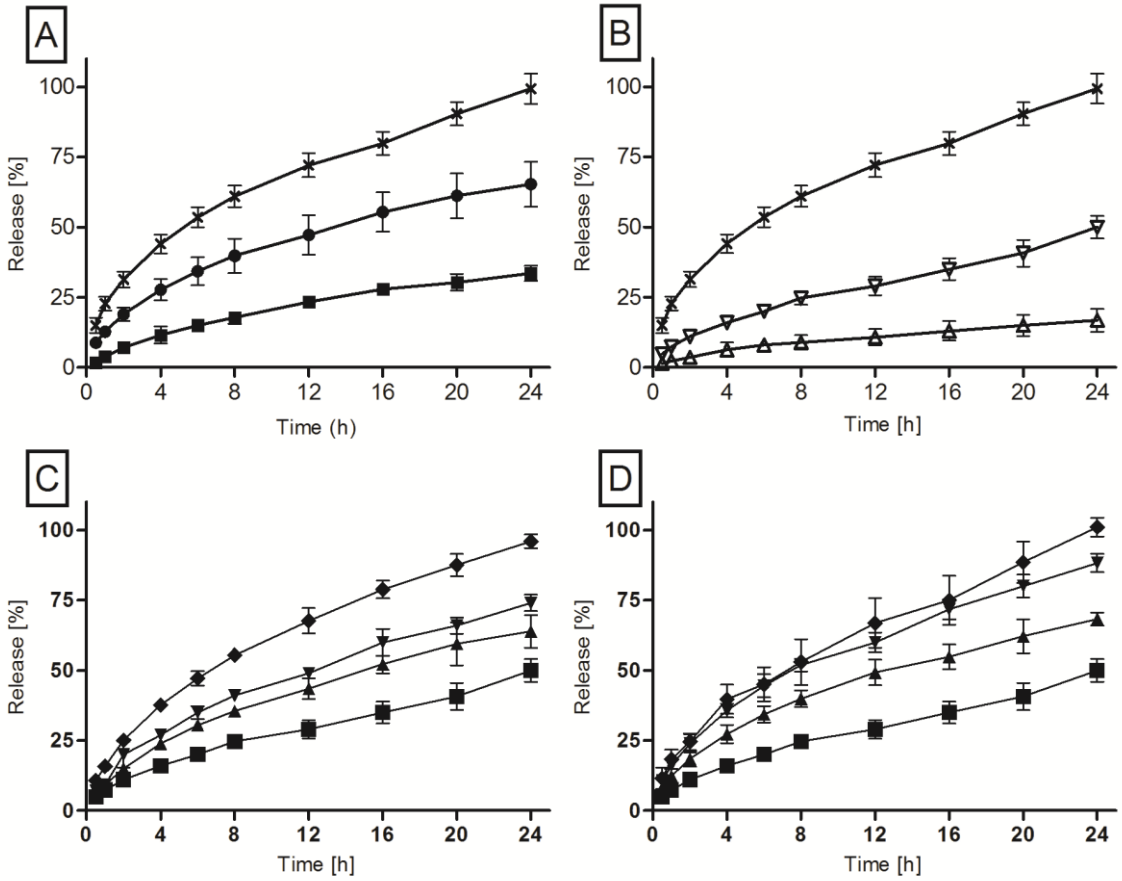


Figure 4. Mean dissolution profiles (± S.D.) of Pearlbond matrices in function of (A) drug load: 50% (■), 60% (●) and 65% MPT (x); (B) drug solubility: 65wt.% TH (Δ), Dyph (▽) and MPT (x); pore former (C) PEG 4000 or (D) Tween 80: Dyph/Pearlbond 65/35 (■) with 2 (▲), 5 (▼) and 10% (♦) of pore former, respectively.

The influence of drug load on the release is illustrated in Figure 4A. By incorporating 50, 60 and 65wt.% MPT in the TPUR matrix, the release after 24h is 33, 66 and 100%, respectively. These findings can be correlated to the percolation theory [200-201] as a minimum amount of MPT (percolation threshold) is needed to generate sufficient pores in the inert TPUR matrix in order to ensure sufficient diffusional channels throughout the entire matrix allowing dissolution and release of the entire drug content. The release mechanism from the TPUR matrices is entirely diffusion controlled as no changes in tablet dimensions

(diameter/height) and tablet geometry (biconvex tablets) were observed for any of the formulations: no swelling or erosion occurred upon wetting of the TPUR matrices. At constant drug load, the drug release profiles were independent of the TPUR grade incorporated in the formulation (data not shown). Figure 4B illustrates the effect of drug solubility on the release profiles (at a 65wt.% drug load). While the highly soluble MPT (aqueous solubility >1000 mg/mL) ensures a complete release after 24h, the release of Th (10mg/mL) and Dyph (333mg/mL) was, due to their lower aqueous solubility, limited to 20 and 50%, respectively. The addition of a pore former was required to ensure complete release of these drugs: Figure 4C and 4D represent the effect of PEG 4000 (hydrophilic substance) and Tween 80 (surfactant) on the release of Dyph. A gradual increase in drug release is observed in function of the amount of pore-former. The addition of PEG 4000 and Tween 80 to the formulation not only facilitated drug release from the TPUR matrices by generating extra diffusional channels for the API, it also enabled the production of matrices with a higher drug load (>65wt.%) as the melting of PEG 4000 and the liquid Tween 80 phase acted as a lubricant during HME/IM processing. A P539 formulation with a 70% MPT load and 10% PEG 4000 could be processed into high quality tablets; obviously this higher drug load compromised the sustained release capacities of the formulation (complete release already after 12h, data not shown). In addition to the lubricating effect of the pore formers, the addition of 5 and 10% Tween 80 to the formulation (Dyph/P539 65/35) reduced Dyph crystallinity to 76% and 67%, respectively, thus lowering the rotational friction during HMEand improving processability. Similar results were obtained when PEG 4000 was used as pore-former (data not shown). Figure 5 illustrates the correlation between tablet porosity and *in vitro* drug release of a MPT/P539 65/35 formulation: the dissolution of interconnecting drug clusters creates additional pores through which the remaining drug can dissolve, creating an empty porous TPUR matrix after 24 h. The formation of additional pores during

dissolution and the creation of an empty porous TPUR matrix was confirmed via AFM and SEM experiments (Figure 6). Prior to dissolution, needle-like MPT crystals were detected at the surface of the tablet, whereas after dissolution pores of approximately 10µm were observed.

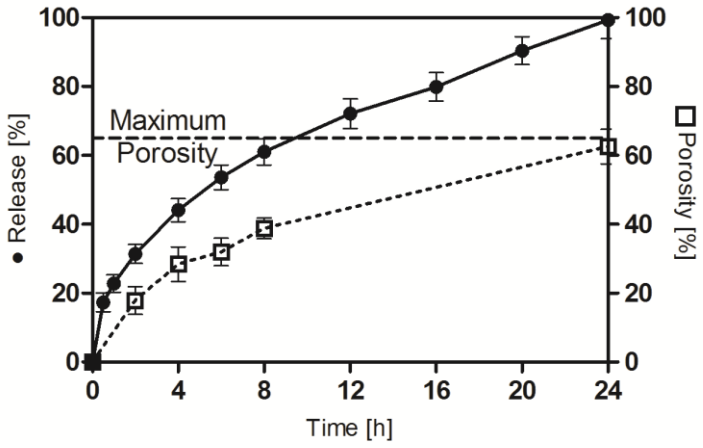


Figure 5. Mean dissolution profile (± S.D.) of MPT/Pearlbond 65/35 in correlation with the tablet porosity.

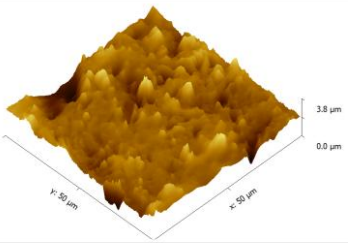
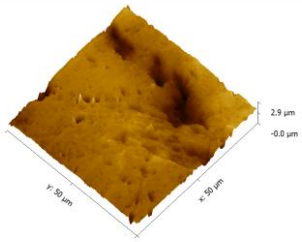
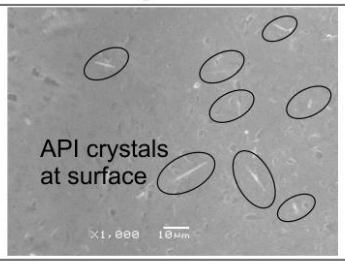
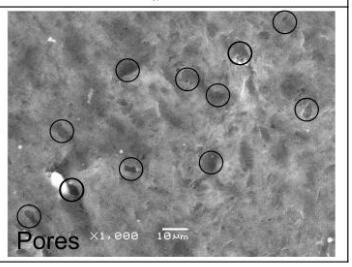
Formulation TPUR/API 35/65	Before dissolution	After dissolution (24h)
Porosity	2.1 ± 0.8%	63.0 ± 0.6%
AFM		
SEM		

Figure 6. Tablet characterization before and after dissolution: porosity (He pycnometry), AFM and SEM images.

Raman mapping

To evaluate the distribution homogeneity of the crystalline API, Raman microscopic mapping was performed on the tablets. Six areas were mapped and each area was analyzed using MCR analysis to determine the true underlying factors contributing to the spectral variation. The spectral range studied (800-1500cm^{-1}) contained the fingerprint region of both components of the formulation. No spectral difference was observed in any of the six evaluated area: crystalline API was homogeneously distributed at the surface of the tablet (mapping in supporting information).

Oral toxicity: Simulator human intestinal microbial ecosystem (SHIME)

Toxicological reports of TPUR have been widely described for their use in (breast) implants, intravaginal rings, stents, coating, etc. [16, 25, 184-185, 187, 202-204]. However, no data about the toxicity of TPUR are available upon oral intake. While the SHIME study does not provide an entire toxicological report, it can give a first impression about the impact of the gastro-intestinal fluids on the integrity of TPUR and the effect of TPUR on the microbial flora. Upon oral intake, the formulation passes the intestinal environment where chemical and/or enzymatic reactions can affect the polymer structure. Also, the human colon, which is colonized by a complex microbial community, can modify the polymer structure and may in turn be influenced by exposure to the polymer. To this end, P523 and T85A (2g/l) were added to the SHIME system to determine its intestinal stability and its possible impact on microbial metabolism indicators (pH, short chain fatty acids [205] and bacteria). No significant differences were observed in bacterial count (Figure 7), short chain fatty acids and pH (data not shown). The polymer structure of T85A was not altered during gastro-intestinal transit as MDSC and FTIR showed similar thermal behavior and spectra, respectively. The structure of P523, on the other hand, was affected as the peaks at 1100, 1275 and 1325cm^{-1}

disappeared after exposure to the SHIME media. The first peak was linked to symmetrical ester stretch vibration [206], whereas the other two were assigned to chemical changes in the amorphous SS region of TPUR [206]. Previous research [207-208] already described that polyether-based polyurethanes are more resistant to biodegradation than polyester-based polyurethanes. This first toxicity screening of T85A revealed no evidence of chemical and/or enzymatic reaction after exposure to the intestinal environment, whereas P523 showed signs of ester linkage degradation/hydrolysis. This first indication, regarding TPUR toxicity upon oral administration, was considered positive as the activity or composition of the GI bacterial community, the pH values and the presence of short chain fatty acids were not altered after exposure to both polymers.

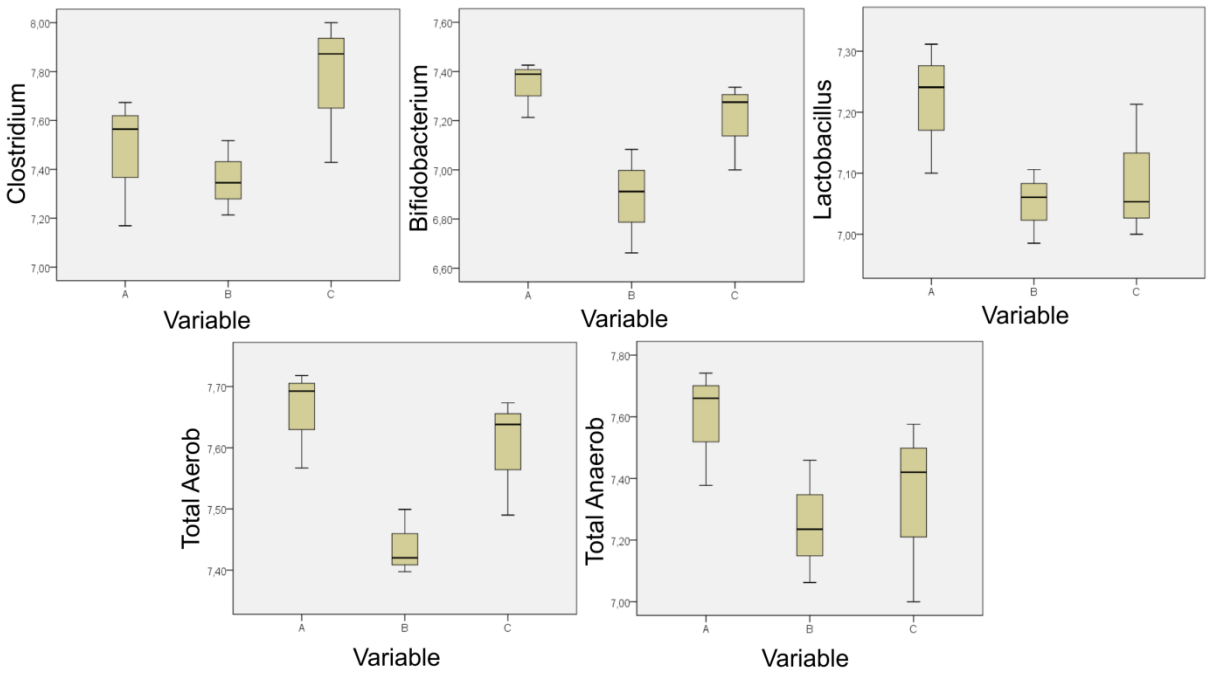


Figure 7. Boxplot curves of bacterial counts of the SHIME experiment after exposure of (A) P539, (B) T85A and (C) control. The polymer concentration was 2g/l in both treatment groups; no polymer was used in the control group.

In vivo evaluation

Figure 8 illustrates the *in vitro* dissolution profiles and the mean plasma concentration-time profiles after oral administration to beagle dogs of MPT tablets (polyurethane matrix, drug load 65wt.%) and the reference formulation (Slow-Lopresor® 200 Divitabs®, drug load 47wt.%). *In vitro* dissolution yielded a complete release of MPT after 12 and 24 h for the reference and the polyurethane matrix, respectively. The reference formulation is subjected to surface erosion of its matrix allowing MPT to escape faster due to the increased surface area, while the tablet geometry of the polyurethane matrix remained unchanged after 24 h dissolution experiments. These differences between *in vitro* drug release patterns were also reflected in their *in vivo* behavior. Oral administration of the polyurethane formulation resulted in a lower C_{max} and a more sustained release of MPT (up to 16 h) compared to the reference formulation (up to 12 h). These differences in MPT plasma concentration, however, were not statistically significant. Moreover, intact TPUR tablets, which still contained 13% of their initial MPT content, were collected from the faeces of the dogs. No remnants of the reference formulation were found. This is probably attributed to the fast gastro-intestinal (GI) transit time in dogs in combination with a limited amount of fluids in the dog [144], thereby limiting MPT dissolution from the polyurethane matrix. The reference formulation is, compared to the polyurethane matrix, less susceptible to the GI transit time and the limited fluids as surface erosion altered the surface area of the formulation. Other pharmacokinetic parameters (AUC, t_{max} and $HVD_{t50\%Cmax}$) did not differ significantly ($p>0.05$).

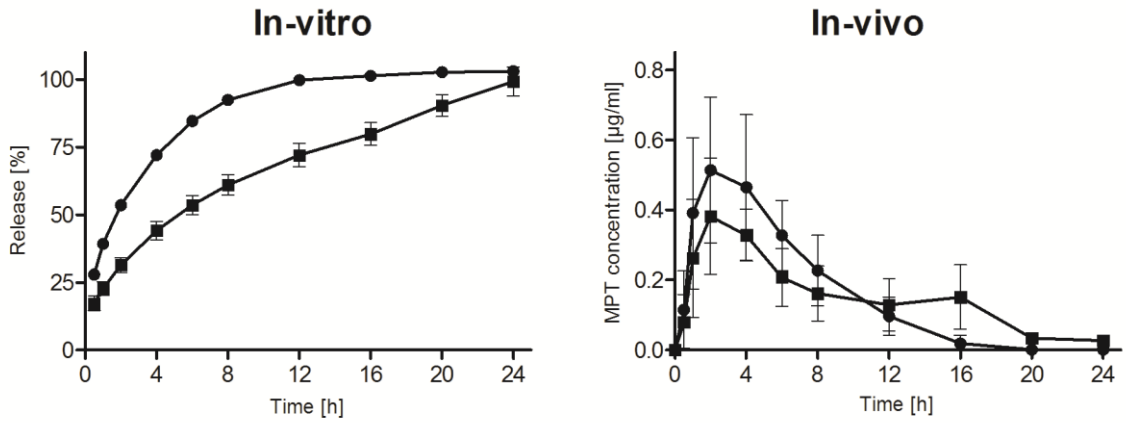


Figure 8. *In vitro* dissolution experiments and mean MPT plasma concentration (± S.D.) after oral administration of 200mg MPT (normalized dose) to dogs (n=6) as tablets containing MPT/Pearlbond 65/35 (■) and as Slow-Lopresor 200 Divitabs® (●)

Conclusion

This study demonstrated that TPUR polymers are promising matrix formers to produce oral controlled release formulations. Sustained release (*in vitro* and *in vivo*) of MPT, a highly water-soluble drug, was achieved, while diprophylline required a drug release modifier (Tween 80 or PEG 4000). The high drug load in combination with controlled release capacities is noteworthy in the field of formulations produced via HME/IM.

Acknowledgments

The authors acknowledge Mr. Daniël Tensy, Jana De Bodt and Veerle Boterberg for their contribution. Merquinsa is acknowledged for generously supplying the TPUR polymers. The Department of Morphology at the Faculty of Veterinary Medicine (Ghent University, Belgium), is acknowledged for the photomicrographs.

Supporting information

Raman Mapping: the spectral range studied (800-1500cm^{-1}) contains the fingerprint region of both components. For each mapped area, two MCR analysis were done. Firstly, as the tablet is composed by two elements, a 2 factors MCR was performed. Two identical spectra were systematically obtained (SF1), the MCR analysis wasn't able to separate the two contributions in the spectra signifying the homogeneity of the spectra within the monitored area.

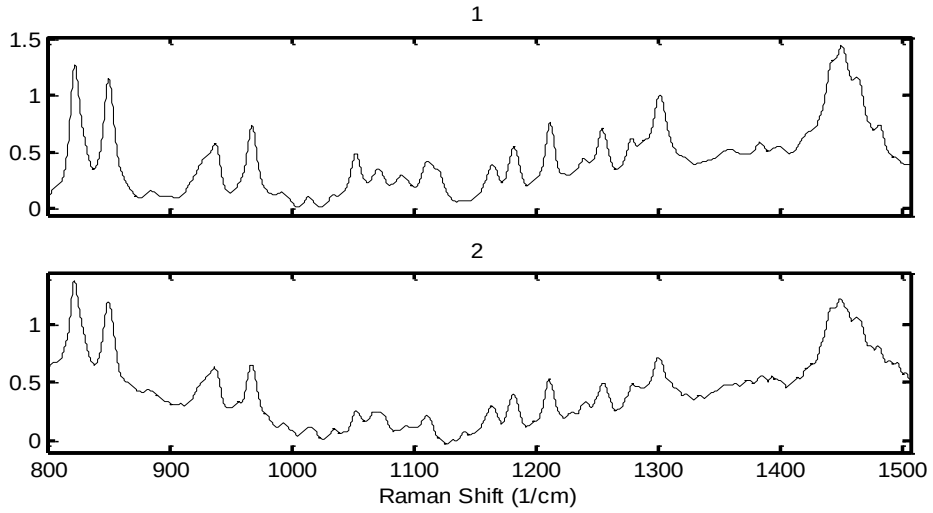


Figure S1. Spectra 1 and 2 obtained after a 2 factors MCR analysis.

The homogeneity of the tablet can also be visualized with 2D plots of a 2 factors MCR analysis (SF2).

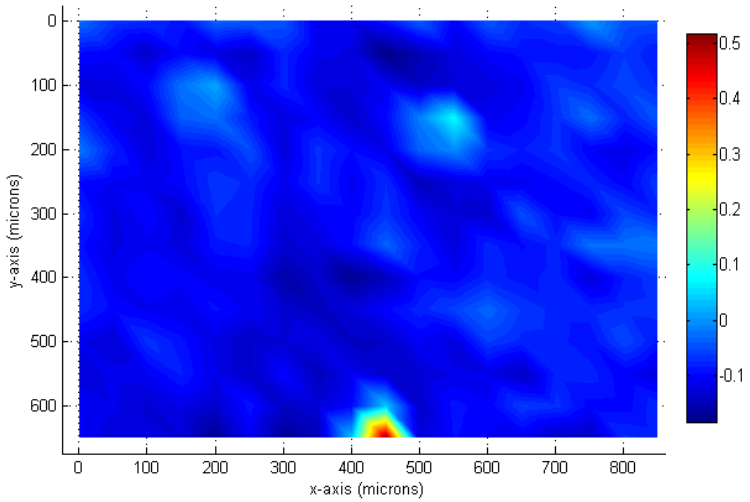


Figure S2. Raman mapping of an area of the surface of an IM-tablet containing 65% MPT and 35% TPUR: red and blue color corresponding to spectral differences

Secondly, an auto MCR was performed and always resulted in only one spectra, a supplemental indication of the homogeneity of the spectra within the monitored areas.

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CHAPTER 5

Release characteristics of polyurethane tablets containing dicarboxylic acids as release modifiers – a case study with diprophylline

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Introduction

Hot melt extrusion (HME) combined with injection molding (IM) as downstream processing step is a suitable technique to manufacture solid dosage forms with high dimensional precision [53, 70, 155, 209]. The use of polyurethanes as carrier for the production of sustained release formulations is favorable due to their highly elastomeric character, superior tensile strength, crack resistance and inherent lubricity. They have been successfully used for many years as drug release controlling polymers in vaginal rings [16, 25, 184], stents [185], coatings [186], implants [187], and medical tubings [122]. The inert, non-ionic and water-insoluble nature of polyurethanes enables them to release the incorporated API in a sustained manner, even at high drug loadings (>50wt.%) [121]. However, depending on the properties of the drug the addition of a third component is required in the formulation to ensure complete drug release. The development of a polyurethane-based biomaterial, for instance, required the use of a pore former to alter the release characteristics of an antibacterial agent (cefadroxil) to prevent bacterial adhesion and growth on its surface. The highest release rate was observed when bovine serum albumin (BSA) was incorporated in the TPUR matrix, compared with polyethylene glycol (PEG 1450) and mannitol, possibly due to the different aqueous solubility of the pore formers although further investigation was necessary [210]. In the development of an antifungal catheter, PEG 2000 and BSA were added to control the release of fluconazole in a water-swellable polyurethane matrix. The addition of PEG resulted in faster release profiles, whereas BSA was able to control the release over a longer period, which was attributed to its higher molecular weight (69 000 and 2000 g/mol for BSA and PEG, respectively) [211]. An oral TPUR application, containing mixtures of TPUR and diprophylline required the incorporation

(2, 5 and 10%) of a pore former (PEG 4000) or a surfactant (Tween 80) to ensure complete drug release over a 24 h period [121].

This paper evaluates the effect of dicarboxylic acids on the release characteristics of diprophylline from polyurethane matrices processed via hot-melt extrusion and injection molding. Malonic, succinic, maleic and glutaric acid were selected as dicarboxylic acids as their differences in aqueous solubility, melting point, pKa, polarity and chemical structure allows to identify the critical parameters towards the release enhancing effect from the polyurethane matrix.

Experimental Section

Materials

Diprophylline (Dyph, 7-(2,3-dihydroxypropyl)-theophylline) was embedded as drug in the thermoplastic polyurethane (TPUR) matrix. Tecoflex 72D (T72D, a medical-grade polyurethane) was obtained from Merquinsa (a Lubrizol company, Ohio, USA). Malonic, succinic, maleic and glutaric acid were purchased from Sigma (St-Louis, USA). The chemical structures of all materials are detailed in Figure 1, while the chemical properties of the dicarboxylic acids are listed in Table 1. Distances between various atoms were determined via Chem 3D Pro (PerkinElmer, Massachusetts, USA).

Table 1: Chemical characteristics of dicarboxylic acids

Dicarboxylic acid	COOH -R- COOH	pKa_1	T_m (°C)	Solubility in H_2O (g/L)	logP
Malonic	CH_2	2.8	135	1400	-0.81
Succinic	CH_2CH_2	4.2	184	60	-0.59
Maleic	CH=CH	1.9*	135	790	-0.5
Glutaric	$(CH_2)_3$	4.3	95	430	-0.29

* Low pKa due to intramolecular H-bonding

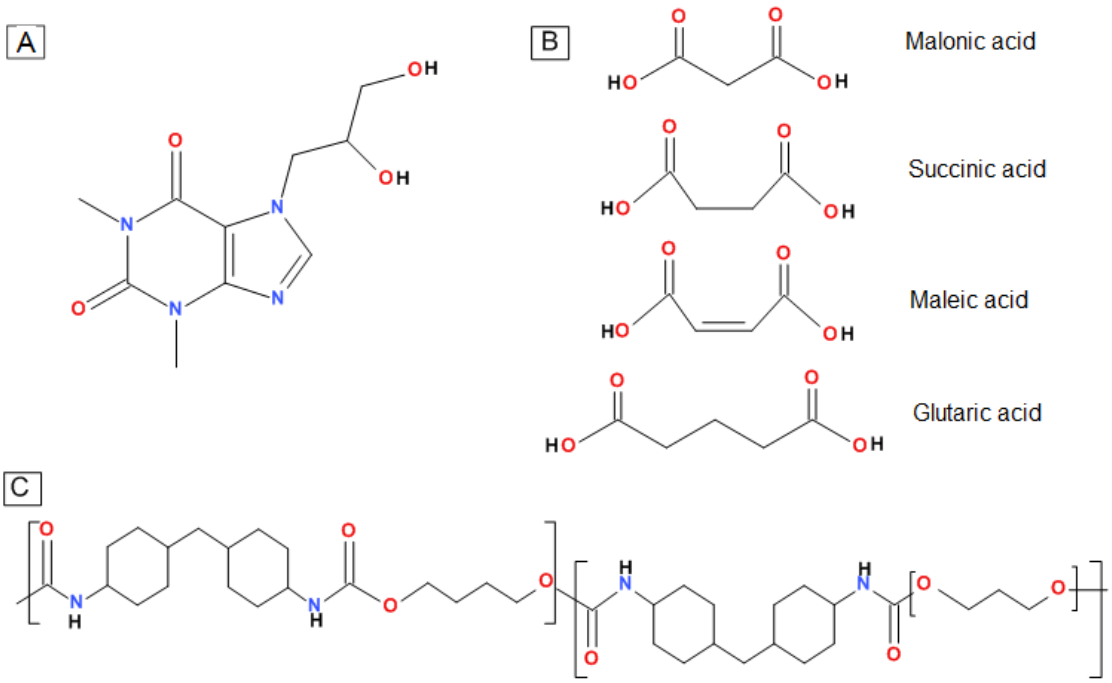

Figure 1. Chemical structure of (A) diprophylline, (B) dicarboxylic acids and (C) Tecoflex 72D thermoplastic polyurethane.

Thermal analysis

The glass transition temperature (Tg) and melting point (T_m) of pure components, physical mixtures and injection molded tablets were analyzed in Tzero pans (TA instruments, Zellik, Belgium) by modulated differential scanning calorimetry (MDSC Q2000, TA Instruments, Leatherhead, UK) using a heating rate of 2°C/min. The modulation period and amplitude were set at 1min and 0.318°C, respectively (heat-iso method). Dry nitrogen at a flow rate of 50mL/min was used to purge the MDSC cell. All results were analyzed using the TA Instruments Universal Analysis 2000 software. Samples (± 5mg) were run in Tzero pans (TA Instruments, Zellik, Belgium). MDSC heat capacity calibration was done via small sapphire disks, placed in a Tzero pan. Analysis of the thermal characteristics (T_m and T_g) was done via a heating/cool/heat run between -70 and 140°C. The melting enthalpy (in the total heat flow signal), $T_{melt\text{-}max}$ (i.e. inflection point of melting endotherm) and $T_{melt\text{-}onset}$ (i.e. start of melting endotherm) were analyzed in the first heating cycle. Analysis of the glass transition

temperature was done in the first and second heating cycle for the injection molded tablets and the physical mixtures, respectively. All results were analyzed using the TA Instruments Universal Analysis 2000 software.

X-ray diffraction (XRD)

The crystallinity of the samples was determined via X-ray diffraction using a D5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 kV and current of 40 mA in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1 s/step).

Karl Fischer

The water content of all dicarboxylic acids was determined by volumetric Karl Fischer titration using a V30 volumetric KF titrator (Mettler Toledo, USA). Methanol (Hydranal, Sigma Aldrich, Germany) was used as solvent. Before titration, 1g was dissolved in methanol during 1000 s. All measurements were performed in triplicate.

Fourier Transform Infrared Spectroscopy

Attenuated total reflection Fourier-transform infrared (ATR FT-IR) spectroscopy was performed on pure substances, physical mixtures and heated physical mixtures in order to identify molecular changes upon heating. Physical mixtures of Dyph and dicarboxylic acid (PM acid) at a molar ratio of 1/1 were compared with their respective PM after heating (2°C/min up to 140°C) and recooling to room temperature (heat-treated PM).

Spectra (i.e. 10 samples per physical mixture, 1 spectrum per sample, 40 spectra for PM acid and 40 spectra for PM acid heated) were recorded using a Nicolet iS5 ATR FT-IR spectrometer (Thermo Fisher Scientific). A diamond ATR crystal was pressed against the samples. Each spectrum was collected in the 4000 - 550 cm^{-1} range with a resolution of 2 cm^{-1} and averaged over 32 scans. FTIR spectral data analysis was done using SIMCA P+ v.12.0.1

(Umetrics, Umeå, Sweden). The spectral ranges of 1000-1120cm^{-1} and 880-780cm^{-1} were evaluated via principal component analysis. All collected FTIR spectra were preprocessed using standard normal variation (SNV)

Production of injection molded tablets

Physical mixtures of drug and polymer were extruded at 140°C using a co-rotating twin-screw extruder at 100rpm (Haake MiniLab II Micro Compounder, Thermo Electron, Karslruhe, Germany). The API/TPUR ratios (wt.%) used in this study were 75/25, 65/35 and 50/50 with a processing temperature of 140°C. Biconvex tablets (diameter: 10mm/height: 5mm) were produced via injection molding (Haake MiniJet System, Thermo Electron). The injection pressure was 800bar during 10s, in combination with a post-pressure of 400bar for 5s.

***In vitro* drug release**

Drug release from the injection molded tablets was determined using the paddle method on a VK 7010 dissolution system (VanKel Industies, New Jersey, USA) with a paddle speed of 100rpm. Distilled water was used as dissolution medium (900mL) at 37 ± 0.5°C. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h and spectrophotometrically analyzed for Dyph concentration at 274nm.

Results and Discussion

The standard formulation: processability, release and solid state characterization

Processing of TPUR/Dyph mixtures via HME and IM at 140°C required a minimum of 25% of thermoplastic polymer to provide sufficient plasticity to the formulations, as Dyph remained mainly crystalline during thermal processing. Mixtures with higher drug loads (>75wt.%) could not be processed as the powder fraction was too high to ensure an adequate flow in the extruder (i.e. too high screw torque). Dyph release (Figure 2A) from the standard formulation was incomplete: 9, 41 and 55% Dyph was released after 24h from TPUR matrices with drug loads of 50, 65 and 75%, respectively. This indicated that - despite the high drug load - a continuous interconnecting network was not achieved in the TPUR matrix and that a release modifier is required to enhance Dyph release. Although 2 polymorphs of Dyph with distinct melting temperatures, melting enthalpies and crystallographic spectra (Figure 2B and 2C) have been described, after thermal processing only Form I (T_m 162°C, 175J/g, a thermodynamically stable form) was detected in the DSC signal of TPUR/Dyph matrices. This observation was confirmed via XRD (Figure 2C). The formation of the kinetically stable Form II (T_m 150°C, 135J/g) has been described after recrystallization from solvents/melts [212].

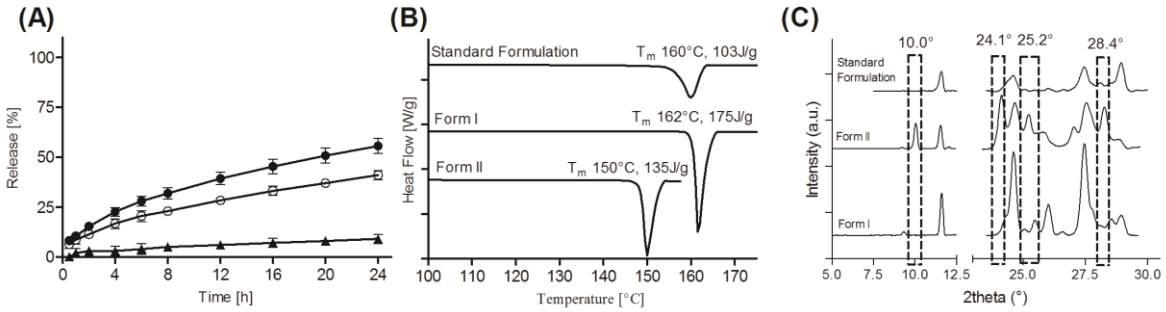

Figure 2. (A) Mean dissolution profiles (± S.D.) of the standard formulation Dyph/TPUR at different ratios (wt.%): (▲) 50/50, (□) 65/35 and (●)75/25; (B) thermal analysis via MDSC and (C) XRD-diffractograms confirming the presence of Dyph form I in the standard formulation.

Addition of dicarboxylic acids as drug release modifiers

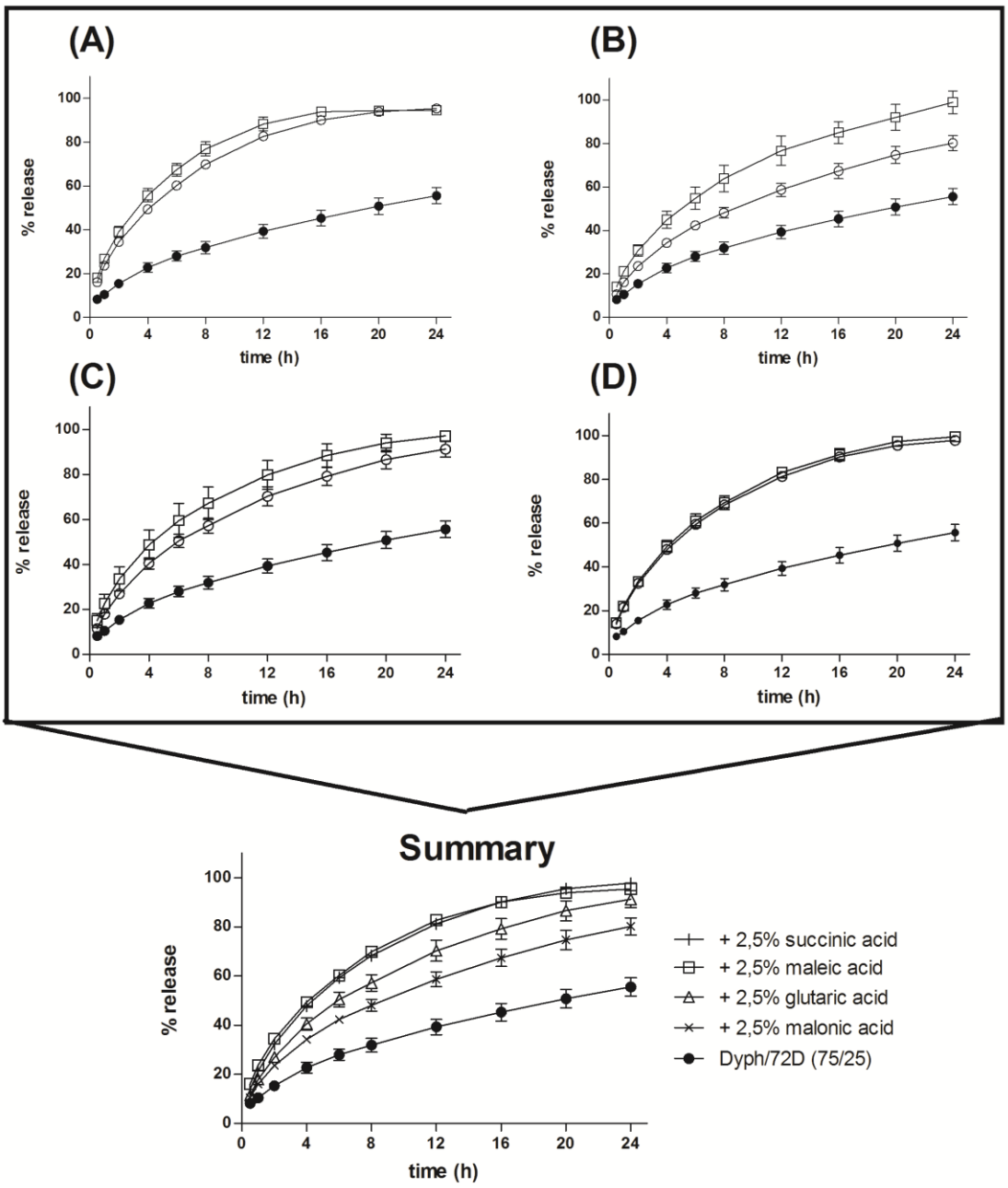

Figure 3. Mean dissolution profiles (± S.D.) of the standard formulation Dyph/TPUR (75/25) (●) with dicarboxylic acids as drug release modifiers: (A) maleic acid, (B) malonic acid, (C) glutaric acid and (D) succinic acid: 2.5% (○) and 5% (□); (Summary) comparison of the profiles Dyph/TPUR (75/25) with the addition of 2.5% dicarboxylic acids.

Figure 3 evidences that the release of Dyph was improved via the addition of dicarboxylic acids. This improvement was concentration driven, as higher concentrations of dicarboxylic acids induced faster drug release. However, figure 3E shows that the solubility of the dicarboxylic acids is not the main contributing factor for the enhanced release rate. Malonic acid (Fig 3B), having the highest water solubility (1400g/L), was the least successful drug release modifier. No correlation was found between the drug release modifying capacity and logP, pKa or Tm of the dicarboxylic acids. Succinic and maleic acid yielded the highest release modifying effect, which might indicate that the specific chemical structure of these two acids (i.e. two methylene groups between the carboxylgroups) is important for their superior drug release altering capacity.

The effect of dicarboxylic acids on drug release was not linked to changes in polymorphic structure of Dyph. XRD profiles of thermally processed Dyph/TPUR matrices in combination with maleic acid (Figure 4) only showed signals of the innate crystallographic form of Dyph (i.e. Form I) as the specific peaks of Dyph Form II (10.0, 24.1, 25.2 and 28.2°) were absent in the formulation. Moreover, there was no correlation found between the water content of the dicarboxylic acids and their drug release modifying capacity. Karl Fisher experiments indicated that the water content of all dicarboxylic acids was similar and lower than 1% ($\pm$ 0.05, n=3, data not shown).

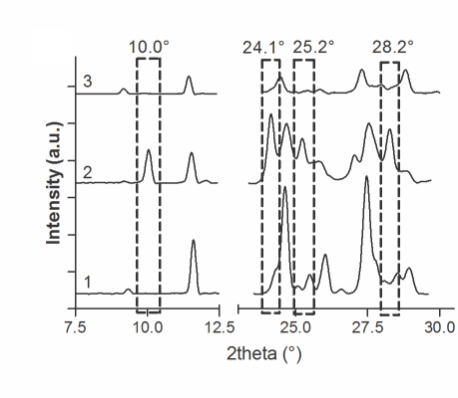

Figure 4. XRD diffractograms of (1) Dyph form I, (2) Dyph form II, (3) standard formulation + 5% maleic acid

Interaction between diprophylline and dicarboxylic acids

The probability of interactions between the different dicarboxylic acids and Dyph were evaluated via thermal analysis (MDSC) and spectroscopic analysis (ATR-FTIR combined with PCA-analysis).

MDSC

The thermal results presented in this section are, for the sake of clarity, limited to a comparison between malonic and maleic acid, as both dicarboxylic acids have the same T_m (134°C), but their impact on the release characteristics is markedly different (the lowest and highest drug release modifying capacity was attributed to malonic and maleic acid, respectively).

The themograms of the physical mixtures revealed an interaction between Dyph and both dicarboxylic acids based on the reduction of the thermal parameters ($T_{melt\text{-}max}$, $T_{melt\text{-}onset}$ and degree of crystallinity) of Dyph during the first heating cycle. The interaction between a crystalline API and an excipient can induce, depending on their respective molar ratio, (partial) dissolution of the API, and as the resulting smaller API crystals are intrinsically less stable, peak broadening of the melting endotherm is observed. These phenomena were more pronounced when Dyph was combined with maleic acid compared to malonic acid (Figure 5, left). The second heating cycle of Dyph/dicarboxylic acid mixtures revealed a glass transition signal which was constant in combinations with malonic acid, whereas Tg varied when maleic acid was used, indicating a change in molecular mobility due to interactions at a molecular level (Figure 5, middle). These thermal results of the physical mixtures provide a clear indication of stronger interactions between Dyph and maleic acid, compared to Dyph/malonic acid mixtures. Thermal investigation of the injection molded tablets (IM) illustrated similar effects (Figure 5, right): the addition of 5% malonic and maleic acid reduced $T_{melt\text{-}max}$ of Dyph

from 162 to 159 and 154°C, respectively. Moreover, without the addition of dicarboxylic acids, 80% of the Dyph fraction remained crystalline in a TPUR matrix. The degree of crystallinity of Dyph in formulations processed with malonic acid was not affected, whereas Dyph crystallinity was reduced to 73 and 68%, respectively, when 2.5 and 5% maleic acid was used as release modifier. These results confirmed the higher affinity between Dyph and maleic acid, compared to malonic acid.

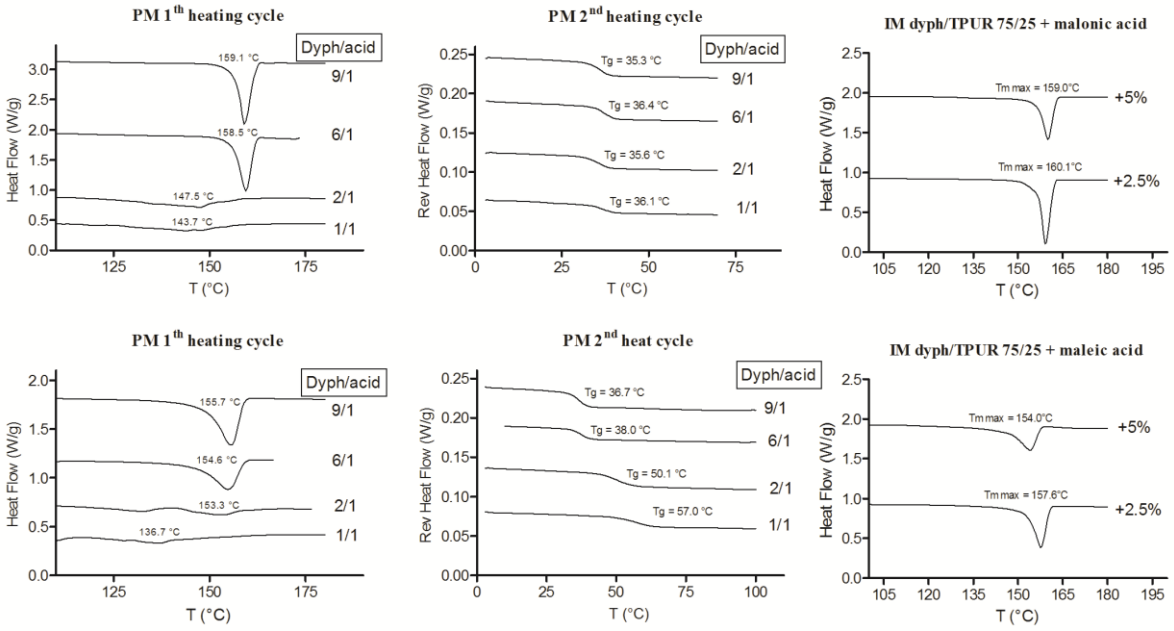

Figure 5. Thermograms of physical mixtures (PM) of Dyph and dicarboxylic acids (molar ratio: 9/1, 6/1, 2/1 and 1/1) during the 1st (left, to analyse $T_{melt-max}$) and 2nd heating cycle (middle, to analyse Tg), and of an HME/IM-processed Dyph/TPUR mixture (ratio: 75/25) in combination with 2.5 and 5% dicarboxylic acids (right) during the 1st heating cycle. Formulations contained malonic acid (top) and maleic acid (bottom).

ATR-FTIR

As thermal analysis indicated the importance of molecular interactions for the release-enhancing effect of dicarboxylic acid in a TPUR matrix, the affinity between the different dicarboxylic acids and Dyph was further explored via FTIR analysis.

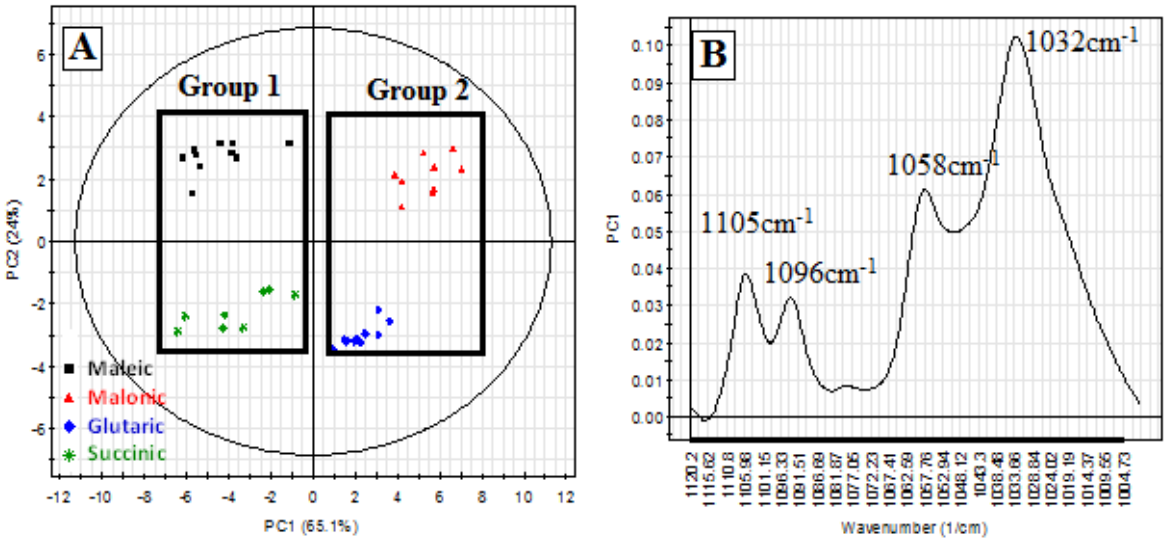

Figure 6. A) PC1 versus PC2 scores plot obtained after PCA of 1000-1120cm^{-1} spectral range of the FTIR spectra obtained after heat-treatment (heating rate: 2°C/min to 140°C) of physical mixtures of Dyph and dicarboxylic acids. Each point represents one sample and each symbol represents a different physical mixture. B) PC1 loadings plot obtained after PCA of the FTIR spectra from the 4 physical mixtures heated.

Principal component analysis of the FTIR spectra of the heat-treated PM was performed using the 1000-1120cm^{-1} spectral range. All preprocessed FTIR spectra were decomposed into four principal components (PCs) explaining 98.6% of the total spectral variance where PC1 accounted for 65.1%, PC2 24%, PC3 6.1%, and PC4 3.4% of the spectral variance, respectively. Figure 6A illustrates the scores clustering according to PC1 and PC2. Interestingly, PC1 distinguishes two groups: mixtures with succinic and maleic acid (i.e. dicarboxylic acids inducing the highest drug release modifying capacity, Fig. 3) and mixtures with malonic and glutaric acid (having the lowest drug release modifying capacity, Fig. 3).

Examination of the PC1 loadings plot (Figure 6B) to identify the spectral variability responsible for this clustering in group 1 and 2 revealed four important peaks, all attributed to the chemical structure of Dyph: 1105 and 1096cm^{-1} of the C-O stretching of the secondary alcohol, 1058cm^{-1} of the C-O stretching of the primary alcohol, and 1032cm^{-1} of the C-N stretching of the tertiary aliphatic amine [213].

Figure 7A and 7B illustrate the FTIR spectra of the physical mixtures (full line) and the heat-treated samples (dotted lines) over the 1000-1120cm^{-1} spectral range. Before heating, the peaks of interest were identical for all PM, independent of the type of dicarboxylic acid. Although the intensity of C-O stretching of the primary and secondary alcohol decreased upon heating and cooling of all samples, these peaks (1 and 2 on Figure 7) completely disappeared in the heat-treated mixtures containing maleic and succinic acid. The peak indicative of C-N stretching of tertiary aliphatic amines shifted towards lower wavenumbers (peak 3 on Figure 7). This shift was larger in combination with maleic and succinic acid. A new peak was formed at 820cm^{-1} and 812cm^{-1} for the heat-treated samples of Dyph/maleic acid and Dyph/succinic acid, respectively (peak 4 and 5 on Figure 7). This was attributed to a C-H vibration shift due to the interaction between both components [213]. These spectral changes clearly confirmed the more extensive interactions between Dyph and maleic/succinic acid (compared to malonic/glutaric acid). A structural fit between the primary and secondary alcohol of Dyph and both carboxylic groups of the acids is, most likely, at the origin of this enhanced interaction (Figure 7E): the distance (i.e. two methyl groups) between the two oxygens groups of the carbonyl of maleic (2.7Å) and succinic acid (2.5Å) is similar to the distance between the two hydroxyl groups of Dyph (2.8Å). Hence, 2 H-bonds can easily be formed, yielding more interactions and the complete disappearing of their respective C-O stretch peaks. Malonic acid (i.e. one methyl group) and glutaric acid (i.e. three methyl groups, Figure 7E) did not structurally match with Dyph, resulting in a lower degree of molecular

interactions (distance between oxygens of the carbonyl group being 3.9 and 4.7Å for malonic and glutaric acid, respectively). Hence, the peak of the C-O stretch was still observed in these peaks, although its intensity had dropped.

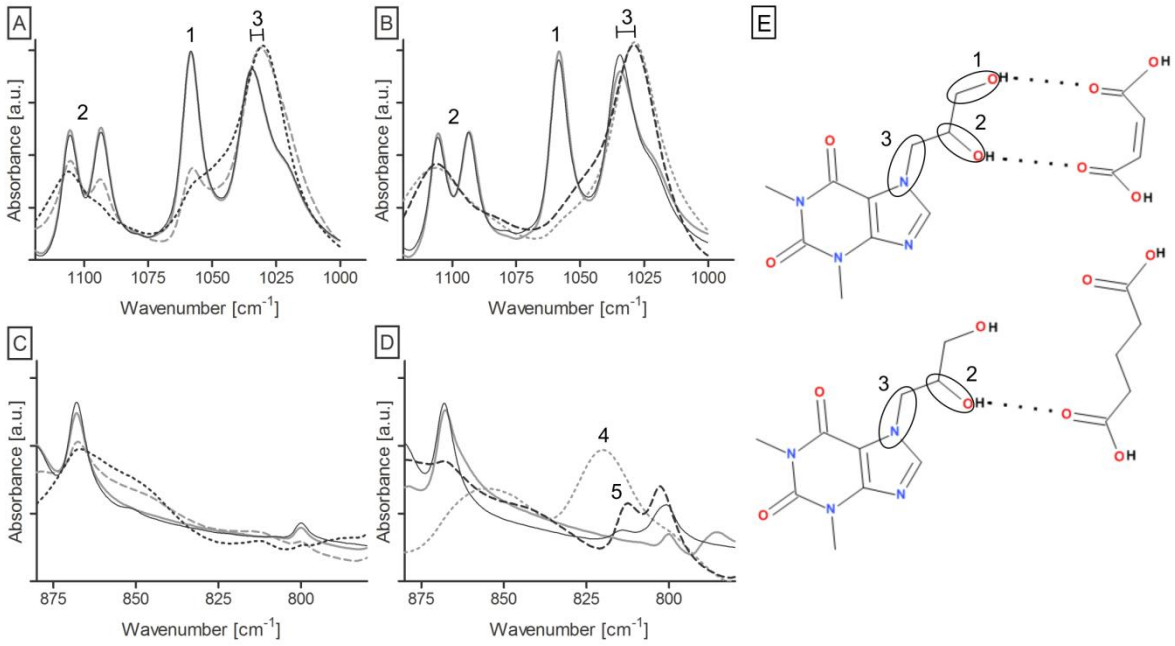

Figure 7. FTIR spectra of physical mixtures (full line) and heat-treated physical mixtures (dotted lines) of Dyph and dicarboxylic acid (molar ratio 1/1) over the 880-780cm^{-1} (bottom) and 1000-1120cm^{-1} (top) spectral region: (A, C) mixtures with malonic (grey) and glutaric acid (black); (B, D) mixtures with succinic (black) and maleic acid (grey); (E) formation of H-bond(s) between Dyph and maleic (top) or glutaric acid (bottom).

To confirm that stronger interactions between Dyph and maleic/succinic acid are due to a structural fit between these components, the interaction between fumaric acid (enantiomeric form of maleic acid) and Dyph was monitored. The carboxylic acid groups of fumaric acid are in trans-form (both COOH at the opposite side of the backbone), while in maleic acid they are in cis-form (similar side of the backbone). FTIR spectra and *in vitro* release data illustrated that fumaric acid did not interact with Dyph to the same extent as maleic acid (data not shown): the C-O stretch of both hydroxyl groups and the shift of C-N stretch in Dyph were less affected in this combination. Moreover, *in vitro* Dyph release was

lower for fumaric acid in comparison to maleic acid formulations: 39 and 50% after 4 h for fumaric and maleic acid, respectively. These observations confirmed that the superior release modifying capacity of maleic/succinic acid is attributed to a structural fit between Dyph and dicarboxylic acids.

Ester bond formation between the OH-groups of Dyph and maleic/succinic acid was excluded as the addition of a drop of 0.5g/ml LiBr solution to a heat-treated Dyph/maleic acid sample neutralized the spectral changes, confirming the reversible nature of the molecular interactions between Dyph and maleic acid and the absence of an irreversible ester-bond. The addition of a LiBr solution results in a breakdown of the reversible inter- and intra-molecular H-bonds, since the bromide anion acts as a strong nucleophilic component, whereas Li^+ interacts with the carbonyl group [214].

Conclusion

A high dosed sustained release formulation was developed via hot melt extrusion and injection molding. Despite the high drug load (75wt.% Dyph), a drug release modifying agent was essential to release the entire Dyph fraction in a sustained manner from the TPUR matrix. Succinic and maleic acid had a superior release modifying capacity which was attributed to more intense molecular interaction with Dyph (H-bonds). A structural fit between the primary and secondary alcohol of Dyph and both carboxylic groups of the acids was at the origin of this enhanced interaction.

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GENERAL CONSLUSIONS AND FUTURE PERSPECTIVES

The objective of this doctoral thesis was to evaluate the use of polymethacrylates, quaternized polymethacrylates, modified polymethacrylates, polyoxazolines and polyurethanes for the development of immediate and sustained release formulations via hot melt extrusion (HME) and injection molding (IM). Modifications were made on pharmaceutically approved polymers and two non-conventional polymers were evaluated with the goal of expanding the range of polymers currently used for HME/IM. Despite the extensive research being conducted today, researchers should face the reality: the number of marketed products manufactured via HME and/or IM as processing technique has been disappointing. This work encourages an update of the regulatory framework. Currently, there are no regulatory approval processes specifically for novel excipients. Information about the quality and safety of new excipients is only reviewed by the health authorities in the context of a new drug application causing difficulties for both manufacturers and the users of these excipients. This work also encourages formulation researchers to think outside-the-box. There really is a need for a more rational design/use of polymer matrix excipients for drug formulation via HME and IM. The polymers from yesterday are not satisfactory enough to deal with today's problems. To this end, the use of thermoplastic polyurethanes is especially promising. They allow the production of a high drug loaded formulation, thereby diminishing

the amount of excipient needed and creating a major advantage for the patient's compliance and the environment.

Nevertheless, a few topics can be identified for future investigation/are subject for improvement:

- There exist thermoplastic polyurethanes (TPUR) that are hydrophilic and water swellable. Evaluating those types of polyurethanes (PU) via HME/IM would be interesting.
- Using other high dosed BCS class I API's in combination with TPUR.
- The evaluation of different types of TPUR via HME/IM: TPUR are available in various molecular weights, different types (polyester, polyether, polycarbonates, *etc.*) of SS, different SS lengths, and variable SS/HS ratios which makes them attractive candidates to alter drug release performances based on polymer composition.
- Thermoplastic polyurethanes (TPUR) are often available in pellet-form. Finding processing steps to produce TPUR in powder form would be beneficial.
- An investigation on how to produce the used formulation on a more industrial scale (upscaling).
- Evaluating the use of polyurethanes for vaginal/rectal use would be interesting as these routes of administration are subjected to less regulatory obligations.
- Polyurethanes are in this work evaluated via HME and IM. Processing the PU via other manufacturing techniques (melt granulating, direct compression) would increase the amount of possible applications. Preliminary tests evidenced that melt granulating PU could also lead to high drug load

formulation, which upon direct compression can result in very rigid tablets. Possible applications can be found in the field of drug abuse (e.g. crushing rilatin and taking it sublingual or snorting it to increase its potency).

- An evaluation of the type of polymers that can be used on a micro-molding device. Miniaturized drug delivery systems are especially interesting for patients with a daily pill burden.
- Polymers are widely used for various applications in all types of industry. Researchers should reach out and learn from those other domains in order to use that knowledge in the field of pharmaceutical technology. The problem is often that manufacturers of novel excipients only disclose their sensitive information (e.g. molecular structure, specific additives) in confidentiality. This makes the formulation research and the physicochemically characterization difficult as the researcher is unaware of all the 'ingredients' in the polymer. A more close collaboration with the industry would be beneficial to create trust, recognition and find mutual beneficial projects. To this end, the research valorization would increase and it would create more transparency resulting possibly in a more positive public opinion about governmental sponsored research.

SUMMARY

Hot melt extrusion (HME) is an established process that has been used for almost a century. The combination with injection molding (IM) enables the processing of materials with high dimensional precision. These techniques rely on obtaining a homogeneous system via a substantial energy input, provided by elevated temperature, high shear force, and pressure. Despite the extensive research being conducted today, the number of marketed products manufactured via HME and/or IM as processing technique has been disappointing.

The objective of this doctoral thesis was, therefore, to evaluate the use of polymethacrylates, quaternized polymethacrylates, modified polymethacrylates, polyoxazolines and polyurethanes for the development of immediate and sustained release formulations via HME/IM. Modifications were made on pharmaceutically approved polymers and two non-conventional polymers were evaluated with the goal of expanding the range of polymers currently used for HME/IM.

Chapter 1 investigated a polymethacrylate polymer, Eudragit® E PO, as drug delivery matrix for immediate release purposes. A formulation IBP/EudrE 30/70 (wt.%) was processed via hot melt extrusion and injection molding, and subsequently physicochemically characterized. The release profile, however, was pH-dependent (only immediate release in acidic environments up to pH 3). The aim was to create a pH-independent release formulation

via the quaternization of the polymer (i.e. protonating the polymer's amine function) or via the creation of a low pH microenvironment during dissolution with the aid of dicarboxylic acids (succinic, glutaric and adipic acid). Both resulted in a pH-independent (up to pH5)

immediate release formulation. However, the presence of a positively charged polymer induced stability issues (recrystallization of API) and the formulations containing dicarboxylic acids were classified as mechanically unstable. Hence, further research is needed to obtain a pH-independent immediate release formulation via hot melt extrusion and injection molding.

In **chapter 2** several Eudragit E PO (n-butyl-, dimethylaminoethyl-, methyl-methacrylate-terpolymer) analogues were synthesized via free radical polymerization. These polymers were processed via hot melt extrusion and injection molding, and evaluated as carriers to produce immediate release solid solution tablets. Three chemical modifications increased the glass transition temperature of the polymer: (a) substitution of n-butyl by t-butyl groups, (b) reduction of the dimethylaminoethyl methacrylate (DMAEMA) content and (c) incorporation of a bulky isobornyl repeating unit. These structural modifications revealed the possibility to increase the mechanical stability of the tablets via altering the polymer's Tg without influencing the drug release characteristics and glassy solid solution forming properties. The presence of DMAEMA units proved to be crucial with respect to API/polymer interaction (essential in creating glassy solid solutions) and drug release characteristics. Moreover, these chemical modifications accentuate the need for a more rational design of (methacrylate) polymer matrix excipients for drug formulation via hot melt extrusion and injection molding.

Chapter 3 evaluated poly(2-ethyl-2-oxazoline)s (PEtOx) as matrix excipient for the production of oral solid dosage forms via hot melt extrusion (HME) followed by injection molding (IM). Using metoprolol tartrate as good water-soluble model drug, it was demonstrated that the drug release can be delayed via HME/IM, with the release rate controlled by the molecular weight of the PEtOx. Using fenofibrate as lipophilic model drug, the drug dissolution rate was strongly enhanced. Hence, PEtOx polymers are a potentially interesting class of polymers to serve as matrix for controlled released formulations. Future research should, therefore, focus on the toxicity analysis of PEtOx, improving the release characteristics of the formulation (e.g. by investigating the influence of longer alkyl side chains or higher PEtOx MW), elaborating stability studies and the development of pharmaceutical grade PEtOx.

Chapter 4 evaluated thermoplastic polyurethanes (TPUR) as matrix excipients for the production of oral solid dosage forms via hot melt extrusion (HME) in combination with injection molding (IM). It was demonstrated that TPURs enabled the production of solid dispersions – crystalline API in a crystalline carrier – at an extrusion temperature below the drug melting temperature (Tm) with a drug content up to 65% (wt.%). The release of metoprolol tartrate (MPT) was controlled over 24h, whereas a complete release of diprophylline (Dyph) was only possible in combination with a drug release modifier: polyethylene glycol 4000 (PEG 4000) or Tween 80. No burst release nor a change in tablet size and geometry was detected for any of the formulations after dissolution testing. The total matrix porosity increased gradually upon drug release. Oral administration of TPUR did not affect the GI ecosystem (pH, bacterial count, short chain fatty acids), monitored via the Simulator of the Human Intestinal Microbial Ecosystem (SHIME). The high drug load

(65wt.%) in combination with (*in vitro* and *in vivo*) controlled release capacity of the formulations, is noteworthy in the field of formulations produced via HME/IM.

In **chapter 5**, the influence of several dicarboxylic acids on the release characteristics of polyurethane tablets with a high drug load was investigated. Mixtures of diprophylline (Dyph) and thermoplastic polyurethane (TPUR) (ratio: 50/50, 65/35 and 75/25 wt.%) were hot-melt extruded (HME) and injection molded (IM) with the addition of 1, 2.5, 5 and 10wt.% dicarboxylic acid as release modifier. Incorporating malonic, succinic, maleic and glutaric acid in the TPUR matrices enhanced drug release, in function of the dicarboxylic acid concentration in the formulation. No correlation was found between the water solubility, melting point, logP and pKa of the acids and their drug release modifying capacity. Succinic and maleic acid had the highest drug release modifying capacity which was linked to more intense molecular interactions with Dyph. A structural fit between the primary and secondary alcohol of Dyph and both carboxylic groups of the acids was at the origin of this enhanced interaction.

It can be concluded that this doctoral thesis accentuated the need for a more rational design of polymer matrix excipients for drug formulation via hot melt extrusion and injection molding

SAMENVATTING

Hot melt extrusie (HME) is een productieproces die nu bijna een eeuw wordt gehanteerd. De combinatie met spuitgieten (injection molding, IM) maakt het mogelijk om finale producten te bekomen met een hoge dimensionele nauwkeurigheid. Beide technieken resulteren in een homogeen systeem met behulp van een aanzienlijke energietoevoer, geleverd door de verhoogde temperatuur, de hoge afschuifkracht en druk. Ondanks verschillende studies en uitgebreid onderzoek de afgelopen jaren, is het aantal geproduceerde producten via HME en IM teleurstellend. Vandaar het doel van dit proefschrift om het gebruik van polymethacrylaten, gekwaterniseerde polymethacrylaten, structureel gewijzigde polymethacrylaten, polyoxazolines en polyurethanen te evalueren in de ontwikkeling van formulaties die zorgen voor een onmiddellijke en aanhoudende vrijstelling van het geneesmiddel. Wijzigingen werden aangebracht op farmaceutisch goedgekeurde polymeren en twee niet-conventionele polymeren werden geëvalueerd met als doel het aantal polymeren die momenteel gebruikt worden voor HME/IM uit te breiden.

Hoofdstuk 1 evalueerde een polymethacrylaat polymeer, Eudragit® E PO, als drug delivery matrix voor onmiddellijke geneesmiddel vrijstelling. De formulatie IBP/EudrE 30/70 (wt.%) werd verwerkt via hot melt extrusie en spuitgieten, en vervolgens fysicochemisch gekarakteriseerd. Het vrijstellingsprofiel was echter pH-afhankelijk (alleen onmiddellijke geneesmiddelvrijstelling in zure milieus tot pH 3). Het doel was om een pH-onafhankelijke

geneesmiddelvrijstelling te bekomen via de kwaternisatie van het polymeer (protonatie van de aminefunctie van het polymeer) of via de creatie van een micromilieu met lage pH met behulp van dicarbonzuren (barnsteenzuur, glutaarzuur en adipinezuur). Beide modificaties resulteerden in een pH-onafhankelijke (tot pH 5) onmiddellijke geneesmiddelvrijstelling. De aanwezigheid van een positief geladen polymeer induceerde echter stabiliteitsproblemen (herkristallisatie van API) en de formulaties die dicarbonzuren bevatten werden als mechanisch onstabiel beschouwd. Verder onderzoek is daarom nodig om een pH-onafhankelijke onmiddellijke geneesmiddelvrijstelling te bekomen via hot melt extrusie en spuitgieten.

In **hoofdstuk 2** werden verschillende Eudragit E PO analogen (n-butyl-, dimethylaminoethyl-, methyl-methacrylaat-terpolymer) gesynthetiseerd via vrije radicale polymerisatie. Deze polymeren werden verwerkt via hot melt extrusie en spuitgieten en geëvalueerd als carriers om tabletten te produceren die zorgden voor een onmiddellijke geneesmiddelenvrijgave. Drie chemische modificaties werden doorgevoerd om de glastransitietemperatuur (Tg) van het polymeer te verhogen: (a) de substitutie van de n-butyl groepen door t-butyl groepen, (b) een afname van het aantal dimethylaminoethyl methacrylaat (DMAEMA) groepen en (c) de toevoeging van extra component die sterische hinder induceert: isobornyl methacrylaat. Deze structurele modificaties toonden aan dat het mogelijk was om de mechanische stabiliteit van de tabletten te verhogen door de Tg van het polymeer te verhogen, zonder de geneesmiddelenvrijstelling te wijzigen. Het aantal DMAEMA eenheden in het polymeer bleek cruciaal te zijn met betrekking tot de geneesmiddel-polymeer interactie (essentieel om een ‘glassy solid solution’ te creëren) en de vrijstelling van het geneesmiddel. Bovendien accentueerden deze chemische modificaties de nood aan een meer

rationeel design van (methacrylaat)polymeren als carriërs voor verwerking via hot melt extrusie en spuitgieten.

Hoofdstuk 3 evalueerde poly(2-ethyl-2-oxazoline)s (PEtOx) als matrix excipienten voor de productie van een orale vaste formulatie via hot melt extrusie (HME), gevolgd door spuitgieten (injection molding, IM). Door metoprolol tartrate te gebruiken als hydrofiel geneesmiddel, werd aangetoond dat de geneesmiddelvrijstellingssnelheid kan vertraagd worden via HME/IM met controle van de vrijstellingssnelheid via het moleculair gewicht van de PEtOx. Ook werd aangetoond dat, door fenofibraat te gebruiken als lipofiel geneesmiddel, de geneesmiddelvrijstellingssnelheid fors toenam. Bijgevolg vormen PEtOx polymeren een potentieel interessante klasse bruikbaar in farmaceutische formulaties. Verder onderzoek is echter noodzakelijk met de focus op: (a) toxiciteit analyse van de PEtOx polymeren, (b) verdere optimalisatie van de vrijstellingsprofielen, door bijvoorbeeld de invloed van PEtOx met langere alkyl zijketens te onderzoeken, (c) stabiliteitsstudies en (d) de ontwikkeling van een farmaceutisch veilig PEtOx polymeer.

Hoofdstuk 4 analyseerde de thermoplastische polyurethanen (TPUR) als matrix excipienten voor de productie van orale vaste formulaties via hot melt extrusie (HME) en spuitgieten (injection molding, IM). Er werd aangetoond dat de TPURs het toelieten om solid dispersions - kristallijn geneesmiddel in een kristallijne carrier - te produceren met een hoge geneesmiddelbelading (65wt.%) bij een procestemperatuur die lager ligt dan de smelttemperatuur van het geneesmiddel. De vrijstelling van metoprolol tartrate (MPT) werd gecontroleerd gedurende een periode van 24u, terwijl een volledige vrijstelling van diprophylline (Dyph) slechts mogelijk was met behulp van een additief: polyethylene glycol

4000 (PEG 4000) of Tween 80. Er werd geen burst vrijstelling of verandering in tablet geometrie en grootte gedetecteerd bij de tabletten na dissolutie. De totale matrix porositeit steeg gradueel in functie van het vrijgestelde geneesmiddel. Orale toediening van TPUR beïnvloedde het gastrointestinaal (GI) ecosysteem (pH, aantal bacteriën, korte vetzuren) niet, wat werd aangetoond door middel van SHIME (Simulator of the Human Intestional Microbial Ecosystem). De hoge geneesmiddelbelading (65wt.%) in combinatie met de (*in vitro* en *in vivo*) gecontroleerde vrijstellingsprofielen is noemenswaardig voor formulaties geproduceerd door middel van HME/IM.

In **hoofdstuk 5** werd de invloed van verschillende dicarbonzuren op de vrijstellingsprofielen van polyurethane tabletten met een hoge geneesmiddelbelading onderzocht. Formulaties van diprophylline (Dyph) en thermoplastisch polyurethane (TPUR) (ratio: 50/50, 65/35 and 75/25 wt.%) werden geproduceerd via hot melt extrusive (HME) en spuitgieten (injection molding, IM). Aan deze formulaties werd vervolgens 1, 2.5, 5 en 10wt% dicarbonzuur toegevoegd om hun invloed op het vrijstellingsprofiel te onderzoeken. Door de incorporatie van malonzuur, barnsteenzuur, maleïnezuur en glutaarzuur in de TPUR matrices, nam de geneesmiddelvrijstellingssnelheid toe in functie van de concentratie van dicarbonzuur. Er werd geen correlatie vastgesteld tussen de wateroplosbaarheid, smeltpunt, logP en Pka van de dicarbonzuren en hun invloed op de geneesmiddelvrijstelling. Barnsteenzuur en maleïnezuur hadden de grootste invloed op het vrijstellingsprofiel van de formulatie. Een meer intense interactie tussen beide zuren en diprophylline lag aan de oorzaak hiervan door een structurele ‘fit’ tussen het primaire en de secundair alcohol van diprophylline en beide carbonzure groepen van de zuren.

Er kan worden geconcludeerd dat deze doctoraatsthesis de nood naar een meer rationeel design van polymeer matrix excipienten beklemtoont om verbeterde formulaties te produceren via hot melt extrusie en spuitgieten.

PERSONAL DATA

Name:	Claeys Bart
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Date of birth:	21/05/1987
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EDUCATION

2010- 2014	**PhD researcher**, development and manufacturing of new medicine formulations at the laboratory of Pharmaceutical Technology Ghent University (Belgium)
2011-2013	**Master of Science in Business Economics**, graduated cum laude, Ghent University (Belgium) Masterthesis: Entrepreneurial research scientists and their strive for business familiarity
2008-2010	**Master in Pharmaceutical Sciences (Drug development)**, graduated magna cum laude, Ghent University (Belgium) Masterthesis: Determination of surface energy using different approaches.
2005-2008	**Bachelor in Pharmaceutical Sciences** Ghent University (Belgium)

EXPERIENCE (WORK)

2014- Present	**Medical Scientific Liaison Infectious Disease** Janssen, Pharmaceutical Companies of Johnson and Johnson
2010- 2014	**PhD Researcher** Ghent University (Belgium)

- Patent filed: Polyurethanes as oral drug delivery platform (PCT, P2013/039-polyurethanes)
- Research project: Non-conventional polymers as matrix excipients for hot melt extruded oral-release formulations;
- Teaching assistant of practical courses "Galenica" (3rd bachelor Pharmaceutical Sciences and 2nd Master Pharmaceutical sciences);
- Guidance of research thesis (1st Master Pharmaceutical sciences and Master of Industrial Pharmacy)
- Development and manufacturing of new medicine formulations.

2010	**Pharmacist** Omnia Apotheek, Koksijde (Belgium)

2009 **Erasmus Program**
Institut für Pharmazeutische Technologie und Biopharmazie, Düsseldorf (Germany)

- Research project: Determination of surface energy using different approaches.

2008 **Summer Internship**
Departments of Pharmaceutics, Pharmaceutical Chemistry and Bioengineering, Salt Lake City, Utah (USA)

- Research project: Silk-elastinlike polymers for spatial and temoral control of virus mediated solid tumor gene therapy.

PERSONAL SKILLS

Mother tongue: Dutch

Other languages

	UNDERSTANDING		SPEAKING		WRITING
	Listening	Reading	Spoken interaction	Spoken production	
French	B2	B2	B1	B1	B1
German	B1	B1	B1	B1	A2
Practical German, Level 2, Universitairy Center for Language Education, Ghent, Belgium					
English	C1	C1	C1	C1	C1
Advanced academic English: Writing skilss, Ghent University, Ghent, Belgium					

Common European Framework for Languages:
Levels: A1/A2: Basic user – B1/B2: Independent user – C1/C2: Proficient user

Communication skills

- Collaborative skills and team player:
  professional: during PhD collaboration with different laboratories; social: member of student union (GFK), member student union (Doopcomité GFK);
- Social and good ability to adapt to multicultural environments gained through my work experience abroad (Düsseldorf, Germany and Salt Lake City, Utah, USA).

Organisational/ managerial skills

- Organize planning of experiments;
- Guidance of masterthesis (Master Pharmaceutical Science and Industrial Pharmacy);
- Responsible for a team of 5 lifeguards, 07/2009, Koksijde, Belgium;
- Lifeguard during the summer at the Belgian coast, 2004-2008, Koksijde, Belgium;
- Team captain of basketballteam Racing Bruges.

Additional Information

- Played in the basketball team of Racing Bruges (1994-2007);
- Now practicing triathlon.

International Publications

B. Claeys, A. Vervaeck, C. Vervaet, J.P. Remon, R. Hoogenboom, B.G. De Geest, Poly (2-ethyl-2-oxazoline) as Matrix Excipient for Drug Formulation by Hot Melt Extrusion and Injection Molding, Macromolecular Rapid Communications, 33 (2012) 1701-1707.

B. Claeys, R.D. Coen, B.G. De Geest, V.R. de la Rosa, R. Hoogenboom, R. Carleer, P. Adriaensens, J.P. Remon, C. Vervaet, Structural modifications of polymethacrylates: Impact on thermal behavior and release characteristics of glassy solid solutions, European Journal of Pharmaceutics and Biopharmaceutics, 85 (2013) 1206-1214.

B. Claeys, S. De Bruyn, L. Hansen, T. De Beer, J.P. Remon, C. Vervaet, Structural modifications of polymethacrylates: Release characteristics of polyurethane tablets containing dicarboxylic acids as release modifiers - a case study with diprophylline, International Journal of Pharmaceutics, 477 (2014) 244-250.

B. Claeys, A. Vervaeck, X.K.D. Hillewaere, S. Possemiers, L. Hansen, T. De Beer, J.P. Remon, C. Vervaet, Thermoplastic Polyurethanes for the Manufacturing of Highly Dosed Oral Sustained Release Matrices via Hot Melt Extrusion and Injection Molding, European Journal of Pharmaceutics and Biopharmaceutics, 90 (2015) 44-52.

B. Claeys, S. De Bruyn, B.G. De Geest, J.P. Remon, C. Vervaet, The creation of a pH-independent immediate release polymethacrylate formulation via quaternization of the polymer or the addition of acids – An observational study, Drug Development and Industrial Pharmacy, accepted for publication.

A. Almeida, **B. Claeys**, J.P Remon, C. Vervaet, Hot-Melt-Extrusion: Pharmaceutical Applications: Hot-melt Extrusion Developments in the Pharmaceutical Industry. In D. Douroumis (Ed.) (2012), A. John Wiley & Sons, Ltd., Publication, UK, ISBN: 9780470711187

Oral Presentations

A new class of polymers to produce high-dosed sustained release oral drug formulations via hot melt extrusion: polyurethanes, 9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lisbon, Portugal, April 2014;

Polyurethanes: a new class of polymers to produce high-dosed sustained release oral drug formulations via hot melt extrusion, Meeting of the Belgian-Dutch Biopharmaceutical Society, Ghent, Belgium, December 2013;

Poster Presentations

Structural modifications of polymethacrylates: the impact on the thermal behavior and release characteristics of solid solutions, AAPS annual meeting and exposition, Chicago, USA, October 2012;

Structural modifications of polymethacrylates: the impact on their thermal behavior and release characteristics – A case study with ibuprofen, APV, Istanbul, March 2012;

Attended workshop, lectures

- Master in Business Economics, 2013-2011
- Meeting of the Belgian-Dutch Biopharmaceutical Society, Ghent, Belgium, 2013
- 17th Forum of Pharmaceutical Sciences, Spa, Belgium, 2013;
- Annual PSSRC Symposium, Lille, France, 2013;
- Closing conference of the INTERREG "2 Mers Seas Zeeën" IDEA project, Villeneuve-d'Ascq, France, 2013;
- AAPS annual meeting and exposition, Chicago, USA, 2012;
- 8th World meeting on Pharmaceutics and Biopharmaceutics and Pharmaceutical Technology, Istanbul, Turkey, 2012;
- Controlled Release Workshop, Darmstadt, Germany, 2011;
- INTERREG "2 Mers Seas Zeeën" IDEA meeting, Cambridge, UK, 2011;

Training

- Introductory Statistics, Ghent, Belgium, 2013;
- Introduction to Polyurethanes, Smithers Rapra, Shrewsbury, England, 2013;
- Fundamentals of HPLC, Etten-Leur, The Netherlands, 2011;
- Advanced academic English: Writing skills, Ghent, Belgium, 2011;
- Project Management, University of Ghent, Belgium, 2010.