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).