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PARTIALLY HYDROLYZED POLYVINYL ALCOHOL AS FUNCTIONAL EXCIPIENT IN ORAL SOLID DOSAGE FORMS PREPARED VIA EXTRUSION

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LIST OF ABBREVIATIONS

ADI	acceptable daily intake
ANOVA	analysis of variance
API	active pharmaceutical ingredient
AR	aspect ratio
AUC	area under the curve
BCS	biopharmaceutical classification system
CEL	celecoxib
cGMP	current good manufacturing practice
C_{max}	peak plasma concentration
CTC	compressibility, tabletability and compactability
DH	degree of hydrolysis
DP	degree of polymerization
DOE	design of experiment
DSC	differential scanning calorimetry
DTGS	deuterated triglycerine sulfate
DVS	dynamic vapor sorption
EFSA	European food safety authority
ESI	electrospray ionization
FDA	food and drug administration
FDC	fixed-dose combination
FT-IR	Fourier transform infrared
GPC	gel permeation chromatography

HCT	hydrochlorothiazide
HME	hot-melt extrusion
HPLC	high performance liquid chromatography
HPMCAS	hydroxypropylmethylcellulose acetaat succinaat
IAR	immediately after ejection axial recovery
KF	Karl Fischer
LOD	loss on drying
MCC	microcrystalline cellulose
MDSC	modulated differential scanning calorimetry
MRM	multiple reaction mode
MS	mass spectrometry
NCE	new chemical entities
NMR	nuclear magnetic resonance
NOAEL	no observed adverse effect level
PPI	polymeric precipitation inhibitor
PSD	particle size distribution
PVA	polyvinyl alcohol
R&D	research and development
RH	relative humidity
SEM	scanning electron microscopy
$\mathbf{t_{max}}$	time to reach peak plasma concentration
$\mathbf{T_c}$	crystallization temperature
$\mathbf{T_g}$	glass transition temperature
TGA	thermogravimetric analysis
$\mathbf{T_m}$	melting temperature
XRD	X-ray diffraction

OUTLINE AND OBJECTIVES

For decades' innovation in the pharmaceutical industry has focused on the introduction of novel drug compounds, and little attention was paid to the optimization of the manufacturing process of drug products. Based on the (mis)belief that regulatory demands could only be met using batch technologies and that the introduction of novel manufacturing techniques would delay market introduction of a new product (e.g. reduce the time span during which the research and development (R&D) costs of innovator drugs can be recovered), batch processing was the golden standard for most unit operations in pharmaceutical manufacturing. Furthermore, post-approval changes to the manufacturing process were discouraged, because notification of the competent authorities is required, as each modification could have an impact on drug product quality, safety and efficacy. As a result, pharmaceutical manufacturing of drug product has in most cases been synonymous to batch processing despite its inherent advantages, such as more batch-to-batch variability, higher costs and difficult scale-up. However, over the past 10 years there has been a slow shift in the pharmaceutical industry from batch towards continuous processing of drug products, stimulated by initiatives of the regulatory authorities to increase process understanding as well as the need to improve efficiency and reduce costs (materials, energy, waste) of pharmaceutical drug products due to lower profit margins (given the pressure of generics as well as lower health budgets). Therefore, the introduction of continuous manufacturing techniques, which are already well established in e.g. the food and chemical industry, has been intensively studied by academic institutions in collaboration with manufacturers of brand and generic drug products, focusing on several essential unit operations (e.g. powder feeding, blending, dry/wet granulation, compaction, coating) as well as on the incorporation of process analyzers in a continuous manufacturing line.

Within the framework of continuous processing, extrusion (e.g. a process that converts raw materials into a product of uniform shape and density by forcing it through a die under controlled conditions) can be applied for different applications, depending on the manufacturing conditions: hot-melt extrusion (HME) and extrusion-spheronization.

Applying heat during HME in combination with thermoplastic materials embeds a drug in a polymeric matrix, thus modifying the drug release pattern depending on the physicochemical properties of the polymeric phase: hydrophilic polymers (e.g. polyvinylpyrrolidone, polyethylene oxide) are used to prepare immediate release formulations and allow to improve the release rate and bioavailability of a poorly water-soluble drug via the formation of solid solutions or solid dispersions. In contrast, embedding the drug in hydrophobic polymers (e.g. ethylene vinyl acetate, polyurethanes) yields sustained release matrices. While HME relies on heat to soften the formulation, a liquid (e.g. water) is added prior to extrusion in the extrusion/spheronization process, thus forming a wet plastic mass that can be extruded through narrow die openings. The resulting cylindrical extrudates are shaped into dense spherical particles during spheronization, and after drying the spherical particles (e.g. pellets) are formulated into a multiparticulate sustained release drug delivery system by applying a release-controlling polymeric membrane on the surface of the pellets.

Next to the introduction of continuous manufacturing as an innovation tool in the pharmaceutical industry, formulators are also constantly looking for novel excipients which provide specific properties to a formulation and which (preferably) can be used for a broad range of drug products. Although partially hydrolyzed polyvinyl alcohol (PVA), a water-soluble synthetic polymer, is already used as viscosity-enhancing or stabilizing agent in liquid dosage forms, its use as pharmaceutical excipient in oral solid dosage forms has been limited. Since several grades of PVA are available (e.g. different degree of hydrolysis (DH) and polymerization, which influences the water solubility and viscosity of the polymer), this polymer can be a potential excipient in different applications of solid dosage forms and/or to impart a broad range of characteristics to a specific drug product.

Based on the introduction of continuous manufacturing techniques in the pharmaceutical industry (extrusion being one of them) and the search for novel pharmaceutical excipients, this study evaluates the use of partially hydrolyzed PVA in solid dosage forms processed via HME and via extrusion/spheronization.

The aim of the first part of this project is to evaluate partially hydrolyzed PVA with different DH as carrier in HME, focusing on its effect on processing of poorly water-soluble drugs. As tableting of a hot-melt extruded polymeric formulation is a possible downstream processing

technique in order to formulate the final dosage forms, this research was extended to evaluate the impact of HME on the mechanical properties of PVA-based tablets.

The second part of this project evaluated partially hydrolyzed PVA as pelletisation aid in extrusion/spheronization, aiming to formulate pellets with a high drug load (> 70%), evaluating pellets with a single drug as well as pellets containing two drugs (e.g. suitable for combination therapy using a single drug product). Pellet properties such as size, sphericity, aspect ratio (AR) and *in vitro* drug release were measured.

Introduction

PARTIALLY HYDROLYZED POLYVINYL ALCOHOL AS FUNCTIONAL EXCIPIENT IN ORAL SOLID DOSAGE FORMS PREPARED VIA EXTRUSION

1 EXTRUSION

In the first part of this introduction, extrusion is reviewed as a continuous manufacturing process that converts raw materials into a product of uniform shape and density by forcing it through a die under controlled conditions (feed rate, temperature and pressure). This technique can be broadly classified in hot-melt extrusion (HME) (molten system) and extrusion/spheronization (wet plastic system). The process and equipment used in both systems are summarized below.

1.1 Hot-melt extrusion

HME is a process, whereby heat is used to control the viscosity of raw materials in order to flow through the barrel and the die of the extruder. This technique has received much attention in the pharmaceutical industry, as it is a viable method to obtain different drug delivery systems including granules, pellets, films and tablets, and offers distinct advantages compared to other conventional techniques such as a solvent-free process (environmental friendly), the ability to be operated as a continuous process, reduced costs (limited number processing steps) (Crowley et al., 2007). HME can be used for several applications, mainly depending on the physicochemical properties of the thermoplastic polymer. Hydrophilic polymers (e.g. polyvinylpyrrolidone, polyethylene oxide) are used to improve the bioavailability of poorly soluble drugs (Biopharmaceutical Classification System (BCS) Class II or IV) via the formation of solid solutions or solid dispersions, whereby the drug is (molecularly) dispersed in the polymer (Miller et al., 2007). Hydrophobic polymers (e.g. ethylene vinyl acetate, polyurethanes) are used to obtain matrix systems. In a matrix system the drug is homogenously distributed in the carrier, and drug release occurs via drug diffusion (pores, swelling matrix) (Repka et al., 2004). Recently, HME has also been evaluated as potentially powerful tool for taste masking (Maniruzzaman et al., 2014). However, besides several advantages of HME, a major drawback is related to the thermal processing of material, which limits its applicability for thermo-sensitive drugs.

HME is generally divided into four sections: (a) feeding of the extruder, (b) conveying of mass and entry into the die, (c) flow through the die and (d) exit from the die and downstream processing.

1.1.1 Feeders

In HME, the formulation (e.g. drug and thermoplastic polymer) can either be premixed or individual gauged inside the barrel of the extruder. The feeding equipment used is required to ensure a constant and accurate material throughput, however this is rather challenging, mainly at low feed rates, as fluctuations in flow rates could occur due to powder cohesion or electrostatic charging. Two types of feeders are available: volumetric and gravimetric feeding systems. Volumetric feeders use a screw conveyor running at a constant speed to discharge powder from a hopper at a constant rate (e.g. L/min), but require free-flowing powders in order to guarantee a consistent filling of the screws and are not able to adjust for variations in density. In the pharmaceutical industry, gravimetric or loss-in-weight feeders are preferred, where a volumetric feeder is associated with a weighing platform (load cell) to control the discharge of powder from a hopper at a constant weight per unit time (e.g. kg/min). A feedback control system monitors the actual feed rate and compensates, if necessary, for variations in density (Figure 1). Different mechanism could be used to dispense powders such as vibration, belt and rotary valve, yet screw-driven types are the most common (Repka et al., 2013).

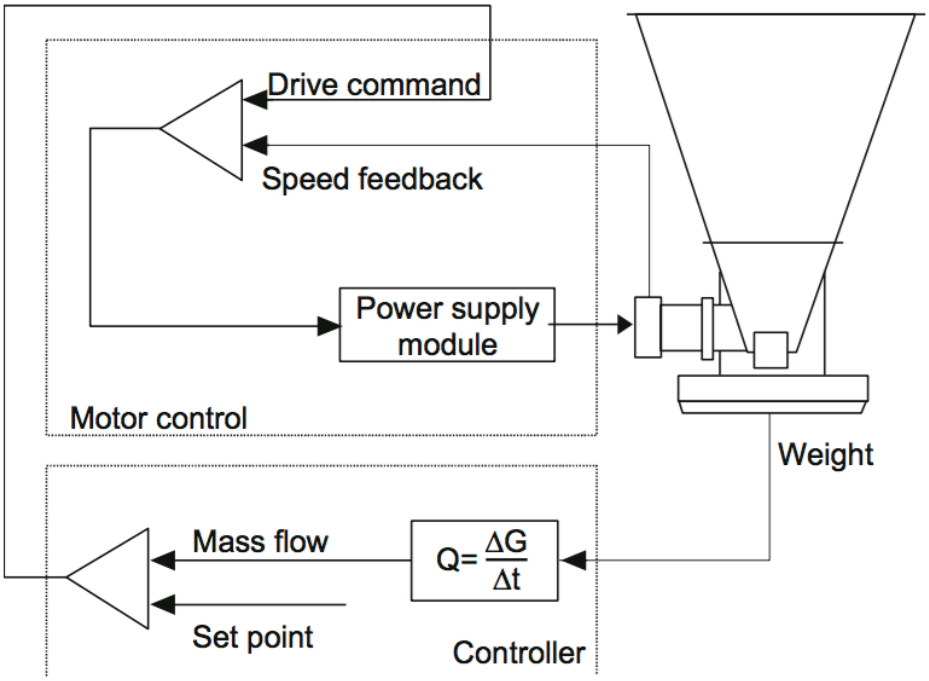

Figure 1. Loss-in-weight feeder with feedback control (Repka et al., 2013).

1.1.2 Extruders

The extruder consists of a temperature-controlled barrel, which either contains a piston (ram extruder) or screw(s) (screw extruder). The principle of a ram extruder is based on a ram or piston which pushes the molten mass through the die. This technique is mainly applied for precision extrusion of highly valuable materials that are only available in small amounts. The main disadvantages of ram extrusion are poor temperature uniformity and low homogeneity in comparison with screw extrusion. Two types of screw extruders are available: single- and twin-screw extruders, which both provide more shear stress and intensive mixing. Twin-screw extruders are preferred compared to single-screw extruders, because of easier material feed, more intensive mixing, shorter residence time and less tendency to overheat the materials (Swarbrick, 2006). The different types of twin-screw extruders can be broadly classified as counter-rotating (opposite direction) or co-rotating (same direction) and as intermeshing or non-intermeshing, whereby the latter has screws where the flights of one screw do not protrude into the channel of the other screw (Rauwendaal, 1981). In the pharmaceutical industry, co-rotating intermeshing extruders are preferred, because counter-rotating extruders induce air entrapment, higher pressures and have a low maximum screw

speed/output. In contrast, co-rotating extruders have screws which wipe each other clean (self-wiping) and can be operated at higher screw speeds/output for materials that are not thermo-sensitive (Whelan and Dunning, 1994).

The design of the screws has an important influence on extrusion efficiency (e.g. shear rate, residence time). Different screw elements can be fitted on a shaft, such as conveying elements or kneading elements. Conveying elements transport material through the barrel, while kneading elements ensure distributive or dispersive mixing of the drug inside the carrier. In general, three zones are identified inside the barrel, (a) feeding zone, (b) compression or melting zone and (c) metering zone (Liu et al., 2001). In the feeding zone material is transported from the feeder into the melting zone, whereby the throughput is mainly determined by the feed rate and not by the extruder screw speed (starve-fed). Subsequently, the material enters the melting or compression zone, which contains kneading and conveying elements to ensure proper melting and mixing (either distributive or dispersive) of the material. In the end, the plastic melt flows into the metering zone, the pressure increases and the plastic melt is pumped through the die (Figure 2) (Giles et al., 2004).

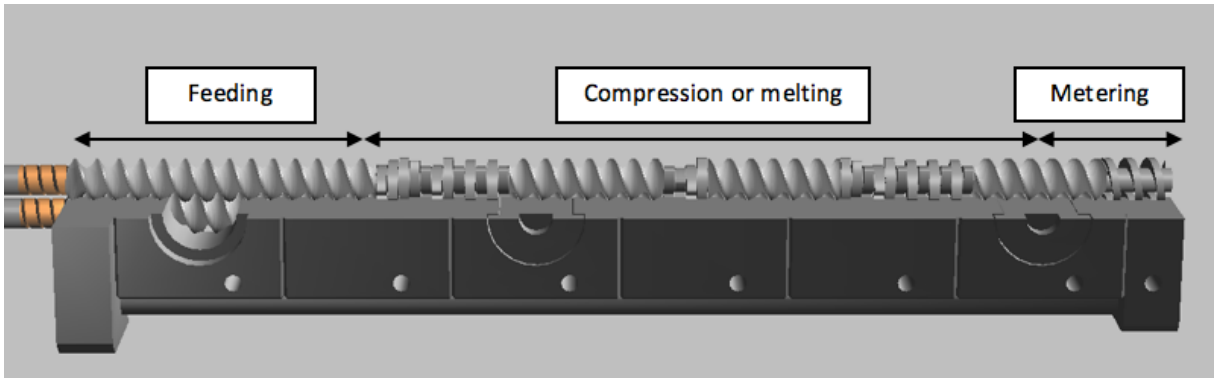

Figure 2. Barrel of a twin-screw extruder with three zones: feeding zone, compression or melting zone and metering zone (Obtained from Thermo Fisher Scientific®).

Hot-melt extruders are available in different sizes (e.g. lab, pilot or production scale) characterized by the length-to-diameter ratio (L/D) and diameter of the screws. In case of extruders used in pharmaceutical applications L/D values typically range between 20 to 40:1

(mm). Screw diameter depends on the extruder size, e.g. 11, 16 and 24 mm for a lab-scale, pilot-scale and production-scale extruder, respectively. The L/D and screw diameter are important parameters during scale-up of an extrusion process (Maniruzzaman et al., 2012). Additionally, some smaller lab-scale extruders (e.g. Haake MiniLab Micro Compounder) are available, however these extruders contain two conical screws to build up pressure inside the barrel instead of two parallel screws and can therefore not be used for scale-up experiments. They are mainly used for compounding smaller amounts of material (e.g. 5-10 g).

1.1.3 Die

The die is the assembly at the end of the extruder that shapes the plastic melt. Several extrusion dies are available, which can be classified based upon their shape. In the pharmaceutical industry, flat and annular dies are most common. Flat dies convert the circular shape of the extrusion chamber into a thin, wide sheet and are used to produce films for applications in transdermal, transmucosal and transungual delivery (e.g. bio-adhesive films) (Repka and McGinity, 2001). Annular extrusion dies yield cylindrical extrudates and are used to manufacture medical devices (e.g. tubing) (Guo and Stehr, 2001). An ideal extrusion die should meet three requirements (a) provide a uniform flow rate, (b) maintain a uniform melt temperature and (c) produce a melt with the same shear history (Whelan and Dunning, 1994). These requirements are important during die design, for example, in order to obtain films with equal thickness for a flat die, different path lengths have to be taken into account (shorter path length in the middle of the die versus the sides). Otherwise films would be thicker in the middle than at the sides, therefore the sides of a flat die are enlarged versus the middle (Figure 3) (Ghebre-Selassie and Martin, 2003).

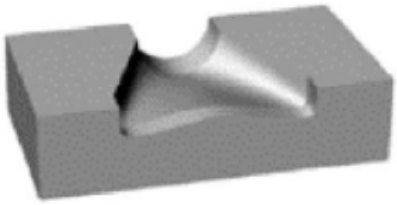

Figure 3. Flat die corrected to obtain films with uniform thickness (Ghebre-Selassie and Martin, 2003).

As the extrudate leaves the die, some 'post-extrusion effects' could appear related to the viscoelastic behavior of the polymer, such as die swell and sharkskin. Die swell is a phenomenon, which occurs if a polymer flows through an orifice or tube and the diameter/thickness of the extrudate is increased compared to the diameter/thickness of the die. This effect is mainly attributed to the elastic portion of the viscoelastic behavior of the polymer. In HME, polymers are subjected to high shear forces and are stretched into the flow direction before exiting the die. As the extrudate exits the die, polymer molecules relax and recoil causing die swell (Miller, 1963). Sharkskin is a surface effect which causes transverse ridges and/or rough surface. This effect is explained by different velocity in the extrusion die. The melt near the border of the die moves very slowly compared to other areas in the melt, and these high stresses on the free surface can cause cracks (Denn, 2001). Both effects can be diminished or avoided if shear forces are reduced (e.g. higher temperature, lower flow rates).

1.1.4 Downstream processing

Usually the extrudate is cooled down, milled and filled into capsules or tablets. Nowadays, due to an increased interest in continuous manufacturing, a lot of research is performed on downstream equipment, whereby the extrudate is immediately transformed into its final dosage form (e.g. films, tablets, pellets). The development of this equipment is rather challenging in the pharmaceutical industry, as dimensions need to be precise in order to deliver the right dose to the patients. Many downstream equipment originates from the plastic industry, and therefore research is required to evaluate their use in pharmaceutical

applications. Several publications have already evaluated different downstream processes to obtain solid dosage forms and are listed below.

Injection molding refers to a process, whereby a melt is injected into the mold under controlled conditions (pressure and temperature). The melt cools down inside the cavity and solidifies. In the end, the mold is opened and the final drug product is removed. Injection molding is already successfully applied for the production of different conventional and innovative drug delivery systems. Claeys et al. used injection molding to produce sustained release matrix tablets of thermoplastic polyurethanes (Claeys et al., 2015). Rathbone et al. produced an intravaginal insert from the biodegradable polyester poly(ϵ-caprolactone) via injection molding (Rathbone et al., 2002).

Calendering uses two counter rotating rolls with multiple cavities shaped as half the form of the desired dosage form. The extrudate is placed between those rolls, and during rotation cavities are filled with melt, the melt cools down and solidifies, subsequently the dosage form is liberated during rotation. Recently, Vynckier et al. evaluated calendering for continuous production of fixed-dose combinations (FDC) containing a plasticized ethylcellulose core with metoprolol tartrate and a plasticized polyethylene oxide coat with hydrochlorothiazide (HCT). Calendering was identified as a promising technique, however further optimization is essential when a rate-controlling polymer coat is applied via co-extrusion as the coat thickness was not uniform (Vynckier et al., 2015).

Pelletizer/Spheronizer is a process, whereby the extrudate is cut in small cylindrical pellets by a rotary knife with several cutting faces. Afterwards, those pellets are placed inside a spheronizer to obtain spherical pellets. Young et al. produced controlled-release pellets of theophylline and an experimental acrylic polymer (Eudragit® Preparation 4135F) by HME followed by spheronization (Young et al., 2002).

Chill rolls are mainly used to control the cooling rate of the extrudate. They are designed as two rolls with a defined gap in between and rotate at a defined roll speed. The temperature of the rolls can be adjusted to obtain a specific cooling rate. A controlled cooling rate is important for amorphous and semi-crystalline materials, as recrystallization due to uncontrolled cooling could have a major influence on drug release (Swarbrick, 2006). Mididoddi et al. extruded hydroxypropylcellulose and/or polyethylene oxide films containing

ketoconazole, and used chill rolls to quench-cool the film, which prevented recrystallization (solid solution) (Mididoddi and Repka, 2007).

1.2 Extrusion/spheronization

In an extrusion/spheronization process, a liquid is added to the formulation to obtain a plastic mass, which can be extruded through the narrow die openings of the extruder. The cylindrical extrudates are then transformed into spherical pellets by spheronization on a rotating friction plate. After drying, those spherical pellets are used to formulate multiparticulate drug delivery systems, which can be classified into reservoir and matrix systems. In reservoir systems, a drug-containing core is surrounded by a (generally polymeric) membrane, which controls drug release rate, whereby in matrix systems, a drug is embedded in a solid carrier material, which controls the release rate of the drug (Siepmann et al., 2006).

Multiple unit dosage forms (e.g. pellets) are becoming more important due to their distinct pharmacological and technological advantages compared to single unit dosage forms (e.g. tablets), such as (Dukic-Ott et al., 2009):

- Reduced variability of drug plasma profiles due to a generally short gastro-intestinal residence time
- Minimal local irritation in the gastrointestinal tract
- Less risk of dose dumping
- Flexibility to blend pellets with different drug components, incompatible drugs or drugs with different release profile
- Flexibility to produce dosage forms with different strength without process or formulation changes
- Low dusting
- Easy to coat and to fill into capsules

However, there are some drawbacks encountered with extrusion/spheronization, including the addition of water during wet granulation, which limits the use of drugs sensitive to hydrolysis. Additionally, it is still a challenge to predict from the physicochemical properties

of a drug, whether satisfactory pellets will be formed, due to numerous influencing factors (Fitzpatrick et al., 2006; Tomer et al., 2002).

Extrusion/spheronization is a multistep process involving four different unit operations, (a) wet granulation, (b) extrusion, (c) spheronization and (d) drying.

1.2.1 Granulation

The first objective in an extrusion/spheronization process is to obtain a wet mass with sufficient plasticity and deformation characteristics, by mixing excipient(s), drug(s) and a liquid binder. This process, called wet granulation, can be performed in a wide range of equipment, classified as batch- or continuous granulators. Typically, wet granulation was a batch-wise process operated in a planetary mixer, whereby a mixer blade simultaneously rotates about two axes, the symmetry axis of the bowl and the axis of the mixer blade. Other types of batch granulators are sigma blade mixers or high-shear mixers. Nowadays, continuous granulators are available, including instant granulators (e.g. Nica M6 Instant Mixer) and twin-screw extruders. Instant granulators contain a rapidly rotating disk onto which powder and liquid binder are fed. In contrast, screw extruders blend dry powders and a liquid binder by the action of the screws (Vervaet and Remon, 2005). Depending on the type of equipment different kinds of strain and shear forces are applied onto the wet powder mass, which affect the properties during the subsequent unit operations, such as extrusion and spheronization. Vervaet et al. reported that large amounts of energy induced by high-shear granulation, for example, could influence extrusion behavior of the wet powder mass, because energy is partly transformed to heat, which increases temperature and causes evaporation of the granulation liquid (Vervaet et al., 1995). Schmidt et al. showed that granulation methods (planetary mixer, high-shear mixer and twin-screw extruder) applying different shear forces affected pellet properties, as granulators with high-shear forces required a higher water content for successful pelletisation (Schmidt and Kleinebudde, 1999). Recently, Bryan et al. confirmed the influence of mixer type (planetary mixer or miniature screw extruder) on the powder wet mass during extrusion/spheronization. The high-shear mixer yielded smaller pellets, possibly due to a higher maximum shear strain rate during mixing, whereby smaller microcrystalline cellulose (MCC) particles are formed, which bound water more tightly inside the MCC network.

Therefore, less water was available at the surface for agglomeration and plasticity of the paste was reduced (Bryan et al., 2015). These findings emphasize two critical variables during wet granulation: the amount of granulation liquid added to the formulation and the uniform distribution of the fluid through the powder mass.

1.2.2 Extrusion

During extrusion, the wet powder mass is transformed into rod shaped particles with uniform diameter. The extrusion process could be performed in three different types of extruders, classified based on their feeder mechanism: screw-feed, gravity-feed or piston-feed extruders. Screw-feed extruders contain one or two screws that transport and compress the wet powder mass towards the die or screen. The screen, a perforated endplate, contains multiple perforations holes, which can have different dimensions (thickness and diameter). Various screw-feed extruders are available depending on the extrusion endplate: axial, dome and radial extruders. Axial and dome screw extruders transport the wet powder mass in the same direction of the screws towards a flat or dome-shaped screen, respectively. The extrusion screen of radial screw-feed extruders is placed around the screws and thus the plastic mass is extruded perpendicular to the screws. As axial and dome screw extruders contain an extrusion endplate, higher forces are generated onto the wet powder mass, resulting in a higher density and more heat production compared to radial screw extruders. Gravity-feed extruders transport the material by gravitational forces and are subdivided in cylinder, gear and radial extruders. The cylinder-type extruders contain two rolls, a solid roll and a perforated roll, whereby the solid roll forces the material through the perforated roll. In gear-type extruders, material is forced between two gears with perforations at the base of the gear (between the teeth of the gear). Axial-type extruders wipe the wet powder mass against the screen via rotating blades. The main difference with screw-feed extruders is that gravity-feed extruders do not compress the plastic mass before extrusion. As last, piston-feed or ram extruders push the material through a die or screen with a piston or ram and is mainly applied for research purposes (Trivedi et al., 2007).

Water content is a critical parameter, as this influences plasticity and cohesiveness of the wet powder mass. However, during extrusion, higher stresses are applied and water movements

or liquid phase migration could occur, which influences extrudate/pellet quality. Extensive water movement may lead to shark-skinned extrudates (too dry), or result in extrudates with different water content, which turn into spheres of different sizes. Liquid phase migration was determined by a competition between (a) the time needed to pass through the extruder (which depends on production rate and geometry) and (b) the rate of percolation of the liquid through the matrix (which depends on applied pressure and permeability of the solid matrix) (Rough et al., 2002). Therefore, several papers investigated factors influencing water movements during ram-extrusion. The extrusion force-ram displacement profiles obtained during extrusion of wet masses were divided in three stages: (a) compression, where materials are consolidated under slight pressure, (b) steady state, where pressure is required to maintain constant flow and (c) forced flow, where higher pressures are required to maintain flow (Figure 4) (Parikh, 2009).

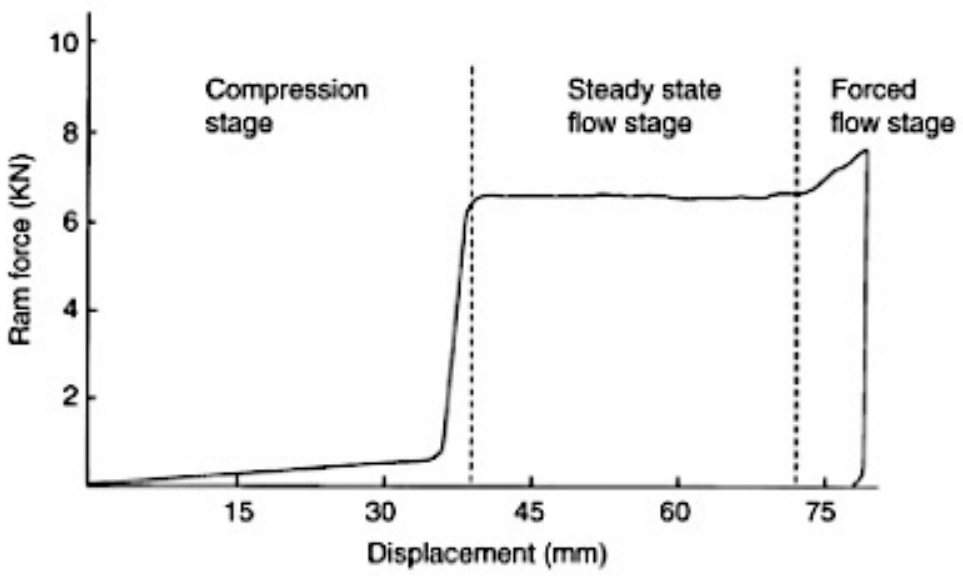

Figure 4. An extrusion force-displacement profile for a microcrystalline cellulose-lactose water mixture showing three stages of extrusion on a ram extruder: compression, steady state flow, and forced flow (Parikh, 2009).

Rough et al. examined the influence of initial water content, extruder speed and die geometry on liquid phase migration. This study showed that the length of compression stage and steady state pressure were reduced at higher initial bulk water content, due to the fact that lower

forces are required to extrude the soft paste, which reduced the potential of liquid migration. Furthermore, slower extrusion speeds produced extrusion force-displacement curves with a delayed onset of extrusion (longer compression stage) and lower extrusion pressure, which steadily increased due to water loss. This was explained because at slower extrusion speed water could move more freely through the voids between the particles (higher porosity), and a less uniform water content was obtained inside the extrudates. Die length hardly affected final water content, however smaller die diameters raised the pressure inside the extruder, which induced water separation (Rough et al., 2000; Tomer and Newton, 1999). Zhang et al. compared the performance of two laboratory-scale extruders, a multi-holed die ram extruder and a roller screen extruder. The latter produced smaller pellets and had a wider size distribution, which was attributed to differences in density of the extrudates. Lower densities were obtained for roller screen extruders and thus resulted in a lower cohesive strength (Zhang et al., 2013).

1.2.3 Spheronization

The cylindrical extrudates are subsequently shaped by rotational and frictional forces into spherical pellets. This process, called spheronization or marumerization, is performed in a bowl with fixed sidewalls and a rapidly rotating bottom plate or friction plate. The friction plate has a grooved surface with different geometries to increase frictional forces: cross-hatched, radial and striated edges (Figure 5). The cross-hatched pattern is preferred, as independent of plate diameter, the pattern (groove size and spacing) remains the same. In contrast with radial and striated edges, the groove size and spacing changes with increasing diameter, which is more challenging during manufacturing and scaling-up.

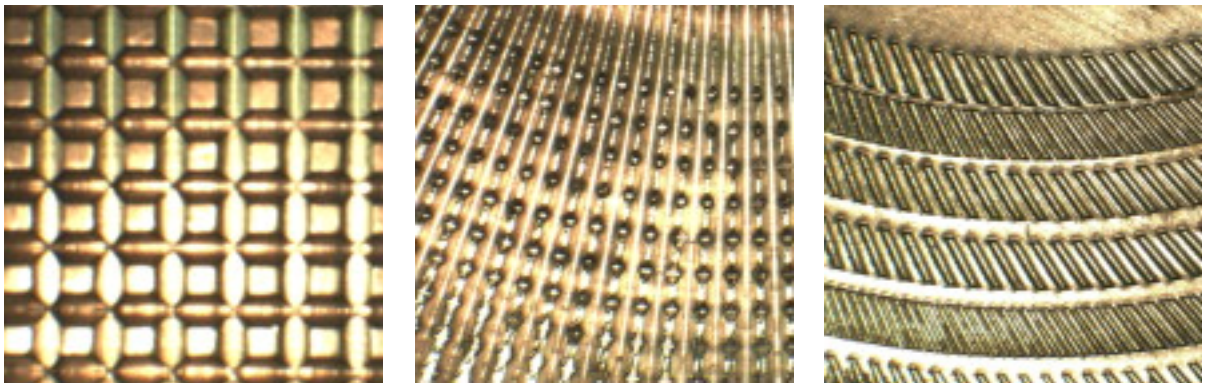

Figure 5. Friction plate designs: cross-hatch pattern (left), radial pattern (middle) and striated edge pattern (right) (Michie et al., 2012).

The extrudates used for spheronization should meet specific requirements, in order to produce pellets with required properties (e.g. uniform pellet size, spherical shape, low friability, smooth surface). Fielden et al. summarized requirements for successful spheronization of the cylindrical extrudate (Swarbrick, 2006):

- The extrudate should possess sufficient mechanical strength when wet, yet it must be brittle enough to be broken into smaller lengths in the spheronizer, but not be so friable that it disintegrates completely.
- The extrudate must be plastic to enable the cylindrical rods to be rolled into spheres by the action of the friction plate.
- The extrudate must be non-adhesive to itself in order that each spherical pellet remains discrete throughout the process.

Two pelletisation mechanisms have been described. Rowe et al. characterized spheronization by breakage of the extrudates in smaller rod-shaped particles with a length equal to their diameter, followed by plastic deformation due to collision of particles with other particles, friction plate or sidewalls of the bowl (Rowe, 1985). Baert et al. suggested another mechanism, whereby the smaller rod-shaped particles are twisted, resulting in two distinct parts with a flat side and a round side. The frictional and rotational forces during spheronization process fold the edges of the flat side together like a flower forming the cavity observed in certain pellets (Baert et al., 1993). Recently, Koester et al. further developed these

pelletisation mechanism, as it was observed that fine particles attach to the surface of larger fragments in regions subjected to lower mechanical stress (e.g. waist region) (Koester and Thommes, 2010) (Figure 6).

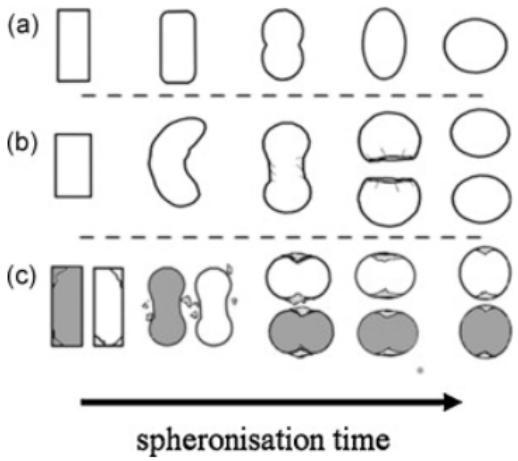

Figure 6. Pellet-forming mechanism according to (a) Rowe, (b) Baert and (c) Koester (Koester et al., 2012).

The most critical process parameters during spheronization that influence the yield and quality of the pellets, are the design of the grooves, spheronizer load, rotational speed of the friction plate and residence time in the spheronizer. Michie et al. evaluated the influence of friction plate design (cross-hatch, radial, striated edge pattern) and spheronizer load on the pellet properties obtained by extrusion/spheronization. The sieve fraction containing most pellets was identical for the three friction plates (1-1.4 mm), but the highest yield was obtained with the striated edge pattern. However, pellets produced with a striated edge friction plate had a reduced mechanical strength, which might be a drawback. The spheronizer load had an impact on pellet size and mechanical strength of the pellets. A higher spheronizer load resulted in a larger median pellet size and mechanically stronger pellets, because particles will move slower and thus endure a less impact with the sidewalls (Michie et al., 2012). Newton et al. investigated the influence of spheronizer speed and residence time onto pellet properties. Higher spheronizer speeds break cylindrical extrudates into shorter length particles, and less time is required to obtain spherical pellets. However, when spheronization speed was too high, particles were smaller and less spherical (Newton et al., 1995). Podczeck et al. investigated the influence of standing time of the extrudate and rotation speed of the spheronizer plate on the properties of the pellets. The latter was defined as the linear

peripheral velocity of the friction plate, which depends on the rotational speed and diameter of the friction plate. This parameter is important during scale-up, because by adjusting spheronizer speed from a small friction plate diameter to a larger plate diameter, the linear peripheral velocity could be kept the same. This study showed that pellets with higher density and surface tensile strength were obtained, when extrudates were immediately spheronized or higher linear peripheral velocities were used. This phenomenon was linked to the penetration of water at longer standing times which increased swelling of MCC fibers, resulting in a more porous structure. Additionally, a higher linear peripheral velocity increased the forces onto the extrudates, resulting in more adhesion between the particles (Podczeck and Newton, 2014).

1.2.4 Drying

In the final step, spherical pellets are dried using different drying techniques (static or dynamic), including open atmosphere, desiccation, conventional hot air oven or tray-drying, fluidized bed, microwave-drying and freeze drying. The influence of the drying technique onto pellet properties have been investigated in different studies. Bashaiwoldu et al. evaluated the influence of four different drying techniques (freeze-drying, fluid-bed drying, hot air oven and desiccation with silicagel) on the structural and mechanical properties of pellets. The main difference between pellets obtained with various drying techniques was observed in the pellet porosity. Freeze drying and fluidized bed resulted in pellets with high porosity, as shrinkage of MCC pellets was suppressed due to rapid water evaporation. In contrast, water evaporation was slower during desiccation and hot air oven, thus more time was allowed for MCC to shrink, resulting in smaller pellets with a lower porosity. The higher porosity of these pellets is correlated with a reduction of their mechanical strength, which can be a disadvantage during further processing (e.g. coating) (Bashaiwoldu et al., 2004). Bataille et al. compared oven and microwave drying, whereby pellets dried with microwaves resulted in a higher porosity compared to oven dried pellets (Bataille et al., 1993). This result corresponded with the data of a previous study, as microwave drying is much faster than oven drying.

1.2.5 Downstream processing

Multiparticulates (e.g. pellets) can be easily filled into hard-gelatin capsules or sachets to obtain the final dosage form. However, pellets are frequently used to apply a cosmetic (e.g. identification), protective (e.g. physical stability) or functional coat (e.g. controlled release).

Coating can be performed using different coating equipment: conventional coating pan, perforated coating pan or fluidized bed. The coating pan rotates on an inclined axis and is designed without or with perforations for conventional and perforated coating, respectively. Perforated coating pans are able to dry solid dosage forms faster, as air could be forced through the perforations of the pan. However, smaller dosage forms (e.g. pellets) are generally coated in fluidized bed coaters (e.g. Würster system), whereby air is used to fluidize the pellets inside the container, and polymeric solutions or dispersions are applied using a top, bottom or tangential spray-atomization technique. Wesdyk et al. evaluated the influence of different spray modes (top, bottom or tangential) on film thickness of pellets with various sizes. Bottom spray atomization showed to be largely depended on pellet size, as larger pellets obtained a thicker film compared to smaller pellets, possibly due to a different fluidization pattern and/or velocity. Pellets coated via top spray atomization had variable thicknesses independent of pellet size, and is therefore mainly used for taste or odor masking. In contrast, tangential spray atomization yielded pellets with uniform coating (Wesdyk et al., 1993).

Recently, *tableting* of pellets has received more attention, because production rate for capsules is low compared to tablets, and thus costs are higher. Moreover, capsules cannot be divided to obtain smaller dosage forms. However, compaction of pellets is challenging as tablets should disintegrate rapidly and drug release may not be affected during compaction. Furthermore, the coat of reservoir-type coated pellets should be able to withstand compaction pressure, so that no ruptures could occur (Abdul et al., 2010).

2 POLYVINYL ALCOHOL

In the second part of this introduction, the synthesis of partially hydrolyzed polyvinyl alcohol (PVA), the functional excipient evaluated in this project, is reviewed, because this determines molecular weight and residual content of acetyl groups. These properties are important depending the application, as they mainly control water solubility and viscosity.

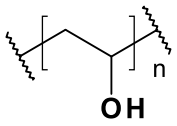

Figure 7. Structure of polyvinyl alcohol polymer.

2.1 Synthesis

As the monomer of PVA, vinyl alcohol, is chemically unstable, due to the keto-enol tautomeric equilibrium which lies on the acetaldehyde side (Figure 8) (Milosavljevic and Thomas, 2001; Wu and Lien, 1996), PVA is derived from vinyl acetate.

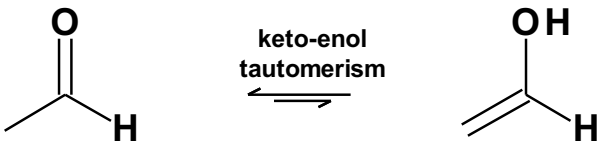

Figure 8. Keto-enol tautomerisation of acetaldehyde and vinyl alcohol.

Vinyl acetate is mainly produced by ethylene gas-phase process, whereby ethylene reacts exothermically with acetic acid and oxygen on solid bed catalysts, yielding vinyl acetate and water. Catalysts used in industry contain palladium and alkali metal salts on carrier materials (Figure 9) (Roscher, 2000; Samanos et al., 1971).

Figure 9. Synthesis of vinyl acetate.

Polyvinyl acetate, used for production of PVA, is formed by polymerization of vinyl acetate using free radical polymerization, whereby a hydrogen atom is removed from the acetate group. The growing radical is transferred to the vinyl acetate monomer, which then reinitiates the polymerization (Figure 10) (Brydson, 2013).

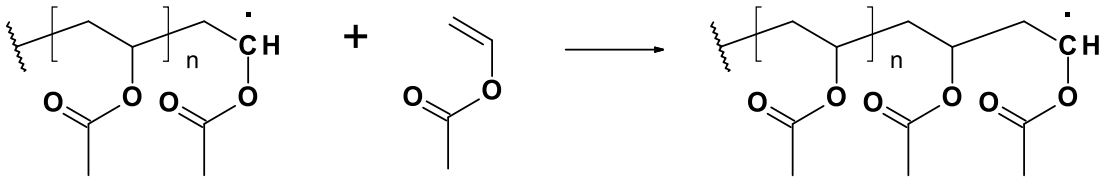

Figure 10. Polymerization of polyvinyl acetate.

Afterwards, PVA is prepared by transesterification (alcoholysis) of polyvinyl acetate in the presence of sodium hydroxide, which act as catalyst (Figure 11) (Dimonie et al., 1978).

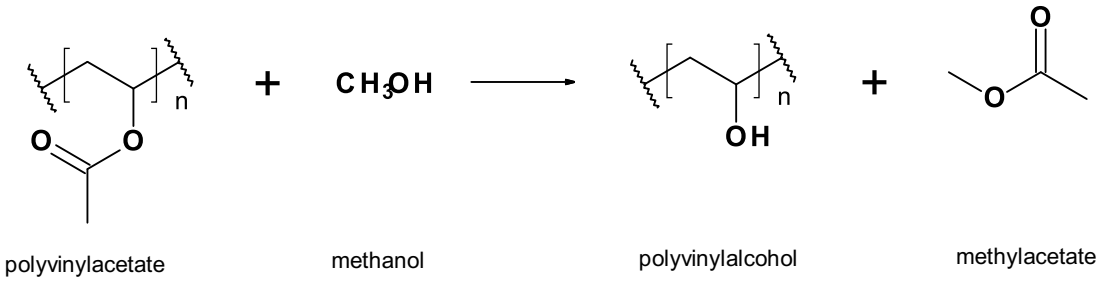

Figure 11. Synthesis of polyvinyl alcohol.

2.2 Properties

Physical properties of PVA mainly depend on molecular weight and residual content of acetyl groups (degree of hydrolysis, DH). The molecular weight of PVA is controlled by the degree of polymerization (DP) of vinyl acetate and influences the viscosity of aqueous solutions, whereas hydrolysis conditions (catalyst concentration, reaction temperature and reaction time) control DH (Erbil, 2000). As DH and DP can be controlled separately, a wide range of PVA are available for different applications. The principal grades of PVA produced are classified as fully hydrolyzed (97.5% - 99.5% DH) and partially hydrolyzed (80 – 97.5% DH), whereby different DP are available (based on the viscosity of a 4% aqueous solution of PVA at 20°C), such as a low viscosity group (DP 500 - 5 mPa.s), a medium viscosity group (DP 1700 - 20-30 mPa.s), and a high viscosity group (DP 2000 - 40-50 mPa.s).

2.2.1 Solubility in water

The solubility of PVA mainly depends on DH and to a lesser extent on DP. The many hydroxyl groups available in fully hydrolyzed PVA cause a high affinity to water, however strong hydrogen bonding between intra- and intermolecular hydroxyl groups greatly impedes its aqueous solubility. In contrast, partially hydrolyzed PVA contains residual acetate groups which weaken intra- and intermolecular hydrogen bonding between hydroxyl groups, increasing water solubility. Figure 12 shows the solubility of PVA as function of DH at temperatures of 20 and 40°C (Hassan and Peppas, 2000). Small amounts of residual acetate groups (e.g. 2-3 mol%) cause a significant change in the solubility at 40°C: fully hydrolyzed PVA (e.g. DH 99%) is only slightly soluble, while partially hydrolyzed PVA (e.g. < DH 96%) is almost completely soluble. At a dissolution temperature of 20°C, partially hydrolyzed PVA DH < 88% is almost completely soluble, however a sharp reduction of solubility was observed at higher DH.

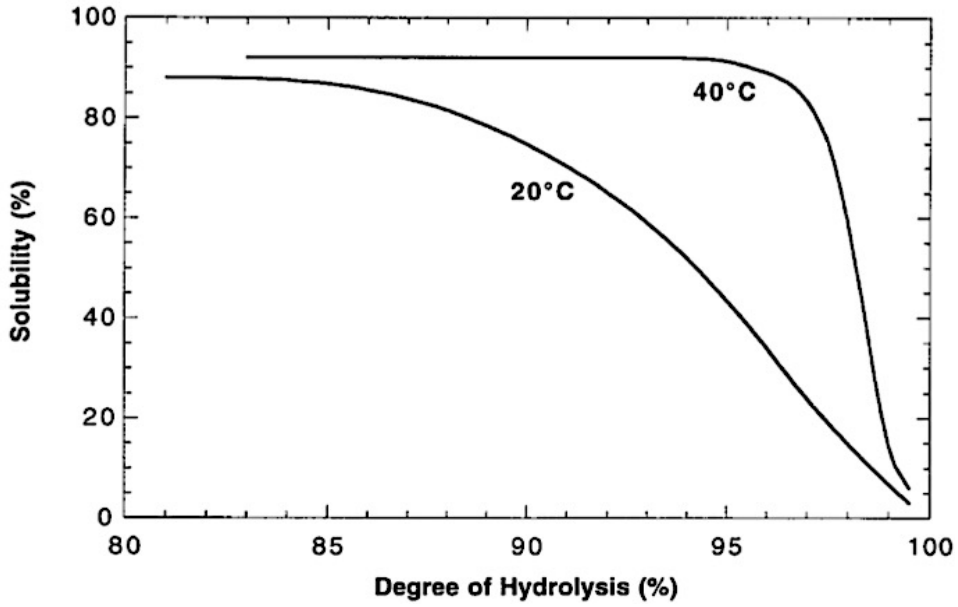

Figure 12. Solubility in water as function of degree of hydrolysis at dissolution temperatures of 20°C and 40°C (number average molecular weight of $\overline{M}_n$ = 77000 g/mol) (Hassan and Peppas, 2000).

Furthermore, solubility of PVA also depends on DP. Figure 13 shows the solubility of PVA with different DH (80–98%) and DP (500–2400) against dissolution temperature. DP mainly influences fully hydrolyzed PVA (e.g. 98%), PVA with a lower DP having a higher solubility. The solubility of partially hydrolyzed PVA was relatively independent of DP. Additionally, figure 13 shows the solubility of PVA with DH 80%, which has a much higher solubility at lower temperatures compared to PVA DH 88%, however solubility sharply decreases at higher temperatures and results in phase separation of the aqueous solution (Finch, 1992). This phenomenon, known as the 'cloud point', observed for PVA-grades with DH lower than 83%, is linked to the disruption of hydrogen bonding between PVA and water molecules at elevated temperatures. In addition, the higher content of residual acetate groups formed associates (micelles) (Aladjoff et al., 1982). The temperature at which phase separation occurred was lower for polymers with more hydrophobic acetate groups in their structure (Briscoe et al., 2000).

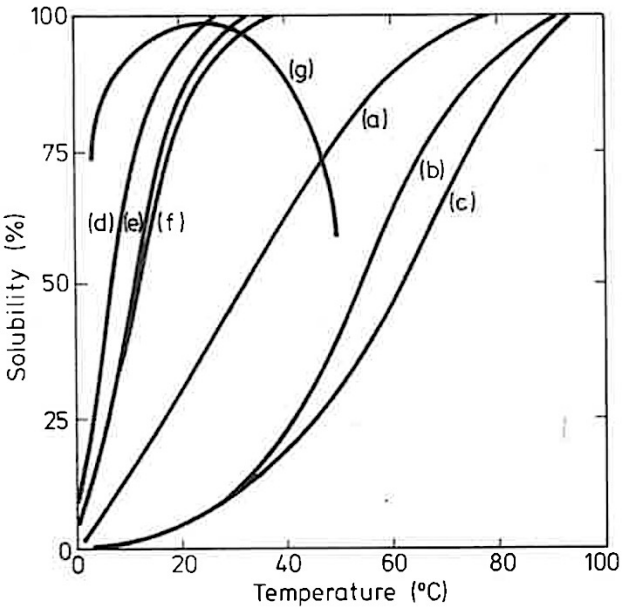

Figure 13. Solubility of polyvinyl alcohol with different degree of hydrolysis (DH 98-99% (a,b,c); DH 87-89 (d,e,f); DH 78-81% (g)) and degree of polymerization (DP 500-600 (a,d); DP 1700-1800 (b,e); DP 2000-2100 (g); DP 2400-2500 (c,f)) in relation to solution temperature (Finch, 1992).

Further studies revealed that the solubility of PVA could change after heat treatment. Kenney et al. studied crystallinity of PVA in relation with water resistance and observed that after heat treatment crystallinity of PVA increased and thus water solubility decreased (Kenney and Willcock.Gw, 1966). However, this phenomenon depended on DH: a major effect was noticed with fully hydrolyzed PVA, but with partially hydrolyzed PVA no change in solubility was seen, unless an extreme heat treatment of 180°C for 1h was performed (Finch, 1992).

2.2.2 Viscosity

The viscosity of aqueous PVA solutions depends on DP, DH, concentration and temperature. Fully hydrolyzed PVA solution have a higher apparent viscosity compared to partially hydrolyzed PVA, however viscosity increases again for solution containing PVA with lower DH (e.g. < 72.5%) (Figure 14). Fully hydrolyzed PVA must be heated above 80°C before complete dissolution in water, as thermal energy is required to disrupt intra- and intermolecular

hydrogen bonding. Upon cooling, intra- and intermolecular hydrogen bonding are able to re-form, and thus gradually increase the viscosity of PVA solution.

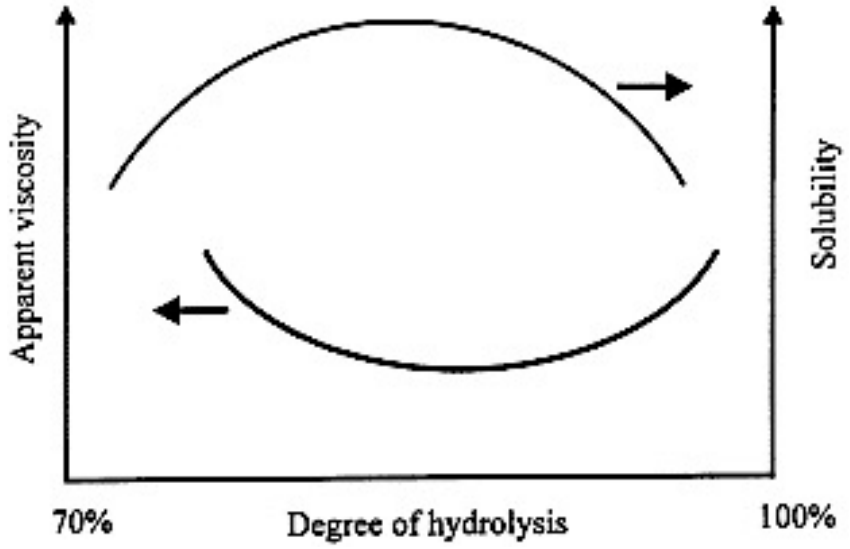

Figure 14. Schematic diagram of the interrelationship between apparent viscosity and degree of hydrolysis, and between solubility and degree of hydrolysis for aqueous polyvinyl alcohol solutions; other conditions are fixed (Briscoe et al., 2000).

Partially hydrolyzed PVA is more readily soluble in water at room temperature and a lower apparent viscosity was observed, due to the presence of residual acetate groups which disrupt inter- and intramolecular hydrogen bonding. However, viscosity of PVA with lower DH (e.g. 72.5%) was higher, as the presence of more hydrophobic acetate groups enhances hydrogen bonding between PVA and water molecules. Therefore, a higher viscosity due to interaction between solute and solvent is anticipated (Briscoe et al., 2000).

2.3 Toxicology

Initially, toxicity of PVA was evaluated for use as an indirect food additive in products which are in contact with food, whereby the US Food and Drug Administration (FDA) approved PVA films for applications where it is in contact with food. Later, oral toxicity was examined by

European Food Safety Authority (EFSA) to estimate the safety of PVA as food additive (e.g. film coating of tablets). Studies have shown that PVA was minimally absorbed after oral administration and had limited acute oral toxicity (LD_{50} 15-20 g/kg). Furthermore, PVA is not mutagenic or clastogenic, and the No Observed Adverse Effect Level (NOAEL) of orally administered PVA in male and female rats was 5000 mg/kg body weight/day in the 90-day dietary study (DeMerlis and Schoneker, 2003). Therefore, the joint FAO/WHO Expert Committee on Food Additives established an Acceptable Daily Intake (ADI) for PVA of 50 mg/kg body weight per day.

2.4 Applications

2.4.1 Non-pharmaceutical applications

PVA polymers, which are available in different DH and DP, can be used in various industries and applications, such as:

In the *textile industry*, PVA polymers are used for the production of the fibre 'Vinylon', which is carried out by wet spinning or dry spinning from aqueous PVA solutions. Different water-soluble and highly water-resistant PVA fibers can be produced depending their application. Water resistant fibers are produced by heat treatment and partial acetalization. The fibers are used in the production of clothes, fishing nets, ropes, … (Sakurada, 1985). In addition, PVA is used in warp sizing, because of its high mechanical strength as a film, which is necessary to prevent abrasion of the yarn during weaving, and ease of desizing, as it is readily soluble in water (Anandjiwala et al., 1995).

In the *adhesives industry*, PVA is used as remoistenable adhesive in post stamps and envelopes. The earliest adhesives were Arabic gum and potato starch derivatives, but they tended to deteriorate by cracking, peeling and yellowing. Later, PVA was used because of its distinct advantages, such as longer lifetime and less sensitive to water absorption (Sharkey, 1987).

In the *paper industry*, PVA is used to improve mechanical properties of paper sheets. Paper consists out of a network of cellulose and non-cellulose fibers (e.g. hemicellulose and lignin),

which are held together by hydrogen bonds. The mechanical strength of paper sheets is improved by dipping sheets in a PVA solution, which increased inter-fiber bonding (Nada et al., 2000; Nada et al., 1996).

In the *packaging industry,* PVA is used, because of its biodegradability and gas barrier properties (e.g. against oxygen and aromas). Two techniques are mainly applied for PVA film production: film casting from viscous water solution and blow extrusion from melts. Blow extrusion, which is most frequently used for packaging films, is a technique whereby an extruded tube is inflated by air to form a large cylinder. PVA films are used in various applications, depending their DH and thus water solubility. Fully hydrolyzed PVA grades are used in food packaging to prevent oxidation, whereas partially hydrolyzed PVA grades are used in packing of hygienic articles or laundry bags (Alexy et al., 2002; Moroi, 1988; Piergiovanni and Limbo, 2015).

Other applications of PVA are emulsion stabilizers in coatings (Budhlall et al., 2003), thickening agents in cosmetics (Guillot et al., 1982) …

2.4.2 Pharmaceutical applications

In the pharmaceutical industry, PVA polymers are mainly used in liquid and semi-solid formulations, such as:

In *artificial tears*, PVA is added to prolong the residence time of the drug within the external eye to prolong drug absorption. Studies have shown that PVA at a concentration of 1.4% does not interfere with corneal wound healing, increases ocular contact time and retains clear vision (Hardberger et al., 1975; Murube et al., 1998). In addition, PVA can be used as stabilizing agent in *emulsions*. Sakai et al. improved stability of latonoprost, which is sensitive to hydrolysis, by formulating latanoprost as ophthalmic lipid emulsion, whereby PVA was added as emulsifier (Sakai et al., 2005).

Cross-linked PVA polymers are used for production of *hydrogels*, which are three-dimensional polymeric networks capable to swell in water or biological fluids without going into dissolution due to the crosslinks. PVA can be cross-linked using chemical agents (e.g. gluteraldehyde,

acetaldehyde) or via physical crosslinking (e.g. due to crystallite formation by repeated freeze-thawing cycles). The latter technique is preferred in pharmaceutical applications, as no toxic agents are used and a higher mechanical strength of cross-linked PVA is obtained. Hydrogels can be used in various applications including: controlled release matrices and bio-adhesives (Hassan and Peppas, 2000). Mandal et al. studied PVA hydrogels, focusing on swellable controlled delivery systems for miconazole nitrate. Therefore, a PVA solution was mixed with miconazole nitrate and cross-linked by freeze-thawing. The number of freeze-thawing cycles did not affect drug release mechanism (Fickian diffusion), however the swelling of PVA hydrogels was reduced with increasing freeze-thawing cycles due to a higher degree of crystallinity (Mandal, 2000). Peppas et al. examined the muco-adhesive characteristics of PVA hydrogels produced by freeze-thawing. Adhesion studies showed that maximum adhesion was reached after two freeze-thawing cycles, and although additional cycles improved stability of the network, the adhesive properties were reduced (Peppas and Mongia, 1997). Hayes et al. evaluated the biomechanical properties of PVA hydrogels as polymeric implants of the knee meniscus. Crosslinking was performed by addition of salts (e.g. sodium sulfate) to aqueous PVA solutions (salting out), followed by freeze-thawing cycles. Studies have shown that higher crosslinking densities were obtained due to the salting out effect of PVA. The mechanical properties of PVA hydrogels were comparable with human meniscus and no acute cytotoxicity was observed (Hayes et al., 2016). Li et al. developed PVA hydrogel nanoparticles for protein/peptide drug delivery. A solution of PVA and bovine serum albumin was homogenized with silicone oil to obtain a water-in-oil emulsion, and was subsequently exposed to several freeze-thawing cycles. The water-in-oil emulsion was conversed into a suspension of PVA hydrogel nanoparticles in silicon oil (Li et al., 1998).

The use of PVA in oral *solid* dosage forms is rather limited. Morita et al. developed a new controlled release system based on the swelling behavior of PVA. The system is a coated tablet with tablet core containing drug, PVA and an agent which controls the swelling of PVA (e.g. salts, such as sodium sulfate, trisodium citrate and sodium chloride). Initially drug release was controlled by the polymer membrane, which contains a water-soluble (e.g. hydroxypropylmethylcellulose) and a water-insoluble polymer (e.g. ethylcellulose). The water-soluble polymer in the core dissolves, forming pores in the membrane. The aqueous medium penetrates through the pores into the tablet core and the swelling-controlling agent

in the core dissolves. This agent delays the swelling of PVA, but gradually diffuses out of the system. Thereafter, PVA starts to swell, whereby the coating of the tablet cracks (Figure 15). After removal of the outer-layer, drug release is controlled by the PVA carrier. Different release patterns (e.g. zero-order, two phase zero-order) could be obtained by varying the swelling controlling agent (type, concentration) and PVA properties (DH, concentration) (Morita et al., 2000).

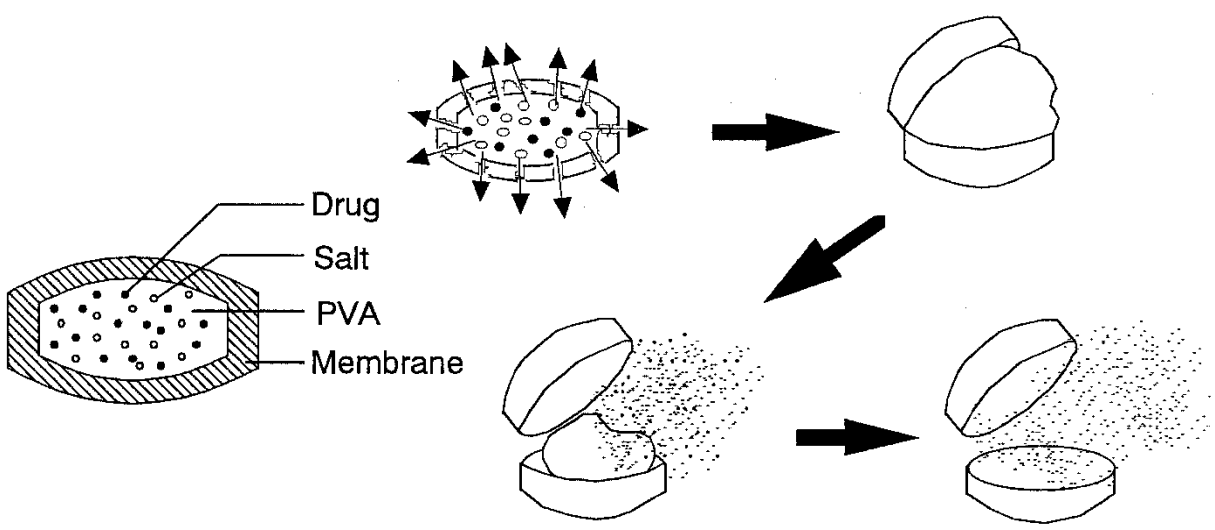

Figure 15. Structure of a swelling controlled release system and schematic diagram of the drug release (Morita et al., 2000).

Recently, PVA-filaments (diameter 1.75-3 mm) were evaluated as drug carrier for 3D printed tablets prepared by fused deposition modelling. This process uses pre-prepared thermoplastic polymer filaments as an 'ink', which are passed through a nozzle under elevated temperature. The software-controlled heated nozzle deposits the semi-liquid material in a layer-by-layer pattern to form a 3D structure. Goyanes et al. manufactured mechanically strong tablets containing fluorescein as model drug. Different controlled-release profiles were obtained by changing the degree of infill percentage, which is the amount of material that was included inside the internal structure of the printed tablet. In example, a tablet with 25% infill, means that 25% of the interior volume of the tablet was occupied by polymer (Goyanes et al., 2014). Skowyra et al. produced prednisolone controlled-release tablets by fused deposition modeling (Skowyra et al., 2015). 3D printing is a promising method to produce patient-tailored

medicines, however drug loading of PVA-filaments was limited (e.g. 0.29% fluorescein or 1.9% prednisolone) and the API incorporated in the filaments must be thermostable.

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1

HOT-MELT EXTRUSION WITH POLYVINYL ALCOHOL FOR ORAL IMMEDIATE RELEASE APPLICATIONS

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ABSTRACT

The purpose of this study was to evaluate polyvinyl alcohol as carrier for oral immediate release dosage forms produced via hot-melt extrusion. Different non-plasticized polyvinyl alcohol grades (LM 25, LM 22, 505 and 4-88, having a degree of hydrolysis of 33-38%, 47-53%, 72-75% and 88%, respectively) and a plasticized polyvinyl alcohol grade (DS0312.2 with a degree of hydrolysis of 73%) were characterized via thermogravimetric analysis, differential scanning calorimetry and X-ray diffraction. Polyvinyl alcohol formulations produced by hot-melt extrusion (2 - 3 mm die) were evaluated in function of degree of hydroxylation, extrusion temperature (100°C - 180°C) and hydrochlorothiazide (used as model drug) concentration (5 – 15%). Higher extrusion temperatures were necessary to extrude polyvinyl alcohol with higher degree of hydrolysis. X-ray diffraction patterns proved the ability of polyvinyl alcohol with higher degree of hydrolysis (> 70%) to solubilize hydrochlorothiazide up to 15%. Drug release was affected by the degree of hydrolysis, dissolution medium and drug load. The highest hydrochlorothiazide release rate was observed from hot-melt extruded polyvinyl alcohol samples with a high degree of hydrolysis. While drug release from extrudates consisting of polyvinyl alcohol with a low degree of hydrolysis was affected by ionic strength, there was no influence of pH and ionic strength on hydrochlorothiazide release from polyvinyl alcohol samples with a higher degree of hydrolysis. Drug release was also influenced by drug loading. Design of experiments was used to evaluate drug release in formulations combining non-plasticized and plasticized polyvinyl alcohol (LM 25, LM 22 or 505 combined with DS0312.2). The influence of extrusion temperature (130-160°C) and the ratio between the polyvinyl alcohol grades (20/60, 40/40, 60/20, %wt/wt) was also evaluated. Drug release was enhanced using polyvinyl alcohol with a higher degree of hydrolysis (72/75% > 47/53% > 33/38%) and from formulations with a larger fraction of plasticized polyvinyl alcohol (DS0312.2). Extrusion temperature had a minor impact on drug release.

KEYWORDS: hot-melt extrusion, polyvinyl alcohol, immediate release, design of experiments

INTRODUCTION

The number of New Chemical Entities (NCE) which are classified as class II or IV drugs according to the Biopharmaceutical Classification System (BCS) have increased over the last decade (Nkansah et al., 2013). Class II and IV drugs are characterized by low oral bioavailability, mainly due to their poor aqueous solubility. Therefore, several techniques to improve solubility of poorly water-soluble drugs have been developed: inclusion complexes in cyclodextrins (Joudieh et al., 2009), self-emulsifying drug delivery systems (Porter et al., 2008), nanocrystals (Junghanns and Muller, 2008; Shegokar and Muller, 2010), coacervation (De Jaeghere et al., 2013), solid dispersions (Janssens and Van den Mooter, 2009). The latter technique (where the drug is (molecularly) dispersed in a carrier) can be prepared via solvent evaporation (Dave et al., 2012), fusion methods (Gorajana et al., 2013), complexation (Taupitz et al., 2013), spray-drying (Jang et al., 2013) or hot-melt extrusion (HME) (Mohammed et al., 2012). For pharmaceutical applications HME is considered an effective process to formulate immediate release dosage forms of poorly water-soluble drugs via the formation of solid dispersions or solutions since it has many advantages over conventional approaches, such as a solvent-free process, the possibility to be operated as continuous process, a limited number of processing steps (Maniruzzaman et al., 2013; Repka et al., 2012). Several water-soluble polymeric carriers suitable for HME applications have been identified (e.g. hydroxypropylcellulose, polyethylene oxide, poly(vinyl pyrrolidone) (Crowley et al., 2007), polyvinyl alcohol (PVA) (Dawson and Stevens, 2002)).

Partially hydrolyzed PVA, used for pharmaceutical applications, is a copolymer of vinyl acetate and vinyl alcohol, and is synthesized by polymerization of vinyl acetate followed by partial hydrolysis (in the presence of aqueous sodium hydroxide) to substitute part of the acetate groups on the polymer backbone by a hydroxyl function. The synthesis conditions (e.g. catalyst concentration, reaction temperature and time) determine the degree of hydrolysis (DH) of PVA (typically the content varies between 30 and 99 mol%) and molecular weight, which both influence the water solubility (Hallensleben, 2000). Its hydrophilic, non-toxic (DeMerlis and Schoneker, 2003), non-carcinogenic and biodegradable (Thellen et al., 2013) properties make partially hydrolyzed PVA an interesting polymer for pharmaceutical applications and it is

currently used as stabilizing agent in emulsions, viscosity-increasing agent in ophthalmic formulations and for lubrication purposes in artificial tears (Rowe et al., 2006).

The purpose of this study was to process different partially hydrolyzed PVA-grades via HME and to evaluate them as carrier for oral immediate-release dosage forms to formulate solid dispersions in order to improve the release rate of poorly water-soluble drugs (using hydrochlorothiazide (HCT) as model drug).

MATERIALS AND METHODS

Materials

Several PVA-grades (obtained from Kuraray, Hattersheim am Main, Germany) with varying DH were evaluated: type LM 25 (33-38% hydrolyzed), type LM 22 (47-53% hydrolyzed), type 505 (72-75% hydrolyzed). In addition, a plasticized PVA grade (type DS0312.2, 73% hydrolyzed, Kuraray, Hattersheim am Main, Germany) and a pharmaceutical PVA grade (type 4-88, 88% hydrolyzed, provided by Merck, Darmstadt, Germany) were included in the study. The LM-grades were end group-modified with carboxylic acid to provide good aqueous dispersibility. HCT (Utag, Amsterdam, Netherlands) was used as model drug.

Hot-melt extrusion and production of mini-tablets

In a first screening study to allow material characterization (extrusion temperature, drug solubility in polymer), PVA with different DH and physical mixtures of HCT/PVA were processed using a co-rotating twin-screw mini-extruder (Haake MiniLab II Micro Compounder, Thermo Electron, Karlsruhe, Germany), operating at a screw speed of 60 rpm and a processing temperature ranging from 130-180°C. The extruder was equipped with a pneumatic feeder, two Archimedes screws and a 2 mm cylindrical die. At room temperature, the extrudates were manually cut, using surgical blades, into mini-tablets of 2 mm length. Based on the results of the initial screening study a number of HCT/PVA mixtures were selected and hot-melt extruded using a co-rotating, fully intermeshing twin screw extruder (Prism Eurolab 16, Thermo Fisher, Germany), operating at a screw speed of 100 rpm and processing temperatures of 130-180°C in order to evaluate the processability and characteristics of these formulations on a pilot-scale extruder. The extruder was equipped with a gravimetric feeder, two Archimedes screws with 3 mixing zones and a cylindrical die of 3 mm. At room temperature, the extrudates were manually cut, using surgical blades, into mini-tablets of 2 mm length.

Karl Fischer coulometric titration

The water content of the different PVA-grades was quantified via Karl Fischer (KF) coulometric titration. The measurements were performed with a V30 Compact Volumetric KF titrator (Mettler Toledo, Zaventem, Belgium). PVA (0.5 – 1 g) was added into the reaction cell that contained Hydranal®-Methanol dry (Sigma-Aldrich, Germany) as solvent, and Hydranal®-Composite 5 (1-component, Sigma-Aldrich, Germany) was used as titrant.

X-ray diffraction

The crystallinity of PVA, physical mixtures of PVA/HCT and extruded samples was investigated by means of X-ray diffraction (XRD). The XRD patterns were determined using a D5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 V in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1s/step).

Thermal analysis

Thermogravimetric analysis (TGA) (Hi-res TGA 2950, TA instruments, Leatherhead, UK) was employed to investigate the thermal stability of the different PVA-grades. Samples (± 15 mg) were equilibrated at 25°C and heated to 600°C at a heating rate of 10°C/min while recording the weight loss.

Glass transition temperature (T_g), crystallization temperature (T_c), melting point (T_m) of pure components and extruded samples were analyzed by differential scanning calorimetry (DSC), using a Q2000 DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. Dry nitrogen at a flow rate of 50 ml/min was used to purge the differential scanning calorimetry (DSC) cell. The samples were evaluated with a heating rate of 2°C/min and 10°C/min during 3 cycles (heating, cooling and heating) from -20 to 220°C. Measurements were performed in triplicate. All results were analyzed using the TA Instruments Universal Analysis 2000 software.

The degree of relative crystallinity of PVA was calculated with reference to the enthalpy of fusion (ΔH_f^*) of the perfect PVA crystal (138.6 J/g) (Mallapragada et al., 1997), with the following formula:

$$X_c = \left(\frac{\Delta Hf}{\Delta Hf*} \right) x\ 100$$

Gel permeation chromatography

Molecular weight of PVA-grades was measured via gel permeation chromatography (GPC) (Waters, Manchester, UK). Separation was carried out using a GRAM analytical 10 µm pre-column (8.0 x 50mm), in combination with GRAM analytical 30 Å and GRAM analytical 1000 Å GPC columns (10µm, 8.0 x 300 mm) (PSS, Mainz, Germany), stored in a Merck Hitachi column oven L-7300 (Tokyo, Japan) at 40°C. Elution was performed with N,N-dimethylacetamide (Sigma-aldrich, Buchs, Switzerland)/demineralized water (90/10) at a flow rate of 1 ml/min. Columns were calibrated with poly(methyl methacrylate).

***In vitro* drug release**

Drug release from PVA-based extrudates was determined using USP apparatus 1 (baskets), in a VK 7010 dissolution system combined with a VK 8000 automatic sampling station (Vankel Industries, New Jersey, USA). The release rate from extrudates containing 15 mg HCT was tested in demineralized water, 0.1 N HCl (pH 1.0), dissolution media pH 7.4 with varying ionic strength (0-0.14 M) and dissolution media with an ionic strength of 0.14 with varying pH (1-9) (900 ml, at a temperature of 37±0.5°C), while the rotational speed of the baskets was 100 rpm. Samples of 5 ml were withdrawn at 10, 20, 30, 40, 50, 60, 70, 80, 100 and 120 min and spectrophotometrically analyzed for HCT at 272 nm by means of a Shimadzu UV-1650PC UV-VIS double beam spectrophotometer (Antwerp, Belgium). Each batch was evaluated in triplicate.

Experimental design methodology

A D-optimal design with 21 experiments, including 3 center points, was performed to study the influence of three process variables on drug release: PVA grade (type 505, type LM 22 and LM 25), amount of plasticized PVA (type DS0312.2) (20 - 60, %wt/wt) and extrusion temperature (130 - 180°C). 20% HCT was incorporated in all formulations. An overview of the performed design of experiment (DOE) is given in Table 1. The experimental design results were analyzed using MODDE 10.1 software (Umetrics, Umeå, Sweden).

Table 1. Design of experiments.

RUN	DS0312.2 (%) / PVA (%)	PVA GRADE	Extr.T (°C)	% Release (60 min)
1	20/60	505	130	-
2	40/40	505	155	68.88
3	60/20	LM 22	155	80.75
4	20/60	LM 22	155	18.71
5	40/40	LM22	180	38.96
6	40/40	505	155	58.43
7	20/60	505	180	56.81
8	60/20	LM 25	130	45.38
9	40/40	505	155	64.08
10	20/60	LM 22	130	20.37
11	60/20	505	180	85.95
12	60/20	LM 22	130	64.13
13	60/20	LM 25	180	64.02
14	20/60	LM 25	180	22.89
15	60/20	LM 22	180	74.67
16	40/40	LM 25	155	16.68
17	20/60	LM 22	180	28.67
18	60/20	505	130	83.57
19	40/40	LM 22	130	37.39
20	20/60	LM 25	130	9.92
21	40/40	505	155	51.91

RESULTS AND DISCUSSION

The initial weight loss up to a temperature of 150°C during TGA of the PVA-grades was due to the presence of water in PVA. This was confirmed via KF titration as the water content of all samples ranged from 1.0 to 3.7%. The onset of thermal polymer degradation was detected at 210°C for the plasticized PVA grade and at 240°C for the non-plasticized PVA-grades, indicating that PVA polymers are stable under the process conditions used in the study (a maximum extrusion temperature of 180°C was used).

DSC detected a higher T_g for all non-plasticized PVA-grades during the second heating phase (Table 2), as the plasticizing effect of water was lost due to the evaporation of water during the first heating phase (Hassan and Peppas, 2000). In contrast, the T_g of plasticized PVA (type DS0312.2) was not affected by heating due to the presence of a non-volatile plasticizer.

Table 2. General properties and thermal behavior (differential scanning calorimetry, using a cooling/heating rate of 10°C/min) of five different types of polyvinyl alcohol. ([a]) Peak too broad for quantification.

	GENERAL PROPERTIES			THERMAL BEHAVIOR			
				1st HEATING		2nd HEATING	
	Type	DH	Mw (g/mol)	T_g (°C)	T_m (°C)	T_g (°C)	T_m (°C)
Non-plasticized	**LM 25**	**33 – 38**	48991	38.6	-	44.6	-
	LM 22	**47 – 53**	47835	40.1	-	48.7	-
	505	**72 -75**	126543	46.2	154.3	60.8	142.7
	4-88	**88**	92881	45.7	162.3	67.0	143.6
Plast.	**DS0312.2**	**73**	120064	46.0	153.4	41.4	-[a]

Although the supplier did not disclose specific information about the plasticizer in type DS0312.2, chemical information based on Raman spectra (Figure 1) suggested the presence of sorbitol as a plasticizer for PVA. In addition, DSC measurements detected a melting peak at

98.7°C, which corresponds with the T_m of sorbitol. The different types of PVA had a different melting behavior: melting endotherms were not detected for PVA with a low DH (< 50%), whereas melting peaks were observed for PVA with high DH (> 70%).

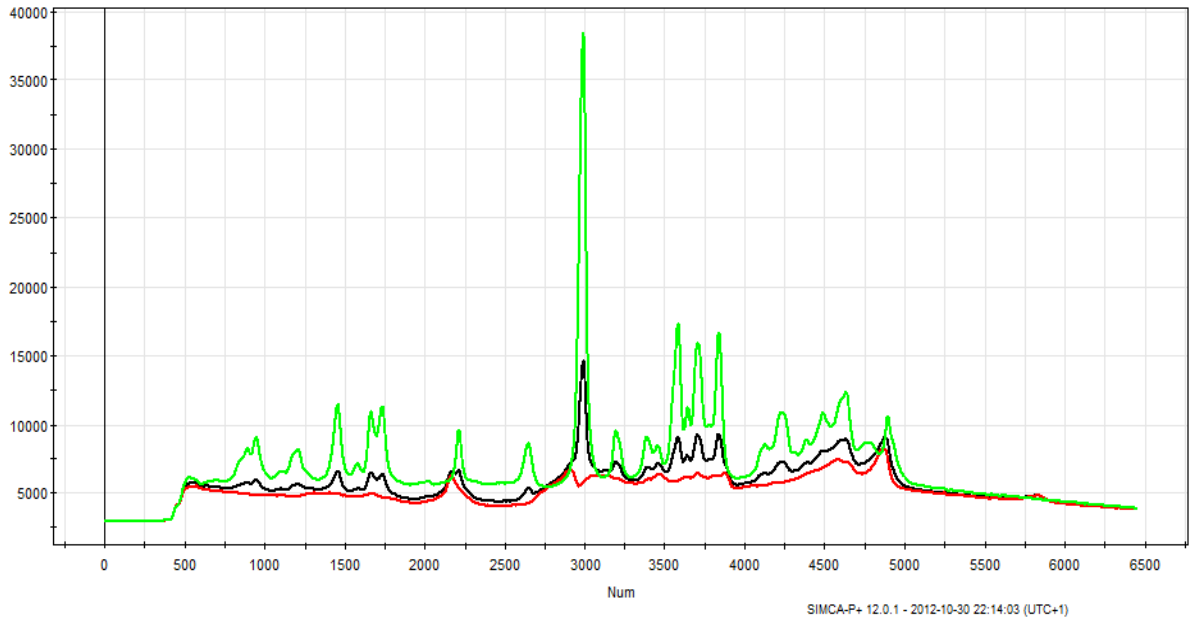

Figure 1. Raman spectra of polyvinyl alcohol (red), sorbitol (green) and plasticized polyvinyl alcohol (type DS0312.2) (black).

This difference in crystallinity was also reflected in the XRD patterns of the different PVA powders (Figure 2): whereas a diffuse halo was observed for PVA-grades with a low DH (due to their higher content of amorphous polyvinyl acetate), crystalline reflections at 2θ = 19.9° and 20.2° were detected in samples with high DH (Bunn, 1948). The semi-crystalline nature of these PVA-grades was confirmed based on the fusion enthalpy of the DSC melting peaks: 16.9±1.7% crystallinity for type 505 (72-75% hydrolyzed) and 32.1±3.6% crystallinity for type 4-88 (88% hydrolyzed), respectively. The correlation between crystallinity and DH is linked to intermolecular hydrogen bonding between the polymer chains (Assender and Windle, 1998), whereby PVA-grades with a high DH (which contain more vinyl alcohol units), could recrystallize upon cooling due to hydrogen bonding. Recrystallization of PVA was affected by the heating/cooling rate during DSC measurements: while PVA_{505} (72 – 75%) did not

recrystallize at heating/cooling rate of 2°C/min, a melting endotherm of PVA crystals after cooling at 10°C/min. In contrast, PVA with low DH (< 50%, LM25 and LM22) did not recrystallize during cooling, as the higher number of vinyl acetate units disrupted hydrogen bonding between vinyl alcohol.

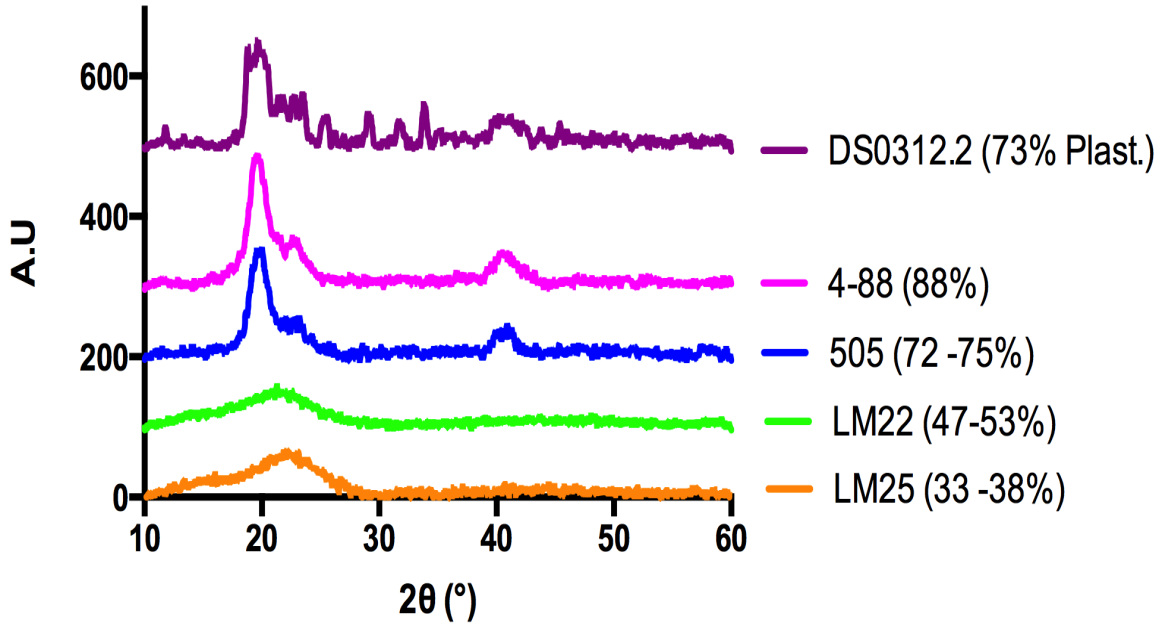

Figure 2. X-ray diffraction profiles of the different polyvinyl alcohol grades.

The processability of PVA formulations via HME (3 mm die) was evaluated in function of DH and extrusion temperature. The extrusion behavior of the non-plasticized PVA-grades differed depending on their DH: while PVA_{LM25} (33 - 38%) and PVA_{LM22} (47 - 53%) were easily processable at a temperature of 100°C, higher temperatures (160-180°C) were required to process PVA_{505} (72 - 75%) and $PVA_{4\text{-}88}$ (88%), as their crystalline nature required higher temperatures for processing via HME. These extrusion temperatures were correlated with the DSC profiles observed for the different PVA-grades (Table 2). In addition, PVA-grades with a higher DH had a higher molecular weight (Table 2), and therefore higher extrusion temperatures were required during the extrusion process to lower the flow viscosity of these

PVA-grades. Physical mixtures of plasticized PVA and HCT could not be processed via HME: temperatures below 150°C yielded too high torque values, while processing above 150°C (e.g. above the melting point of this polymer grade) yielded a completely liquefied formulation. In contrast, mixtures of plasticized and non-plasticized PVA-grades in a ratio of at least 3 to 1 were extrudable between 130 and 180°C. Combinations of plasticized and non-plasticized PVA were used in a DOE to evaluate the effect of PVA mixtures in drug release.

The XRD patterns of HCT and physical mixtures of PVA/HCT showed the crystalline nature of HCT at 2θ = 17°. After extrusion, transparent extrudates were obtained up to 15% HCT content in combination with PVA with a high DH, no HCT crystals were detected in these samples (Figure 3). In contrast, even at 10% HCT load formulations containing PVA with a lower DH were opaque. These PVA-grades were only able to solubilize 5% HCT.

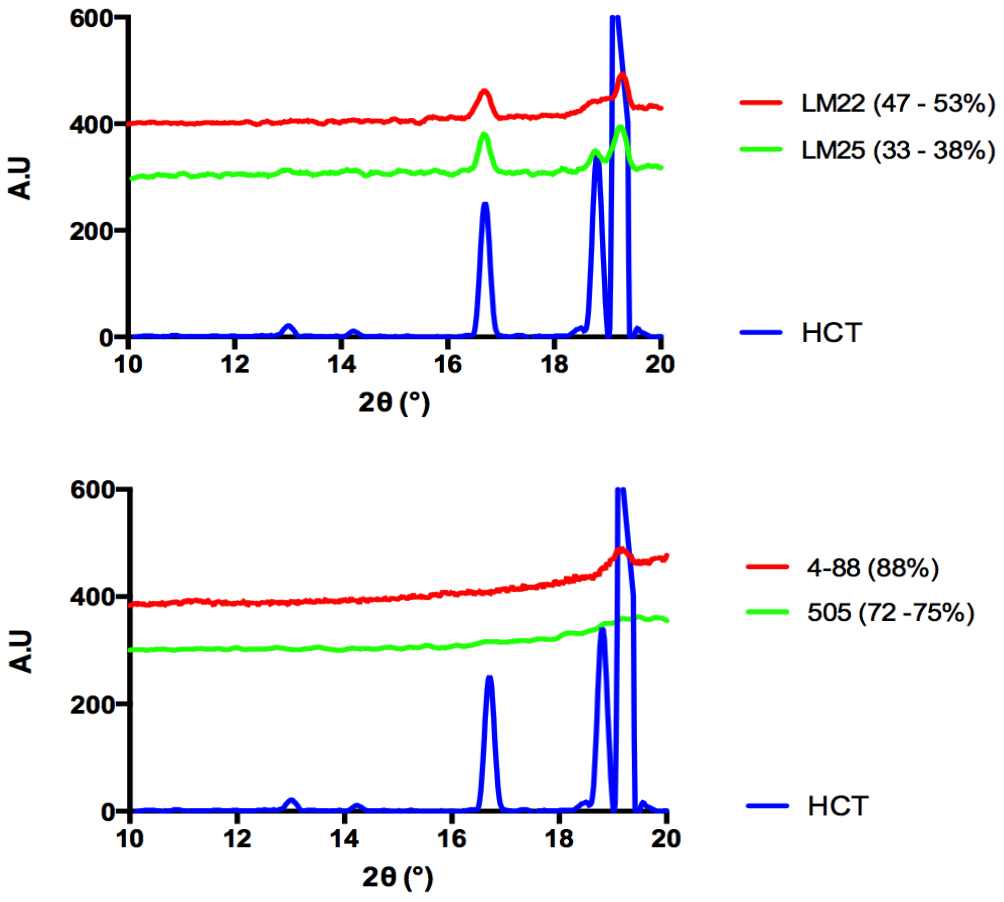

Figure 3. X-ray diffraction-profiles of hot-melt extruded formulations containing different grades of polyvinyl alcohol in combination with hydrochlorothiazide (ratio: 85/15).

The influence of pH on HCT release from PVA-based extrudates was evaluated in a pH range 1 to 9, using dissolution media with a constant ionic strength of 0.14M (Figure 4).

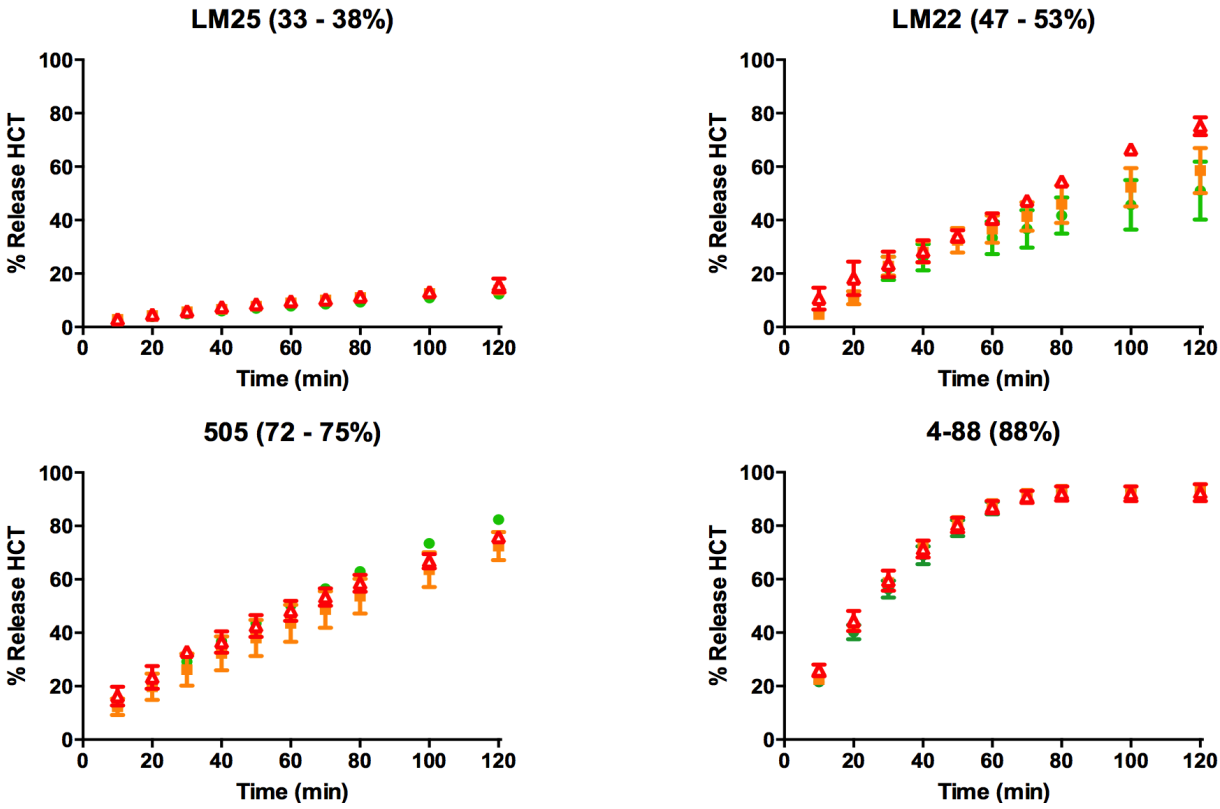

Figure 4. Dissolution profiles (n=3) of hot-melt extruded formulations containing different grades of polyvinyl alcohol in combination with hydrochlorothiazide (ratio: 85/15) in function of the pH of the dissolution medium (pH 1 (•); pH 4.5 (■); pH 9 (Δ)). Ionic strength of all dissolution media was 0.14M.

Although PVA_{LM25} (33 - 38%) and PVA_{LM22} (47 - 53%) were chemically end modified with carboxylic groups, which could potentially reduce the release rate from these formulations at lower pH values, only the release rate from $PVA_{LM\ 22}$ (47 – 53%) was slightly affected at pH 1. HCT release from PVA_{505} (72-75%)- and $PVA_{4\text{-}88}$ (88%)-based formulations was independent of pH. The effect of ionic strength of the dissolution medium (pH 7.4) on HCT release was significant for PVA matrices with a low DH, while no effect on formulations containing PVA with a higher DH (> 70%) was detected (Figure 5).

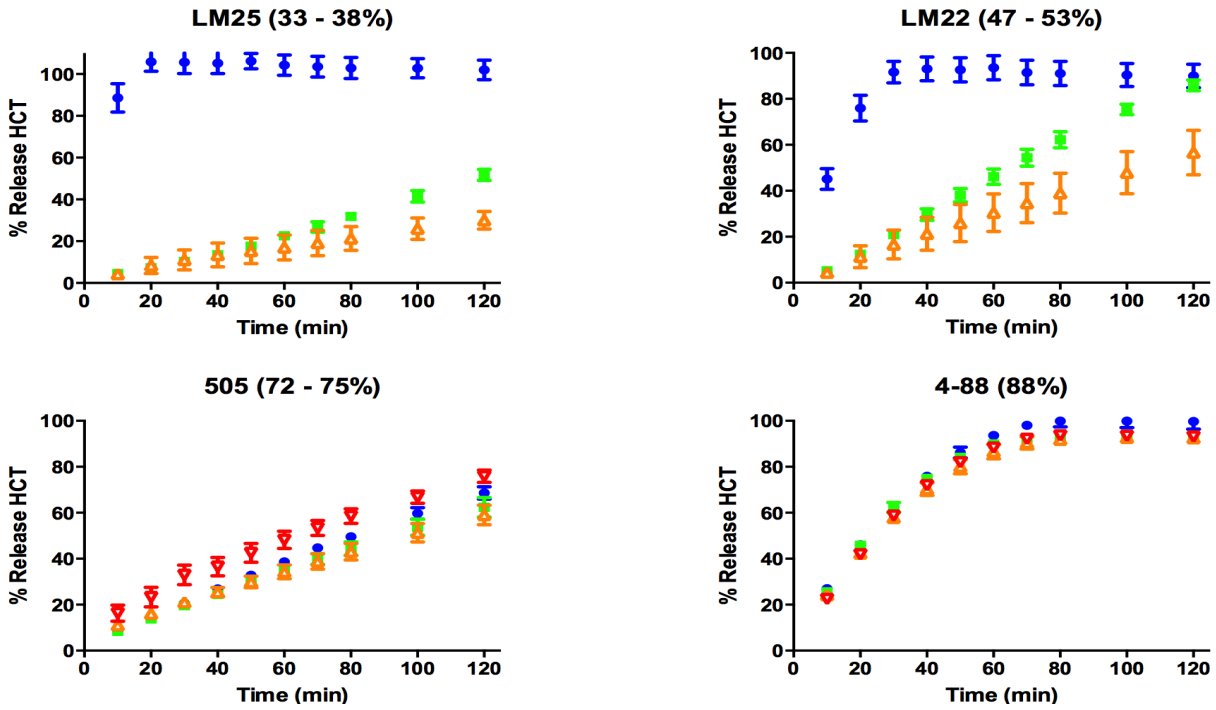

Figure 5. Dissolution profiles (n=3) of hot-melt extruded formulations containing different grades of polyvinyl alcohol in combination with hydrochlorothiazide (ratio: 85/15) in function of ionic strength of the dissolution medium (0 M (•); 0.018 M (■); 0.089 M (Δ); 0.14 M (∇). pH of all dissolution media was 7.4.

The influence of drug load on drug release was investigated with formulations containing 5-15% HCT (Figure 6). Drug release from $PVA_{4\text{-}88}$ formulations containing 5 and 15% HCT after 120 min was 51% and 92%, respectively, indicating that amorphous or dissolved HCT clusters in PVA were released faster at higher drug concentrations. The same phenomenon was seen for all PVA types. Kim, C.J. and Lee, P.I. revealed similar results with PVA beads (Kim and Lee, 1992).

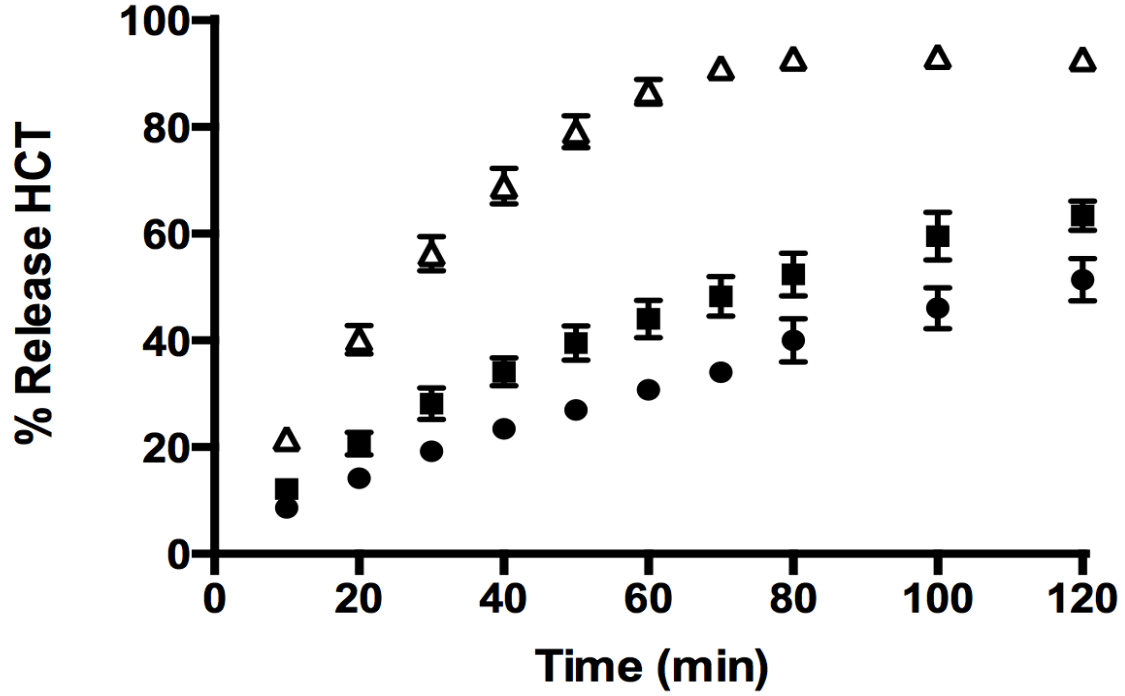

Figure 6. Dissolution profiles (n=3) of hot-melt extruded formulation containing polyvinyl alcohol 4-88 (88%) and hydrochlorothiazide in 0.1 N HCl in function of hydrochlorothiazide concentration: 5% (•), 10% (■) 15% (Δ).

The D-optimal experimental design existing of 21 experiments (Table 1) was used to evaluate the influence of PVA grade (type 505, type LM 22 and LM 25), added amount of plasticized PVA (type DS0312.2) (amo) and extrusion temperature (T) upon drug release after 60 minutes. From the experimental results (Table 1), a quadratic regression model was calculated for the response variable using Modde 10.1:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{11}X_1^2 + b_{33}X_3^2 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3$$

where b_1, b_2 and b_3 represent the coefficients of the main factors X (e.g. temperature (T), PVA type (LM22, LM25 or 505) and amount plasticized PVA (amo)). Similarly, b11 and b33 represent the second order coefficients while b12, b13 and b23 are the interaction coefficients.

In first instance, the raw data (design results) were evaluated using a replicate plot, in which the ideal outcome is that the variability of repeated experiments is much less than the overall variability (plot not shown). The effects of the studied variables were graphically and

statistically interpreted using the Modde software and by the normal probability plot and the algorithm of Dong (De Beer et al., 2011). The significant effects and interactions are shown for the evaluated response variable (Figure 7).

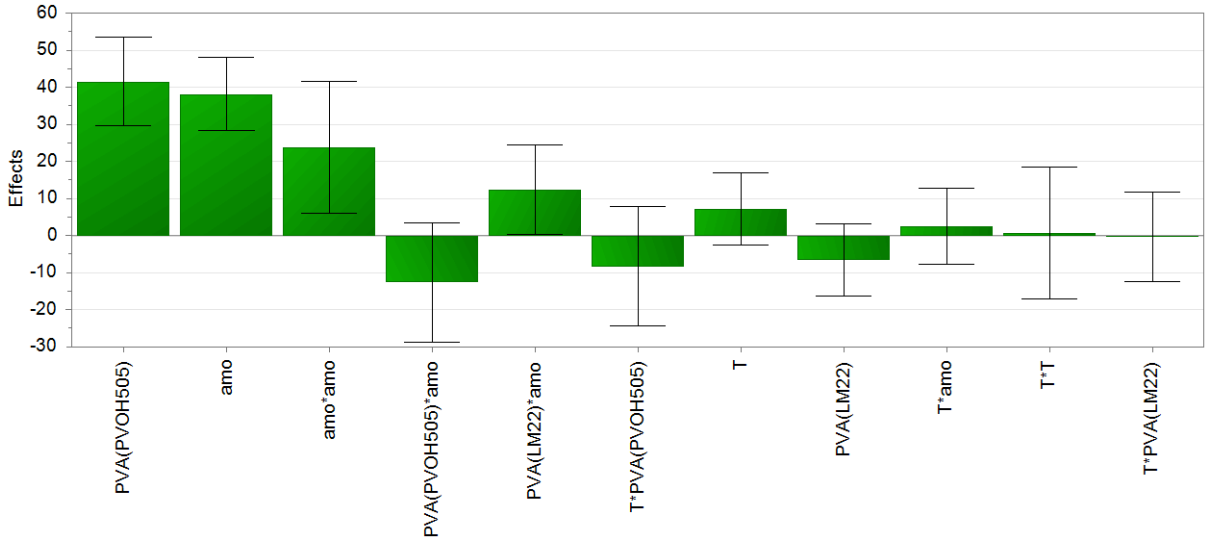

Figure 7. Effect plots of main factors (extrusion temperature (T), polyvinyl alcohol grade, amount plasticized polyvinyl alcohol (amo)), second order factors and interactions.

Using PVA_{505} (72 – 75%) had a positive significant effect on amount of drug released after 60 min, which confirmed earlier results that drug release was faster for formulations containing PVA with a higher DH. Increasing the amount of plasticized PVA (type DS0312.2) in the formulation revealed an improved drug release for formulations containing higher concentrations of plasticized PVA (type DS0312.2). The effect of extrusion temperature (T) was not significant. There were no significant interactions. After fitting the regression model, the goodness of fit (R^2) and the goodness of prediction (Q^2) were evaluated. The least significant regression coefficients were excluded provided that Q^2 increased. As extrusion temperature was not significant, Q^2 decreased when excluded. Therefore, the resultant equation was:

$$y = 4.89(T) - 16.47(PVA\ LM25) - 2.30\ (PVA\ LM22) + 18.77\ (PVA\ 505) + 21.31(amo) + 9.90(amo^2)$$

Based on this calculated model for the drug release after 60 min (=y), contour plots were derived showing how both added amount of plasticized PVA (amo) and applied extrusion temperature (T) for each PVA type (LM25, LM22, 505) influence drug release (Figure 8). The contour plots confirm improved drug release for combinations containing PVA with a higher DH and higher concentrations of plasticized PVA, e.g. PVA_{LM25} formulations containing 20% and 60% DS0312.2 released maximum 15% and maximum 55% HCT after 60 min, respectively.

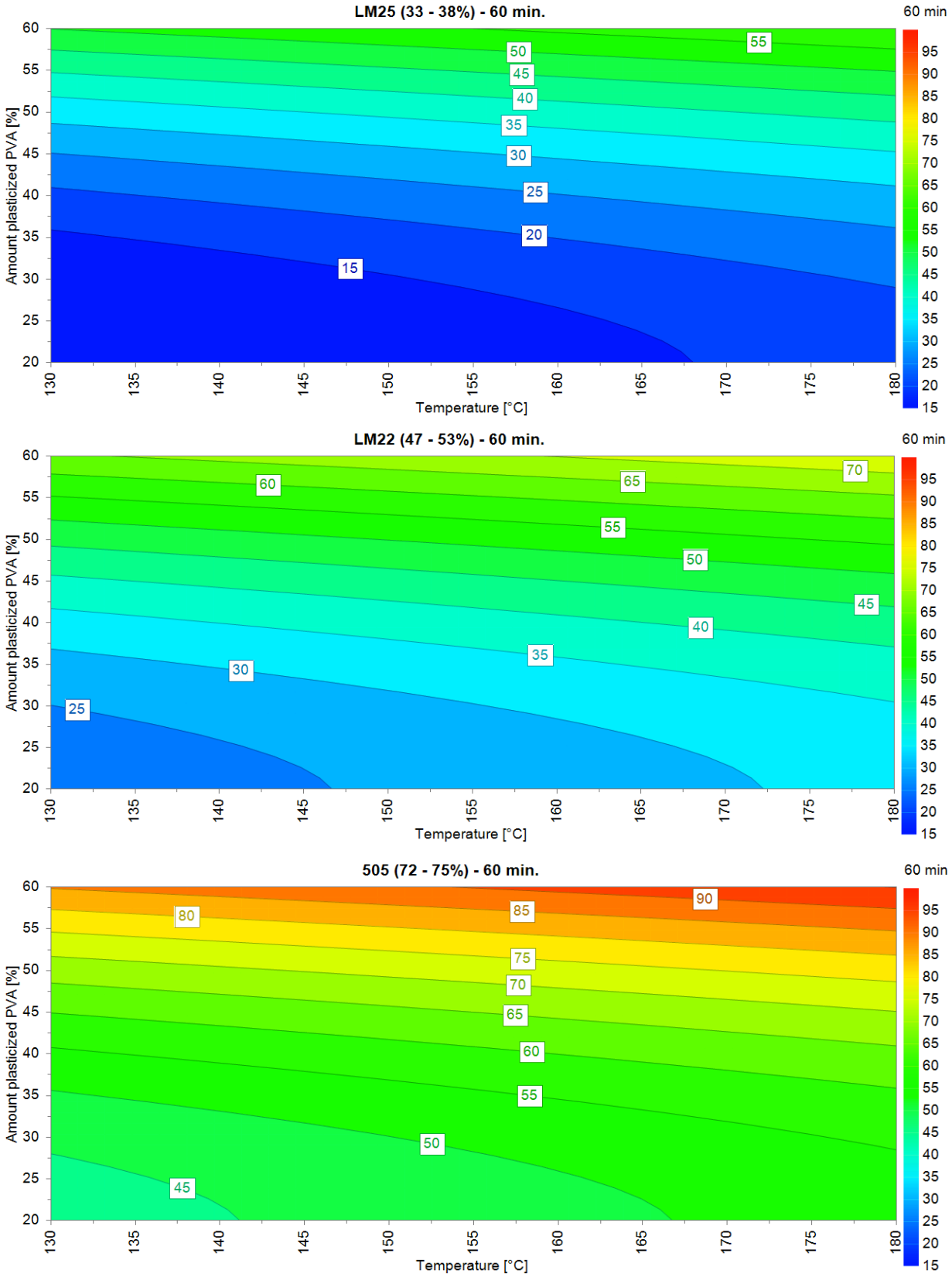

Figure 8. Contour plots of drug release (0.1 N HCl, 60 min) from blends of non-plasticized polyvinyl alcohol (A. LM25, B. LM22, C. 505) and plasticized polyvinyl alcohol (type DS0312.2) in function of the concentration of plasticized polyvinyl alcohol and the extrusion temperature.

This observation was valid for all PVA-grades. The design model was then used to determine a combination of factors leading to complete HCT release within 60 min: 11.76% PVA_{505}, 68.24% added plasticized PVA (type DS0312.2) and 130°C extrusion temperature. As the predicted formulation was out of the initial experimental range of the design, this formulation was tested, to evaluate the model prediction. The dissolution profile (Figure 9) proved indeed that HCT was completely released after 60 minutes.

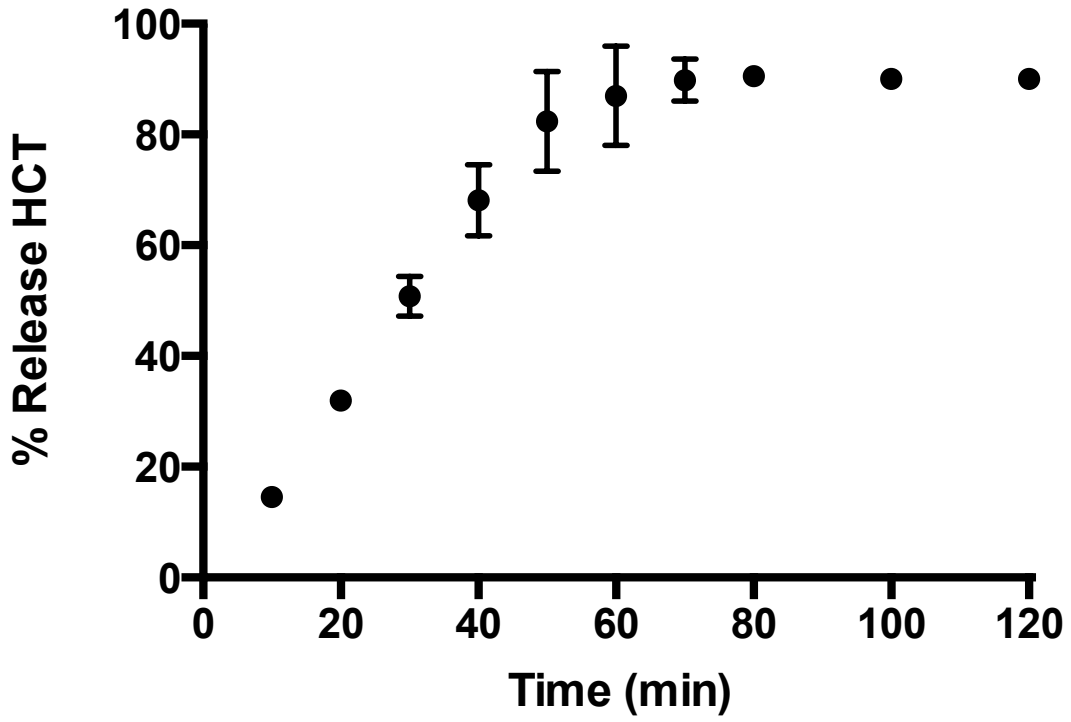

Figure 9. Dissolution profile (n=3) of hot-melt extruded formulation containing 11.76% polyvinyl alcohol 505 (72-75%), 68.24% plasticized polyvinyl alcohol (type DS0312.2) and 20% hydrochlorothiazide in 0.1 N HCl.

CONCLUSIONS

PVA polymers were identified as promising carriers for HME applications, as PVA with high DH were able to solubilize HCT up to 15%. The fastest drug release was obtained from PVA formulations with a high DH, whereby HCT release was independent of pH and ionic strength. Thereby, the two-dimensional contour plots confirmed faster drug release rate for combinations containing PVA with high DH, and higher concentrations of plasticized PVA. However, high extrusion temperatures were required which could hamper its application for thermo-sensitive drugs.

Acknowledgement

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2

THE INFLUENCE OF PLASTICIZERS ON THE PROPERTIES OF HOT-MELT EXTRUDED POLYVINYL ALCOHOL

Parts of this chapter are published in:

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ABSTRACT

Polyvinyl alcohol (degree of hydrolysis > 70%) requires higher extrusion temperatures, which could hamper its application for thermo-sensitive drugs. Therefore, the purpose of this study was to investigate the effect of sorbitol, a water-soluble plasticizer, on the thermal properties of hot-melt extruded polyvinyl alcohol (degree of hydrolysis > 70%). The melting of polyvinyl alcohol/sorbitol mixture was required to establish molecular interactions between polyvinyl alcohol and sorbitol. These molecular interactions were reflected in the hot-melt extrusion behavior: whereas an extrusion temperature of 180°C was necessary to process physical mixtures of polyvinyl alcohol (degree of hydrolysis > 70%) and sorbitol, only 140°C was necessary during re-extrusion (after quench cooling and cryomilling) of the polyvinyl alcohol/sorbitol mixture. In addition, the *in vitro* and *in vivo* drug release of plasticized polyvinyl alcohol was examined; whereas the celecoxib/polyvinyl alcohol/sorbitol system was able to maintain supersaturation during *in vitro* dissolution (0.1 N HCl) compared to Celebrex®, the *in vivo* pharmacokinetic parameters ($AUC_{0\text{-}24h}$, C_{max} and t_{max}) were highly comparable.

KEYWORDS: hot-melt extrusion, polyvinyl alcohol, immediate release, supersaturation, plasticizer

INTRODUCTION

The bioavailability of approximately 40% of the novel drug candidates is limited due to poor aqueous solubility and/or permeability (Ahuja et al., 2007). Hot-melt extrusion (HME), a technique whereby heat is used to embed a drug in a hydrophilic thermoplastic carrier, was already successfully applied to improve solubility, and thus bioavailability of several poorly soluble drugs, including fenofibrate (Kalivoda et al., 2012), itraconazole (Verreck et al., 2003) and nimodipin (Zheng et al., 2007). The solubility was enhanced due to the formation of solid dispersions, which increased drug surface area available for dissolution and improved drug wettability (Vasconcelos et al., 2007). Solid dispersions were originally defined by Chio and Riegelman as 'a dispersion of one or more active ingredients in an inert carrier at the solid state' (Chiou and Riegelman, 1971). The choice of the carrier is important, because this influences physicochemical stability of the solid dispersion (e.g. crystallization of the drug from its amorphous state), as well as processing conditions (e.g. extrusion temperature). Carriers used in HME to improve drug solubility, are required to be safe, thermoplastic, thermally/physically stable and water soluble (Janssens and Van den Mooter, 2009). Polymeric carriers are mostly used, and have been classified in natural product based-polymers, mainly cellulose derivatives (e.g. hydroxypropylcellulose, hydroxypropylmethylcellulose) and fully synthetic polymers (e.g polyvinylpyrrolidone, polyethyleneglycol, polyvinyl alcohol (PVA)) (Vasconcelos et al., 2007).

The previous chapter has shown that partially hydrolyzed PVA with a high degree of hydrolysis (DH) (> 70%) was a promising carrier for HME, as it is non-toxic, water-soluble and drug release was independent of pH or ionic strength. However, due to the presence of intra- and intermolecular hydrogen bonding between hydroxyl groups, high extrusion temperatures (e.g. 180°C) were required to process PVA with high DH, which limits its applicability for thermo-sensitive drugs. Different techniques are able to improve processability and decrease extrusion temperature of PVA by disrupting intra- and intermolecular hydrogen bonding, such as: (1) blending with other polymers, (2) co-polymerization, (3) adding plasticizers with low molecular weight (Wu et al., 2012). Until now, the use of appropriate plasticizers is the easiest method to modify the processing temperature of PVA with high DH. Different plasticizers,

mostly polyols, have been used with PVA, such as glycerin (Jang and Lee, 2003), low molecular weight polyethylene glycol (Lim and Wan, 1994) and sorbitol (Mohsin et al., 2011).

The purpose of this study was to investigate the effect of a water-soluble plasticizer (e.g. sorbitol) on the thermal properties of hot-melt extruded PVA with high DH. In addition, the *in vitro* and *in vivo* drug release of plasticized PVA was examined.

MATERIALS AND METHODS

Materials

PVA-grades with varying DH were evaluated: a technical grade PVA_{505} (DH 72-75%) (obtained from Kuraray, Hattersheim am Main, Germany) and a pharmaceutical grade $PVA_{4\text{-}88}$ (DH 88%, provided by Merck, Darmstadt, Germany). Celecoxib (CEL) (Sanico, Turnhout, Belgium), a Biopharmaceutical Classification System (BCS) class II drug (Turner et al., 2012), was used as model drug. Sorbitol (Fagron, Waregem, Belgium) was used as water-soluble plasticizer of PVA.

Hot-melt extrusion

Mixtures of PVA/sorbitol were processed using a co-rotating, fully intermeshing twin screw extruder (Prism Eurolab 16, Thermo Fisher, Germany), operating at a screw speed of 100 rpm and processing temperatures of 180°C. The extruder was equipped with a gravimetric feeder, two Archimedes screws with 3 mixing zones and a cylindrical die of 3 mm. Afterwards, the extrudates were quench-cooled in liquid nitrogen, (cryo-)milled and sieved through a 300 µm sieve.

Mixtures of (cryo-)milled PVA/sorbitol extrudate (<300 µm) and CEL were processed using a co-rotating twin screw extruder (Haake MiniLab II Micro Compounder, Thermo Electron, Karlsruhe, Germany), operating at a screw speed of 60 rpm and a processing temperature of 140-160°C. The extruder was equipped with a pneumatic feeder, two Archimedes screws and a 2 mm cylindrical die. The extrudates were quench-cooled in liquid nitrogen, (cryo-)milled and sieved through a 300 µm sieve.

Thermal analysis

Glass transition temperature (T_g), crystallization temperature (T_c), melting point (T_m) of pure components, extruded and (cryo-)milled samples were analyzed by differential scanning calorimetry (DSC), using a Q2000 DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. Dry nitrogen at a flow rate of 50 ml/min was used to purge the differential scanning calorimetry (DSC) cell. The samples, loaded in non-hermetic aluminum T_{zero} pans, were evaluated according to DSC conditions (heating rate: 10°C/min) during 3 cycles (heating, cooling and heating) from -20 to 220°C. Measurements were performed in triplicate. All results were analyzed using the TA Instruments Universal Analysis 2000 software.

Karl Fischer coulometric titration

The water content of the different PVA-grades was quantified via Karl Fischer (KF) coulometric titration. The measurements were performed with a V30 Compact Volumetric KF titrator (Mettler Toledo, Zaventem, Belgium). PVA (0.5 – 1 g) was added into the reaction cell that contained Hydranal®-Methanol dry (Sigma-Aldrich, Germany) as solvent, and Hydranal®-Composite 5 (1-component, Sigma-Aldrich, Germany) was used as titrant.

X-ray diffraction

The crystallinity of PVA and CEL was investigated by means of X-ray diffraction (XRD). The XRD patterns were determined using a D5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 V in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1s/step).

Fourier transform infrared analysis

A Nicolet iS5 (Thermo Scientific, Massachusetts, United States) Fourier transform infrared (FT-IR) spectrometer with a deuterated triglycine sulfate (DTGS) detector was used. All spectra

were recorded in the 4000 – 400 cm^{-1} range with a 4 cm^{-1} resolution. Once recorded, the spectra were normalized.

***In vitro* drug release**

The *in vitro* drug release of CEL was investigated for PVA formulations containing 15 mg CEL formulated as physical mixture or (cryo-)milled extrudate. CEL release from PVA formulations and from a commercially available CEL formulation (Celebrex®, a capsule formulation containing 37.4% CEL) was determined using a 0.1 N HCl (pH 1.0) dissolution medium. PVA/CEL formulations were filled into hard-gelatin capsules prior to dissolution testing. CEL concentrations were spectrophotometrically analyzed at 250 nm by means of a Shimadzu UV-1650PC UV-VIS double beam spectrophotometer (Antwerpen, Belgium). Each batch was evaluated in triplicate.

Bioavailability study

The study was approved by the Ethical Committee of the Faculty of Veterinary Medicine (Ghent University, Belgium). A cross-over study in dogs (n = 6, body weight varying between 10 and 15 kg) was performed to determine the bioavailability of CEL after oral administration of the (cryo-)milled PVA extrudate and Celebrex® formulation. The dogs received a hard-gelatin capsule (n°0) containing 5 mg/kg body weight CEL, formulated as the (cryo-)milled extrudate or Celebrex® formulation. The washout period between sessions was 2 weeks. Blood samples (2 ml) were taken prior to each treatment day (=blank sample) and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h after administration by puncturing the vena jugularis. The blood samples were collected in dry heparinized tubes and within 1 h after collection blood was centrifuged for 10 min at 1500 *xg* and kept frozen at -20°C until analysis.

Determination of celecoxib plasma concentration

CEL plasma concentrations were determined based on the high performance liquid chromatography – mass spectrometry (HPLC-MS) method developed by Nkansah et al. (Nkansah et al., 2013) using indomethacin as internal standard. The chromatographic system consisted of an Agilent 1100 series (Agilent, Heilbronn, Germany), whereby separation was carried out using a Luna C18 column (50 mm x 2.0 mm, particle size 3 µm; Phenomenex, Torrance, CA). The injection volume was 5 µL. Gradient elution was performed with a flow rate of 0.2 ml/min starting at 50% eluent A (5 mM ammonium formate with 0.1% formic acid). Eluent B (acetonitrile) was linearly increased from 50% to 70% during 3 min. The initial conditions were regained over a 0.2 min time interval, followed by a 7 min equilibration time prior to the next injection. This resulted in an overall run time of 10 min. Detection was performed using a API 3000 triple quadrupole mass spectrometer (AB Sciex, Framingham, MA) equipped with an electrospray ionization source in the electrospray negative ion mode (ESI-). Nitrogen was used as both drying and nebulizing gas. Product ions were detected using the multiple reaction-monitoring (MRM) mode, using argon as collision gas. The capillary voltage and source temperature were optimized at -4.2 kV and 300°C, respectively. The collision energy and cone voltage were optimized for each compound individually. Data were collected and processed using the Analyst software (AB Sciex, Framingham, MA). The peak plasma concentration (C_{max}), the time to reach C_{max} (t_{max}), and the extent of absorption ($AUC_{0\text{-}24h}$) were determined.

RESULTS AND DISCUSSION

PVA polymers with high DH (> 70%) were most promising as carrier in HME, as drug release was independent of pH and ionic strength. However, the higher temperature required for HME (180°C) of these PVA samples (type 505 and 4-88) due to their semi-crystalline nature hampered their use as carriers for thermo-sensitive drugs (e.g. CEL) (Sovizi, 2010). Therefore, the addition of a plasticizer was evaluated to broaden the application of PVA for HME. The most commonly used plasticizers for PVA were polyols (e.g. polyethylene glycol, glycerol, sorbitol), where hydrogen bonding between the polyols and PVA reduced inter- and intra-molecular hydrogen bonding in the PVA polymer chains (Wu et al., 2012). Sorbitol was selected as low molecular weight and water-soluble plasticizer, because sorbitol as solid plasticizer easily could be homogenized and processed during HME.

Whereas no effect of sorbitol (in a concentration up to 40%) during the first DSC heating cycle was observed, a lower T_g and T_m were detected during the second heating cycle of all samples (Table 1).

Table 1. Thermal behavior of polyvinyl alcohol/sorbitol mixtures as a function of sorbitol concentration, using a cooling/heating rate of 10°C/min.

		1st HEATING		2nd HEATING	
Type PVA	**Sorbitol % (m/m)**	**T_g (°C)**	**$T_{m\ (onset)}$ (°C)**	**T_g (°C)**	**$T_{m\ (onset)}$ (°C)**
505	**0**	46.2	154.3	60.8	142.7
(DH 72/75%)	**10**	46.3	150.7	57.7	142.1
	20	46.1	153.3	50.9	136.6
	30	46.2	148.5	41.0	131.2
	40	46.8	169.5	35.4	123.1
4-88	**0**	45.7	162.3	67.0	143.6
(DH 88%)	**10**	48.0	161.5	52.9	134.5
	20	46.8	160.1	37.1	128.9
	30	46.1	132.1	13.7	126.9
	40	40.0	138.6	13.1	126.4

This indicated that the melting of the sorbitol/PVA mixtures was required to establish molecular interactions between the polymer and sorbitol, thus affecting the thermal properties of the formulations via the plasticizing effect of sorbitol on the PVA polymer. The effect of sorbitol was linked to its concentration as more interactions can be established between the OH-groups of both components, thus disrupting the structural regularity of PVA (Mohsin et al., 2011). Sorbitol concentration was limited to 40% as a higher concentration in the PVA/sorbitol mixture yielded a liquefied mass after extrusion. Sorbitol also had a more pronounced impact on PVA with the highest DH ($PVA_{4\text{-}88}$) as more intramolecular interactions can be destroyed due to the addition of sorbitol.

The effect of sorbitol on the thermal properties during DSC was also reflected in the HME behavior of the sorbitol/PVA mixtures. Whereas an extrusion temperature of 180°C was required to process physical mixtures of PVA and sorbitol (e.g. similar condition as for HME-processing of pure PVA-grades with a high DH), re-extrusion of PVA/sorbitol mixture (after quench-cooling and (cryo-)milling) required a lower temperature for efficient extrusion at low torque: 160°C for mixtures containing 10-30% sorbitol and 140°C with 40% sorbitol. There was no difference in extrusion temperature between mixtures containing PVA_{505} (72-75%) or $PVA_{4\text{-}88}$ (88%). Moisture content of the (cryo-)milled material was similar to un-milled PVA/sorbitol mixtures, thus water sorption during (cryo-)milling did not contribute to the observed lower extrusion temperature for the (cryo-)milled PVA/sorbitol formulations.

Combining the (cryo-)milled plasticized PVA-grades (containing 40% sorbitol) with 15 % CEL (melting point 160.6°C) also allowed HME processing at 140°C. Under these conditions both PVA carriers (type 505 and 4-88) were able to solubilize the entire CEL fraction as confirmed by the XRD patterns (Figure 1) and DSC analysis (Figure 2).

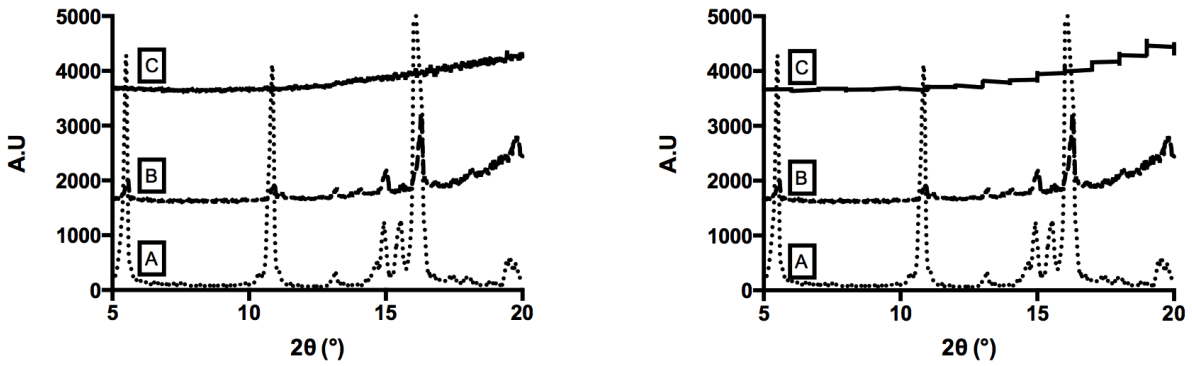

Figure 1. X-ray diffraction profile of celecoxib (A), and physical mixture (B) or extrudate (C) containing plasticized polyvinyl alcohol type 505 (72-75%) (left) or type 4-88 (88%) (right) and celecoxib (15%).

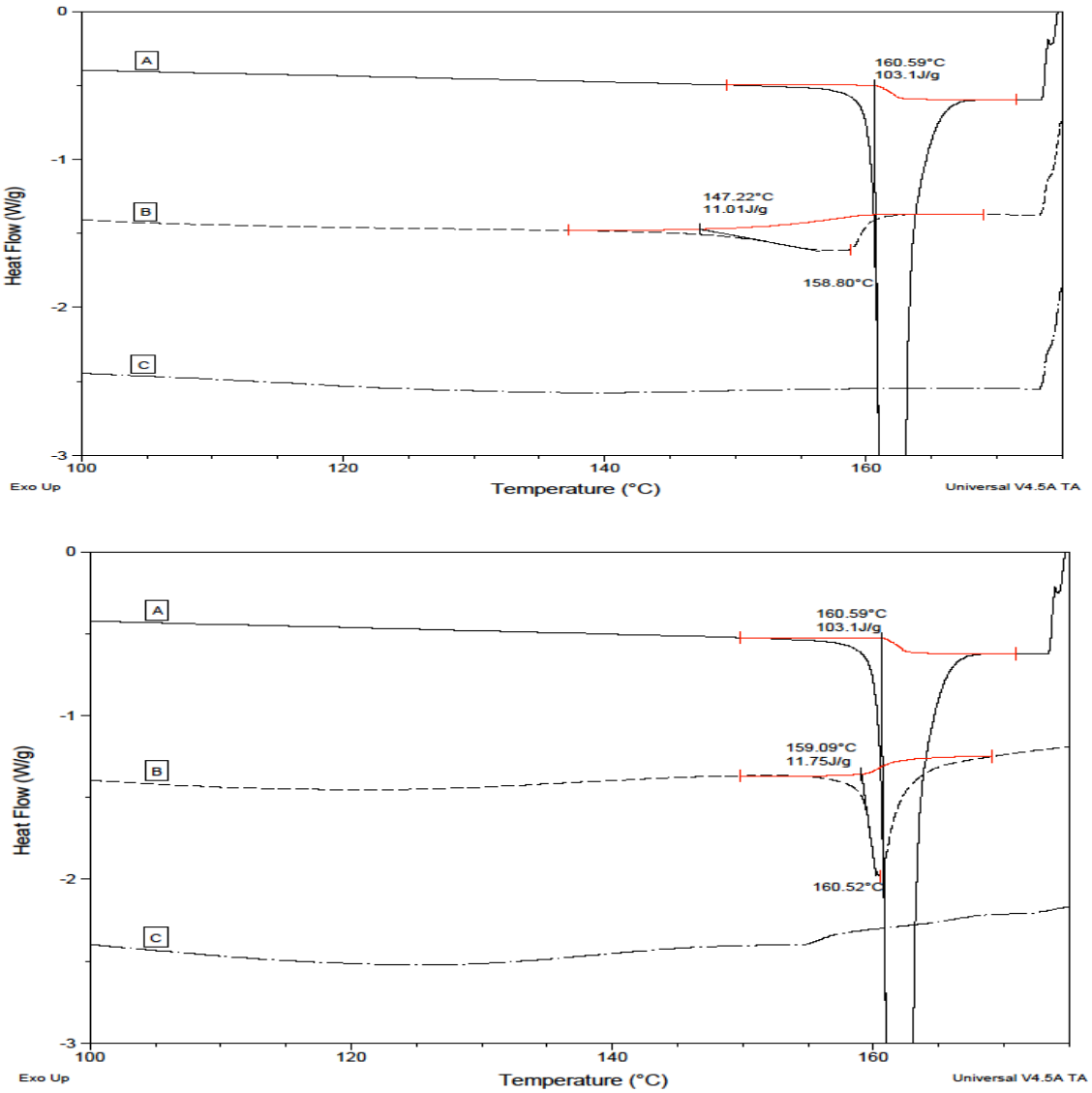

Figure 2. Differential scanning calorimetry of celecoxib (A), and physical mixture (B) or extrudate (C) containing plasticized polyvinyl alcohol type 505 (72-75%) (above) or type 4-88 (88%) (under) and celecoxib (15%).

FTIR spectroscopy (Figure 3) showed characteristic peaks of CEL at 3331.4 and 3225.8 cm^{-1}, which corresponded to N-H stretching in the SO_2NH_2 group. While those bands were clearly visible in the physical mixture, they broadened after extrusion, likely due to hydrogen bonding between the acidic hydrogen of N-H as hydrogen donor from CEL and O-H as hydrogen acceptor of PVA (Fouad et al., 2011).

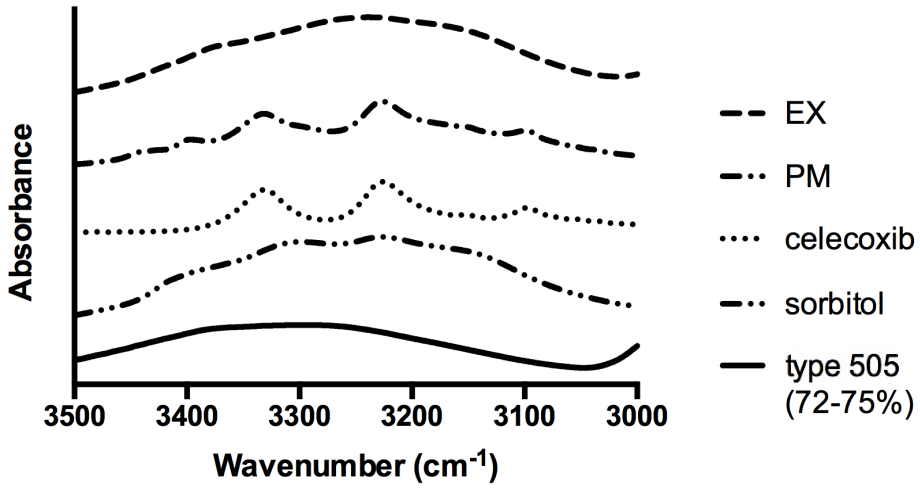

Figure 3. Fourier transform infrared spectra of physical mixture (PM) or extrudate (EX) both containing 15% celecoxib and pure compounds (polyvinyl alcohol type 505 (72-75%), sorbitol and celecoxib).

The *in vitro* dissolution resulted in a fast release of CEL from the PVA mixtures (Figure 4). It is important to note that these dissolution tests were performed under non-sink conditions in 0.1N HCl and that the CEL/PVA/sorbitol system was able to maintain supersaturation during the length of the dissolution test. In contrast, CEL release from the commercially available formulation (Celebrex®) was much slower in the medium and was equivalent to the maximum solubility of CEL in 0.1N HCl (3 mg/L). PVA has already been reported as a polymeric precipitation inhibitor (PPI), able to stabilize supersaturation of drugs (caffeine (Gift et al., 2008), danazol (Warren et al., 2010), estradiol (Megrab et al., 1995) and tacrolimus (Overhoff et al., 2008)) via drug/polymer interactions. In addition to the lower extrusion temperature of this formulation during HME, this could be an important feature to improve the bioavailability of solubility-limited drugs (BSC class II).

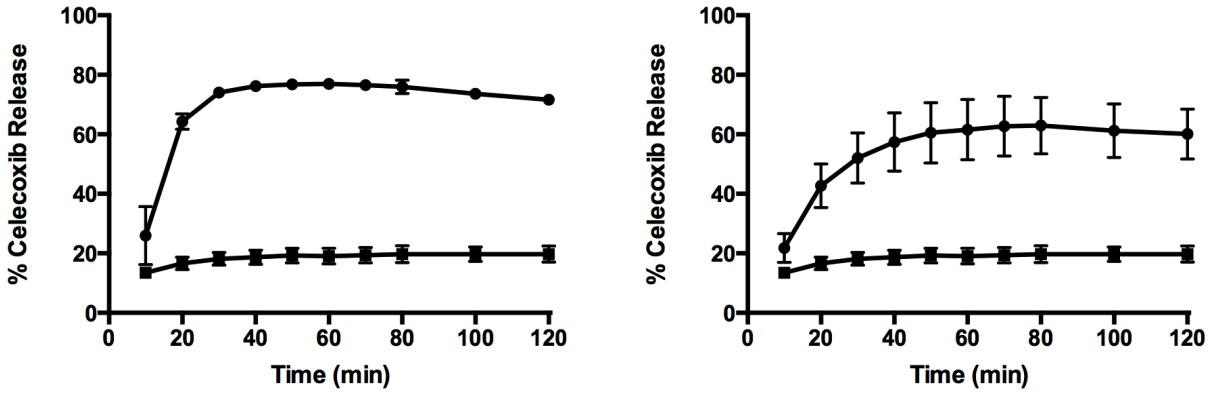

Figure 4. Dissolution profiles (n=3) of Celebrex® (■) and hot-melt extruded formulation containing plasticized polyvinyl alcohol type 505 (72-75%) (left) or type 4-88 (88%) (right) (•) in capsules containing 15 mg celecoxib in 0.1N HCl pH 1.

The influence of *in vitro* supersaturation on *in vivo* bioavailability was investigated after oral administration of the formulations to dogs (Figure 5).

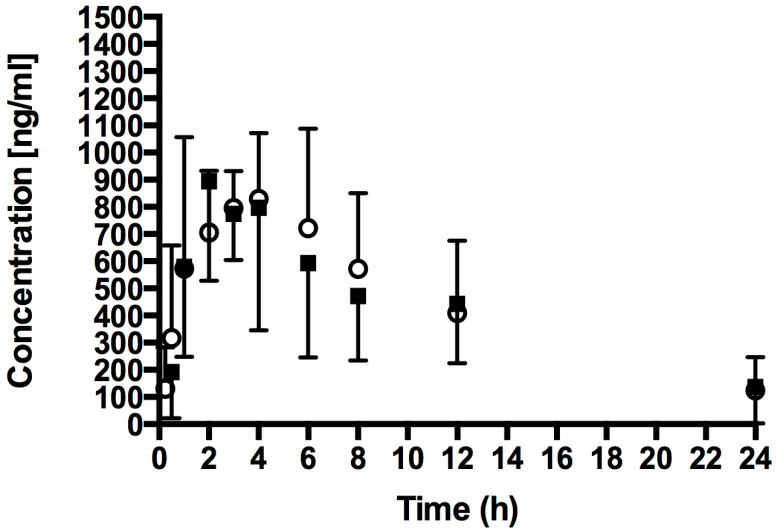

Figure 5. Average plasma concentration vs time profiles of celecoxib (5 mg/kg) after oral administration of capsules containing Celebrex® (■) or the hot-melt extruded formulation with plasticized polyvinyl alcohol type 505 (72-75%) (O) in dogs (n=6).

Despite the significant differences of the *in vitro* release profiles, all pharmacokinetic parameters were equally good, as (cryo-)milled plasticized PVA (containing 40% sorbitol) with 15% CEL was able to obtain the same bioavailability as the reference, which was Celebrex®, a commercially available formulation (Table 2).

Table 2. Pharmacokinetic parameters of celecoxib (5 mg/kg) after oral administration of capsules containing Celebrex® or the hot-melt extruded formulation with plasticized polyvinyl alcohol type 505 in dogs (n=6).

	Celebrex®	**PVA type 505 (72-75%)**
$AUC_{0\text{-}24h}$ (ng.h/ml)	9869.3 ± 4508.3	10176.2 ± 4188.2
C_{max} (ng/ml)	1035.8 ± 336.8	1000.2 ± 193.7
t_{max} (h)	3.5 ± 1.5	3.0 ± 1.9
Rel. bioavailability F (%)		96.6

This discrepancy between *in vitro* and *in vivo* behavior could be due to the fact that *in vitro* dissolution was limited by the solubility of CEL combined with the fixed volume of dissolution media available. In contrast, following *in vivo* administration sink conditions are more likely based on the high permeability of CEL, whereby the rate-limiting factor was shifted to its dissolution rate. Therefore, a number of reasons could influence *in vivo* dissolution rate, such as incomplete dissolution of the PVA carrier, rapid *in vivo* diffusion of the PVA polymers after dissolution (making CEL more prone to precipitation) … Furthermore, *in vivo* dissolution of hydrophobic compounds such as CEL (log P = 3.5) could be influenced by presence of endogenous compounds (e.g. lecithin), which are able to form micelles, and improve solubility (Shono et al., 2009). However, this study emphasize that caution needs to be taken for *in vitro*/*in vivo* correlations.

CONCLUSIONS

PVA polymers with high DH were identified as promising carriers for HME, however high extrusion temperatures were required which could limit their applicability for thermo-sensitive drugs. Therefore, PVA was plasticized with sorbitol, whereby melting of PVA/sorbitol mixtures was required to lower the extrusion temperature to 140°C. The *in vitro* dissolution profiles of CEL were significantly improved compared to Celebrex®, as CEL was in a state of supersaturation, and moreover PVA was able to stabilize supersaturation for at least 2h. However, the enhanced *in vitro* dissolution was not reflected in the *in vivo* bioavailability.

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3

THE IMPACT OF HOT-MELT EXTRUSION ON THE TABLETING BEHAVIOUR OF POLYVINYL ALCOHOL

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ABSTRACT

There is evidence that processing techniques like hot-melt extrusion could alter the mechanical properties of pharmaceuticals, which may impede further processability (e.g. tableting). The purpose of this study was to evaluate if hot-melt extrusion has an impact on the tableting behavior of polyvinyl alcohol – formulations. Mixtures of partially hydrolyzed polyvinyl alcohol grades (with a degree of hydrolysis of 75 and 88%) and sorbitol (0, 10 and 40%) were extruded, (cryo-)milled and compressed into compacts of 350±10 mg. Before compression all intermediate products were characterized for their solid-state (glass transition and melting temperature, crystallinity) and material properties (particle size, moisture content, moisture sorption). Because both polyvinyl alcohol grades required higher extrusion temperatures (e.g. 180 °C), sorbitol was added to polyvinyl alcohol as plasticizing agent to allow extrusion at 140°C. Compaction experiments were performed on both physical mixtures and (cryo-)milled extrudates of polyvinyl alcohol-sorbitol. By measuring tablet tensile strength and porosity in function of compaction pressure, tableting behavior was compared before and after hot-melt extrusion by means of the compressibility, tabletability and compactibility profiles. A higher amorphous content in the formulation (as a result of hot-melt extrusion) negatively influenced the tableting behavior (e.g. lower tablet tensile strength). Hot-melt extrusion altered the mechanical properties towards more elastically deforming materials, thereby increasing tablet elastic recovery during decompression. The lower tensile strengths resulted from a combined effect of less interparticulate bonding areas (because of higher elastic recovery) and weaker bonding strengths per unit bonding area (between glassy particles).

KEYWORDS: hot-melt extrusion, tableting, elastic recovery, polyvinyl alcohol, oral drug delivery, immediate release.

INTRODUCTION

Due to the application of high-throughput screening and medicinal chemistry as drug selection procedures, there has been a significant increase in the number of new chemical entities (NCE) that are poorly water-soluble. To overcome solubility-related problems pharmaceutical research has shifted its focus to new formulation strategies where solid dispersions are a viable technique to improve the (oral) bioavailability of poorly water-soluble drug compounds (Janssens and Van den Mooter, 2009; Leuner and Dressman, 2000). Different approaches are reported to (molecularly) disperse the active pharmaceutical ingredient (API) in its carrier (Moneghini et al., 2001; Paudel et al., 2013; Sethia and Squillante, 2004), whereby hot-melt extrusion (HME) of polymeric formulations has the advantage of being a continuous manufacturing process that is generally applicable on industrial scale, without the requirement of further drying steps (Breitenbach, 2002).

In a previous paper we evaluated partially hydrolyzed polyvinyl alcohol (PVA) as carriers for immediate release applications processed via HME, whereby PVA-grades with a high degree of hydrolysis (DH) (70 – 90%) were identified as the most promising grades, since drug release from these polymeric solid solutions was independent of pH and ionic strength. However, due to their high melting point onset (150-170°C) higher extrusion temperatures were required to extrude these polymers, and sorbitol was added as a plasticizer of PVA-based formulations in order to sufficiently decrease the process temperature during HME (De Jaeghere et al., 2015).

Although various downstream processes for HME are available (injection molding, calendering, milling in combination with tableting), the latter remains an important technique to process hot-melt extruded formulations into their final dosage form (Treffer et al., 2013). Therefore, our previous research on HME of PVA-grades was extended to investigate the processability of PVA and sorbitol/PVA carriers after HME into tablets via milling and compression. Investigations into the impact of solid dispersion manufacturing techniques such as HME on the tableting behavior of pharmaceutical polymers has so far been limited (Agrawal et al., 2013; Boersen et al., 2013; Dinunzio et al., 2012; Mohammed et al., 2012) with minimal focus on the mechanical properties of the pure components. These properties are of

great importance in solid dosage form development and manufacturing, as they describe the behavior of a material subjected to an applied stress during compression (Iyer et al., 2013). In this study, PVA and sorbitol/PVA mixtures were processed by HME, characterized, milled and eventually processed into tablets via compression. Compressibility, tabletability and compactibility (CTC) profiles of those tablets were drafted and compared with the physical mixtures in order to evaluate the impact of different processing steps on the mechanical properties of these materials. Axial recoveries of the tablets were calculated and linked to the CTC-profiles. The focus of this research paper is essential since altered mechanical properties may impede further processability of the materials during tableting.

MATERIALS AND METHODS

Materials

Two types of PVA were used, a technical grade PVA_{505} (72-75% hydrolyzed) obtained from Kuraray (Hattersheim am Main, Germany) and a pharmaceutical grade $PVA_{4\text{-}88}$ (88% hydrolyzed) obtained from Merck (Darmstadt, Germany). Sorbitol (Fagron, Waregem, Belgium) was used as water-soluble plasticizer.

Hot-melt extrusion

Physical mixtures of PVA and sorbitol (0, 10, 40%) were processed via HME according to the method described by De Jaeghere et al. (2015) using a co-rotating, fully intermeshing twin-screw extruder (Prism Eurolab 16, Thermo Fisher, Germany) operating at a screw-speed of 100 rpm and a process temperature of 180°C across the entire barrel. The extruder was equipped with a gravimetric feeder (0.300 kg/h), two co-rotating twin-screws with 3 mixing zones and a cylindrical die of 3 mm. The extrudates were quench-cooled with liquid nitrogen, (cryo)-milled and sieved through a 300 µm sieve.

Tableting

Tablets (350 ± 10 mg) of physical mixtures and (cryo-)milled extrudates of PVA/sorbitol were prepared using a rotary tablet press (MODUL™ P, GEA Pharma Systems, Courtoy™, Halle, Belgium) equipped with a round concave (radius: 24mm) Euro B punch of 12 mm diameter at a tableting speed of 5 rpm. The compaction pressure ranged from 100 to 400 MPa after a pre-compression at 17 MPa. Tablets used for thermal analysis were compacted at 305 MPa, after pre-compression at 17 MPa. All tablets were immediately after compression characterized for tablet strength, dimensions and mass.

Thermal analysis

Differential scanning calorimetry (DSC) was performed before and after sample manipulation (HME, (cryo-)milling, tableting), whereby melting temperature (T_m), glass transition temperature (T_g), crystallization temperature (T_c) and heat of fusion (ΔH_f) were analyzed with a Q2000 DSC (TA Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. The DSC cell was purged with dry nitrogen at a flow rate of 50 ml/min. The samples were evaluated according to DSC conditions (heating rate of 10°C/min) during 3 cycles (heating, cooling and heating) from -20 to 200°C. Crystallinity (%) was calculated with reference to the enthalpy of fusion (ΔH_f^*) of a perfect PVA crystal (138.6 J/g) (Mallapragada et al., 1997) with the following formula:

$$X_c = \left(\frac{\Delta Hf}{\Delta Hf_*} \right) x\ 100$$

All results were analyzed in triplicate using the TA instruments Universal Analysis 2000 software. A one-way analysis of variance (ANOVA) was performed with SPSS Statistics 23 (IBM, New York, United States) to detect significant differences in T_g or T_m during extrusion, (cryo-) milling and tableting of both PVA-grades. Tukey analysis was used to determine differences in T_g and T_m between extrusion, (cryo-)milling and tableting.

X-ray diffraction

The crystallinity of PVA, sorbitol and CEL was investigated by means of X-ray diffraction (XRD). The XRD patterns were determined using a D5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with a voltage of 40 V in the angular range of $10° < 2\theta < 60°$ using a step scan mode (step width = 0.02°, counting time = 1s/step).

Solid-state ^{1}H-nuclear magnetic resonance

Solid-state ^{1}H-wideline nuclear magnetic resonance (NMR) measurements were carried out at ambient temperature on a Varian Inova 400 spectrometer in a dedicated wide-line probe

equipped with a 5 mm coil using the solid echo method (Mens et al., 2008). The samples were placed in 5 mm glass tubes, which were closed tightly with Teflon stoppers.

The T_{1H} relaxation decay times (spin-lattice relaxation in the lab frame) were measured by placing an inversion recovery filter in front of the solid echo part ($180°_{x'}$ - t - $90°_{x'}$ - t_{se} - $90°_{y'}$ - t_{se} - acquire). The length of the 90° pulse (t_{90}) was set to 1.6 µs and spectra were recorded with a spectral width of 2 MHz (0.5 µs dwell time), allowing an accurate determination of the echo maximum which is formed at $\tau = (3t_{90}/2 + 2t_{se}) = 7$ µs and this time point is calibrated to time zero. The integrated proton signal intensity was analyzed mono- or bi-exponentially as a function of the variable inversion time t according to:

$$I(t) = I_0^S \left(1 - 2\exp\left(-{}^{t}/_{T_{1H^S}}\right)\right) + I_0^L \left(1 - 2\exp\left(-{}^{t}/_{T_{1H^L}}\right)\right) + C^{ste}$$

'S' and 'L' refer to the fractions with short and long decay time, respectively.

All experimental data were analyzed using a non-linear least-squares fit (Levenberg-Marquardt algorithm). A preparation delay of 5 times the longest T_{1H} relaxation decay time was always respected between successive accumulations to obtain quantitative results.

Particle size distribution

Particle size distribution (PSD) of the powders was measured by laser diffraction (Mastersizer-S long bench, Malvern Instruments, Malvern, UK). The measurements were done via dry dispersion method in volumetrical distribution mode using a 300 RF lens combined with a dry powder feeder (Malvern Instruments, Malvern, UK) at a feeding rate of 3.0 G and a jet pressure of 2.0 Bar. Measurements were performed in triplicate.

Dynamic vapor sorption

Dynamic vapor sorption (DVS Advantage, Surface Measurement Systems, Middlesex, UK) was used to assess the overall hygroscopicity of the materials. Approximately 10-20 mg of sample was placed into the instrument microbalance where it was dried under a stream of dry

nitrogen at 25°C until equilibrium (e.g. a weight change of less than 0.002% per minute during at least 15 min). The samples were subsequently exposed to various relative humidities (RH) at 25°C, increasing from 0 to 80% in steps of 20%, from 80 to 90% and from 90 to 98% allowing equilibration at each interval.

Tablet Evaluation

All tablet evaluations were performed on ten tablets.

Tensile strength, breaking force and dimensions

Tablet breaking force, diameter and thickness were determined using a hardness tester (Type HT10, Sotax, Basel, Switzerland). Tablet diametric tensile strength of the tablets (MPa) was derived using the following equation of Fell and Newton (1968):

$$Tablet\ Tensile\ Strength\ (\sigma_t) = \frac{2P}{\pi D t}$$

where P, D and t denote the diametric breaking force (N), tablet diameter (mm) and tablet thickness (mm), respectively. This formula can be used for double-convex cylindrical tablets as was reported by Podczeck et al. (Podczeck et al., 2013).

Tablet porosity

The porosity of the formed compacts was calculated using the following equation:

$$Tablet\ Porosity = 1 - \frac{\rho_{app}}{\rho_{true}}$$

where ρ_{app} and ρ_{true} denote the apparent and true density (g/ml), respectively. Apparent density was calculated by dividing the tablet mass by the volume of the tablet, while the true density of all powders was measured using helium pycnometry (AccuPyc 1330, Micrometrics,

Norcross, U.S.A) at an equilibration rate of 0.0050 psig/min with the number of purges set to 10.

Tablet compaction characterization

Compacts were prepared at different compaction pressures (100 to 400 MPa with a pre-compression of 17 MPa), and tableting behavior (tabletability, compressibility and compactibility) was evaluated.

Tabletability was analyzed by plotting tablet tensile strength to the compaction pressure. *Compressibility* was analyzed by assessment of the tablet volume reduction (tablet porosity normalized by compaction pressure). *Compactibility* of pharmaceutical powders is generally described by use of the Ryshkewitch equation:

$$\sigma_t = \sigma_0 \, e^{-bP}$$

where σ_t and σ_0 denotes the tablet tensile strength (MPa) and limiting tablet tensile strength at zero porosity (MPa), respectively, b is an empirical constant and P denotes the tablet porosity (Ryshkewitch, 1953).

Axial recovery

Axial recovery of the tablets immediately after ejection (IAR) was calculated by use of the Armstrong and Haines-Nutt equation (Armstrong and Haines-Nutt, 1972):

$$IAR\ (\%) = \left(\frac{T_a - T_{id}}{T_{id}}\right) x\ 100$$

where T_a denotes the tablet height immediately after ejection (mm) and T_{id} the tablet height under maximum compression force at main compression (mm). The dimensions of 10 tablets, manufactured at equal conditions, were used to calculate the % IAR of each formulation at 4 compaction pressures.

RESULTS AND DISCUSSION

Characterization

Previous research work already proved the thermal stability of PVA_{505} and $PVA_{4\text{-}88}$ by means of thermogravimitric analysis (TGA). This technique showed an onset of thermal polymer degradation at 240°C, which indicated that PVA polymers are stable under the process conditions used in this study (e.g. a maximum extrusion temperature of 180°C) (De Jaeghere et al., 2015). Furthermore, the ability of sorbitol to act as low molecular weight plasticizer of PVA was identified. Therefore, melting of PVA/sorbitol mixtures was required to establish molecular interactions between polymer and sorbitol, as no effect of sorbitol was observed during first DSC heating cycle. The plasticizing effect of sorbitol was linked to its concentration as more interactions can be established between the OH-groups of both components, thus disrupting the structural regularity of PVA (De Jaeghere et al., 2015). DSC analysis was used to examine the influence of extrusion, (cryo-)milling and tableting on the physicochemical properties of PVA and sorbitol. T_g of sorbitol was lower in the (cryo-)milled extrudates due to their higher water content (an increase of 1-1.5% was observed compared to HME samples): after HME and (cryo-)milling T_g was -8.1±0.3°C and -15.5±0.1°C, respectively, for PVA_{505} and -3.6±0.2°C and -14.5±1.6°C, respectively, for $PVA_{4\text{-}88}$. Analysis of variance (ANOVA) showed no significant difference ($p > 0.05$) in T_g of both PVA-grades during extrusion, cryo-milling and tableting, however significant difference ($p < 0.05$) was observed in T_m of both PVA-grades, which was slightly increased during processing (Table 1).

Table 1. Thermal properties of non-plasticized and plasticized (containing 40% sorbitol) polyvinyl alcohol after extrusion, (cryo-)milling and tableting using a heating rate of 10°C/min. The significance of the results was determined with analysis of variance. Means of T_g (^{a,b}) or T_m (^{c,d}) in the same column with different superscripts are different at the 0.05 level of significance (Tukey) (n = 3).

				505 (72-75%)	**4-88 (88%)**
NON-PLASTICIZED (0% sorbitol)	**1st heating**		**T_g (°C)**	44.9 ± 2.1	48.1 ± 3.5
			$T_{m\ (ons.)}$ (°C)	155.0 ± 1.4	164.1 ± 1.6
	2nd heating		**T_g (°C)**	62.0 ± 0.7	67.1 ± 1.0
			$T_{m\ (ons.)}$ (°C)	131.5 ± 6.6	144.7 ± 9.6
PLASTICIZED (40% sorbitol)	**2nd heating**	**EXTRUSION**	**T_g (°C)**	34.3 ± 3.2^a	38.6 ± 1.1^a
			$T_{m\ (ons.)}$ (°C)	117.7 ± 2.4^c	133.1 ± 4.7^c
		CRYOMILLING	**T_g (°C)**	30.5 ± 2.5^a	37.9 ± 3.4^a
			$T_{m\ (ons.)}$ (°C)	121.8 ± 5.2^c	149.1 ± 3.3^d
		TABLETING	**T_g (°C)**	31.6 ± 1.5^a	38.2 ± 5.0^a
			$T_{m\ (ons.)}$ (°C)	131.2 ± 3.8^d	149.1 ± 2.2^d

DSC analysis showed endothermic peaks between 60-75°C and after 1-week XRD patterns showed some degree of crystallinity in the samples (Figure 1). This phenomena was linked to the crystallization of sorbitol polymorphs during storage (Nezzal et al., 2009; Sztatisz et al., 1977). Due to this (re)-crystallization of sorbitol, the plasticizing effect of sorbitol was reduced and T_m of PVA slightly increased.

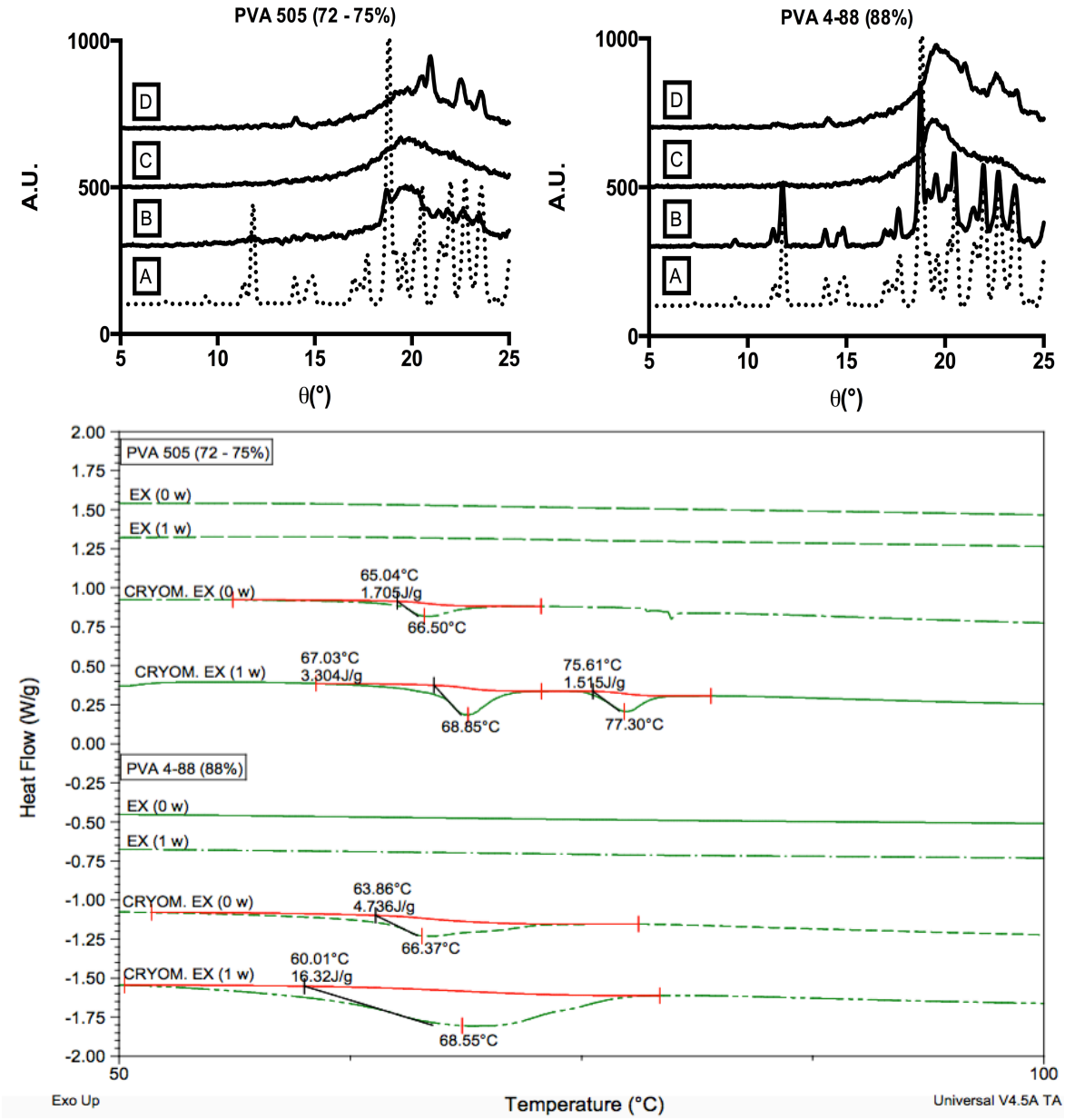

Figure 1. X-ray diffraction patterns (above) of sorbitol (A), physical mixture polyvinyl alcohol/sorbitol (60:40) (B), (cryo-)milled extrudate (C) and (cryo-)milled extrudate after 1 week (D). Differential scanning calorimetry profiles (under) of extrudate (EX) and (cryo-)milled extrudate at time point 0 and after 1-week.

Furthermore, solid-state ^{1}H-wideline NMR (Table 2) was performed, whereby a short relaxation decay time of 6.3s was found for semi-crystalline $PVA_{4\text{-}88}$, and a long relaxation decay time of 26.3s for crystalline sorbitol. After extrusion, $PVA_{4\text{-}88}$ and sorbitol interacted with each other, as both fractions (I_0^S and I_0^L) were changed compared to the physical mixtures and the relaxation decay times of $PVA_{4\text{-}88}$ and sorbitol were decreased. However, phase separation was observed for extrudates containing 40% sorbitol, as evidenced by the presence

of 2 relaxation decay times. Therefore, experiments were repeated with extrudates containing less sorbitol (e.g. 10%), whereby only one relaxation decay time of 14.2s was observed, which could mean that sorbitol was homogenized with $PVA_{4\text{-}88}$ and more stable inside the extrudates. This result was linked to the DSC results whereas no recrystallization of sorbitol was observed.

Table 2. Solid-state ^{1}H-wideline nuclear magnetic resonance relaxation decay times (T_{1H}) and fractions (I_O) of $PVA_{4\text{-}88}$, sorbitol, physical mixtures (PM) and extrudates (EX) containing 40% and 10% sorbitol.

Sample	T_{1H}^{S} (s)	I_o^{S} (%)	T_{1H}^{L} (s)	I_o^{L} (%)
$PVA_{4\text{-}88}$	6.3	100.0		
Sorbitol			26.3	100.0
$PVA_{4\text{-}88}$-Sorbitol (60:40) PM	6.0	63.4	25.4	36.6
$PVA_{4\text{-}88}$-Sorbitol (60:40) EX	3.5	88.0	15.7	12.0
$PVA_{4\text{-}88}$-Sorbitol (90:10) EX			14.2	100.0

PSD of both PVA-grades and sorbitol were measured by means of laser diffraction (Table 3). Although all powders were sieved to a fraction smaller than 300 µm, d_{90} –values exceeded 300 µm for all samples as there was a tendency for the material to agglomerate during the measurements. Fine powders are more subjected to agglomeration since their small particle size increases surface-mass ratio, which favors the bonding (Parikh, 2010).

Table 3. Mean particle size distribution of physical mixtures (PM) and (cryo-)milled extrudates (EX) of polyvinyl alcohol/sorbitol formulations, measured via dry laser diffraction (n=3).

		d_{10} (µm)	**d_{50} (µm)**	**d_{90} (µm)**
PVA_{505}	**PM**	47.6 ± 5.96	204.3 ± 4.74	404.1 ± 32.98
	EX	68.8 ± 0.07	187.6 ± 0.69	359.1 ± 6.39
$PVA_{4\text{-}88}$	**PM**	22.9 ± 0.52	164.4 ± 16.71	544.0 ± 7.41
	EX	73.4 ± 4.43	203.0 ± 5.78	367.2 ± 4.15

DVS was used to calculate moisture sorption and desorption isotherms in order to assess the hygroscopic behavior of the PVA/sorbitol mixtures (physical mixtures and (cryo-)milled extrudates) (Figure 2).

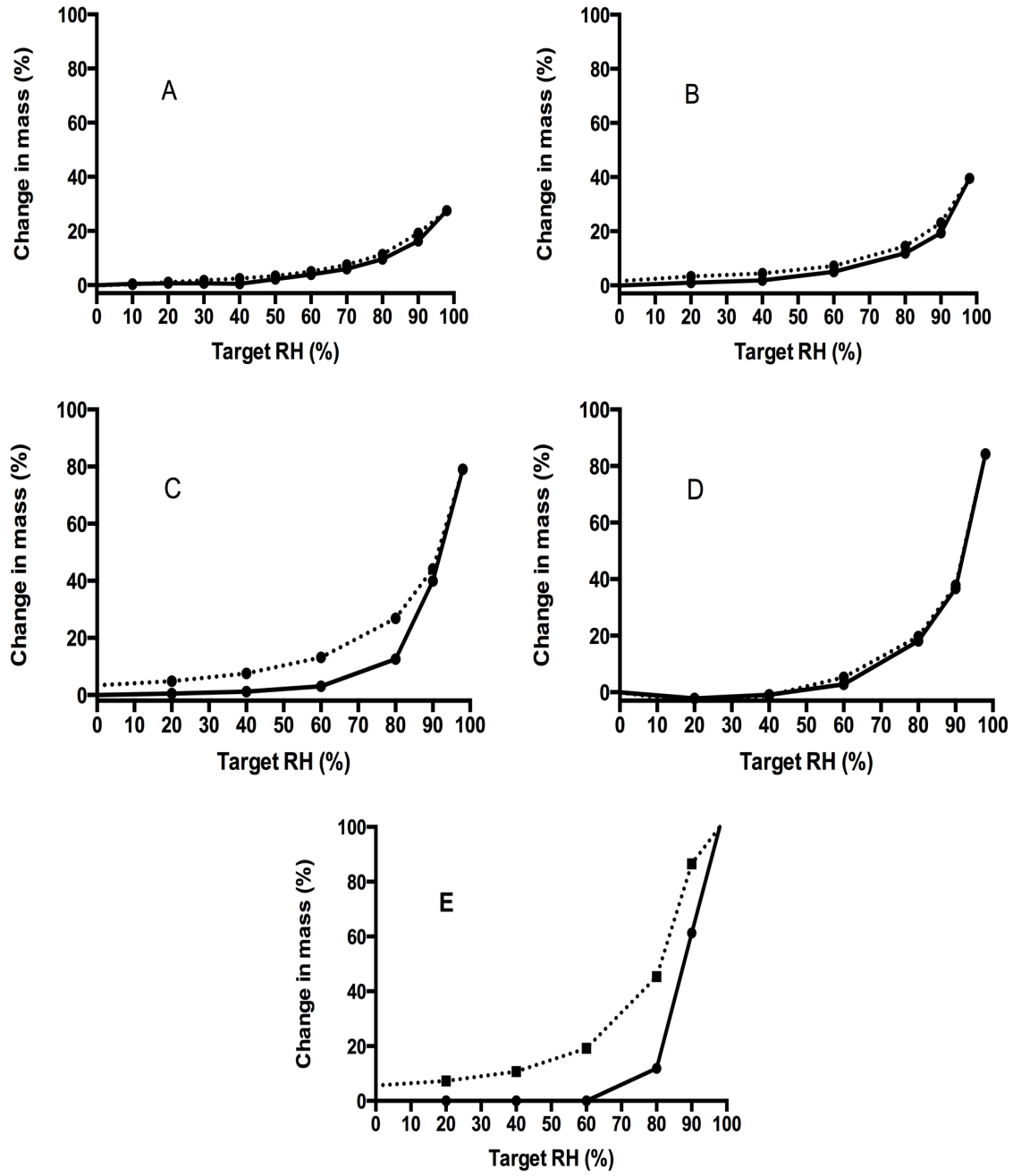

Figure 2. Dynamic vapor sorption (_) and desorption (…) curves of $PVA_{4\text{-}88}$ (A), $PVA_{4\text{-}88}$ (cryo-)milled extrudate (B), $PVA_{4\text{-}88}$/sorbitol (60:40) physical mixture (C), $PVA_{4\text{-}88}$/sorbitol (60:40) (cryo-)milled extrudate (D) and sorbitol (E) at 21°C.

The influence of sorbitol was clearly visible at extreme conditions (21°C/98%RH) as non-extruded PVA (A) had a water content of 30%, which increased up to 80% by addition of sorbitol (C). This was expected from the sorption isotherms of crystalline sorbitol which revealed water contents >80% at equal conditions. The level of hysteresis was negligible for pure PVA before and after extrusion (A,B) which could be attributed to intermolecular hydrogen bonding between the polymer chains (Assender and Windle, 1998), whereby the hydroxyl groups of PVA are not available for binding with water molecules. Interestingly, when comparing PVA/sorbitol (60:40) before and after extrusion (C,D) there was a remarkable difference in the level of hysteresis. While for the non-extruded formulation hysteresis was clearly present, it became negligible for the extruded formulation. This was explained by DSC data which showed that interactions between PVA and sorbitol only occurred when sorbitol was melted by HME (De Jaeghere et al., 2015). The resulting extrudates are dense particles (Page and Maurer, 2014). It has been described in literature that for amorphous sugars the packing of molecules affected the water sorption behavior. In dense glassy particles, adsorption of water occurs mainly on the surfaces (weak interactions) because of the absence of pores penetrable to water (Jouppila, 2006). This is applicable for the PVA/sorbitol extrudates, since DSC results revealed that amorphous sorbitol clusters are present in the PVA carrier (separate T_g for sorbitol and PVA). The moisture content of all formulations was lower (< 5%) at laboratory conditions (35-60% RH).

Tablet properties

Tabletability

Tabletability describes the relationship between tensile strength of a tablet and compaction pressure exerted on these tablets (Figure 3) (Joiris et al., 1998). A strong increase of tablet strength was observed at low compaction pressures for most mixtures, however the curves levelled off at higher compaction pressures. This was explained by the phenomenon of elastic recovery, which occurred after removal of the compaction load (e.g. decompression).

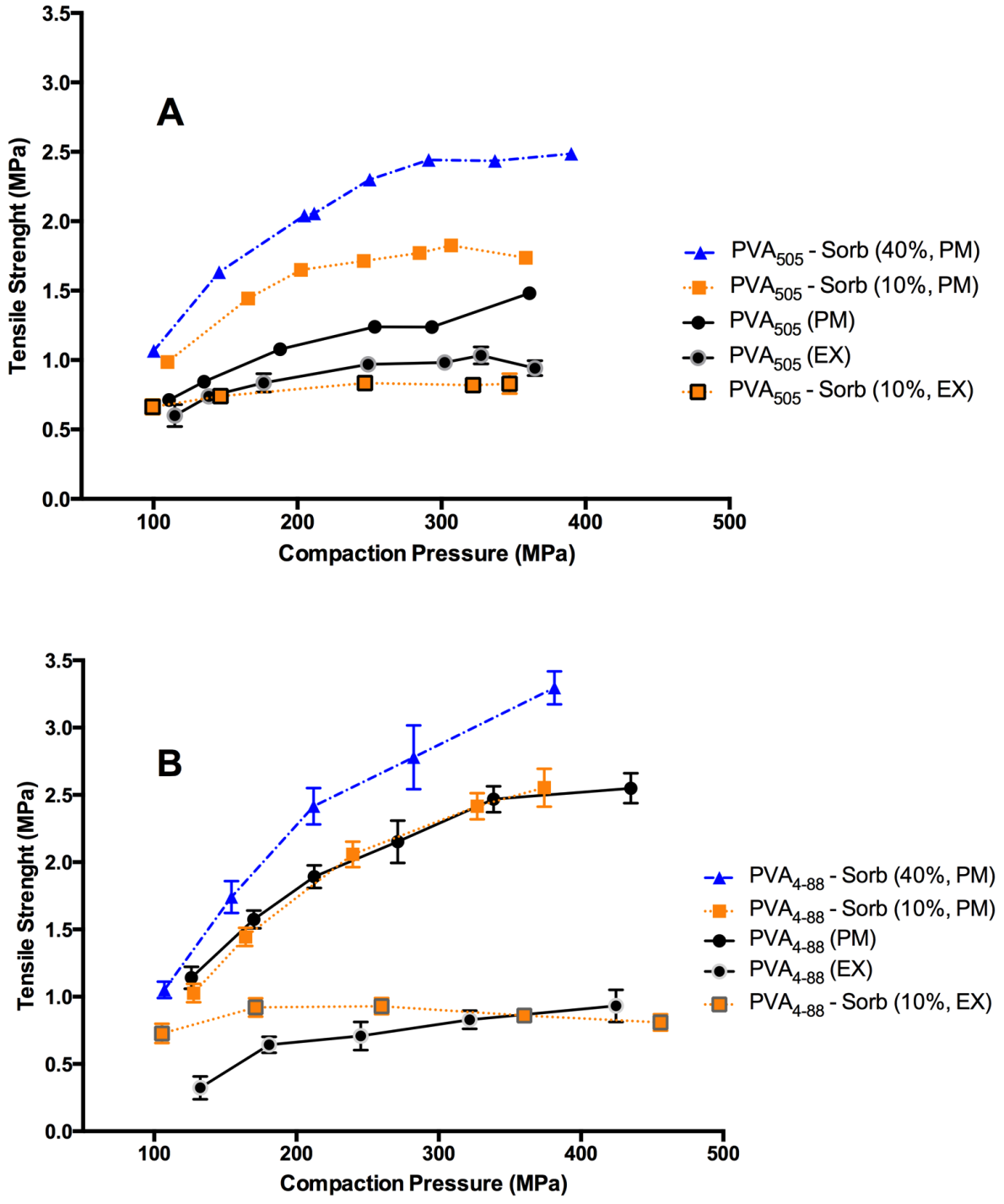

Figure 3. Tabletability of physical mixtures (PM) and hot-melt extruded (EX) samples formulated with PVA_{505} (A) or $PVA_{4\text{-}88}$ (B), in combination with 0, 10 or 40% sorbitol (n=10).

As powders are compressed, particles come in closer contact by volume reduction mechanisms (particle rearrangements, fragmentation, plastic/elastic deformation), which reduce tablet porosity. This leads to a steep increase in the bonding area and consequently in

tensile strength of the tablets (Duberg and Nyström, 1986). In the low-pressure region, elastic recovery of the tablet after compression was negligible and the tablet strength increased linear with the compaction pressure. At higher compaction pressures, tablet porosity was already reduced considerably so further increase of the compaction pressure led to elastic deformation rather than a further decrease in porosity (Sun and Grant, 2001). Inevitable, such particles store elastic energy, which is linked to a certain elastic recovery at decompression, thereby reducing the bonding area. The associated reduced points of contact between neighboring particles in the tablet caused a level off in tensile strength (Sun, 2011). In general, tabletability curves of the extrudates were lower than those of the physical mixtures and the increase in tablet strength was limited (e.g. level off at lower compaction pressures). These results were in line with earlier findings on the tabletability of HME materials (Agrawal et al., 2013; Boersen et al., 2013). While the tensile strength of physical mixtures increased in function of the concentration of crystalline sorbitol (a value of 2.5 MPa was recorded for 40% sorbitol at a compaction pressure of 300 MPa), the tensile strength of extruded samples was lower at higher amorphous sorbitol content (at 40% sorbitol content the tablets manufactured at various compaction pressures were even too soft for measuring the diametrical breaking force) (Figure 3, A). In addition, maximum tabletability (e.g. highest tensile strength) was obtained at lower compaction pressures for extrudates compared to physical mixtures, at about 200 MPa and > 400 MPa, respectively (Figure 3, B). Differences in particle size (Table 3) could explain the lower position of the curves but could not explain the limited increase in tablet strength and the early level off at lower compaction pressures. Agrawal et al. attributed this to the possible weaker interactions between glassy materials resulting in tablets with lower tensile strengths (Agrawal et al., 2013). In this study it was hypothesized that the process of HME altered the mechanical properties of the PVA/sorbitol-carrier and therefore changed its volume reduction mechanism towards a more elastically deforming material. Iyer et al. reported an increase in the elasticity of melt-extruded hydroxypropylmethylcellulose acetate succinate (HPMCAS) and linked this with a likely higher elastic recovery after compression (Iyer et al., 2013). It is possible that the HME-process induced a similar change in mechanical properties of PVA/sorbitol, leading to an increased elastic deformation and hence higher elastic recoveries with increasing amorphous fraction (Figure 1: the absence of sharp crystalline peaks in the XRD-data of (cryo-)milled extrudates compared to the physical

mixtures). Boersen et al. reported similar findings, where brittle fracture index experiments showed a reduction in the plasticity of HME-powders (Boersen et al., 2013).

Comparison of figures A and B indicated that physical mixtures of non-extruded $PVA_{4\text{-}88}$ yielded tablets of higher tensile strengths than physical mixtures of PVA_{505} at equal compaction pressures (an increase of 80% in tensile strength was recorded at a compaction pressure of 300 MPa). This was explained by the differences in crystalline content of both polymers, since PVA is a semi-crystalline polymer (Agrawal et al., 2013). The crystalline content of pure $PVA_{4\text{-}88}$ (32.1%) was significantly higher compared to pure PVA_{505} (16.6%), which resulted in 'stronger' tablets, and HME reduced the crystallinity of $PVA_{4\text{-}88}$ significantly (21.4%) compared to PVA_{505} (14.4%) as the higher extrusion temperatures disrupted inter- and intramolecular hydrogen bonding. Additionally, differences in PSD of the physical mixtures (Table 3) also contributed to this phenomenon.

Tabletability on its own does not provide a fundamental understanding of the tableting behavior of pharmaceutical powders, since bonding area (reflected by compressibility) and bonding strength per unit bonding area (reflected by compactibility) also determine the tensile strength of tablets. Only by simultaneously analyzing particle size, compressibility, compactibility and tabletability, an extensive insight in the tablet properties can be obtained (Sun and Grant, 2001).

Compressibility

Compressibility of a material is its ability to be reduced in volume as a result of an applied pressure (Joiris et al., 1998). The compressibility profiles showed similar trends as tabletability, with physical mixtures having greater compressibility (e.g. yielding lower tablet porosities) compared to the extrudates (Figure 4). While the lowest tablet porosities were observed for physical mixtures with higher content of crystalline sorbitol, porosities increased in extrudates with more amorphous content (e.g. high sorbitol content). In addition, maximum compressibility (e.g. lowest tablet porosity) was obtained at a lower compaction pressures for extrudates containing (amorphous) sorbitol compared to physical mixtures, at about 250 MPa and >400 MPa, respectively (Figure 4).

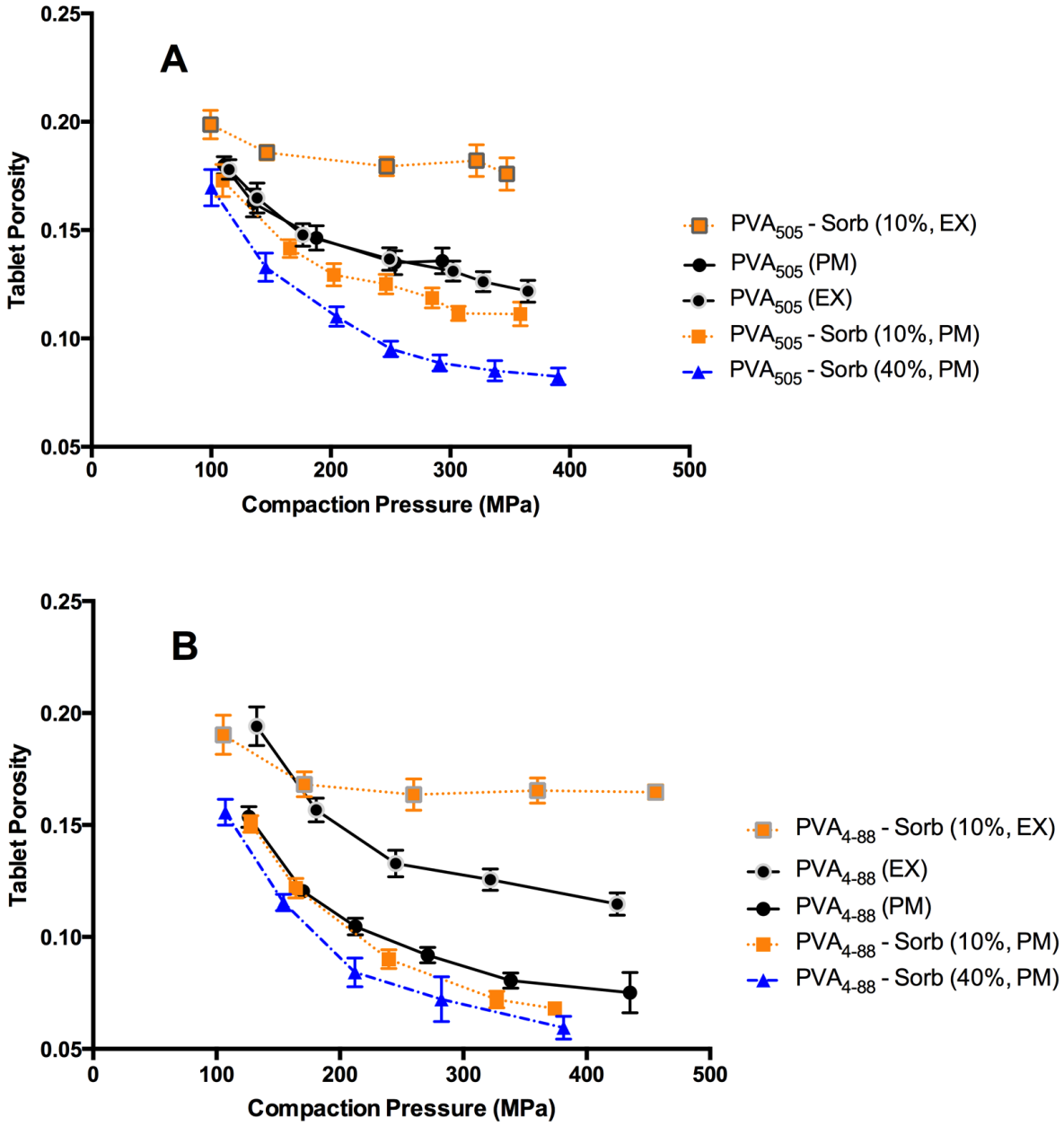

Figure 4. Compressibility of physical mixtures (PM) and hot-melt extruded (EX) samples formulated with PVA_{505} (A) and $PVA_{4\text{-}88}$ (B), in combination with 0, 10 or 40% sorbitol (n=10).

The differences between physical mixtures and extrudates were linked to HME. Higher amorphous content in the extrudates induced an early level off in the compressibility profiles, resulting in constant tablet porosity at higher compaction pressures because of the effect of elastic recovery (Figure 4). These results were in line with tabletability profiles where an early flattening was observed in tablet tensile strength of the extrudates. Therefore, the

assumption of an altered volume reduction mechanism due to HME was strengthened. If HME altered the mechanical properties of PVA/sorbitol towards a more elastically deforming material, the stored elastic energy increased in function of the applied external force and hence resulted in more elastic recovery of the tablets during decompression (Sun and Grant, 2001). Therefore, the reduced porosity due elastic deformation was counteracted by the elastic recovery causing a level off in the curve.

By comparing tablet porosities at equal compaction pressures for physical mixtures of PVA_{505} and $PVA_{4\text{-}88}$, it was clear that particle size had a strong influence. Lower tablet porosities were detected with $PVA_{4\text{-}88}$ –mixtures (tablet porosity was 0.14 and 0.08 for physical mixtures with $PVA_{4\text{-}88}$ and PVA_{505}, respectively), since these had smaller particle sizes (Table 3). However, the effect of extrusion on the pure polymers was clearly visible. While for PVA_{505} the curves of physical mixtures and extrudates are superimposed (Figure 4,A), this is not the case for $PVA_{4\text{-}88}$ since higher tablet porosities were reached for the extrudates of $PVA_{4\text{-}88}$ (Figure 4,B). This was explained by the differences in crystalline content of both polymers. Extrusion of pure $PVA_{4\text{-}88}$ increased the amorphous fraction of the semi-crystalline polymer, which favored elastic deformation and hence increased the elastic recovery. This was not the case for pure PVA_{505}, since the crystalline content did not change remarkably.

Compactibility

Compactibility describes the relationship between tensile strength and porosity (Figure 5). Tablet tensile strength decreased exponentially with increasing porosities, as described by the Ryshkewitch equation (Ryshkewitch, 1953). Although physical mixtures and extrudates showed large differences in tabletability (e.g. tensile strengths), these differences were less distinct when tablet tensile strength was plotted at zero porosity, especially for PVA_{505}.

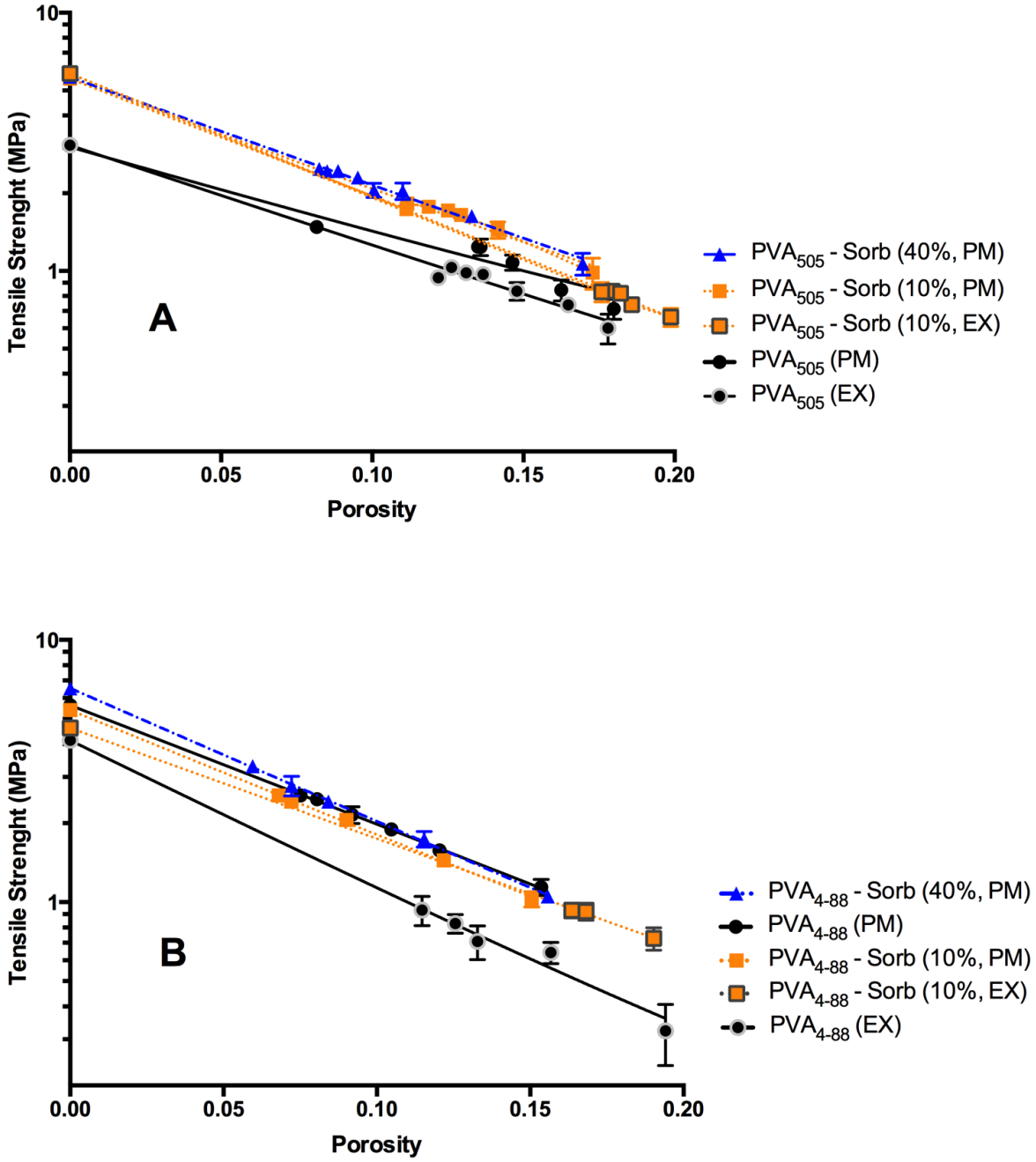

Figure 5. Compactibility of physical mixtures (PM) and hot-melt extruded (EX) samples formulated with PVA_{505} (A) or $PVA_{4\text{-}88}$ (B), in combination with 0, 10 or 40% sorbitol (n=10).

Since compactibility can be used to quantify bonding strength between particles at zero porosity (Joiris et al., 1998; Maarschalk et al., 1996; Sun, 2011), these results suggested that the higher tensile strength was more related to the interparticulate bonding area (e.g. compressibility) compared to the bonding strength per unit bonding area (e.g. compactibility).

However, compactibility curves of both PVA-types gave evidence of weaker interactions between glassy materials (Agrawal et al., 2013) since compression of physical mixtures with increasing sorbitol content (e.g. higher crystalline fraction) resulted in a higher tensile strength at zero porosities. This effect was clearly reflected in the lower position of the compactibility curve of pure $PVA_{4\text{-}88}$ extrudates compared to the physical mixture (Figure 5, B), which was linked to the lower crystalline content of the semi-crystalline polymer after HME. This effect was not significant for PVA_{505} and therefore those curves (PM vs. EX) were almost superimposed at zero porosity (Figure 5,A), indicating that almost no changes in bonding strength occurred. In general, this study revealed that differences in tablet tensile strength for PVA/sorbitol carriers were the result of altered interparticulate bonding areas (elastic recovery and particle size) combined with a change in the bonding strengths for glassy materials (Agrawal et al., 2013) after extrusion.

Axial recovery

Axial recovery of the tablets calculated immediately after tablet ejection was selected as the "out-of-die" recovery descriptor. For each formulation, IAR was calculated for tablets of non-extruded physical mixtures and extruded mixtures at 4 compaction pressures. The results are shown in Figure 6 as a ratio of the IAR before and after extrusion in function of the compaction pressure.

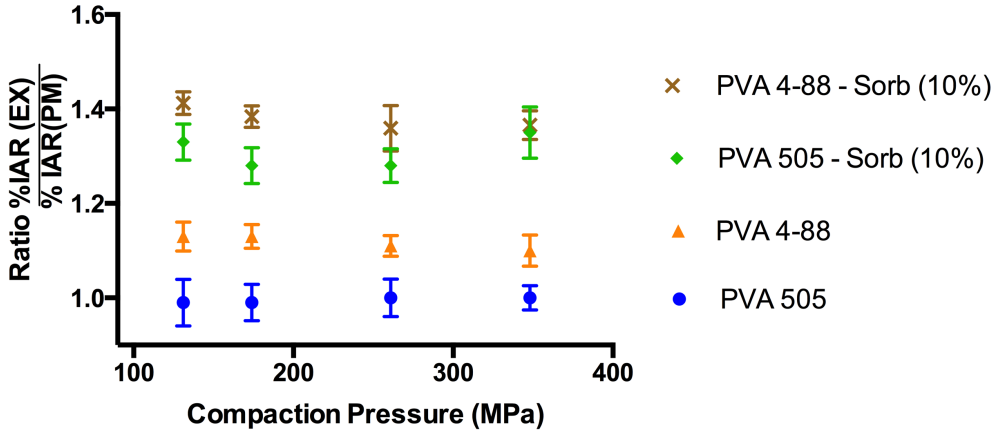

Figure 6. Immediately after ejection axial recover-ratio of physical mixtures (PM) and hot-melt extruded samples (EX) at various compaction pressures for formulations containing polyvinyl alcohol and sorbitol (n=10).

All calculated ratios were higher or equal to the value 1 indicating that tablets of extruded powders experienced higher or equal IAR compared to tablets of their physical mixtures (e.g. not subjected to HME). Only for pure PVA_{505}, HME had no impact on the IAR-ratio of the tablets (ratio = 1), as no change in crystalline content of pure PVA_{505}-polymer was observed after HME. However, IAR-ratios of pure $PVA_{4\text{-}88}$ were > 1 since HME affected the amorphous content of the polymer. The addition of sorbitol to the formulations, which changed from crystalline to amorphous state after HME, resulted in higher %IAR ratios of the tablets. These results showed that the higher amorphous content of formulations due to HME was reflected in the IAR of the tablets. Additionally, these results were in line with the CTC-profiles and confirmed the hypothesis that due to HME, materials were transformed towards a more amorphous state, hereby experiencing more elastic deformation during compression.

CONCLUSIONS

This study demonstrated that HME could alter the mechanical properties of PVA/sorbitol carriers, thereby negatively affecting the tableting behavior (e.g. lowering tablet tensile strength) with increasing amorphous content. This resulted from a combined effect of less interparticulate bonding areas (because of higher elastic recoveries) and weaker bonding strengths per unit bonding area (e.g. lower tensile strengths at zero porosity). In general, it can be concluded that it will be necessary to further optimize the formulation (e.g. plasticizer content) in order to improve the tableting behavior of PVA/sorbitol extrudates.

Acknowledgements

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4

THE USE OF PARTIALLY HYDROLYZED POLYVINYL ALCOHOL IN THE PRODUCTION OF HIGH DRUG-LOADED PELLETS FOR IMMEDIATE RELEASE USING EXTRUSION/SPHERONIZATION

De Jaeghere, W., Vercruysse, J., Remon, J.P., Vervaet, C., 2016. The use of partially hydrolyzed polyvinyl alcohol in the production of high drug-loaded pellets for immediate release using extrusion/spheronization. *(In preparation)*

ABSTRACT

Partially hydrolyzed polyvinyl alcohol was evaluated as pelletisation aid for the production of pellets with a high acetaminophen concentration (> 70%). It was found that the inclusion of a minimal microcrystalline cellulose concentration was required to overcome problems related to the tackiness effect of partially hydrolyzed polyvinyl alcohol. Fifteen formulations were screened with varying acetaminophen concentration (70-90%) and partially hydrolyzed polyvinyl alcohol/microcrystalline cellulose ratio (0/100-50/50), whereby a formulation containing 70% acetaminophen, 6% partially hydrolyzed polyvinyl alcohol and 24% microcrystalline cellulose was the most promising formulation with a narrow particle size distribution (with a low span), low aspect ratio (≤ 1.2), good sphericity (> 0.9) and low friability (< 1%). Polyvinyl alcohol-based pellets with a high drug load were also evaluated for a fixed-dose combination application, combining acetaminophen with tramadol hydrochloride in a ratio of 325/37.5 (w/w). The optimal water content was lower compared to the acetaminophen formulation, due to a higher aqueous solubility of tramadol hydrochloride, while the overall pellet quality (span, aspect ratio, sphericity and friability) was slightly decreased. The *in vitro* dissolution profiles showed complete tramadol hydrochloride and acetaminophen release within 10 and 20 min, respectively.

KEYWORDS: extrusion, spheronization, polyvinyl alcohol, pellets

INTRODUCTION

Multiparticulate drug delivery systems (e.g. pellets) are important for therapeutic applications due to their distinct advantages compared to single unit systems such as reproducible and generally short gastric/intestinal residence time, flexibility to blend pellets with different compositions or release patterns (personalized medicines), and low risk of dose dumping (Dukic-Ott et al., 2007). Pellets, which for pharmaceutical applications are defined as small (between 0.5 and 2.00 mm), free-flowing, spherical particles, can be obtained by solution or suspension layering of cores, powder layering, spray congealing, melt spheronization or extrusion/spheronization (Lustig-Gustafsson et al., 1999). The latter is the best option to produce pellets with high drug load. However, this technique requires specific properties of the formulation during the different steps of the process: (a) a cohesive wet mass which does not adhere to the extruder and retains some degree of rigidity; (b) the extrudates need to be brittle enough to break into smaller extrudates and contain some degree of plasticity to deform into spheres (Swarbrick, 2006). As most drug molecules do not exhibit these characteristics, microcrystalline cellulose (MCC) is conventionally included as excipient to obtain formulations with sufficient rigidity, plasticity and water absorbing capacity. However, the use of MCC has distinct disadvantages, such as higher batch-to-batch variability due to its natural origin, long disintegration times (or even no disintegration at all), incompatibility with certain drugs (e.g. ranitidine) (Basit et al., 1999). Furthermore, the drug load in MCC-based pellets is limited (Mallipeddi et al., 2010), which restricts the use of those pellets in fixed-dose combinations (FDC), whereby two or more drugs are combined inside the pellets. Combination drug therapy is recommended for elderly and long-term care patients in order to facilitate patient compliance (Raffa, 2001). Therefore, several alternatives such as biopolymers (e.g. starch, chitosan) or synthetic polymers (e.g. hydroxypropylmethylcellulose, polyethylene oxide) are proposed in order to decrease MCC concentration in the pellets. However, these materials have inferior properties (e.g., less water holding capacity, ionic polymers require granulation liquid with a specific pH) for extrusion/spheronization, compared to MCC (Dukic-Ott et al., 2009).

In his study, partially hydrolyzed polyvinyl alcohol (PVA) is evaluated as pelletisation aid in high drug-loaded pellets produced by extrusion/spheronization, whereby pellet properties (e.g. aspect ratio (AR), sphericity, particle size distribution (PSD)…) were compared with MCC pellets as a reference. Single-drug pellets as well as pellets for FDC therapy were investigated, the latter combining acetaminophen with tramadol hydrochloride.

MATERIALS AND METHODS

Materials

A pharmaceutical grade $PVA_{4\text{-}88}$ (88% hydrolyzed), obtained from Merck (Darmstadt, Germany), and microcrystalline cellulose (MCC) (Avicel® PH101) (FMC Wallingstown, Little Island, Cork, Ireland) were used as pelletisation aids. Micronized acetaminophen (Atabay, Istanbul, Turkey) and tramadol hydrochloride (Proto Chemicals, Mitlödi, Switzerland) were used as model drugs. Demineralized water or an aqueous solution of PVA were used as granulation liquid.

Production of pellets

Active pharmaceutical ingredient (API), PVA and Avicel® PH101 or API and Avicel® PH101 (batch size: 200g) were mixed in different ratios during 5 min in a planetary mixer (Kenwood Chief, Hampshire, UK), using a K-shaped mixing arm (Table 1). Demineralized water or a PVA aqueous solution (prepared by dissolving PVA in demineralized water at 80°C and cooled down to room temperature prior to addition) was gradually added to the powder mixture, while mixing was continued during 10 min. The wet mass was extruded at an extrusion speed of 100 rpm using a single screw extruder (Dome extruder DG-L1, Fuji Paudal, Tokyo, Japan) equipped with a dome-shaped extrusion screen with 1.0 mm perforations. The resulting extrudates were spheronized for 1 min at a speed of 1000 rpm using a spheronizer having a cross-hatched geometry friction plate (Caleva Model 15, Caleva, Sturminster Newton, Dorset, UK). The pellets were oven dried for 24h at 40°C. Each batch of pellets was sieved for 5 min at 2 mm amplitude using a sieve shaker (Retsch, Haan, Germany) to obtain the 710-1000 µm size fraction.

Table 1. Composition of pellet formulations.

	Concentration (%)				
Form.	Acetaminophen	PVA	MCC	Ratio (PVA/MCC)	Water content (%)*
1	70	0	30	0/100	-
2	70	1.5	28.5	5/95	53.3
3	70	3	27	10/90	46.2
4	70	6	24	20/80	38.3
5	70	15	15	50/50	-
6	80	0	20	0/100	-
7	80	1	19	5/95	43.3
8	80	2	18	10/90	40.6
9	80	4	16	20/80	33.2
10	80	10	10	50/50	22.9
11	90	0	10	0/100	-
12	90	0.5	9.5	5/95	36.3
13	90	1	9	10/90	35.0
14	90	2	8	20/80	30.2
15	90	5	5	50/50	24.5
16	-	-	100	-	120
17	50	-	50	-	55.7

*Water content was calculated as a percentage of the total dry weight of each formulation

Characterization

Pellet size and shape

The size and shape of the pellets were determined using dynamic image analysis (QicPic, Clausthal-Zellerfeld, Germany). D_{10}, D_{50} and D_{90}, which are the respective particle sizes at 10, 50 and 90% cumulative undersize, were determined (Kooiman et al., 2009). Furthermore, the width of the PSD was determined by calculating the span, as follows:

$$Span\ (\mu m) = D_{90} - D_{10}$$

An independent sample t-test was performed with SPSS Statistics 23 (IBM, New York, United States) to detect significant differences in span between formulations. The shape of the pellets was expressed as AR and sphericity. AR was defined as the ratio of the maximal and minimal Feret diameter ($Feret_{max}$ and $Feret_{min}$, respectively).

$$AR = \frac{Feret_{max}}{Feret_{min}}$$

Sphericity was defined as the ratio between the perimeter of a circle that has the same projected area (A) as the particle (P_{EQPC}) to the measured perimeter (P_{REAL}), and is thus a value between 0 and 1 (Yu and Hancock, 2008).

$$Sphericity = \frac{P_{EQPC}}{P_{REAL}} = \frac{2\sqrt{\pi A}}{P_{REAL}}$$

The measurements were performed in triplicate.

Loss on drying

After drying, the residual moisture content of the pellets was analyzed by loss on drying (LOD) using a Mettler LP16 moisture analyzer, including an infrared dryer and a Mettler PM460 balance (Mettler-Toledo, Zaventem, Belgium). A sample of approximately 2 g was dried at 105°C until the rate of change was less than 0.1% LOD per 30s and the % LOD was then recorded. The measurements were performed in triplicate.

Friability

Pellet friability was determined using a friabilator equipped with an abrasion drum (Pharma Test, Hainburg, Germany). Approximately 10 g pellets within the size range of 710-1000 µm were accurately weighed and added to the abrasion drum together with 200 glass beads (4

mm in diameter). The friabilator was set at 25 rpm during 10 min. At the end of the run, the content of the abrasion drum was sieved using a 500 µm sieve and the fraction below 500 µm was accurately weighed. Friability was measured in triplicate and calculated as follows:

$$Friability\ (\%) = \frac{Fraction < 500\ \mu m\ (g)}{Total\ sample\ (g)}\ x\ 100$$

Image analysis

Photomicrographs of pellets were taken with a digital camera (Camedia® C-3030 Zoom, Olympus, Tokyo, Japan), linked with a stereomicroscope system (SZX9 DF PL 1.5x, Olympus, Tokyo, Japan). A cold light source (Highlight 2100, Olympus, Germany) and a ring light guide (LG-R66, Olympus, Germany) were used to obtain top light illumination of the pellets against a dark surface.

Scanning electron microscopy (SEM) was used to determine differences in pellet surface morphology. Prior to imaging, samples were coated with a thin gold layer. SEM images were recorded using a tabletop SEM (PHENOM™, FEI Company).

***In vitro* dissolution**

Drug release from pellets was determined using USP apparatus 2 (paddles), in a VK 7010 dissolution system combined with VK 8000 automatic sampling station (Vankel Industries, New Jersey, USA). The amount of pellets corresponding to 500 mg acetaminophen or 325 mg acetaminophen and 37.5 mg tramadol hydrochloride were placed in 0.1 N HCl pH 1 (900 ml, at a temperature of 37 ± 0.5°C), while the rotational speed of the paddles was 100 rpm. Samples of 5 ml were withdrawn at 10, 20, 30, 40, 50, 60, 70, 80, 100 and 120 min (without medium replacement) and spectrophotometrically analyzed for acetaminophen concentration at 244 nm by means of a Shimadzu UV-1650PC UV-VIS double beam spectrophotometer (Antwerpen, Belgium). The acetaminophen content in the samples was determined by linear regression using a calibration curve between 1.5 and 15 µg/ml. Tramadol hydrochloride was analyzed via high performance liquid chromatography (HPLC). The HPLC

system (Merck-Hitachi D-7000, Tokyo, Japan) consisted of a pump (Merck-Hitachi L-7200), an autosampler (Merck-Hitachi L-7250), a LichroSpher 100 RP-8 column (4.6 x 150 mm, 5µm) (Merck Millipore, Darmstadt, Germany), and an UV-detector (Merck-Hitachi L-7400) set at 272 nm. For the preparation of the mobile phase, 0.05 M monobasic potassium phosphate was mixed with acetonitrile (Biosolve, Valkenswaard, the Netherlands) in a ratio 4:1 (vol/vol). The analyses were performed at 25°C, and the flow rate was set at 1 ml/min. A volume of 25 µL was injected onto the HPLC system. Each formulation was evaluated in triplicate.

RESULTS AND DISCUSSION

When processing acetaminophen and MCC formulations via extrusion/spheronization the drug load was limited to 50% in order to obtain pellets of acceptable quality. At higher drug content process yield as well as pellet properties (shape, size) were negatively affected. Therefore, PVA was incorporated in the formulation and evaluated as pelletisation aid in order to increase the maximum achievable drug concentration in the pellets while maintaining pellet quality. However, preliminary studies have shown that the inclusion of at least 5% MCC was required to overcome problems related to the tackiness effect of PVA during extrusion. MCC acts like a 'molecular sponge', which is able to absorb and retain large quantities of water due to its large surface area and high internal porosity, and therefore hold water when pressure was applied during extrusion (Fielden et al., 1988).

To assess the impact of PVA on pellet quality formulations were processed with varying acetaminophen concentration (70-90%) and PVA/MCC ratio (0/100 to 50/50; w/w) (Table 1). The highly drug loaded formulations without PVA could not be spheronized, as the extrudates were too brittle and fragmented during spheronization (F1, F6 and F11). Formulation 5, containing 15% PVA, was not processable as the extrudates were too sticky rendering spheronization impossible.

A lower water content was required for formulations containing more acetaminophen and having a higher PVA/MCC ratio, which was linked to the lower MCC concentration in these samples and the water-holding capacity of MCC (Chatlapalli and Rohera, 1998) (Verheyen et al., 2009). Additionally, when Law et al. combined hydrophilic polymers (sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose and polyvinylpyrrolidone) with MCC to improve extrusion/spheronization, the results indicated that the inclusion of adhesive polymers required lower levels of water for successful extrusion/spheronization (Law and Deasy, 1998). Similarly, those formulations with a higher PVA concentration required less water for extrusion/spheronization purposes based on the tackiness of PVA when wetted.

Pellets were manufactured via extrusion/spheronization either after addition of PVA as a dry powder (e.g. dry mixture of PVA, MCC and drug wetted with pure water) or as an aqueous dispersion (e.g. dry mixture of MCC and drug wetted with aqueous PVA solution). However, some formulations could not be processed via the wet addition method, either because the PVA concentration was too high compared to the available amount of water resulting in a too viscous granulation liquid (e.g. F10: 43.7% (w/w) PVA dispersion required for wetting) or the extrudates were too brittle and could not be spheronized, possibly due to the low PVA/MCC content (F12 and F13). After drying, the residual moisture content was below 1.5% for all formulations.

The PSD of different formulations (after wet and dry addition of PVA) were compared with reference pellets made of pure MCC pellets (F16) (Figure 1).

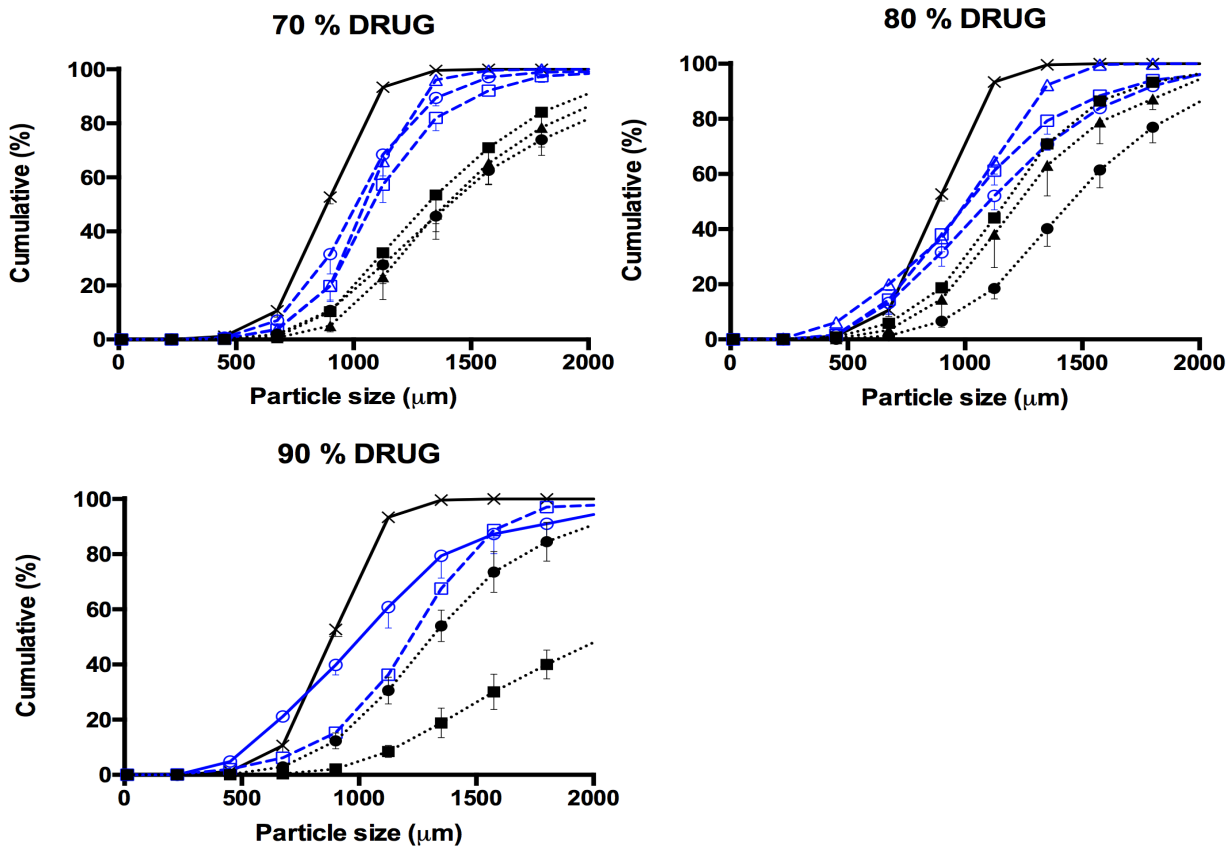

Figure 1. Particle size distributions (mean ± standard deviation, n=3) of formulations containing 70% drug (Form. 2 (o), 3 (□), 4 (Δ)), 80% drug (Form. 7 (o), 8 (□), 9 (Δ)) or 90% drug (Form. 14 (o), 15 (□)) and polyvinyl alcohol added dry (black closed symbol) or wet (blue open symbol). Microcrystalline cellulose pellets were used as reference (X).

Overall the pellet size of formulations containing PVA was higher compared to the reference (Figure 1, Table 2).

		PVA method addition	
	Formulation	Dry	Wet
70 %	F2	1486 ± 348[a]	640 ± 23[b]
	F3	1040 ± 85[a]	679 ± 52[b]
	F4	1158 ± 197[a]	467 ± 32[b]
80 %	F7	1198 ± 181[a]	1114 ± 64[a]
	F8	926 ± 42[a]	998 ± 35[a]
	F9	965 ± 68[a]	803 ± 22[b]
90 %	F14	1143 ± 198[a]	1172 ± 355[a]
	F15	2338 ± 253[a]	805 ± 73[b]
Ref.	MCC	434 ± 19	

Table 2. Span (d_{90}-d_{10}, μm) (mean ± standard deviation, n=3) of formulations as a function of drug concentration (70-90%), polyvinyl alcohol/microcrystalline cellulose ratio (0/100 – 50/50). Polyvinyl alcohol was added either as dry powder or aqueous dispersion. The significance of the results was determined with independent sample t-test. Span values in the same row with different superscripts are different at the 0.05 level of significance.

During extrusion it was observed that extrudates containing PVA were less brittle compared to MCC extrudates; Hence, PVA-containing extrudates broke into longer segments during spheronization, yielding larger pellets.

An independent sample t-test was used to detect significant differences in span between formulations either processed with PVA in dry powder form or as aqueous dispersion. In general, addition of PVA in the formulation as an aqueous dispersion significantly ($P < 0.05$) reduced span values, possibly due to a more homogeneous distribution of the PVA solution, which acts as a liquid binder. Chatlapalli also reported that a liquid binder (e.g. hydroxypropylcellulose in isopropyl alcohol) was more effective than a binder added in powdered form (Chatlapalli and Rohera, 1998). At higher PVA/MCC ratio the PSD was narrower (e.g. a lower span). Formulation 4 processed via the wet addition method of PVA resulted in the lowest span (467 ± 32 μm) which was not significantly different ($p > 0.05$) from the reference MCC pellets. However, it was observed that increasing the drug load from 70%

to 90% (hence lowering the amount of PVA and MCC in the pellets) had a negative influence on the span. This indicated that PVA and MCC were essential to provide sufficient rigidity, plasticity and water absorbing capacity to allow production of spheres with narrow PSD (Wlosnewski et al., 2010). Overall, the span values of formulations containing PVA were higher, and thus PSD broader.

The pellet morphology was measured in terms of AR and sphericity, whereby the fraction 710-1000 µm fraction of MCC pellets was compared with PVA formulations after drying (Figure 2). A mean AR lower or equal to 1.20 is considered as sufficient for pharmaceutical pellets (Krause et al., 2009).

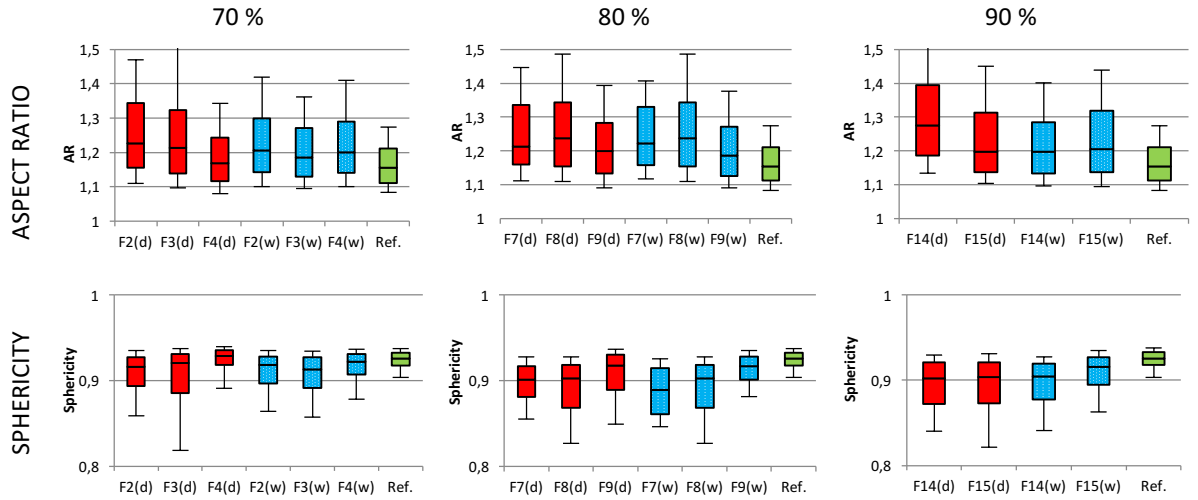

Figure 2. Aspect ratio and sphericity (mean ± standard deviation, n=3) of formulations as a function of polyvinyl alcohol/microcrystalline cellulose ratio (5/95 – 20/80) and drug load (70-90%). Polyvinyl alcohol was added either dry (d) (red) or wet (w) (blue). Microcrystalline cellulose pellets without drug were used as reference (Ref.) (green). Sieve fraction 710-1000 µm was used (n=3).

Wet addition of PVA via an aqueous dispersion yielded a lower AR. However, it should be considered that all PVA formulations had a wider AR range. Due to the wider span of AR, it was hard to distinguish any influence of drug load or addition method of PVA. The sphericity, which was defined as the ratio between the perimeters of an equivalent circle (circle with same projected area as the particle) and the real perimeter, was used to provide more

information about the surface of the pellets. Pellets with a decreased sphericity, contain small scale bumps that enlarge particle perimeter without changing its projected area (Yu and Hancock, 2008). The sphericity of all PVA-formulations was high (>0.85), and thus no small scale bumps were present.

SEM photographs were used to visualize the pellet surface morphology (Figure 3). In agreement with AR and sphericity data, a round sphere with a smooth surface was observed, the structure of the PVA-based pellet being very similar to the MCC pellet.

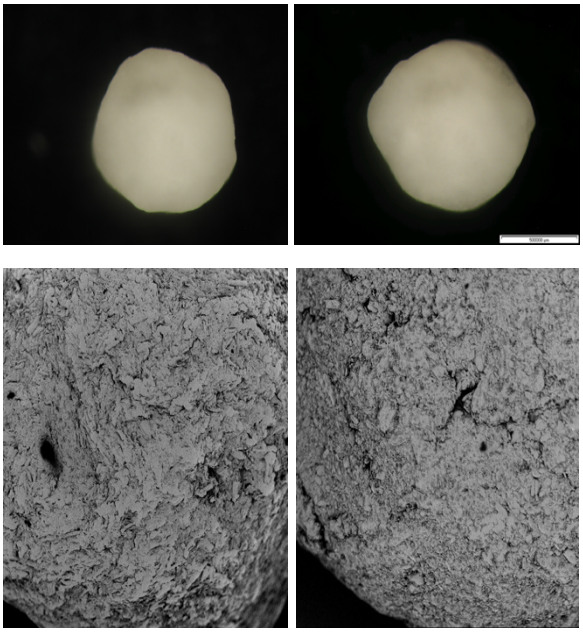

Figure 3. Photomicrographs (top) and scanning electron microscopy image (bottom) of microcrystalline cellulose pellet (left, SEM-magnification x 545) and pellet of formulation 4, containing 70% drug and polyvinyl alcohol solution (right, SEM-magnification x 495) (sieve fraction 710-1000 µm).

The friability (Table 3) was determined to quantify the mechanical properties of the pellets as these must withstand mechanical stress during post-processing steps (e.g. coating, packaging). The friability was slightly higher for pellets with a higher drug load, possibly due to the lower amount of excipients (e.g. PVA and MCC), which mainly determine the mechanical strength of these pellets. Overall wet addition of PVA as a binder in the formulation was the best option to yield pellets with a high mechanical strength. All pellets processed with PVA dispersion have a friability below 1% for all drug loadings (70–90%). Dry

addition of PVA, specifically at higher drug loads, resulted in pellets with a lower mechanical strength.

		PVA method addition	
	Formulation	Dry	Wet
70 %	F2	0.10 ± 0.02	0.15 ± 0.01
	F3	0.39 ± 0.01	0.35 ± 0.02
	F4	0.18 ± 0.02	0.02 ± 0.01
80 %	F7	0.41 ± 0.01	0.66 ± 0.03
	F8	1.12 ± 0.03	0.85 ± 0.04
	F9	1.50 ± 0.04	0.55 ± 0.01
	F10	0.40 ± 0.02	-
90 %	F12	1.35 ± 0.16	-
	F13	1.36 ± 0.23	-
	F14	3.90 ± 0.20	0.35 ± 0.01
	F15	0.56 ± 0.07	0.17 ± 0.01

Table 3. Friability (%) (mean ± standard deviation, n=3 of pellets (710-1000 µm) as a function of drug load and polyvinyl alcohol/microcrystalline cellulose ratio.

The *in vitro* dissolution profiles of pellets with different drug load (70-90%) were compared with MCC pellets (F17) containing 50% acetaminophen (Figure 4). Acetaminophen was completely released after 30, 20 and 10 min for pellets containing 70, 80 or 90% acetaminophen, respectively. It is known that MCC pellets do not disintegrate, and therefore release the drug by diffusion (Kranz et al., 2009). However, pellets containing higher drug load were able to disintegrate and thereby release the drug faster. Furthermore, drug release was independent of PVA addition method, since no difference was observed between formulation processed after addition of PVA as dry powder form and as an aqueous dispersion.

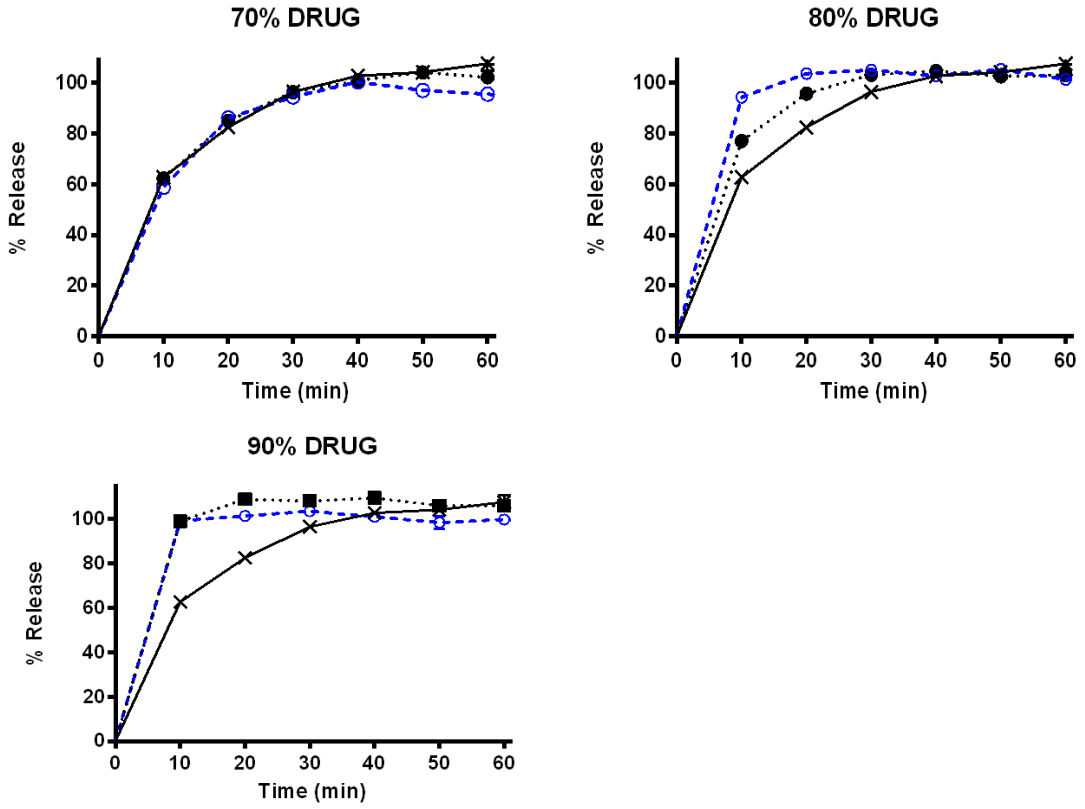

Figure 4. *In vitro* dissolution profiles (mean ± standard deviation, n=3) of pellets with different acetaminophen concentration: formulations 4, 9 and 14 containing 70%, 80% and 90% drug, respectively. Polyvinyl alcohol was added either in dry powder form (black closed symbol) or as aqueous dispersion (blue open symbol). Microcrystalline cellulose pellets without polyvinyl alcohol containing 50% acetaminophen were used as reference (X).

In the second part of this study, pellets with PVA as pelletisation aid were evaluated for a FDC application, combining acetaminophen and tramadol hydrochloride in the pellets. Considering all evaluated parameters (size, size distribution, shape, friability) formulation 4 (containing 70% acetaminophen, 6% PVA and 24% MCC) was identified for further processing into an FDC formulation as it yielded pellets with a narrow PSD, AR below 1.2, a sphericity above 0.9 and a low friability. This formulation was transformed into a FDC containing acetaminophen and tramadol hydrochloride in a ratio of 325/37.5 (w/w) (Table 4).

Concentration (%)	Acetaminophen	Acetaminophen/Tramadol HCl
Acetaminophen	70	62.8
Tramadol HCl	-	7.2
PVA	6	6
MCC	24	24
Water content (%)*	38.3	35

*Water content was calculated as a percentage of the total dry weight of each formulation

Table 4. Composition of pellet formulation containing acetaminophen and acetaminophen/tramadol hydrochloride.

The optimal water content of formulations containing acetaminophen/tramadol hydrochloride was slightly lower compared to acetaminophen formulation, since the aqueous solubility of tramadol hydrochloride (30-100 mg/ml) (Sudha et al., 2010) was higher compared to acetaminophen (14.3 mg/ml) (Kalantzi et al., 2006).

The width of the PSD of the FDC pellets was significantly different ($p < 0.05$) (e.g. higher span value) compared to the other tested formulations. The pellet size parameters (D_{10}, D_{50}, D_{90}) of the acetaminophen/tramadol hydrochloride formulations were higher, possibly due to the higher solubility of tramadol hydrochloride, and thus the lower solid content of the formulation during processing. A higher binder concentration (e.g. PVA) in the formulation resulted in the formation of larger pellets (Table 5).

Formulation	D_{10}	D_{50}	D_{90}	Span (d_{90}-d_{10})
Acetaminophen	804.1 ± 57.0	1054.1 ± 26.6	1271.4 ± 29.5	467 ± 32[a]
Acetaminophen/Tramadol.HCl	1071.1 ± 99.5	1723.2 ± 148.2	2060.4 ± 182.9	989 ± 88[b]
MCC	663.3 ± 24.2	888.0 ± 11.1	1097.5 ± 6.2	434 ± 19[a]

Table 5. Particle size data (D_{10}, D_{50}, D_{90} and span) (mean ± standard deviation, n=3) of formulations containing acetaminophen or acetaminophen/tramadol hydrochloride (325/37.5). Microcrystalline cellulose pellets were used as reference. The significance of the results between formulations was determined with an independent sample t-test. Span values with different superscripts are different at the 0.05 level of significance compared to microcrystalline cellulose (n = 3).

Extrusion/spheronization of the FDC containing acetaminophen and tramadol hydrochloride slightly affected the shape of the pellets, as evidenced by the larger spread of AR and sphericity data (Figure 5), while the friability of the FDC pellets remained low (0.11%).

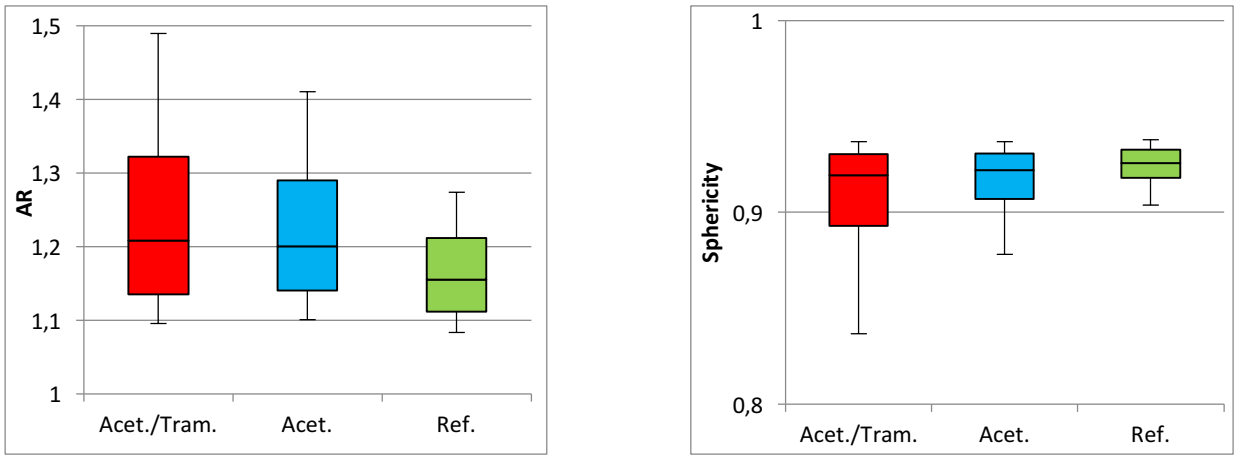

Figure 5. Aspect ratio and sphericity (mean ± standard deviation, n=3) of formulations containing 70% drug either as acetaminophen (blue) or acetaminophen/tramadol hydrochloride (325/37.5) (red). Microcrystalline cellulose pellets without drug were used as reference (Ref.) (green). The 710-1000 µm sieve fraction was used (n=3).

Figure 6 shows the *in vitro* dissolution profiles of FDC pellets with acetaminophen/tramadol hydrochloride.

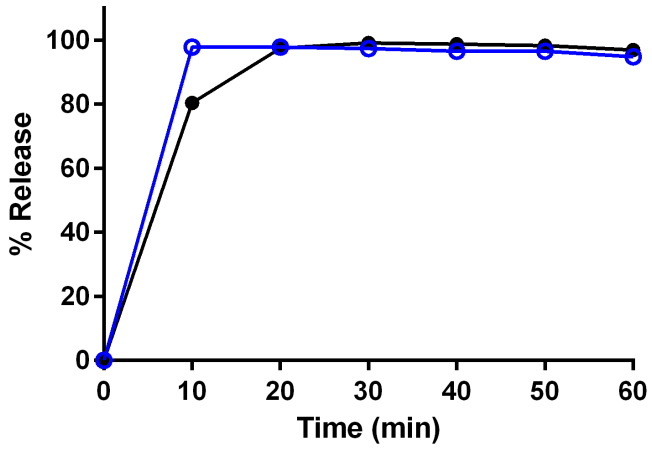

Figure 6. *In vitro* dissolution profiles (mean ± standard deviation, n=3) of acetaminophen (black closed symbol) and tramadol hydrochloride (blue open symbol) from acetaminophen/tramadol hydrochloride pellets.

Tramadol hydrochloride was released within 10 min, whereas acetaminophen was released within 20 min. The faster acetaminophen release from the FDC pellets compared to pellets containing only 70% acetaminophen can be linked to the addition of the highly soluble tramadol hydrochloride, which contributed to a faster disintegration of the pellet.

CONCLUSIONS

This study demonstrates that PVA solution is a promising pelletisation aid for the production of pellets with high acetaminophen concentration (70-90%), since MCC-based pellets with acceptable properties and yield could only be processed up to a concentration of 50% acetaminophen. High drug-loaded pellets were also used to manufacture FDC pellets containing acetaminophen and tramadol hydrochloride. This slightly affected pellet quality (PSD and shape, AR, sphericity and friability). However, *in vitro* drug release of these pellets remained fast.

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5

BROADER INTERNATIONAL CONTEX, RELEVANCE AND FUTURE PERSPECTIVES

The broader international context of this research work relates to two major challenges in pharmaceutical industry: (a) continuous manufacturing and (b) poorly soluble drugs.

a) Continuous manufacturing

The pharmaceutical industry has, in contrast with other industries (e.g. food and chemical), been conservative in its manufacturing concept, and up to now it has mainly relied on batch-wise processing to manufacture most drug products. This preference for batch processes was linked to the regulatory environment and the high profit margin of drug products. As a batch process is defined as a process whereby raw materials are charged into the system at the beginning of the process, and the end product is discharged all at once (Lee et al., 2015), it was imperative in the past for the regulatory authorities to use batch production, because this allowed to verify the quality of a batch after each unit operation before further processing and/or release. However, the disadvantages of batch processes, such as more batch-to-batch variability, higher costs (labor and production) and scale-up issues, have initiated a shift in mentality for pharmaceutical drug product manufacturing.

Nowadays, the pharmaceutical industry is in transition, as profit margins are reduced due to higher costs in research and development (R&D), a cost-constrained healthcare system as well as competition from generic manufacturers (Paul et al., 2010). Therefore, continuous manufacturing has received increasing attention, because this manufacturing concept can significantly reduce production costs while also improving product quality via targeted in-line monitoring of critical quality aspects along the manufacturing line. Furthermore, regulatory authorities recognized the need to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. Therefore, the Food and Drug Administration (FDA) published "Pharmaceutical current Good Manufacturing Practices (cGMPs) for the 21st Century", where continuous manufacturing was defined as a process whereby materials and end product are continuously charged into and discharged from the system, respectively, throughout the duration of the process (Lee et al., 2015).

Continuous manufacturing offers distinct advantages as the capacity of a batch process can only be increased using larger processors, which requires significant investments in equipment

and space throughout development, validation and commercial manufacturing of a drug product. Additionally, scale-up of a batch process is difficult, as process parameters do not scale linearly with the size of the equipment. In contrast, increasing the capacity of a continuous process is straightforward by extending the run time of the process (Vervaet and Remon, 2005). Other advantages of continuous processes are less waste (lower risk of material rejection due to rigorous in-line monitoring during continuous processing), lower environmental footprint (the scale of continuous processors is smaller and less down-time of the equipment) and lower costs (Plumb, 2005).

However, a point of attention of continuous manufacturing (where the 'batch' size is defined by time) is the risk of excessive material waste before steady-state conditions are reached (Vervaet and Remon, 2005) depending on the throughput capacity of the process. Furthermore, continuous manufacturing mostly requires specific equipment which is able to run material in a first-in/first-out mode with stringent control of process conditions, ideally using feed-forward and/or feed-back control loops to minimize the amount of out-of-spec material during continuous processing. Nowadays, equipment for different unit operations is readily available for incorporation in a continuous processing line such as feeders, blenders, extruders, spheronizers, tableting machines. In addition to specific equipment for continuous manufacturing, it is also required to have excipients that are compatible with the continuous manufacturing processes and production equipment (Pifferi et al., 1999).

Historically, pharmaceutical excipients have been seen as cheap and inert ingredients of drug products. However, this view has been changed and today excipients also need to be functional, besides their quality aspects and safety profile (Pifferi and Restani, 2003). Ideally an excipient (a) should perform different functions in a dosage form (e.g. improve stability, enhance release and absorption of the active compound, facilitate manufacturing), (b) can be processed over a broad range of settings, (c) can be processed via different techniques, (d) is available in different grades to create a broad formulation platform. The current project focuses on these aspects, evaluating partially hydrolyzed polyvinyl alcohol (PVA) (a water-soluble polymer which has received limited attention for solid dosage form applications) as a functional excipient in two continuous processes: hot-melt extrusion (HME) (as hydrophilic drug carrier in which the drug is embedded) and extrusion/spheronization (as pelletisation aid in formulations with a high drug load).

In HME only a limited number of polymers are available for pharmaceutical applications (Maniruzzaman et al., 2012) as – in addition to the thermoplastic behavior - non-toxicity and thermal stability are also essential requirements for these materials. Therefore, it was of interest to evaluate PVA as carrier for HME, in order to expand the number of polymers available for this application. In this research work, partially hydrolyzed PVA was evaluated as carrier for oral immediate release applications, whereby only grades with higher degree of hydrolysis (DH) (70-88%) were useful, because drug release from these formulations was independent of pH or ionic strength (in contrast with Eudragit E®, which is only soluble between pH 1-5). However, PVA with higher DH required higher extrusion temperatures (> 180°C) to disrupt intra- and intermolecular hydrogen bonding, which limited the use of partially hydrolyzed PVA as carrier for thermo-sensitive drugs. In contrast, other polymers used for immediate release applications, polyethylene oxide (200 000 Da), for example, could be extruded at 120-140°C (Prodduturi et al., 2005). Therefore, in order to enlarge applicability of partially hydrolyzed PVA, a plasticizer (e.g. sorbitol) was used. The addition of a plasticizer is a common approach to improve processability by decreasing glass transition/melting temperature (T_g, T_m) and thus extrusion temperature. In this work, sorbitol was able to decrease T_g/T_m and thus the extrusion temperature of PVA to a temperature of about 140°C. However, as sorbitol needs to melt before interaction with PVA could occur, an additional processing step (re-extrusion) is required, which is a disadvantage. Furthermore, experiments (differential scanning calorimetry (DSC), X-ray diffraction (XRD)) have shown that sorbitol recrystallizes inside the extrudate upon storage, which can affect the physical stability of the pharmaceutical dosage forms. Overall, partially hydrolyzed PVA is a promising carrier for HME, however major challenges have to be solved (high extrusion temperature, suitable plasticizer) in order to broadly apply PVA as carrier for oral immediate release dosage forms.

PVA was also evaluated as functional excipient in extrusion/spheronization to obtain pellets with a high drug load. Pellets are multiparticulate drug delivery system that offer specific advantages compared to single unit dosage forms (e.g. tablets): reproducible and generally short gastro-intestinal transit time, flexibility to blend pellets with different compositions or release patterns (personalized medicines), and less risk of dose dumping (Dukic-Ott et al., 2007). However, in most cases a relatively large concentration of microcrystalline cellulose (MCC) (Avicel® PH101) must be included in the formulation in order to obtain sufficient

rigidity, plasticity and water absorbing capacity of the formulation, all critical parameters during the extrusion/spheronization process. Therefore, drug load in MCC pellets is often limited (Mallipeddi et al., 2010), which restricts their use, specifically in fixed-dose combinations (FDC) where two or more drugs are combined in a single dosage form. In this work partially hydrolyzed PVA was evaluated as pelletisation aid in high drug loaded pellets (> 70%). Dukic-Ott et al. discussed the properties which are required for an ideal pelletisation aid (Dukic-Ott et al., 2009):

- Yielding pellets with spherical shape, narrow particle size distribution (PSD), smooth surface, sufficient mechanical strength, low friability and desired release characteristics
- Allowing robust processes with high yield
- Appropriate for formulations with many (ideally all) drugs
- Suitable over a broad drug concentration range, especially for high drug loading
- Pure water can be used as wet massing liquid
- No additional excipients are required in the formulation
- Wide concentration ranges of wet massing liquid possible

These properties were compared with the characteristics of PVA. Pellets obtained with partially hydrolyzed PVA and acetaminophen (> 70%) had satisfactory properties (aspect ratio (AR) < 1.2, sphericity > 0.9, narrow PSD and low friability <1%) However, upon inclusion of tramadol hydrochloride, a good water-soluble drug, the pellet quality was slightly decreased. Therefore, further experiments are required to verify if partially hydrolyzed PVA could be applied as pelletisation aid with different drugs. Furthermore, small amounts of MCC (5%) are required to overcome tackiness of PVA. Nevertheless, PVA yielded pellets with high drug loading (> 70%), and water could be used as wet massing liquid. Different alternatives for MCC have already been evaluated, whereby none of them have the same flexibility as MCC. For example, powdered cellulose (Lindner and Kleinebudde, 1994), modified starch (Dukic et al., 2007), chitosan (Santos et al., 2002), hydroxypropylmethyl cellulose (Chatlapalli and Rohera,

1998) required an extra binder to obtain sufficient mechanical strength of the pellets, and some ionic alternatives (e.g. chitosan) are influenced by pH (Santos et al., 2002) or can have ionic interactions with drug compounds (e.g. κ-carrageenan). Therefore, PVA has some distinct advantages compared to other alternatives, which makes it a promising pelletisation aid.

b) Poorly soluble drugs

The use of medicinal chemistry and high-throughput screening has increased the number of poorly soluble drugs. It is believed that 40% of the drugs in development pipelines are class II or class IV products according to the Biopharmaceutical Classification system (BCS), whereby their use is greatly hindered by poor solubility and/or permeability (Keck and Muller, 2006). Therefore, a major challenge in pharmaceutical drug development, is to overcome poor aqueous solubility and thereby enhance bioavailability.

Different methods to improve water-solubility have been described in literature, such as the inclusion of drugs in cyclodextrins (Carrier et al., 2007), self-emulsifying drug delivery systems (Porter et al., 2008), nanocrystals (Shegokar and Muller, 2010), coacervation (De Jaeghere et al., 2013) and solid dispersions. Solid dispersions are defined by Chio and Riegelman as dispersions of one or more active pharmaceutical ingredients (API) in a solid state carrier (Chiou and Riegelman, 1971), and can be prepared via spray-drying or HME.

In this research work, PVA was combined with a poorly water-soluble drug (e.g. celecoxib (CEL)) in HME, which significantly improved the *in vitro* dissolution profiles of CEL. However, CEL was dispersed in amorphous clusters, and this is a critical factor for drug stability (Saerens et al., 2012). The major advantage of PVA is that it contains a high number of hydroxyl functions, which are able to form intermolecular hydrogen bonds and Van der Waals forces. Fourier transform infrared (FT-IR) spectroscopy has shown that CEL and PVA interacted with each other, whereby hydrogen bonding was observed between acidic hydrogen of N-H as hydrogen donor from CEL and O-H as hydrogen acceptor of PVA (Fouad et al., 2011). These drug-polymer interactions contribute to stabilize amorphous CEL inside the extrudate. Additionally, CEL was in a state of supersaturation, and PVA was able to stabilize

supersaturation for at least 2h. This is an important feature of PVA (polymeric precipitation inhibitor (PPI)), as the combination of polymethacrylate and CEL also showed supersaturation, but this formulation was unable to maintain supersaturation (Albers et al., 2009). Therefore, in a broader context the use of PVA contributes to improve bioavailability of poorly soluble drugs.

FUTURE PERSPECTIVES

The aim of this thesis was to evaluate partially hydrolyzed PVA as functional excipient in two specific continuous manufacturing processes, HME and extrusion/spheronization. This research project has shown that PVA is a promising excipient, nevertheless further studies are required to fully exploit the potential of PVA as functional excipient in solid dosage form delivery. A few topics that could be of interest are listed below:

HOT-MELT EXTRUSION

- several grades of PVA (e.g. different DH and polymerization) could be combined to obtain a different drug release profile, because those properties influence water solubility and thus drug release.
- combining PVA with other hydrophilic (e.g. polyvinylpyrrolidone) or hydrophobic (e.g. ethylene vinyl acetate) polymers could also be used to yield different drug release profiles, whereby combinations with hydrophilic polymers could enhance drug release and a more controlled drug release could be obtained with hydrophobic polymers.
- using other plasticizers for PVA (e.g. sugar alcohols, polyethylene glycols), as it was observed that sorbitol recrystallized during storage when used as plasticizer of PVA.
- as sorbitol must melt in order to plasticize PVA, it could be of interest to spray-dry a solution of PVA and plasticizer, whereby this spray-dried powder could be used as carrier in HME.

- nowadays, co-extrusion, whereby two or more materials are extruded through a single die, is evaluated as manufacturing technique for FDC. It would be interesting to use PVA as carrier for co-extrusion, whereby for example grades with a good water solubility are used for the coat (immediate release), and grades with a lower solubility could be used as a core (sustained release).

EXTRUSION-SPHERONIZATION

- in this research work it was shown that solutions of PVA (DH 88%) could be used as pelletisation aid in extrusion/spheronization. Therefore, it could be of interest to use different grades of PVA (e.g. different DH and polymerization) to evaluate the influence on pellet properties (AR, PSD, drug release …).
- Law et al. used hydrophilic polymers in combination with MCC during spray drying. Those spray-dried powders were afterwards used as carrier for extrusion/spheronization. Therefore, it could be of interest to spray-dry a suspension of PVA and MCC to evaluate pellet properties (Law and Deasy, 1998).

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GENERAL CONCLUSIONS

The first objective of this doctoral thesis was to evaluate partially hydrolyzed polyvinyl alcohol (PVA) as carrier in hot-melt extrusion (HME). Additionally, tableting was examined as downstream processing technique for hot-melt extruded PVA formulations.

This study showed that PVA with different degree of hydrolysis (DH) (33-88%) could be processed via HME, whereby processing conditions (e.g. extrusion temperature) and drug release were mainly controlled by DH. PVA grades with a high DH (70-88%) were preferred as carrier for oral solid dosage forms, as drug release was independent of pH and ionic strength. However, high extrusion temperatures were required to disrupt intra- and intermolecular hydrogen bonding, which limits their use for thermo-sensitive drugs.

The addition of sorbitol as plasticizer reduced extrusion temperature of PVA, but sorbitol (added as plasticizer) needed to melt before interaction with PVA occurred. The *in vitro* dissolution profile of solid dispersions containing plasticized PVA and celecoxib (CEL), a poorly soluble drug, was significantly improved, as a state of supersaturation was reached. Moreover, it was observed that PVA acted as a polymeric precipitation inhibitor (PPI), which stabilized supersaturation. Nevertheless, an *in vivo* bioavailability study was unable to demonstrate the advantage of supersaturation.

Furthermore, tableting of hot-melt extruded PVA formulations revealed that the mechanical properties were changed during HME, as lower tablet tensile strengths were obtained using formulations with a higher amorphous content. This was correlated with a combined effect of less interparticulate bonding (because of increased elastic recoveries) and weaker bonding strength per unit bonding area (e.g. lower tensile strength at zero porosity).

The second objective of this doctoral thesis was to evaluate PVA as pelletisation aid during extrusion/spheronization, in order to obtain pellets with a high drug load (> 70%), which are suitable to use with a single drug compound, as well as for fixed-dose combinations (FDC).

Pellets with high acetaminophen concentration (70-90%) and using PVA as pelletisation aid were prepared with satisfactory pellet properties (e.g. aspect ratio (AR), sphericity, *in vitro* drug release…). However, the inclusion of microcrystalline cellulose (MCC) concentration (5%) was required to overcome problems related to the tackiness effect of PVA during extrusion. Additionally, pellets containing a FDC of acetaminophen and tramadol hydrochloride were prepared, yet quality of these FDC pellets was slightly reduced.

Overall, PVA with high DH has shown to be a promising carrier, which could be applied in various pharmaceutical manufacturing processes (e.g. HME and extrusion/spheronization).

SUMMARY

Over the last few years the pharmaceutical industry has rapidly evolved towards the introduction of continuous manufacturing techniques (e.g. extrusion-based techniques), as well as process analyzers which are built inside the manufacturing line. In addition, formulators are constantly looking for new excipients, which provides specific properties to a formulation and can be applied in a broad range of drug products. Within this framework, partially hydrolyzed polyvinyl alcohol (PVA), a water-soluble synthetic copolymer of vinyl acetate and vinyl alcohol, was evaluated as functional excipient in continuous manufacturing techniques.

The first objective of this thesis was to evaluate PVA with different degree of hydrolysis (DH) as carrier in hot-melt extrusion (HME). In addition, the impact of HME on tableting behavior of hot-melt extruded polymeric formulations was investigated. The second objective of this thesis was to study PVA as pelletisation aid in extrusion/spheronization to obtain pellets with a high drug load (> 70%), which can be used to formulate a single drug or a fixed-dose combination (FDC).

Chapter 1 evaluated the use of PVA with different DH (33-88%) as carrier in HME. The polymers were characterized with differential scanning calorimetry (DSC), whereby distinct thermograms were obtained: only a glass transition temperature (T_g) was observed for PVA with low DH (33-53%), whereas a T_g and melting temperature (T_m) were detected for PVA grades with a high DH (72-88%), due to intra- and intermolecular hydrogen bonding. The semi-crystalline nature of the latter was confirmed with X-ray diffraction (XRD), as crystalline reflections were present at 2θ = 19.9° and 20.2°. The differences in DSC profiles were correlated with the extrusion behavior of PVA, as higher extrusion temperatures (e.g. 180°C) were required for PVA with high DH. However, these PVA-grades were most promising as carrier in HME, because higher concentrations hydrochlorothiazide (HCT) (15%) could be solubilized inside the formulation and drug release was independent of pH and ionic strength.

Additionally, a design of experiment (DOE) was performed to evaluate the influence of PVA-grade, added amount of plasticized PVA and extrusion temperature onto drug release after 60 min. Drug release rate was enhanced using PVA with a higher DH or when incorporating more plasticized PVA in the formulation, whereas extrusion temperature had no influence on drug release.

Chapter 2 investigated the effect of sorbitol, a water-soluble plasticizer, on the thermal properties of hot-melt extruded PVA. Various ratios of PVA and sorbitol (100/0 – 60/40) were analyzed via DSC, whereby T_g and T_m only decreased during 2nd DSC heating cycle. This indicated that melting of PVA/sorbitol mixtures was required to establish molecular interactions between polymer and plasticizer. Cryomilled plasticized PVA was subsequently combined with celecoxib (CEL) and could be processed at a lower extrusion temperature of 140°C, yielding a solid dispersion. The *in vitro* dissolution profiles of solid dispersions containing PVA/CEL were significantly improved compared with Celebrex®, a commercially available formulation, as a state of supersaturation was reached. Furthermore, PVA was able to maintain supersaturation for at least 2h, as it acts like a polymeric precipitation inhibitor (PPI). Despite significant improvements during *in vitro* dissolution, all pharmacokinetic parameters ($AUC_{0\text{-}24h}$, C_{max} and t_{max}) were not significantly different. This discrepancy between *in vitro* dissolution and *in vivo* bioavailability could be due to several factors which influence *in vivo* bioavailability of CEL, such as incomplete dissolution of the PVA carrier or rapid *in vivo* diffusion of the PVA polymers after dissolution (making CEL more prone to precipitation). Furthermore, *in vivo* solubility of CEL could be improved, as endogenous compounds (e.g. lecithin) could form micelles, which are able to solubilize hydrophobic compounds. Therefore, this study highlighted that caution needs to be taken for *in vitro*/*in vivo* correlations.

Chapter 3 evaluated the impact of HME on the tableting behavior of PVA formulations. Mixtures of PVA and sorbitol were extruded, (cryo-)milled and compressed into tablets. Before compression all intermediate products were characterized for their solid-state (T_g, T_m, crystallinity) and material properties (particle size, moisture content, moisture sorption). DSC

showed that T_m was slightly increased during processing of both PVA-grades containing 40% sorbitol. This phenomenon was linked to the crystallization of sorbitol, whereby the plasticizing effect of sorbitol was reduced and T_m of PVA slightly increased. XRD and solid-state ^{1}H-wideline NMR were used to confirm phase separation and crystallization of sorbitol during storage. Dynamic vapor sorption (DVS) measurements clearly showed the hygroscopic behavior of sorbitol at extreme conditions (21°C/98%RH), as sorption isotherms from non-extruded PVA shifted after addition of sorbitol. Interestingly, HME had a remarkable effect on the level of hysteresis (difference between sorption and desorption isotherm), while for non-extruded formulations hysteresis was clearly present, it became negligible for the extruded formulations. This was due to interactions between PVA and sorbitol which were only formed when sorbitol melted during HME, forming dense particles where adsorption of water mainly occurred via weak interactions at the surface of the extrudate. Tableting behavior was compared before and after HME by means of the compressibility, tabletability and compactability (CTC) profiles. HME increased the amorphous content of the formulation, which negatively affected tableting behavior (e.g. lower tablet tensile strength). The mechanical properties were altered during processing towards more elastically deforming materials, which increased the elastic recovery during decompression. The lower tensile strength resulted from a combined effect of less interparticulate bonding areas (higher elastic recovery) and weaker bonding strengths per unit bonding area (between glassy particles).

Chapter 4 explored the potential of PVA as pelletisation aid during extrusion/spheronization to obtain pellets with a high acetaminophen concentration (> 70%). Preliminary studies have shown that less than 15% PVA and at least 5% microcrystalline cellulose (MCC) was required in the formulation, to overcome tackiness effect of PVA. Based on these findings, fifteen formulations were selected, containing different acetaminophen concentration (70, 80 or 90%) and various ratios PVA/MCC ratios (0/100 – 50/50). The optimal water content of those formulation was mainly depended on MCC concentration; as less water was needed for formulations containing the lowest concentration of MCC (e.g. higher acetaminophen concentration or PVA/MCC ratio). As PVA was water-soluble, pellets were made either with PVA added as dry powder or pre-dissolved in water. Overall pellet properties (aspect ratio

(AR), sphericity, friability) were superior if PVA was added as dispersion compared to dry addition. A formulation containing 70% acetaminophen, 6% PVA and 24% MCC, was the most promising formulation with a narrow particle size distribution (PSD) (span: 467 ± 32 µm), mean AR ≤ 1.2, sphericity > 0.9 and low friability < 1%. *In vitro* dissolution profiles were mainly controlled by acetaminophen concentration, whereby a faster drug release was obtained for pellets containing the highest drug concentration. Drug release was independent of PVA addition method (dry or wet). Subsequently, this formulation was used to formulate a FDC, whereby acetaminophen was replaced by a fixed ratio of acetaminophen/tramadol hydrochloride (325/37.5). The optimal water content was slightly lower due to the addition of a readily soluble drug, tramadol hydrochloride. Furthermore, the pellets of the FDC were larger compared to the single drug formulation, possibly due to a reduced solid/PVA ratio. Other pellet properties (AR, sphericity and friability) were slightly reduced in quality. However, *in vitro* dissolution profiles resulted in a fast and complete release of tramadol hydrochloride (< 10 min) and acetaminophen (< 20 min).

SAMENVATTING

In de afgelopen jaren, is de farmaceutische industrie snel geëvolueerd met de implementatie van continue productietechnieken (bijv. extrusie), maar ook met analysetechnieken die worden ingebouwd in de productielijn. Daarnaast zijn wetenschappers steeds opzoek naar nieuwe hulpstoffen die de gewenste eigenschappen geven aan de formulatie en die kunnen worden toegepast in verscheidene geneesmiddelproducten. In dit kader, werd partieel gehydrolyseerd polyvinyl alcohol (PVA) als functionele hulpstof geëvalueerd in continue productietechnieken.

Het eerste doel van deze thesis was om PVA met verschillende hydrolysegraad te evalueren als drager in hot-melt extrusie (HME). Daarnaast, werd de impact van HME op het tableteer gedrag van geëxtrudeerde formulaties onderzocht. Het tweede doel van deze thesis was om PVA als hulpstof tijdens extrusie/sferonisatie te bestuderen om hoog gedoseerde pellets aan te maken, welke kunnen worden gebruikt om één geneesmiddel of combinatiepreparaten te formuleren.

In **hoofdstuk 1** werd PVA met verschillende hydrolysegraad geëvalueerd als drager in HME. De polymeren werden gekarakteriseerd met differentiaal scanning calorimetrie (DSC), waarbij verschillende thermogrammen werden verkregen: enkel een glastransitietemperatuur (T_g) was zichtbaar voor PVA met lage hydrolysegraad (33-53%), waarbij een T_g en smelttemperatuur (T_m) werd gedetecteerd voor PVA met hoge hydrolysegraad (72-88%), vanwege intra-en intermoleculaire waterstofbindingen. De semi-kristallijne toestand van de laatstgenoemde werd bevestigd met X-straal diffractie (XRD), want kristallijne reflecties waren aanwezig op 2θ = 19.9° and 20.2°. De verschillen in DSC-profielen waren gecorreleerd met het extrusiegedrag van PVA, aangezien hogere extrusietemperaturen (bijv. 180°C) noodzakelijk waren voor PVA met hoge hydrolysegraad.

Echter, deze PVA-graden waren het meest veelbelovend als drager in HME, aangezien deze een hogere concentratie hydrochloorthiazide (HCT) (15%) konden oplossen in de formulatie, en de geneesmiddelenafgifte onafhankelijk was van pH of ionensterkte. Daarenboven, werd een experimenteel design uitgevoerd om de invloed van PVA-graad, toegevoegde hoeveelheid weekgemaakte PVA en extrusietemperatuur op geneesmiddelenafgifte na 60 min te onderzoeken. Geneesmiddelenafgifte was verbeterd, indien meer PVA met hoge hydrolysegraad of weekgemaakte PVA aanwezig was in de formulatie. Extrusietemperatuur had echter geen invloed op de geneesmiddelenafgifte.

Hoofdstuk 2 onderzocht het effect van sorbitol, een water oplosbare weekmaker, op de thermische eigenschappen van geëxtrudeerd PVA. Verschillende ratio's van PVA en sorbitol (100/0 -60/40) werden geanalyseerd via DSC, waarbij T_g en T_m alleen werd verlaagd gedurende de 2de DSC-opwarmingscyclus. Dit toonde aan dat smelten van PVA/sorbitol mengsels vereist was om moleculaire interacties tussen polymeer en weekmaker te verkrijgen. Cryogeen gemalen en weekgemaakte PVA werd daaropvolgend gemengd met CEL, welke op een lagere temperatuur van 140°C kon geëxtrudeerd worden om een vaste dispersie te verkrijgen. De *in vitro* dissolutieprofielen van vaste dispersies met PVA/CEL waren significant verbeterd in vergelijking met Celebrex®, een commercieel beschikbare formulatie, aangezien supersaturatie werd bekomen. Bovendien, was PVA een precipitatie inhibitor, die instaat was om supersaturatie te behouden gedurende minimaal 2u. Ondanks significante verbeteringen gedurende *in vitro* dissolutie, waren de farmacokinetische parameters ($AUC_{0\text{-}24h}$, C_{max} en t_{max}) niet significant verschillend. Het verschil tussen *in vitro* dissolutie en *in vivo* biologische beschikbaarheid kan door verschillende factoren die de biologische beschikbaarheid van CEL beïnvloeden veroorzaakt worden, zoals onvolledig oplossen van de PVA drager of snelle *in vivo* diffusie van de PVA polymeren na dissolutie, waardoor CEL meer vatbaar is voor precipitatie. Bovendien, kan de *in vivo* oplosbaarheid van CEL verbeterd worden door endogene componenten (bijv. lecithine), die micellen kunnen vormen en de oplosbaarheid van hydrofobe componenten kan verbeteren. Hierdoor, toont deze studie aan dat voorzichtigheid is geboden bij *in vitro*/*in vivo* correlaties.

Hoofdstuk 3 evalueert de impact van HME op het tableteer gedrag van PVA-formulaties. Mengsels van PVA en sorbitol werden geëxtrudeerd, cryogeen gemalen en gecomprimeerd tot tabletten. Voorafgaand het tabletteren werden de fysische (T_g, T_m, kristalliniteit) en materiaal gerelateerde (partikelgrootte, vochtgehalte, vochtopname) eigenschappen van alle intermediaire producten gekarakteriseerd. DSC toonde aan dat de T_m licht verhoogd was tijdens het verwerken van beide PVA-mengsels die 40% sorbitol bevatten. Dit fenomeen werd gelinkt aan de uitkristallisatie van sorbitol, waardoor het weekmakend effect van sorbitol was afgenomen en de T_m van PVA werd verhoogd. XRD en vaste stoffen ^{1}H-NMR werden gebruikt om fase-afscheiding en uitkristallisatie van sorbitol tijdens het bewaren te bewijzen. Dynamische damp sorptie (DVS) metingen toonden het hygroscopisch gedrag van sorbitol in extreme omstandigheden (21°C/98% RV) aan, want sorptie isothermen van niet-geextrudeerd PVA verschoven na toevoegen van sorbitol. HME had een opmerkelijk effect op de hysteresis (verschil tussen sorptie en desorptie isothermen), terwijl voor niet-geextrudeerde formulaties hysteresis duidelijk zichtbaar was, werd deze voor geextrudeerde formulaties verwaarloosbaar. Dit kwam vanwege de interacties tussen PVA en sorbitol die enkel werden gevormd nadat sorbitol was gesmolten gedurende HME. Hierdoor werden dense partikels gevormd, waarbij water enkel werd gebonden via zwakke interacties aan het oppervlak van het extrudaat. Het tableteer gedrag voor- en na- HME werd vergeleken via compresseerbaarheid, tableteerbaarheid en compacteerbaarheid (CTC)-profielen. De amorfe content was verhoogd na HME, waardoor het tableteer gedrag negatief werd beïnvloed (bijv. lagere tabletsterkte). De mechanische eigenschappen werden gedurende verwerking gewijzigd naar elastisch vervormbare materialen, waarbij het elastisch herstel na wegnemen van druk toenam. De lagere tabletsterkte was het resultaat van een gecombineerd effect van minder interparticulaire bindingsruimte (hoger elastisch herstel) en zwakkere bindingssterkte per eenheid bindingsruimte (tussen amorfe partikels).

Hoofdstuk 4 onderzocht de mogelijkheid om PVA te gebruiken als hulpstof tijdens extrusie/sferonisatie, om pellets te bekomen met een hoge paracetamol concentratie (> 70%). De eerste studies hebben aangetoond dat minder dan 15% PVA en minstens 5% microkristallijne cellulose (MCC) noodzakelijk waren in de formulatie, om het klevend effect van PVA te vermijden. Op basis van deze bevindingen werden vijftien formulaties geselecteerd

met verschillende paracetamol concentraties (70, 80, 90%) en PVA/MCC-verhoudingen (0/100-50/50). Aangezien PVA, water oplosbaar was, werden pellets aangemaakt ofwel met PVA toegevoegd als droog poeder of vooraf opgelost in water. In het algemeen waren pellet eigenschappen (aspect ratio (AR), sfericiteit, friabiliteit) beter, indien PVA toegevoegd werd als dispersie in vergelijking met droog poeder. De formulatie bestaande uit 70% paracetamol, 6% PVA en 24% MCC was het meest veelbelovend met een nauwe partikelgrootte distributie (span: 467 ± 32 µm), gemiddelde AR ≤ 1.2, sfericiteit > 0.9 en lage friabiliteit < 1%. *In vitro* dissolutieprofielen waren hoofdzakelijk afhankelijk van het gehalte paracetamol, waarbij een snellere geneesmiddelenvrijstelling werd bekomen voor pellets met een hogere geneesmiddel concentratie. De geneesmiddelenvrijstelling was onafhankelijk van PVA additie methode (droog of nat). Vervolgens, werd deze formulatie gebruikt voor een combinatiepreparaat, waarbij paracetamol werd vervangen door een vaste verhouding paracetamol/tramadol hydrochloride (325/37.5). De optimale hoeveelheid water was iets lager door de toevoeging van een goed water oplosbaar geneesmiddel, tramadol hydrochloride. De pellets van het combinatiepreparaat waren groter dan de pellets met slechts één geneesmiddel, mogelijks door verlaagde verhouding vaste stoffen/PVA. Andere pellet eigenschappen (AR, sfericiteit en friabiliteit) werden iets minder in kwaliteit. De *in vitro* dissolutieprofielen resulteerden in een snelle en volledige vrijgave van tramadol hydrochloride (< 10 min) en paracetamol (< 20 min).

CURRICULUM VITAE

PERSONAL INFORMATION

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EDUCATION

University

2010 – present:	PhD candidate in Pharmaceutical Technology
	Lab. of Pharmaceutical Technology, Ghent University, Belgium
	Scientific promoters: Prof. Dr. Chris Vervaet
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2015 – 2016:	Master after Master in Industrial Pharmacy
	Inter-university programme (UGent, KUL, UA, VUB)
2005 – 2010:	Master in Pharmaceutical Sciences (Drug development)
	Ghent University
	Graduated with distinction

Secondary school

1999 – 2005: Biotechnical Sciences (TSO)
Vrij Agro- en Biotechnisch Instituut (VABI), Roeselare

LANGUAGES

Dutch (native language)
English
French

RESEARCH EXPERIENCE

Sept. '10 – Apr. '16: PhD research: "Partially hydrolyzed polyvinyl alcohol as functional excipient in oral solid dosage forms prepared via extrusion".
Lab. of Pharmaceutical Technology, Ghent University, Belgium
Scientific promoters: Prof. Dr. Chris Vervaet
Prof. Dr. Jean Paul Remon

Sept. '15 – Dec. '16: Master after Master thesis: "Development of formulations for poorly soluble drugs via coacervation".
Lab. of Pharmaceutical Technology, Ghent University, Belgium
Scientific promoters: Prof. Dr. Chris Vervaet
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Jan. '09 – June '09: Master thesis: "Segregation"
Janssen Pharmaceutica, Beerse, Belgium
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WORK EXPERIENCE

Apr.' 16 – present:	Project engineer supervisor Purna Pharmaceuticals NV/SA, Puurs
Oct. '14 – present:	Pharmacist Westlaanapotheek BVBA, Roeselare
Sept.' 10 – Apr. '16:	Organize and teach practical courses of 3rd bachelor pharmaceutical sciences: "Artsenijbereidkunde" and 2nd master pharmaceutical sciences: "Farmaceutische Technologie" Guidance of thesis students (1st master pharmaceutical sciences and Master after Master Industrial pharmacy)
July '10 – Aug. '10:	Pharmacist Westlaanapotheek BVBA, Roeselare
July '09 – June '10:	Pharmacist (Internship) Westlaanapotheek BVBA, Roeselare

INTERNATIONAL PUBLICATIONS

W. De Jaeghere, B.G. De Geest, J. Van Bocxlaer, J.P. Remon, C. Vervaet and A. Antunes da Fonseca, Formulation of poorly water-soluble drugs via coacervation – a pilot study using febantel, Eur. J. Pharm. Biopharm., 85, 930-935 (2013)

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W. De Jaeghere, J. Vercruysse, J.P. Remon and C. Vervaet, The use of partially hydrolyzed polyvinyl alcohol in the production of high drug-loaded pellets for immediate release using extrusion/spheronization. *(In preparation)*

ORAL PRESENTATIONS

Coacervate as drug delivery system
PSSRC Annual meeting, Helsinki (Finland), September 2011

Contributed talk: solid dispersions with polyvinyl alcohol
IDEA meeting, Cambridge (United Kingdom), March 2013

Hot-melt extrusion: polymer blends with polyvinyl alcohol
IDEA closing meeting, Lille (France), June 2013

Hot-melt extrusion: polyvinyl alcohols with different degree of hydrolysis
17th Forum of Pharmaceutical Sciences, Spa (Belgium), October 2013

Hot-melt extrusion of polyvinyl alcohol and plasticizer for oral immediate release applications
1st European conference on pharmaceutics, Reims (France), May 2015

POSTER PRESENTATIONS

Predicting nasal discomfort with the slug mucosal irritation (SMI) assay
AAPS annual meeting and exposition, Chicago (USA), October 2012

Hot-melt extrusion: polymer blends with polyvinyl alcohol
9th World meeting on pharmaceutics, biopharmaceutics and pharmaceutical technology, Lisbon (Portugal), April 2014

ATTENDED WORKSHOPS, COURSES AND LECTURES

Project management, Ghent University, Belgium (2010)

Training days/Workshops IDEA, United Kingdom (2011)

Fundamentals of HPLC, Waters, The Netherlands (2011)

APV Experts' Workshop on hot-melt extrusion, BASF, Germany (2012)

DSC advanced training course, TA Instruments, Belgium (2012)

MDSC advanced training course, TA Instruments, Belgium (2012)

Software training course, TA Instruments, Belgium (2012)

Advanced academic English: writing skills, Ghent University, Belgium (2012)

Design of experiments and multivariate analysis, Ghent University, Belgium (2013)

PhD career focus workshop, Ghent University, Belgium (2014)

Advanced operator training (Modul P tableting course), GEA Courtoy, Belgium (2015)