Title: Hot-melt extrusion of polyvinyl alcohol for oral immediate release applications

Authors: W. De Jaeghere, T. De Beer, J. Van Bocxlaer, J.P. Remon, C. Vervaet

In: International Journal of Pharmaceutics, 492 (1-2), 1-9, 2015.

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

W. De Jaeghere[1], T. De Beer[2], J. Van Bocxlaer[3], J.P. Remon[1], C. Vervaet[1]

[1] Laboratory of Pharmaceutical Technology, Ghent University, Ghent, Belgium

[2] Laboratory of Pharmaceutical Process Analytical Technology, Ghent University, Ghent, Belgium

[3] Laboratory of Medical Biochemistry and Clinical Analysis, Ghent University, Ghent Belgium

Corresponding author:

C. Vervaet

Ghent University, Laboratory of Pharmaceutical Technology

Ottergemsesteenweg 460

9000 Ghent (Belgium)

Tel.: +32 9 264 80 54

Fax: +32 9 222 82 36

E-mail address: Chris.Vervaet@UGent.be

Abstract

The primary purpose of this study was to process partially hydrolyzed PVOH grades (degree of hydroxylation (DH): 33-88%) via HME and to evaluate them as carrier for oral immediate release dosage forms in order to improve the release rate of poorly water soluble drugs (i.e. HCT and CEL) via the formulation of solid dispersions. PVOH grades (DH > 70%) were able to solubilize HCT and CEL up to 15%, but required higher extrusion temperature, due to the crystalline nature of PVOH. The highest drug release rate was observed from hot-melt extruded PVOH samples with a high DH. While drug release from extrudates consisting of PVOH with a low DH was affected by ionic strength, there was no influence of pH and ionic strength on HCT release from PVOH samples with a higher DH. However, PVOH (DH > 70%) required higher extrusion temperatures, which could hamper its application for thermosensitive drugs. Therefore, the secondary purpose was to investigate the effect of sorbitol, a water-soluble plasticizer, on the thermal properties of hot-melt extruded PVOH (DH > 70%). The melting of PVOH/sorbitol mixture was required to establish molecular interactions between PVOH and sorbitol. These molecular interactions were reflected in the HME behavior: whereas an extrusion temperature of 180°C was necessary to process physical mixtures of PVOH (DH > 70%) and sorbitol, only 140°C was necessary during re-extrusion (after quench cooling and cryomilling) of the PVOH/sorbitol mixture. In addition, the *in vitro* and *in vivo* dug release of plasticized PVOH was examined; whereas the CEL/PVOH/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: oral drug delivery, hot-melt extrusion, polyvinyl alcohol, immediate release, supersaturation

1 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 (Mohammed et al., 2012). For pharmaceutical applications hot-melt extrusion (HME) is considered an effective process to formulate immediate release 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. hydroxypropyl cellulose, polyethylene oxide, poly(vinyl pyrrolidone) (Crowley et al., 2007), polyvinyl alcohol (Dawson and Stevens, 2002)).

Partially hydrolyzed polyvinyl alcohol (PVOH), 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 (i.e. catalyst concentration, reaction temperature and time) determine

the degree of hydroxylation of PVOH (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 PVOH 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 primary purpose of this study was to process different partially hydrolyzed PVOH grades via HME and to evaluate them as carrier for oral immediate-release dosage forms in order to improve the release rate of poorly water-soluble drugs (i.e. hydrochlorothiazide (HCT) and celecoxib (CEL)) via the formulation of solid dispersions. A secondary purpose was to investigate the effect of a water-soluble plasticizer (i.e. sorbitol) on the thermal properties of hot-melt extruded PVOH. In addition, the *in vitro* and *in vivo* drug release of plasticized PVOH was examined.

2 MATERIALS AND METHODS

2.1 Materials

Several PVOH grades (obtained from Kuraray, Hattersheim am Main, Germany) with varying degrees of hydrolysis were evaluated: type LM 25 (33-38% hydrolyzed), type LM 22 (47-53% hydrolyzed), type 505 (72-75% hydrolyzed). In addition, a pharmaceutical PVOH grade (type 4-88, 88% hydrolyzed, provided by Merck, Darmstadt, Germany) was included in the study. The LM-grades were end group-modified with carboxylic acid to provide good aqueous dispersibility. Hydrochlorothiazide (HCT) (Utag, Amsterdam, Netherlands), a BCS class III drug (Wu and Benet, 2005), and celecoxib (CEL) (Sanico, Turnhout, Belgium), a BCS class II drug (Turner et al., 2012), were used as model drugs. Sorbitol (Fagron, Waregem, Belgium) was used as water-soluble plasticizer of PVOH.

2.2 Hot-melt extrusion

Pure PVOH, mixtures of PVOH/HCT and mixtures of PVOH/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 130-180°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 either manually cut using surgical blades into mini-tablets of 2 mm length or quench-cooled in liquid nitrogen, cryomilled and sieved through a 300 micron sieve.

Mixtures of cryomilled PVOH/sorbitol extrudate (<300µm) 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°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, cryomilled and sieved through a 300-micron sieve.

2.3 Characterization

2.3.1 Thermal analysis

Thermogravimetric analysis (Hi-res TGA 2950, TA instruments, Leatherhead, UK) was employed to investigate the thermal stability of the different PVOH 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, extruded and cryomilled 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 DSC cell. The samples, loaded in non-hermetic aluminum Tzero pans, were evaluated according to DSC conditions (heating rate: 10°C/min) and heat iso MDSC conditions (heating rate: 2°C/min, amplitude: ± 0.318 °C, period: 60 sec.) 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 PVOH (Xc) was calculated with reference to the enthalpy of fusion (ΔH_f^*) of the perfect PVOH crystal (138.6 J/g) (Mallapragada et al., 1997), with the following formula: $Xc = \frac{\Delta H_f}{\Delta H_f^*} \times 100$, whereby ΔH_f was defined as the enthalpy of fusion of the respective PVOH.

2.3.2 Karl Fisher (KF) coulometric titration

The water content of the different PVOH grades was quantified via KF coulometric titration. The measurements were performed with a V30 Compact Volumetric KF titrator (Mettler Toledo, Zaventem, Belgium). PVOH (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.

2.3.3 X-ray diffraction

The crystallinity of PVOH, HCT and CEL was investigated by means of X-ray diffraction. The X-ray diffraction 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).

2.3.4 *In vitro* drug release

The influence of pH and ionic strength on drug release was investigated for PVOH/HCT extrudates 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 M 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.

The *in vitro* drug release of CEL was investigated for PVOH formulations containing 15 mg CEL formulated as physical mixture or cryomilled extrudate. CEL release from PVOH formulations and from a commercially available CEL formulation (Celebrex®, a capsule formulation containing 37.4% CEL) was determined using the same procedure as for the HCT formulations, but only 0.1 N HCl (pH 1.0) was used as dissolution medium. PVOH/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.

2.3.5 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 cryomilled PVOH extrudate and Celebrex® formulation. The dogs received a hard-gelatin capsule (n°0) containing 5 mg/kg body weight CEL, formulated as the cryomilled 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.

2.3.6 Determination of celecoxib plasma concentration

CEL plasma concentrations were determined based on the 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), 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.

3 RESULTS AND DISCUSSION

3.1 Partially hydrolyzed PVOH

Partially hydrolyzed PVOH was evaluated as carrier for oral immediate release applications, and HCT, which is stable over a wide temperature range, was chosen as model drug (Valladao et al., 1996). Thermal stability of partially hydrolyzed PVOH is a prerequisite for HME. Therefore, thermal gravimetric analysis (TGA) of the partially hydrolyzed PVOH grades was performed. This technique indicated a weight loss up to a temperature of 150°C which was linked to the presence of water in the PVOH polymer as KF titration confirmed that the water content of the samples ranged from 1.0 to 3.7%. The onset of thermal polymer degradation was detected at 240°C, indicating that PVOH polymers are stable under the process conditions used in the study (a maximum extrusion temperature of 180°C was used)(Alexy et al., 2004; Peng and Kong, 2007).

Modulated differential scanning calorimetry (MDSC) (Fig. 1) was used to examine the crystalline nature of PVOH with different degree of hydrolysis (33 – 88%). The non-reversed heat flow of PVOH with high degree of hydrolysis (> 70%) showed two endothermic signals, corresponding with water evaporation and melting of PVOH. In contrast, only water evaporation was observed in PVOH samples with a low degree of hydrolysis (< 50%). Therefore, PVOH with high degree of hydroxylation (>70 %) contain a degree of crystallinity, due to an increased number of OH groups, which are able to form hydrogen bonds. Furthermore, the glass transition temperature was observed in the reversed heat flow for all PVOH grades, which was increased during second heating (Table 1) due to the evaporation of water during the first heating phase (Hassan and Peppas, 2000).

This difference in crystallinity was also reflected in the X-ray diffraction (XRD) patterns of the different PVOH powders (Fig. 2): whereas a diffuse halo was observed for PVOH grades with a low degree of hydroxylation (due to their higher content of amorphous polyvinyl acetate), crystalline reflections at $2\theta = 19.9°$ and 20.2° were detected in samples with a high degree of

hydroxylation (Bunn, 1948). The semi-crystalline nature of these PVOH grades was confirmed based on the fusion enthalpy of the DSC melting peaks: 16.9±1.7% crystallinity for type 505 (72-75%) and 32.1±3.6% crystallinity for type 4-88 (88%), respectively. The correlation between crystallinity and the degree of hydroxylation is linked to intermolecular hydrogen bonding between the polymer chains (Assender and Windle, 1998), whereby PVOH grades with a high degree of hydrolysis (which contain more vinyl alcohol units), could recrystallize upon cooling due to hydrogen bonding. In contrast, PVOH with a low degree of hydrolysis (< 50%, type LM25 and LM22) did not recrystallize during cooling, as the higher number of vinyl acetate units disrupted hydrogen bonding between vinyl alcohols.

The processability of PVOH formulations via HME (3 mm die) was evaluated in function of degree of hydroxylation and extrusion temperature. The extrusion behavior of partially hydrolyzed PVOH grades differed depending on their degree of hydroxylation: while type LM25 (33 - 38%) and LM22 (47 - 53%) were easily processable at a temperature of 100°C, higher temperatures (180°C) were required to process type 505 (72 – 75%) and 4-88 (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 PVOH grades (Table 1). In addition, PVOH grades with a higher degree of hydroxylation had a higher molecular weight (Table 1), and therefore higher extrusion temperatures were required during the extrusion process to lower the flow viscosity of these PVOH grades.

The X-ray diffraction patterns of HCT and physical mixtures of PVOH/HCT showed the crystalline nature of HCT at 2θ = 17°. After extrusion, transparent extrudates were obtained for up to 15% HCT content in combination with PVOH with a high degree of hydroxylation (> 70%), no HCT crystals were detected in these samples (Fig. 3). In contrast, even at 10% HCT load, formulations containing PVOH with a lower degree of hydroxylation (< 50%) were opaque. These PVOH grades were only able to solubilize 5% HCT.

The influence of pH on HCT release from PVOH-based extrudates was evaluated in a pH range 1 to 9, using dissolution media with a constant ionic strength of 0.14M (Fig. 4). Although PVOH type LM25 (33 - 38%) and 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 PVOH type LM 22 (47 – 53%) was slightly affected at pH 1. HCT release from type 505 (72-75%)- and 4-88 (88%)-based formulations was independent of pH. In contrast, the effect of ionic strength of the dissolution medium (pH 7.4) on HCT release was significant for PVOH matrices with a low degree of hydroxylation, while no effect on formulations containing PVOH with a higher degree of hydroxylation (> 70%) was detected (Fig. 5).

The influence of drug load on drug release was investigated with formulations containing 5-15% HCT (Fig. 6). Drug release after 120 min from 4-88 (88%) formulations containing 5 and 15% HCT was 51% and 92%, respectively. This dependency of drug release on drug content was observed for all PVOH types. As HCT is released from PVOH formulations via swelling-controlled diffusion, upon contact of the PVOH formulations with the dissolution medium two phenomena will interact: swelling and true dissolution of PVOH (Colombo, 1993). Initially, PVOH chains swell due to water sorption and therefore, HCT diffuses through this swollen rubbery region. Water sorption also induces dissolution of the polymer matrix. As water sorption will increase in PVOH formulations containing a higher drug load due the higher osmotic pressure, this will enhance polymer swelling, PVOH dissolution and drug release (Kim and Lee, 1992; Lee and Kim, 1991).

3.2 Plasticized partially hydrolyzed PVOH

Based on their ability to solubilize HCT in an HME-processed matrix in combination with their pH and ionic strength independent drug release PVOH polymers with high degree of hydroxylation (> 70%) were promising carriers for HME applications. However, the higher temperature required for HME (180°C) of these PVOH samples (type 505 and 4-88) due to

their semi-crystalline nature hampered their use as carriers for thermosensitive drugs (i.e. CEL) (Sovizi, 2010). Therefore, the addition of a plasticizer was evaluated to broaden the application of PVOH for HME. The most commonly used plasticizers for PVOH were polyols (i.e. polyethylene glycol, glycerol, sorbitol), where hydrogen bonding between the polyols and PVOH reduced inter- and intra-molecular hydrogen bonding in the PVOH 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 1st DSC heating cycle was observed, a lower T_g and T_m were detected during the second heating cycle of all samples (Table 2). This indicated that the melting of the sorbitol/PVOH 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 PVOH 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 PVOH (Mohsin et al., 2011). Sorbitol concentration was limited to 40% as a higher concentration in the PVOH/sorbitol mixture yielded a liquefied mass after extrusion. Sorbitol also had a more pronounced impact on PVOH with the highest degree of hydroxylation (type 4-88) 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/PVOH mixtures. Whereas an extrusion temperature of 180°C was required to process physical mixtures of PVOH and sorbitol (i.e. similar condition as for HME-processing of pure PVOH grades with a high degree of hydroxylation), re-extrusion of PVOH/sorbitol mixture (after quench-cooling and cryomilling) 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 PVOH type 505 (72-75%) or 4-88 (88%). Moisture content of the cryomilled material was similar to unmilled PVOH/sorbitol mixtures, thus water sorption during cryomilling did not contribute to the observed lower extrusion temperature for the cryomilled PVOH/sorbitol formulations.

Combining the cryomilled plasticized PVOH grades (containing 40% sorbitol) with 15 % CEL (melting point 160.6 °C) also allowed HME processing at 140°C. Under these conditions both PVOH matrices (type 505 and 4-88) were able to solubilize the entire CEL fraction as confirmed by the XRD patterns (Fig. 7) and DSC analysis (Fig. 8). FTIR spectroscopy (Fig. 9) 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 (PM), they broadened after extrusion (EX), likely due to hydrogen bonding between the acidic hydrogen of N-H as hydrogen donor from CEL and O-H as hydrogen acceptor of PVOH (Fouad et al., 2011). This resulted in a fast release of CEL from the PVOH mixtures (Fig. 10). It is important to note that these dissolution tests were performed under non-sink conditions in 0.1N HCl and that the CEL/PVOH/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). PVOH has already been reported as a precipitation inhibitor, 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).

The influence of *in vitro* supersaturation on *in vivo* bioavailability was investigated after oral administration of the formulations to dogs (Fig. 11). Despite the significant differences of the *in vitro* release profiles, all pharmacokinetic parameters were equally good, as cryomilled plasticized PVOH (containing 40% sorbitol) with 15% CEL was able to obtain the same

bioavailability as the reference, which was Celebrex®, a commercially available formulation (Table 3). 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 PVOH carrier, rapid *in-vivo* diffusion of the PVOH 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.

4 CONCLUSIONS

PVOH polymers were identified as carriers for HME applications, as PVOH with high degree of hydrolysis were able to solubilize HCT and CEL up to 15%. The fastest drug release was obtained from PVOH formulations with a high degree of hydroxylation, whereby drug release was independent of pH (1 – 9) and ionic strength (0 – 0.14M). However, high extrusion temperatures were required which could hamper its application for thermosensitive drugs. Therefore, PVOH was plasticized with sorbitol, which lowered the extrusion temperature to 140°C. The *in vitro* dissolution profiles of CEL were significantly improved, as CEL was in a state of supersaturation, and moreover PVOH was able to stabilize supersaturation for at least 2h. However, the enhanced *in vitro* dissolution was not reflected in the *in vivo* bioavailability.

Acknowledgement

The authors acknowledge the financial support of the Interreg 2 Seas programme, the support of Merck for providing the pharmaceutical grade PVOH samples and Kuraray for providing the technical grade PVOH samples. The authors also want to thank Mr. D. Tensy for his contribution during the *in vivo* study and Mrs. S. Vande Casteele for her assistance with the LC-MS analyses.

5 REFERENCES

Alexy, P., Lacik, I., Simkova, B., Bakos, D., Pronayova, N., Varosova, M., 2004. Effect of melt processing on thermo-mechanical degradation of poly(vinyl alcohol)s. Polym Degrad Stabil 85, 823-830.

Assender, H.E., Windle, A.H., 1998. Crystallinity in poly(vinyl alcohol). 1. An X-ray diffraction study of atactic PVOH. Polymer 39, 4295-4302.

Bunn, C.W., 1948. Crystal Structure of Polyvinyl Alcohol. Nature 161, 929-930.

Colombo, P., 1993. Swelling-Controlled Release in Hydrogel Matrices for Oral Route. Adv Drug Deliver Rev 11, 37-57.

Crowley, M.M., Zhang, F., Repka, M.A., Thumma, S., Upadhye, S.B., Kumar Battu, S., McGinity, J.W., Martin, C., 2007. Pharmaceutical applications of hot-melt extrusion: part I. Drug Dev Ind Pharm 33, 909-926.

Dave, R.H., Patel, A.D., Donahue, E., Patel, H.H., 2012. To evaluate the effect of addition of an anionic surfactant on solid dispersion using model drug indomethacin. Drug Dev Ind Pharm 38, 930-939.

Dawson, J.C., Stevens, H.G., 2002. Method and apparatus for blowmolding capsules of polyvinylalcohol and blowmolded polyvinylalcohol capsules.

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

DeMerlis, C.C., Schoneker, D.R., 2003. Review of the oral toxicity of polyvinyl alcohol (PVA). Food Chem Toxicol 41, 319-326.

Fouad, E.A., EL-Badry, M., Mahrous, G.M., Alanazi, F.K., Neau, S.H., Alsarra, I.A., 2011. The use of spray-drying to enhance celecoxib solubility. Drug Dev Ind Pharm 37, 1463-1472.

Gift, A.D., Luner, P.E., Luedeman, L., Taylor, L.S., 2008. Influence of Polymeric Excipients on Crystal Hydrate Formation Kinetics in Aqueous Slurries. J Pharm Sci-Us 97, 5198-5211.

Gorajana, A., Ying, C.C., Shuang, Y., Fong, P., Tan, Z., Gupta, J., Talekar, M., Sharma, M., Garg, S., 2013. Development of Solid Dispersion Systems of Dapivirine to Enhance its Solubility. Curr Drug Deliv 10, 309-316.

Hallensleben, M.L., 2000. Ullmann's Encyclopedia of Industrial Chemistry.

Hassan, C.M., Peppas, N.A., 2000. Structure and applications of poly(vinyl alcohol) hydrogels produced by conventional crosslinking or by freezing/thawing methods. Adv Polym Sci 153, 37-65.

Jang, D.J., Sim, T., Oh, E., 2013. Formulation and optimization of spray-dried amlodipine solid dispersion for enhanced oral absorption. Drug Dev Ind Pharm 39, 1133-1141.

Janssens, S., Van den Mooter, G., 2009. Review: physical chemistry of solid dispersions. J Pharm Pharmacol 61, 1571-1586.

Joudieh, S., Bon, P., Martel, B., Skiba, M., Lahiani-Skiba, M., 2009. Cyclodextrin Polymers as Efficient Solubilizers of Albendazole: Complexation and Physico-Chemical Characterization. J Nanosci Nanotechno 9, 132-140.

Junghanns, J.U.A.H., Muller, R.H., 2008. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomed 3, 295-309.

Kim, C.J., Lee, P.I., 1992. Composite Poly(Vinyl Alcohol) Beads for Controlled Drug Delivery. Pharmaceut Res 9, 10-16.

Lee, P.I., Kim, C.J., 1991. Probing the Mechanisms of Drug Release from Hydrogels. J Control Release 16, 229-236.

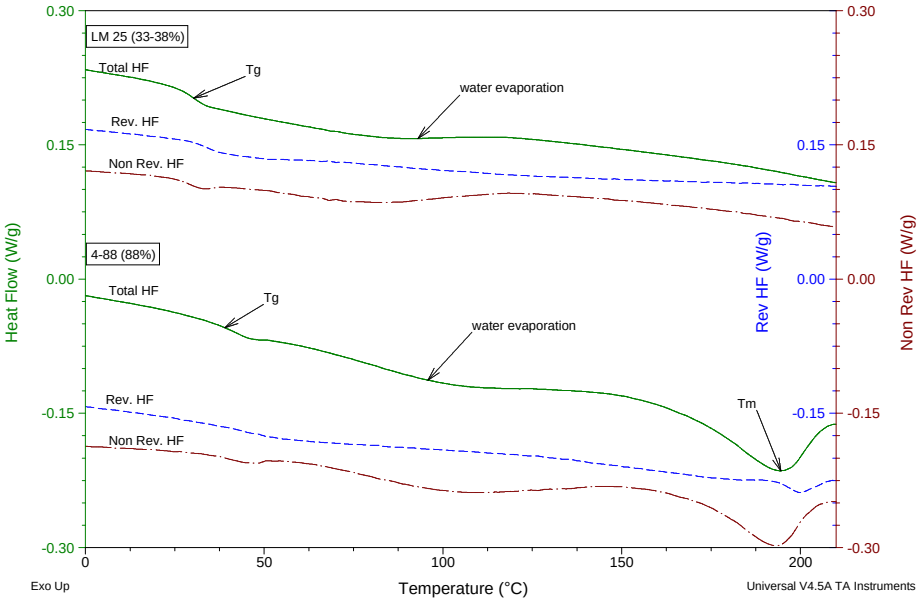
Mallapragada, S.K., Peppas, N.A., Colombo, P., 1997. Crystal dissolution-controlled release systems .2. Metronidazole release from semicrystalline poly(vinyl alcohol) systems. J Biomed Mater Res 36, 125-130.

Maniruzzaman, M., Rana, M.M., Boateng, J.S., Mitchell, J.C., Douroumis, D., 2013. Dissolution enhancement of poorly water-soluble APIs processed by hot-melt extrusion using hydrophilic polymers. Drug Dev Ind Pharm 39, 218-227.

Megrab, N.A., Williams, A.C., Barry, B.W., 1995. Estradiol Permeation through Human Skin and Silastic Membrane - Effects of Propylene-Glycol and Supersaturation. J Control Release 36, 277-294.
Mohammed, N.N., Majumdar, S., Singh, A., Deng, W.B., Murthy, N.S., Pinto, E., Tewari, D., Durig, T., Repka, M.A., 2012. Klucel (TM) EF and ELF polymers for immediate-release oral dosage forms prepared by melt extrusion technology. Aaps Pharmscitech 13, 1158-1169.
Mohsin, M., Hossin, A., Haik, Y., 2011. Thermomechanical properties of poly(vinyl alcohol) plasticized with varying ratios of sorbitol. Mat Sci Eng a-Struct 528, 925-930.
Nkansah, P., Antipas, A., Lu, Y., Varma, M., Rotter, C., Rago, B., El-Kattan, A., Taylor, G., Rubio, M., Litchfield, J., 2013. Development and evaluation of novel solid nanodispersion system for oral delivery of poorly water-soluble drugs. J Control Release 169, 150-161.
Overhoff, K.A., McConville, J.T., Yang, W., Johnston, K.P., Peters, J.I., Williams, R.O., 2008. Effect of stabilizer on the maximum degree and extent of supersaturation and oral absorption of tacrolimus made by ultra-rapid freezing. Pharm Res 25, 167-175.
Peng, Z., Kong, L.X., 2007. A thermal degradation mechanism of polyvinyl alcohol/silica nanocomposites. Polym Degrad Stabil 92, 1061-1071.
Porter, C.J.H., Pouton, C.W., Cuine, J.F., Charman, W.N., 2008. Enhancing intestinal drug solubilisation using lipid-based delivery systems. Adv Drug Deliver Rev 60, 673-691.
Repka, M.A., Shah, S., Lu, J.N., Maddineni, S., Morott, J., Patwardhan, K., Mohammed, N.N., 2012. Melt extrusion: process to product. Expert Opin Drug Del 9, 105-125.
Rowe, R.C., Sheskey, P.J., Owen, S.C., Association, A.P., 2006. Handbook of pharmaceutical excipients. Pharmaceutical Press.
Shegokar, R., Muller, R.H., 2010. Nanocrystals: Industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm 399, 129-139.
Shono, Y., Jantratid, E., Janssen, N., Kesisoglou, F., Mao, Y., Vertzoni, M., Reppas, C., Dressman, J.B., 2009. Prediction of food effects on the absorption of celecoxib based on biorelevant dissolution testing coupled with physiologically based pharmacokinetic modeling. Eur J Pharm Biopharm 73, 107-114.
Sovizi, M.R., 2010. Thermal behavior of drugs. J Therm Anal Calorim 102, 285-289.
Taupitz, T., Dressman, J.B., Buchanan, C.M., Klein, S., 2013. Cyclodextrin-water soluble polymer ternary complexes enhance the solubility and dissolution behaviour of poorly soluble drugs. Case example: Itraconazole. Eur J Pharm Biopharm 83, 378-387.
Thellen, C., Cheney, S., Ratto, J.A., 2013. Melt processing and characterization of polyvinyl alcohol and polyhydroxyalkanoate multilayer films. J Appl Polym Sci 127, 2314-2324.
Turner, D.C., Yin, F.C., Kindt, J.T., Zhang, H.L., 2012. Understanding pharmacokinetic food effects using molecular dynamics simulation coupled with physiologically based pharmacokinetic modeling. Biopharm Drug Dispos 33, 510-521.
Valladao, D.M.S., DeOliveira, L.C.S., Netto, J.Z., Ionashiro, M., 1996. Thermal decomposition of some diuretic agents. J Therm Anal 46, 1291-1299.
Warren, D.B., Benameur, H., Porter, C.J.H., Pouton, C.W., 2010. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: A mechanistic basis for utility. J Drug Target 18, 704-731.
Wu, C.Y., Benet, L.Z., 2005. Predicting drug disposition via application of BCS: Transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharmaceut Res 22, 11-23.
Wu, W.Q., Tian, H.F., Xiang, A.M., 2012. Influence of Polyol Plasticizers on the Properties of Polyvinyl Alcohol Films Fabricated by Melt Processing. J Polym Environ 20, 63-69.

Figures

Fig. 1. MDSC-profiles (total, reversed and non reversed heat flow) of polyvinyl alcohol with different degree of



hydrolysis

Fig. 2. XRD-profiles of the different polyvinyl alcohol grades

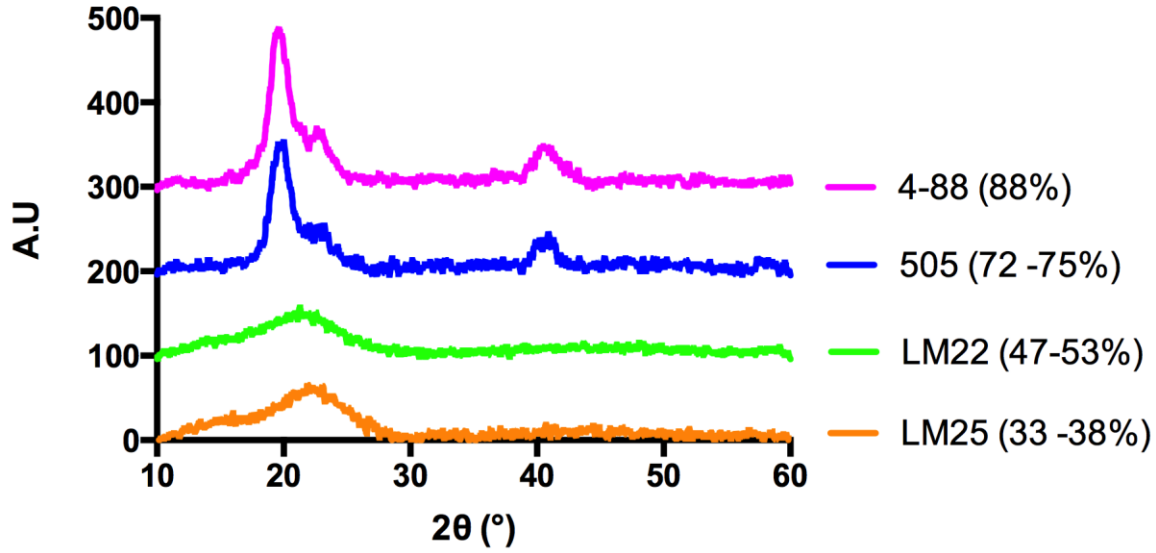


Fig. 3. XRD-profiles of hot-melt extruded formulations containing different grades of polyvinyl alcohol in combination with hydrochlorothiazide (ratio: 85/15)

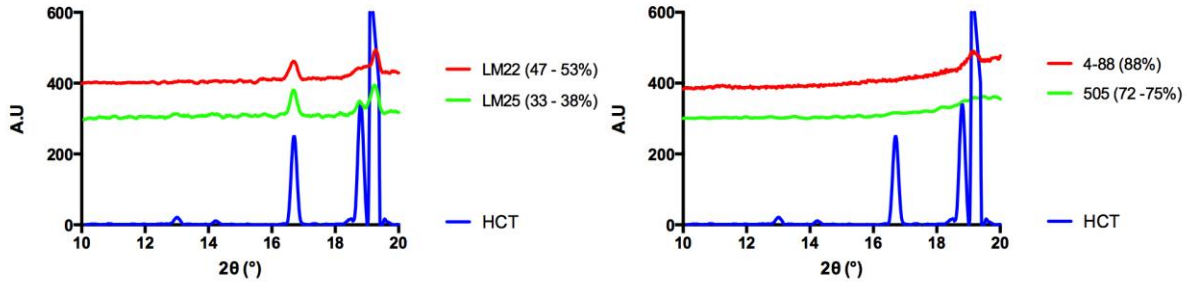


Fig. 4. Dissolution profiles (n=3) of hot-melt extruded formulations containing different grades of polyvinyl alcohol in combination with hydrochlorothiazide (ratio: 85/15) in function of the

pH of the dissolution medium (pH 1 (•); pH 4.5 (■); pH 9 (Δ)). Ionic strength of all dissolution media was 0.14M

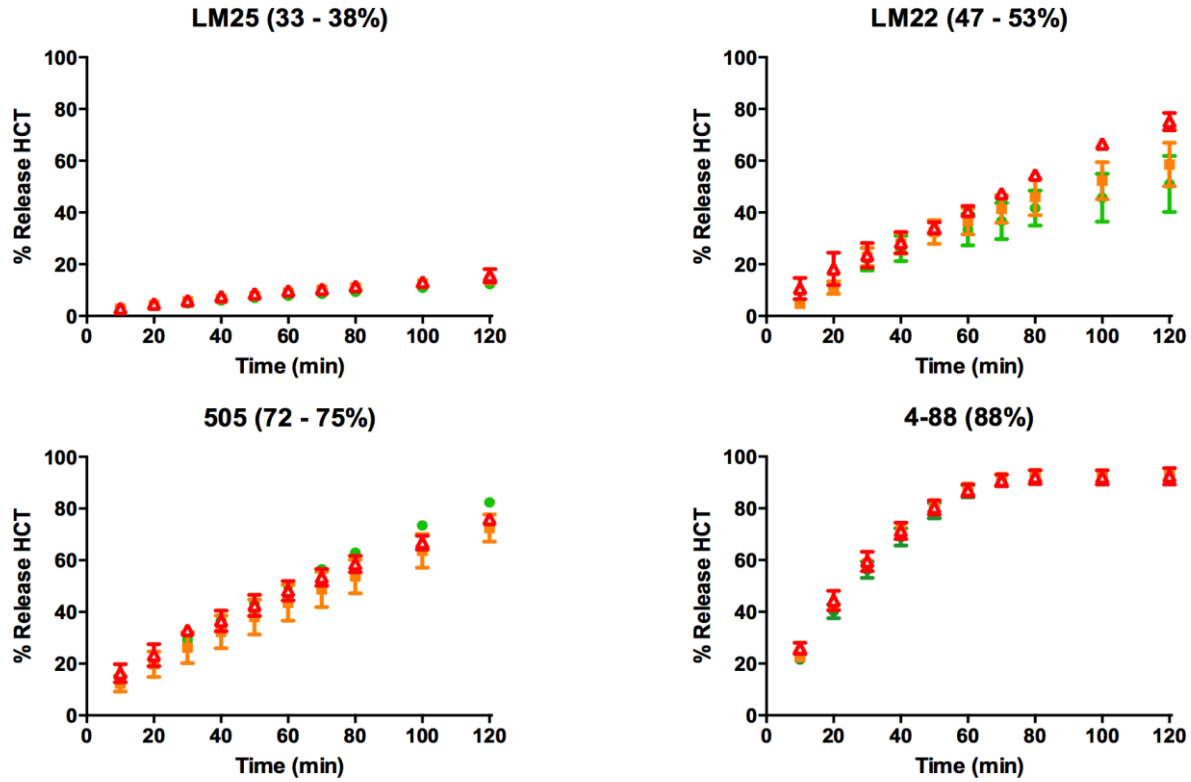


Fig. 5. Dissolution profiles (n=3) of hot-melt extruded formulations containing different grades of polyvinyl alcohol in combination with hydrochlorothiazide (ratio: 85/15) in function of ionic strength of the dissolution medium (0 M (•); 0.018 M (■); 0.089 M (Δ); 0.14 M (∇). pH of all dissolution media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

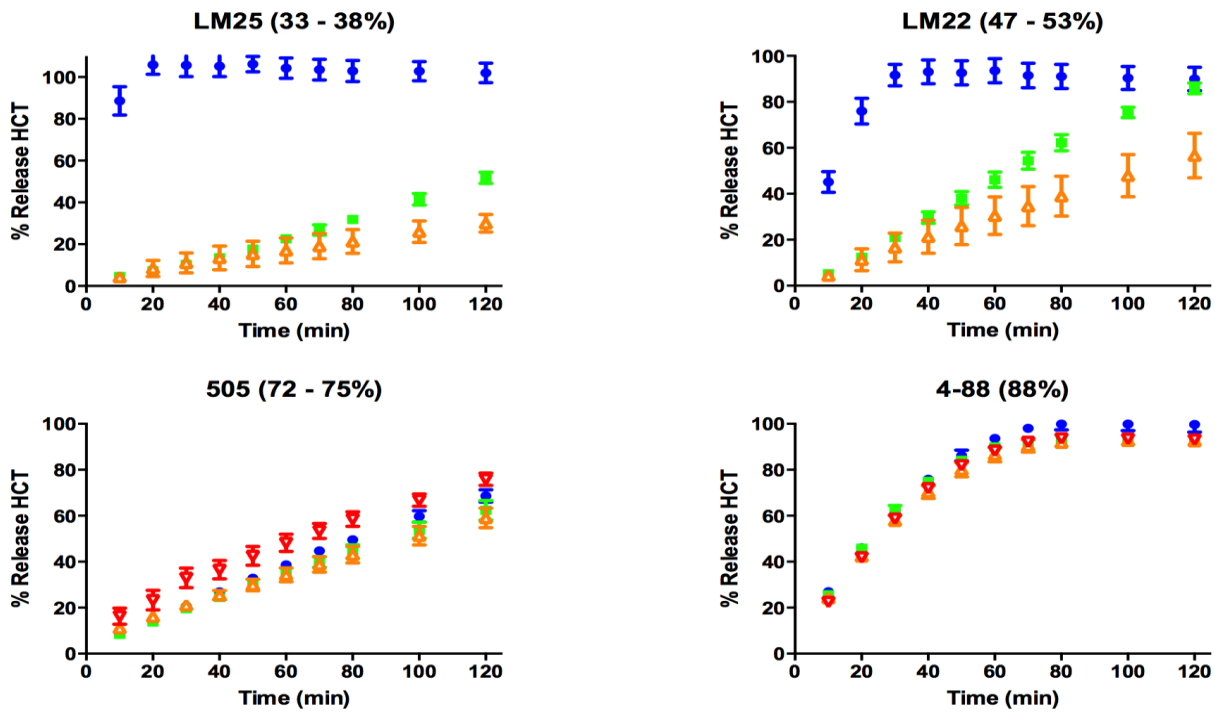


Fig. 6. Dissolution profiles (n=3) of hot-melt extruded formulation containing polyvinyl alcohol type 4-88 (88%) and hydrochlorothiazide in 0.1 N HCl in function of hydrochlorothiazide concentration: 5% (•), 10% (■), 15% (**Δ**)

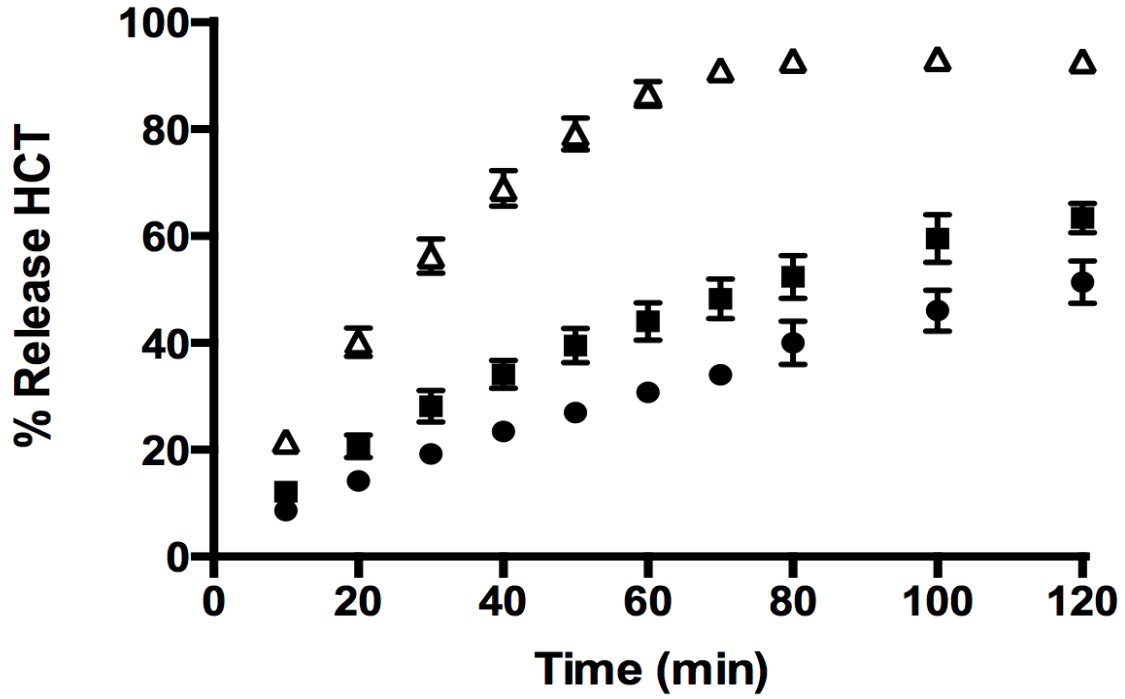


Fig. 7. XRD-profile of celecoxib (A), and physical mixture (B) or extrudate (C) containing plasticized polyvinyl alcohol type 505 (72-75%) (left) or type 4-88 (88%) (right) and celecoxib (15%)

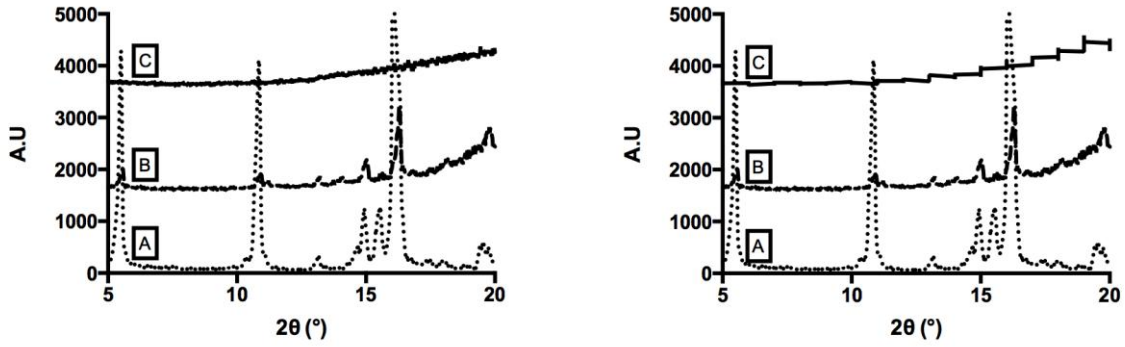


Fig. 8. DSC-profile of celecoxib (A), and physical mixture (B) or extrudate (C) containing plasticized polyvinyl alcohol type 505 (72-75%) (left) or type 4-88 (88%) (right) and celecoxib (15%)

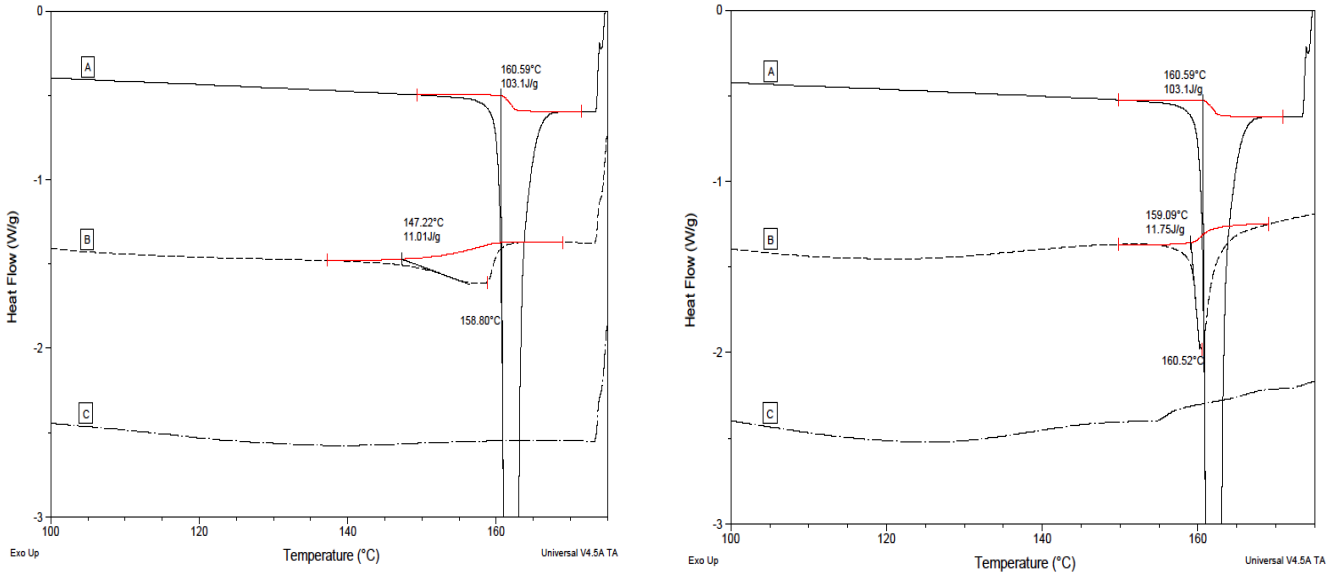


Fig. 9. FTIR spectra of physical mixture (PM) or extrudate (EX) both containing 15% celecoxib and pure compounds (polyvinyl alcohol type 505 (72-75%), sorbitol and celecoxib)

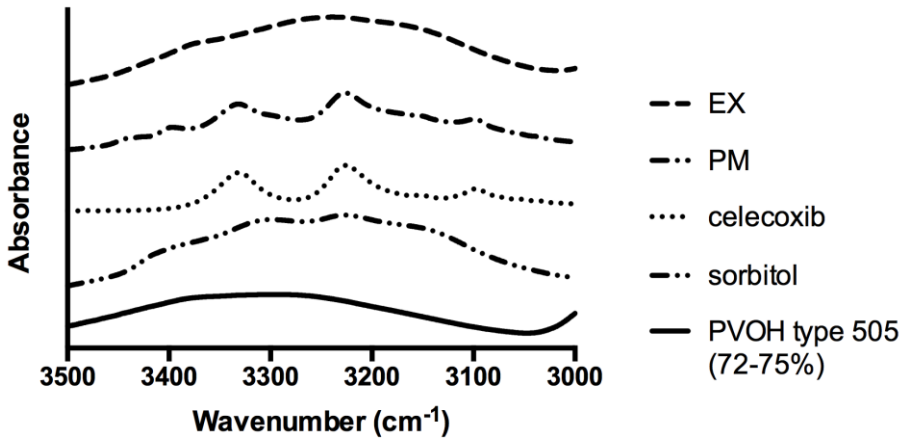


Fig. 10. Dissolution profiles (n=3) of Celebrex® (■) and hot-melt extruded formulation containing plasticized polyvinyl alcohol type 505 (72-75%) (left) or type 4-88 (88%) (right) (•) in capsules containing 15 mg celecoxib in 0.1N HCl pH 1

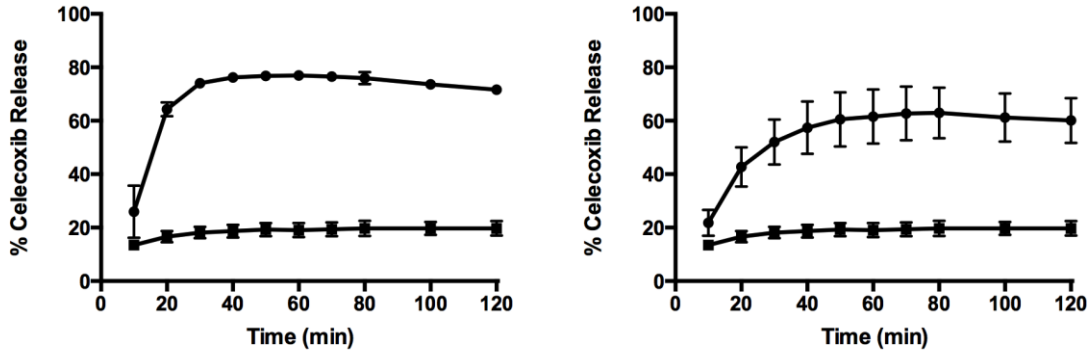
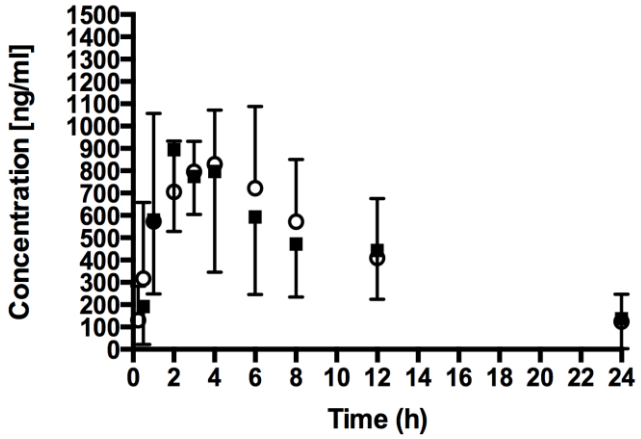


Fig. 11. Average plasma concentration vs time profiles of celecoxib (5 mg/kg) after oral administration of capsules containing Celebrex® (■) or the hot-melt extruded formulation with polyvinyl alcohol type 505 (72-75%) (O) in dogs (n=6)



Tables

Table 1. General properties and thermal behavior (DSC, using a cooling/heating rate of 10°C/min) of the four different types of polyvinyl alcohol

GENERAL PROPERTIES			THERMAL BEHAVIOR			
Type	%OH	Mw (g/mol)	1st HEATING		2nd HEATING	
			T_g (°C)	T_m (°C)	T_g (°C)	T_m (°C)
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

Table 2. 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 PVOH	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

(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
(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

Table 3. Pharmacokinetic parameters of celecoxib (5 mg/kg) after oral administration of capsules containing Celebrex® or the hot-melt extruded formulation with polyvinyl alcohol type 505 in dogs (n=6)

	Celebrex®	**PVOH 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