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Laboratory of Pharmaceutical Technology
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ETHYLENE VINYL ACETATE AS MATRIX FOR ORAL SUSTAINED RELEASE MULTIPLE-UNIT DOSAGE FORMS PRODUCED VIA HOT-MELT EXTRUSION

Master dissertation

Pharm. Kristof DHAENENS
Master of Industrial Pharmacy

Promotors
Prof. Dr. J. P. Remon
Prof. Dr. C. Vervaat
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<tr>
<td>API</td>
<td>Active pharmaceutical ingredient</td>
</tr>
<tr>
<td>BAC</td>
<td>Bronnikov aided correction</td>
</tr>
<tr>
<td>BCS</td>
<td>Biopharmaceutical classification system</td>
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<tr>
<td>DSC</td>
<td>Differential scanning calorimetry</td>
</tr>
<tr>
<td>EVA</td>
<td>Ethylene vinyl acetate</td>
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<tr>
<td>FEGSEM</td>
<td>Field emission gun scanning electron microscope</td>
</tr>
<tr>
<td>GPC</td>
<td>Gel permeation chromatography</td>
</tr>
<tr>
<td>HLB</td>
<td>Hydrophyle-lipophile balance</td>
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<tr>
<td>HME</td>
<td>Hot-melt extrusion</td>
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<tr>
<td>LFD</td>
<td>Large field detector</td>
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<tr>
<td>MBA</td>
<td>Modified Bronnikov algorithm</td>
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<tr>
<td>MDSC</td>
<td>Modulated differential scanning calorimetry</td>
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<tr>
<td>MFI</td>
<td>Melt flow index</td>
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<tr>
<td>MPF</td>
<td>Metoprolol fumarate</td>
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<td>MPS</td>
<td>Metoprolol succinate</td>
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<td>MPT</td>
<td>Metoprolol tartrate</td>
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<tr>
<td>MW</td>
<td>Molecular weight</td>
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<tr>
<td>PE</td>
<td>Polyethylene</td>
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<td>PEO</td>
<td>Polyethylene oxide</td>
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<tr>
<td>PM</td>
<td>Physical mixture</td>
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<tr>
<td>PVA</td>
<td>Polyvinyl acetate</td>
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<td>PVP</td>
<td>Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>RCS</td>
<td>Refrigerated cooling system</td>
</tr>
<tr>
<td>rpm</td>
<td>Rotations per minute</td>
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<tr>
<td>SEM</td>
<td>Scanning electron microscope</td>
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<tr>
<td>SS</td>
<td>Sorbitan sesquioleate</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>TGA</td>
<td>Thermogravimetric analysis</td>
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<td>VA</td>
<td>Vinyl acetate</td>
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<td>XRD</td>
<td>X-ray diffraction</td>
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1. INTRODUCTION

1.1. CONTROLLED RELEASE

1.1.1. General

In recent years increasing attention has been given to the controlled delivery systems, which offer a potential advantage over conventional drug therapy. In standard dosage forms, the drug level in the blood raises, peaks and then declines eventually to almost zero. However, each drug has a therapeutic range above which it is toxic and below which it is ineffective, the minimum toxic concentration and the minimum effective concentration, respectively. A controlled release preparation maintains the drug in the desired therapeutic range with a single dose. Other advantages include localized delivery of the drug to a particular region in the body, which lowers the systemic drug level, a reduced need for follow-up care and improved patient compliance and convenience (Vasudev et al., 1997).

Controlled release dosage forms can be classified into three basic types: sustained release, prolonged action and repeat action dosage forms. As shown in figure 1.1, sustained release products are designed to release bolus (loading dose) to produce an immediate response, followed by a constant dose (maintenance dose; according to zero-order kinetics) required to maintain a therapeutically effective level for some desirable period. Prolonged action formats deliver active ingredients in amounts sufficient to maintain therapeutic levels at a rate which extends the duration of the pharmacological action. Repeat action dosage forms are intended to deliver the equivalent of a single dose drug, and then an additional equivalent dose after a predetermined interval (Remon & Vervaet, 2002). This project is focused on the development of sustained release dosage forms.

Figure 1.1. Sustained release, prolonged action and repeat action dosage forms (Remon & Vervaet, 2002).
1. INTRODUCTION

1.1.2. **Sustained release dosage forms**

We can distinguish sustained release dosage forms between monolithic (non-divided) and multiple-unit (divided) forms. Multiple-unit dosage forms can offer various advantages over monolithic, among which more predictable gastric emptying, less dependence on the state of nutrition, high degree of dispersion in the digestive tract, less risk of dose dumping and less inter- and intra-subject variability (Follonier et al., 1994).

There are three main principles which are used to obtain extended drug action: modification of the biological system, modification of the drug and modification of the dosage form. Modification of the biological system (e.g. inhibition of the renal clearance by probenicid) and modification of the drug (e.g. crystal modifications, drug solubility modifications, chelation products, prodrugs or probiotic use) are in practice not often applied (Remon & Vervaet, 2002; Varshosaz et al., 2006). Modification of the dosage form proves to be the most efficient technique. It is used frequently and based mainly on the following mechanisms: (1) diffusion of the drug species from or through the system; (2) a chemical or enzymatic reaction leading to degradation of the system, or cleaving of the drug from the system; and (3) solvent activation, either through osmosis or swelling of the system. A combination of mechanisms is possible (Langer, 1998).

Polymer-based systems have had an enormous impact on drug therapies. For example as a reservoir system, where the drug is physically entrapped inside a solid polymer shell (Langer, 1998). However, this approach involves coating which is a time consuming and expensive process with possible problems of reproducibility of drug release, dose dumping and no release of ionic species or large molecules (Langer, 1998; De Brabander et al., 2003). To address these problems, drugs were physically embedded in polymers at concentrations high enough to create a series of interconnecting pores through which the drug could subsequently slowly diffuse (a matrix system) (Langer, 1998).

Several studies have shown the possibility to formulate matrices using different types of manufacturing techniques such as extrusion-spherionisation, melt suspension, solvent evaporation, coacervation (Zhou et al., 1995), hot-melt extrusion (Grassi et al., 2003) and melt-granulation (Voinovich et al., 2000).
1. INTRODUCTION

1.2. HOT-MELT EXTRUSION

1.2.1. General

Hot-melt extrusion (HME) is one of the most widely used processing techniques within the plastics industry. This technique was first introduced in the plastics industry in the mid-nineteenth century to prepare polymeric insulation coatings to wires (Crowley et al., 2007). Today melt extrusion has found its place in the array of the pharmaceutical manufacturing operations (Chokshi & Zia, 2004). Extrusion is the process of converting a raw material into a product of uniform shape and density under controlled conditions (Breitenbach, 2002).

1.2.2. Applications

Several research groups have evaluated HME to achieve enhancement in dissolution rates and bioavailability (for poorly water soluble drugs), to modify or control the release of drug (sustained release systems) and masking the bitter taste of an active drug (Chokshi & Zia, 2004 and Forster et al., 2002). Granules, sustained release pellets, matrix tablets, transdermal and transmucosal drug delivery systems and implants are some examples of pharmaceutical forms developed by HME (Crowley et al., 2007). HME is an attractive alternative and has many advantages when compared to traditional pharmaceutical processing methods.

1.2.3. Advantages / Disadvantages

The major advantage is the continuity of the production process as the different production steps (mixing, melting, homogenizing and shaping) are carried out in a single machine. This contributes to a decrease of capital and an increased automation of the production (Henrist & Remon, 1999). Molten polymers during the extrusion process can function as thermal binders and act as drug depots and/or drug retardants upon cooling and solidification. Solvents and water are not necessary; thereby it reduces the number of processing steps and eliminates time-consuming drying steps (Crowley et al., 2007). There are no requirements on the compressibility of the active ingredients. A matrix can be massed into a larger unit independent of compression properties. The intense mixing and agitation imposed by the rotating screw causes de-aggregation of suspended particles in the molten polymer, resulting in more uniform dispersion (Crowley et al., 2007; Sprockel et al., 1997).

The disadvantages are few and mainly related to negative effects of shear force (Sethia & Squillante, 2003). However HME requires a polymer that can be processed at relatively
low temperatures due to the thermal sensitivity of many drugs. All components must be thermally stable at the processing temperature during the short duration of the heating process (Crowley et al., 2007).

1.2.4. **Equipment**

Extrusion processes can be categorized as either ram extrusion or screw extrusion. Screw extrusion consists of a rotating screw inside a heated barrel, while ram extrusion operates with a positive displacement ram capable of generating high pressures to push materials through the die. The major drawback of ram extrusion is limited melting capacity that causes poor temperature uniformity in the extrudate. A screw extruder provides more shear stress and intense mixing what results in extrudates with a higher homogeneity, in comparison with extrudates processed with ram extrusion. At a minimum, a screw extruder consists of three distinct parts: a conveying system for material transport and mixing, a die system for forming, and downstream auxiliary equipment for cooling, cutting or collecting the finishing goods. Individual components within the extruder are the feed hopper, a temperature controlled barrel, rotating screw, die and heating and cooling systems (see figure 1.2.) (Crowley et al., 2007).

![Figure 1.2. Cross section of the single screw extruder (Follonier et al., 1995)](image)

An extruder can have one or more screws, respectively a single, twin- or multiple-screw extruder. The first twin extruders were developed in the late 1930’s. As the name implies twin-screw extruders utilize two screws usually arranged by side. The screw can rotate in the same (co-rotating) or the opposite (counter-rotating) direction. Co-rotating screw extruders are generally of the intermeshing design, and are thus self-wiping. The design minimizes the non-motion and prevents localized overheating of materials within the
extruder. They are industrially the most important type of extruders and have several advantages over the counter-rotating screw extruders such as a higher maximum screw speed and a higher output while achieving good mixing and conveying characteristics (Crowley et al., 2007).

Twin-screw extruders have several advantages over single screw extruders, like easier material feeding, high kneading, and dispersing capacities, less tendency to over-heat and shorter transit time. However single-screw extruders do have the advantage over twin-screw extruders in terms of their mechanical simplicity and more reasonable cost (Crowley et al., 2007).

1.2.5. The melt extrusion process

The theoretical approach to understanding the melt extrusion process is generally presented by dividing the process flow into four sections: feeding the extruder, conveying of mass (mixing and reduction of particle size) and entry through the die, flow through the die, exit from die and down-stream processing (Breitenbach, 2002).

The extrusion channel is conventionally divided into three sections: feed zone, transition zone, and metering zone. The starting material is fed from the hopper directly into the feed section, with screws with deeper flights or flights of greater pitch. This geometry enables the feed material to fall easily into the screw for conveying along the barrel. The material is transported as a solid plug to the transition zone where it is mixed, compressed, melted and plasticized. The heat required to melt or fuse the material is supplied by the heat generated by friction as the material is sheared between the rotating screws and the wall of the barrel in combination with electric or liquid heaters mounted on the barrels. Compression is developed by decreasing the thread pitch but maintaining a constant flight depth or by decreasing flight depth while maintaining a constant thread pitch. Both methods result in increased pressure as the material moves along the barrel. The material reaches the metering zone in the form of a homogeneous plastic melt suitable for extrusion. For an extrudate of uniform thickness, flow must be consistent and without stagnant zones right up to the die entrance. The function of the metering zone is to reduce pulsating flow and ensure a uniform delivery rate through the die cavity. The end-plate die determines the shape of the extruded product (Breitenbach, 2002).

Extrusion processing requires close monitoring and understanding of the various parameters: viscosity and variation of viscosity with shear rate and temperature, elasticity and
extensional flow of the material over hot metal surfaces. Extruders allow in-process monitoring and control of parameters, such as temperature in the extruder, head and die as well as pressure in extruder and die. The main monitoring and controlling parameters are barrel temperatures, feed rate, screw speed, motor load and melt pressure (Chokshi & Zia, 2004).

1.2.6. Materials used in HME

For a pharmaceutical material to be processed by HME, it must be able to deform easily inside the extruder and solidify upon exit. The materials must meet the same levels of purity and safety as those prepared by traditional techniques (Crowley et al., 2007). They must possess some degree of thermal stability in addition to acceptable physical and chemical stability. The thermal stability of each individual compound and of the composite mixture should be sufficient to withstand the production process. HME dosage forms are complex mixtures of active drug and functional excipients. The functional excipients may be broadly classified as matrix carriers, release-modifying agents, bulking agents and various additives (Chokshi & Zia, 2004).

The properties of the active drug substance often limit the formulation and preparation option available to the pharmaceutical scientist in the development of an acceptable dosage form. The HME process is anhydrous, avoiding any potential drug degradation due to hydrolysis. In addition poorly compactable materials can be incorporated into tablets produced by cutting an extruded rod, eliminating any potential tableting problems seen in traditional compressed dosage forms. The active ingredient should be thermally stable to be melt-extruded and thus an initial assessment of thermal, chemical and physical properties of the drug substance is very essential. Depending on the unique properties of the drug substance and the other excipients in the formulation, the drug may be present as undissolved i.e. solid dispersion or completely dissolved in the carrier material i.e. solid solution in the final dosage form. The state of the drug in the dosage form may have profound impact on the processability and stability of the product. In addition to thermal degradation, the active compound may interfere with the functionality of the other components in the formulation (Chokshi & Zia, 2004).

In HME drug delivery systems, the active compound is embedded in a carrier formulation often comprised of one or more “meltable” substances and functional excipients. The meltable substance is generally a polymer or low melting point wax (Crowley et al.,
The selection of the polymer for HME process mainly depends on drug-polymer miscibility, polymer stability and function of final dosage form (Chokshi & Zia, 2004). Carriers used in HME dosage forms have included water insoluble polymers and waxes such as ethylcellulose, poly(ethylene-co-vinyl acetate) or carnauba wax in which the rate of drug release are diffusion controlled. Water soluble polymers have included hydroxpropylcellulose, polyethylene oxide, poly(vinylpyrrolidone) in which the drug is released by a diffusion and erosion mechanism (Crowley et al., 2007).

As mentioned above thermal stability of the individual compounds is a prerequisite for the process, although because of short processing times not all thermolabile compounds are excluded (Chokshi & Zia, 2004). However with the addition of a plasticizer, a HME process can be conducted at lower temperatures and with less torque. Plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between the polymer chains. Generally, both the active ingredient and the polymer will be more stable during the extrusion process due to these improved processing conditions (Crowley et al., 2007).

Drug release can be modified by the addition of various functional excipients. The dissolution rate of the drug can be increased (e.g. super desintegrants, surfactants) or decreased (e.g. swelling agents) (Crowley et al., 2007). For systems that display oxidative or free-radical degradation during processing (even oxygen and moisture may be excluded almost completely) or storage, the addition of antioxidants, acid receptors, and/or light absorbers may be advised (Breitenbach, 2002; Chokshi & Zia, 2004).

1.3. SOLID DISPERSIONS

1.3.1. Definition

By definition, solid dispersions and solid solutions can be differentiated based on the molecular state of the drug in the carrier matrix. If the drug is dissolved at molecular level i.e. the drug forms one phase system with polymer, it is referred as a solid solution; whereas, if the drug is in a two phase system with polymer and forms a microcrystalline dispersion, it is generally referred to as a solid dispersion (Chokshi & Zia, 2004).

Improvement in bioavailability of poorly soluble compounds (Biopharmaceutical Classification System (BCS): Class II) with these systems is primarily based on improved dissolution rates. In the case of solid dispersion, this is achieved by improvement in wetting
behaviour of the hydrophobic drug as well as deagglomeration and micellization of the drug with hydrophilic polymers. In case of solid solutions, improvement in dissolution rate is due to high energy amorphous nature of the drug. Thermodynamically, solid solutions are more unstable compared to solid dispersions because in the solid solution the drug exists in a high energy amorphous form, which is prone to precipitation or crystallization under environmental stress such as moisture and heat (during processing and storage) (Chokshi & Zia, 2004).

Solid dispersions are not only applied for the improvement of the release rate and oral bioavailability. By judicious choice of the carrier it is also possible to delay or slow down the release pattern of drug by formulating it as a solid dispersion. A wide variety of polymers that are poorly soluble or which swell under aqueous conditions have potential as carriers for controlled release dosage forms (Leuner & Dressman, 2000). Insoluble polymer carriers are also used to produce sustained-release pharmaceutical forms. The reason for attenuation of drug release rate is based on the following release mechanism. When a tablet consisting of a solid dispersion of a drug in an insoluble matrix is placed in the dissolution medium, the initial drug release occurs from the tablet’s superficial layers and, consequently, the release rate is relatively fast. As time passes the external layers of the tablet become depleted of the drug and water molecules must travel through long, tortuous channels to reach the drug remaining in the deeper layers of the tablet. Similarly, the drug solution that is formed within the tablet must diffuse through long capillaries to reach the external dissolution medium. The primary reason for the continuously decreasing rate of drug release is the increasing distance that must be traversed by water and drug molecules into, and out of, the tablet, respectively (Islam et al., 2010). Various preparation methods for solid dispersions have been reported in literature.

1.3.2. Methods of preparation

Melting and solvent evaporation methods are the two major processes of preparing solid dispersions. In the melting method, the drug or drug mixture and a carrier are melted together by heating. Then the melted mixture is cooled and solidified. Various modifications of the above basic method are available, including HME. The main advantage of the melting method is its ease and lower cost. The disadvantages include drug degradation, decomposition or evaporation at the melting temperature employed (Leuner & Dressman, 2000). Because of these limitations, the solvent method became more popular for the manufacture of polymer-based solid dispersions.
The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature (Vasconcelos et al., 2007). Many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could now be considered as carrier possibilities. With time, however the ecological and subsequent economic problems associated with the use of organic solvents began to make solvent-based methods more and more problematic. For these reasons, HME is the current method of choice for the solvent-free formation of solid dispersions (Leuner & Dressman, 2000). As previously cited, thermolabile compounds can be processed by HME at elevated temperature because of the short processing time.

In this project solid dispersions for sustained release formulations were manufactured by HME. Metoprolol tartrate was used as model drug and ethylene vinyl acetate copolymer (EVA) as drug carrier.

1.4. ETHYLENE VINYL ACETATE

1.4.1. Structure and synthesis

Ethylene vinyl acetate (EVA; Elvax®) is a thermoplastic high molecular weight copolymer of ethylene and vinyl acetate (VA). Ethylene can be readily copolymerized with VA under high-pressure and temperatures. The reactivity ratios of ethylene and VA are similar, resulting in a random distribution of acetate branches along the length of the polymer chain (Salyer & Kenyon, 1971). EVA is synthesized by free-radical polymerization of ethylene gas and VA using a peroxide catalyst (see figure 1.3.). The physical properties of EVA can be tuned between a rigid and rubbery material by altering the ratio of the co-monomers (Shastri, 2002).

Figure 1.3. Synthesis of EVA (Shastri, 2002).
1.4.2. Properties

The properties of EVA copolymers are mainly determined by their VA contents and their MFI. In general, MFI means the melt flow property of polymer materials at fixed pressure and temperature. Thus, high MFI means superior hot melt extrusion property. The MFI is an indication of the molecular weight (MW) and the viscosity of the polymer. If the MFI is low, the MW and viscosity are high. If the MFI is high, the MW and viscosity are low (www.dupont.com, 2009).

EVA is a kind of semi-crystalline random copolymer (see figure 1.4.) with great industrial importance. Its crystallinity is obviously lower than that of high-density PE because of the incorporation of VA units into the ethylene chains (Zhang et al., 2002). When the VA content is increased, the relative quantity of PE amorphous phase increases and the degree of crystallinity decreases (Brogly et al., 1997). It is known that the degree of crystallinity strongly influences the diffusivity of the polymer for drugs. As the VA content increases, the overall rigidity of the polymer chain decreases and consequently the polymer becomes more rubbery and permeable and hence an increased rate of drug release is observed for drug matrices (Tallury et al., 2007). If the VA content exceeds 50 wt %, the copolymer becomes completely amorphous. Such a change in the phase structure brings about changes in macroproperties of the material. For example, better impact strength and low-temperature properties can be achieved with higher contents of VA component (Zhang et al., 2002).

When VA units are randomly incorporated into the ethylene chains, they separate the chain into crystallizable ethylene sequences of different lengths. In literature, it has been speculated that for the ethylene copolymers with large size branches, only the longer ethylene sequences can pack as the orthorhombic form through so called chain-folded lamellar growth during the primary crystallization process, and the secondary crystallization on subsequent cooling involves predominantly the shorter ethylene sequences. As a result of the latter case, the monoclinic phase is formed. Besides immobile orthorhombic and monoclinic crystalline phases, a third crystalline mobile phase occurs. Such crystalline phase forms during room-temperature aging and melts at the temperature somewhat higher than room temperature on heating. In addition, the amorphous phase also contains two components: an interfacial amorphous phase and a melt-like amorphous phase (Wang et al., 2006).
For random ethylene copolymers, the increase of the comonomer content not only reduces the content but also shortens the average length of the crystallizable ethylene segments. The decrease of the content of the crystallizable ethylene segments brings about the decrease of the crystallinity, whereas the decrease of the average length of crystallizable ethylene segments incurs the increase of the ratio of monoclinic crystals to orthorhombic crystals. Among the crystallizable ethylene segments, the fraction of the shorter ethylene chains increases with the increased comonomer content; this in turn increases the relative content of monoclinic crystals in the crystalline region (Zhang et al, 2002).

Figure 1.4. Morphology of semi-crystalline polymer (www.plastics-elearning.com, 2009).

1.4.3. Toxicology

Typical sources for the induction of adverse tissue response to an implant or other pharmaceutical forms are species that leach out of the polymer matrix. These species are termed as leachants. They include unreacted or residual monomer; residual catalyst and their degradation products; low-MW polymers; fillers; and sterilization agents, such as ethylene oxide. In the case of EVA polymer system, the most likely leachants are unreacted VA and low-MW polyvinyl acetate (PVA). Studies carried out so far suggest PVA and its degradation product polyvinyl alcohol are not toxic. On the other hand, VA is metabolized rapidly in human blood and animal tissue into acetaldehyde, which is a known carcinogen. However, residual VA can be easily removed and hence should not be an issue in future EVA-based implant development (Shastri, 2002).

1.4.4. Applications

Besides several applications in the manufacturing of consumer and industrial goods EVA also found its place in the pharmaceutical industry, mainly in the development of polymeric systems for controlled drug release. The choice of this type of polymer for use in controlled release systems is based on the following characteristics: (1) polymers are
1. INTRODUCTION

biocompatible, non-toxic and do not cause inflammatory reactions; (2) processability (e.g. extrusion) is technically feasible; (3) favorable release properties for many active substances; and (4) solubility and diffusion coefficient of the drug can be varied by the content of VA (Van Laarhoven et al., 2002b).

As cited above, the HME technique is considered as a viable method to develop solid dispersions and solutions. Based on extrusion technology Organon developed two controlled release systems, i.e. Implanon® and NuvaRing®. Both products are made of EVA copolymers. Implanon® is an implant and is designed to release a progestagen for a period of three years. NuvaRing® is a contraceptive vaginal ring, designed to release both a progestagen and an estrogen for a period of 21 days (Van Laarhoven et al., 2002a). EVA is also used as a rate controlling membrane for the controlled delivery of contraceptive hormones to the female reproductive tract (Progestasert®) and lipophilic drugs to the eye or the skin (Ocusert®, Estraderm® and Transderm Nitro®) (Saltzman, 2001).

1.5. METOPROLOL AND SALTS

1.5.1. Structure

Metoprolol fumarate (MPF), succinate (MPS) and tartrate (MPT) appear as white, or almost white, crystalline powders. MPT is very soluble in water and freely soluble in alcohol. MPS is freely soluble in water and slightly soluble in alcohol (Ph. Eur. 6.0, 2009).
1. INTRODUCTION

solubility in water of MPF (± 435 mg/mL) and MPS (± 200 mg/mL) is lower than MPT (＞700 mg/mL) (Ragnarsson et al., 1987). On the basis of permeability and solubility, metoprolol can be categorized as a BCS Class I drug (Yang et al., 2007). Figure 1.5. shows the chemical structures of the different salts of metoprolol.

1.5.2. Pharmacokinetics

Metoprolol is almost completely absorbed following oral administration. The bioavailability is only approximately 50%, because of first-pass metabolism. The drug crosses the blood–brain barrier and placental barrier; it is also excreted into breast milk. Metoprolol undergoes oxidative metabolism in the liver, mainly by CYP2D6 isoenzymes. Plasma drug concentrations may vary considerably between individuals, due to genetically determined differences in the metabolism of the drug, by genetic polymorphism of CYP2D6. Generally over 95% of an oral dose can be recovered in the urine. About 5% of the given dose is excreted in the urine in unchanged form (www.fk.cvz.nl, 2009).

1.5.3. Pharmacodynamics

Metoprolol is a cardioselective β1-receptor blocker without intrinsic sympathicomimetic activity. It blocks stimulation of β1-(myocardial)-adrenergic receptors, usually without affecting β2-(pulmonary, vascular, uterine)-adrenergic receptors. Blocking the adrenergic stimulation of the heart causes a decrease in heart rate, contractility and cardiac output, resulting in a decrease in blood pressure. MPT has a short half-life, therefore it must be taken several times a day or as a controlled release dosage form. This β1-blocker is indicated in the treatment of hypertension, angina pectoris, hyperthyroidism, cardiac arrhythmias, myocardial infarction and as maintenance therapy for migraine headache and heart failure (www.fk.cvz.nl, 2009).

MPT, with its incomplete oral bioavailability (due to extensive first-pass metabolism), short half-life, and multiple daily dosing, is appropriate for a formulation in a once-a-day controlled release dosage form. Therefore, MPT is the ideal candidate to a zero-order controlled release system because it is water-soluble and has a short half-life.

1.6. ADDITIVES

Additives are often included in the formulation to ensure the stability of the polymers during hot-melt extrusion or to modulate the drug release from the extrudates.
1. INTRODUCTION

1.6.1. **Hydrophilic polymers**

Hydrophilic polymers act as swelling agents. When water reaches matrices containing these types of polymers, hydrogen bindings are formed between the water and the polymer. The polymer-water bonding is chosen above the polymer-polymer bonding due to high hydrophilicity. So the polymer chains have the ability to swell, they are getting solvated (Maggi et al., 2001). A hydrogel layer is formed, which regulates the water uptake and the drug release. Highly water-soluble drugs are dissolving and are then mainly released by diffusion, helped by a high drug concentration gradient. When the drug is lower water-soluble, it is mainly released by erosion (Colombo, 2000). It is clear that the drug solubility has an important role in the release rate of drug release. Besides this, drug solubility also has a positive influence on the polymer hydration and on the swelling of the matrix, since polymer hydration only happens when the solid drug has dissolved in the incoming water. Drug solubility also influences the *in vivo* performance, because the drug has to be in a solution to be systemically absorbed and distributed (Li et al., 2008).

1.6.1.1. Polyethylene oxide

Polyethylene oxide is a water-soluble semi-crystalline homopolymer. It consists of ethylene oxide monomers and is available in a lot of molecular weights. PEO is thermoplastic and has a melting range of 57-73°C. We talk about a melting range instead of a melting point, because PEO contains crystals of different sizes. The smaller crystals are melting at a lower temperature. The lower molecular weight PEO has got more small crystals than the high molecular weight PEO. The PEO stability in extrudates depends on the molecular weight of the polymer, the processing temperature, the screw speed and the storing conditions (Crowley et al., 2002).

1.6.2. **Surfactants**

To form a solid dispersion, the drug and the matrix have to be compatible. If this is not the case, a suspension can be formed or two liquid phases can be seen. The resulting solid dispersion is becoming inhomogeneous. To avoid this, we can use surfactants to increase drug homogeneity in the polymer matrices (Greenhalgh et al., 1999).

A surfactant is amphiphilic: it consists of a hydrophilic part and a lipophilic part. Surfactants are located at the interface of several compounds. Both the hydrophilic and the lipophilic part direct themselves to the aqueous side and the non-aqueous side, respectively. They lower the surface tension; the incoming water can be better spread out over the surface
of the matrix, so they improve the wettability. Above a certain concentration value, they form micelles. This concentration is known as the critical micelle concentration. Surfactants can be divided into several groups, according to their charge (non-ionic, cationic, anionic, zwitterionic).

The HLB value stands for the hydrophilic/liphophilic balance. It is an indication of the water-solubility. The higher the HLB-value, the more water-soluble the surfactant is. In this project it was studied the effect of Tween 80 and sorbitan sesquioleate (SS) on the formation of the mini-matrices. The HLB-value of SS is 3.7, so SS is rather hydrophobic. Tween 80 has a higher HLB-value (HLB = 15), it is more hydrophilic.

Besides the addition of surfactant as enhancers of the drug solubility they possess secondary effects on polymer processing and subsequent physical stability of the solid dispersions. Surfactants can act as plasticizers being normally incorporated into pharmaceutical polymers to facilitate thermal processing, to modify drug release from polymeric systems and to enhance the mechanical properties and surface appearance of the dosage form. When incorporated into a polymeric material, a plasticizer improves the workability and flexibility of the polymer by weakening the cohesive interactions between the polymer chains. These result in a reduction in elastic modulus, tensile strength, polymer melt viscosity and glass transition temperature ($T_g$). The polymer toughness and flexibility is improved and lower thermal processing temperatures can be employed. Lowering the polymer $T_g$ with plasticizers, therefore, facilitates thermal stability of the composite materials (Ghebremeskel et al., 2007). When surfactants lower the $T_g$, a change in crystallinity of the carrier polymer occurs. Since drug diffusivity is dependent on the grade of crystallinity of EVA drug release will not only change as a result of a change in wettability.
2. **OBJECTIVE**

The primary objective of this project is the development of a sustained release multiple-unit dosage form of EVA by HME, containing metoprolol salts as model drugs.

In this project the in vitro release of metoprolol salts from extruded mini-tablets was investigated.

Firstly, different parameters influencing the release of this freely soluble drug, namely polymer type (EVA with different contents of VA), drug/polymer ratio and processing temperature, were examined. Furthermore, the dissolution profile of the different salts of metoprolol (MPF, MPS and MPT) was also analyzed. The physicochemical characterization of the extrudates was done by thermal analysis (differential scanning calorimetry; DSC), X-ray diffraction, X-ray tomography, scanning electron microscope (SEM) and digital microscopy.

Secondly, the influence of functional excipients, such as surfactants (Tween 80 and sorbitan sesquioleate) and hydrophilic polymer (polyethylene oxide) on the drug release, was evaluated.

Finally, it was investigated the influence of sorbitan sesquioleate and Tween 80 on the processability of EVA (with different VA contents) and the possible physico-chemical interactions between the polymer and the surfactants.
3. MATERIAL AND METHODS

3.1. MATERIALS

Ethylene vinyl acetate (EVA), with different grades of vinyl acetate (VA), wt% of 40, 28, 15 and 9 (Elvax® 40w, Elvax® 260, Elvax® 550 and Elvax® 750, respectively) were provided by Dupont (Geneva, Switzerland) and it was used as a hydrophobic carrier. Metoprolol tartrate (MPT) (10µm) (Esteve Quimica, Barcelona, Spain) was selected as model drug. Metoprolol fumarate (MPF) and metoprolol succinate (MPS) (Polydrug Laboratories PVT. LTD., Maharashtra, India) were selected to investigate the influence of different drug salts on the in vitro release profile.

The drug release profile was modified by addition of a hydrophilic polymer (polyethylene oxide) and surfactants (sorbitan sesquioleate, Tween 80) to the melt extruded tablets. It was used a PEO with high molecular weight (MW = 7.000.000) (PEO; Sentry™ Polyox™ WSR 303 LEO NF Grade) (Dow Chemical Company, Midland, USA). PEO (Figure 3.1.A) is a non-ionic, semicrystalline, thermoplastic water-soluble homo-polymer. It is manufactured by the heterogeneous catalytic polymerization of ethylene oxide (Zhang & McGinity, 1999).

![Chemical structures](www.sigmaaldrich.com, 2009).

![Figure 3.1. Chemical structures: (A) PEO; (B) sorbitan sesquioleate and (C) Tween 80](www.sigmaaldrich.com, 2009).

It was also investigated the influence of surfactants on the release behavior of MPT from EVA matrices; sorbitan sesquioleate (SS; Arlacel™ 83) (Fagron NV, Waregem, Belgium) is a mixture of the partial esters of sorbitol and its mono- and di-anhydrides with oleic acid. SS (Figure 3.1.B) is a nonionic surfactant with a Hydrophilic-Lipophile Balance (HLB) value of 3.7 (Ph. Eur.6.0, 2009); Tween 80 (Polysorbate 80) (Fagron NV, Waregem,
Belgium) is a mixture of partial esters of fatty acids, mainly oleic acid, with sorbitol and its anhydrides ethoxylated with approximately 20 moles of ethylene oxide for each mole of sorbitol and sorbitol anhydrides. Tween 80 is a nonionic surfactant with a HLB-value of 15 (Figure 3.1.C) (Ph. Eur.6.0, 2009).

3.2. METHODS

3.2.1. Particle size determination

The particle size distribution of EVA powders was determined by laser diffraction (Mastersizer-S long bed, Malvern Instruments, Malvern, UK). The powders were dispersed into the dry powder cell of the Mastersizer and all the measurements were performed in duplicate. The particle size distributions were characterized via D(\(\nu\), 0.1), D(\(\nu\), 0.5), D(\(\nu\), 0.9) and the span. D(\(\nu\), 0.5) (the mass median diameter) represents the size of particle at which 50% of the sample is smaller and 50% is larger than this size. In the same manner D(\(\nu\), 0.1) and D(\(\nu\), 0.9) gives the size of particle for which respectively 10% and 90% of the sample is below this size. The span, a measure of the width of the size distribution, is defined as \([D(\nu, 0.9) - D(\nu, 0.1)] / D(\nu, 0.5)\].

3.2.2. Molecular weight characterization

The molecular weight of EVA40, 28, 15 and 9 was characterized by gel permeation chromatography (GPC). Analyses of the different EVA grades were performed with a Waters Alliance GPCV 2000 GPC equipped with a refractive index detector as concentration detector and an in-line viscometer (Chalmers Tekniska Högskola AB, Göteborg, Sweden). The column set was eluted with 1,2,4-trichlorobenzene (stabilized with Santonox®) at 135 °C. Universal calibration was based on polystyrene standards. Polymers (sample concentration 1mg/mL) were dissolved in 1,2,4-trichlorobenzene and placed in a 135 °C oven for 24h prior to molecular weight measurements.

3.2.3. Hot-melt extrusion

3.2.3.1. Production of the mini-matrices

Physical mixtures of EVA, drug and release modifying agent were made before the actual extrusion process. EVA powders (EVA40, 28, 15 or 9) were pre-mixed with the drug (MPF, MPS or MPT) with or without the release modifying agent (PEO, SS or Tween 80) using a mortar and a pestle, until a homogeneous mixture was obtained (±5min). The surfactants were added drop by drop to the powder mixture. An overview of the composition
of the powder mixtures in the different experiments is shown in Table 3.1. The physical mixtures were manually fed into a co-rotating twin-screw mini-extruder (HAAKE MiniLab II Micro Compounder, Thermo Electron Corporation, Karlsruhe, Germany) at a screw speed of 60 rpm and extruded at different processing temperatures (60, 80, 90, 100, 110 and 120°C). The selection of the screw speed is based on results obtained in a previous study. This machine was equipped with a pneumatic feeder, two archimedes screws and a cylindrical die of 2 mm. The obtained extrudates were cooled down at room temperature and manually cut, using surgical blades, into mini-matrices of 2 mm length.

<table>
<thead>
<tr>
<th>Batch name</th>
<th>Polymer type</th>
<th>Drug type</th>
<th>Polymer/drug ratio</th>
<th>Extrusion temperature °C</th>
</tr>
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<tbody>
<tr>
<td>Influence of polymer type:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>EVA40</td>
<td>MPT</td>
<td>1:1</td>
<td>90</td>
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<td>MPT</td>
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<td>90</td>
</tr>
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<td>MPT</td>
<td>1:1</td>
<td>110</td>
</tr>
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<td>MPT</td>
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<td>110</td>
</tr>
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<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
</tr>
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<td>MPS</td>
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<td>PEO (7M) (%)</td>
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<td>10</td>
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<td>3:2</td>
<td></td>
</tr>
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<td>MPT</td>
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</tr>
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<td>3:2</td>
<td>10</td>
</tr>
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<td>EVA15</td>
<td>MPT</td>
<td>3:2</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>EVA15</td>
<td>MPT</td>
<td>3:2</td>
<td>5</td>
</tr>
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3. MATERIAL AND METHODS

<table>
<thead>
<tr>
<th>Batch name</th>
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<th>Drug type</th>
<th>Polymer/drug ratio</th>
<th>SS (%)</th>
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</tr>
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<td>110</td>
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</tr>
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<td>MPT</td>
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**Influence of addition of sorbitan sesquioleate:**

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<td>90</td>
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</tr>
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</tr>
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<td>34</td>
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<td>4</td>
<td>90</td>
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</tbody>
</table>

**Influence of addition of Tween 80:**

<table>
<thead>
<tr>
<th>Batch name</th>
<th>Polymer type</th>
<th>Drug type</th>
<th>Polymer/drug ratio</th>
<th>Tween 80 (%)</th>
<th>Extrusion temperature (°C)</th>
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</thead>
<tbody>
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<td>35</td>
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<td>MPT</td>
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<td>90</td>
</tr>
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<td>0.5</td>
<td>90</td>
</tr>
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<td>MPT</td>
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<td>90</td>
</tr>
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<td>MPT</td>
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<td>4</td>
<td>90</td>
</tr>
<tr>
<td>39</td>
<td>EVA28</td>
<td>MPT</td>
<td>1:1</td>
<td>0.5</td>
<td>90</td>
</tr>
<tr>
<td>40</td>
<td>EVA28</td>
<td>MPT</td>
<td>1:1</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>41</td>
<td>EVA28</td>
<td>MPT</td>
<td>1:1</td>
<td>4</td>
<td>90</td>
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<tr>
<td>42</td>
<td>EVA28</td>
<td>MPT</td>
<td>3:2</td>
<td>0.5</td>
<td>90</td>
</tr>
<tr>
<td>43</td>
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<td>3:2</td>
<td>1</td>
<td>90</td>
</tr>
<tr>
<td>44</td>
<td>EVA28</td>
<td>MPT</td>
<td>3:2</td>
<td>4</td>
<td>90</td>
</tr>
</tbody>
</table>

3.2.4. **Extrudate characterization**

The surface properties of the extrudates were visually inspected for any possible defects (e.g. shark skinning). The suitability to be cut into mini-matrices (deformation due to cutting, smoothness of the cutting surfaces and the edges), geometric parameters (height and diameter) of mini-tablets before and after dissolution, the 3D dimensions and possible cracks were evaluated using a KH-7700 Digital Microscope (Hirox...
Co, Japan), with an Imaging Device of 1/1.8-inch, 2.11 Mega-pixel CCD Sensor and a maximum pixel resolution of 30 Mega-pixels 6400 (H) × 4800 (V). The Digital microscope is equipped with Hirox Original Lens, MXG-10C model (High Resolution Zoom Lens 10x and high-level optical observation achieved by co-axial vertical lighting) and Objective Lenses OL-70 II with a magnification capacity of 70-700x.

Scanning electron microscopy (SEM) was also used to visualize and evaluate the tablets surface morphology. Photomicrographs were taken with a Field Emission Gun Scanning Electron Microscope (FEGSEM), type Quanta 200F (FEI company, Eindhoven, The Netherlands). The pressure in the chamber was 100Pa and the used detector was a large field detector (LFD).

3.2.5. **X-ray diffraction**

EVA40, 28, 15 and 9 were investigated in terms of crystallinity/amorphicity by means of X-ray diffraction. The crystallinity parts give sharp narrow diffraction peaks while an amorphous component gives a very broad peak (halo). The X-ray patterns were determined using a D-5000 Cu Kα diffractor (λ = 0.154 nm) (Siemens, Karlsruhe, Germany) with an applied current of 40mA. The angular range (2θ) varied from 10 to 60° with steps of 0.02° and the measuring step was 1s/step.

3.2.6. **Thermal Analysis**

The glass transition temperature (T_g), melting point (T_m) and heat of fusion (ΔH) of the different pure components (EVA40, 28, 15, 9 and MPT), powder blends prior to extrusion and hot-melt extruded samples (see table 3.2.) were analysed by differential scanning calorimetry (DSC) and modulated differential scanning calorimetry (MDSC). The DSC instrument used was a Model 2920 from TA Instruments (Leatherhead, UK) running in standard mode and equipped with a refrigerated cooling system (RCS). Samples (5-10mg) were run in closed aluminum pans supplied by TA Instrument; the mass of each empty sample pan was matched with the mass of the empty reference pan to ±0.10mg. Depending of the samples and the determined parameters, the experimental method consisted of 1 single cycle (a heating rate of 20ºC/min from -100 to 180º C) or a 3 cycle analysis (heat, cool, heat). All the samples and starting materials were analyzed in duplicate.

MDSC measurements were carried out using a Q2000 Modulated DSC (TA, Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. Dry nitrogen (grade 5.5 pre-purified) at a flow rate of 50ml/min was used to purge the DSC cell.
The amplitude of the temperature was 0.3°C, the period was 50 s and the underlying heating rate was 2°C/min. The samples were evaluated according to the 3 cycle analysis (heat, cool, heat) from -100 to 180°C. Calibrations for temperature and enthalpy were performed routinely with Indium standard, whereas calibration of the heat capacity was carried out with a sapphire disk with the equivalent literature value at 80°C.

All the results were analyzed using the TA Instruments Universal Analysis 2000 software. Glass transitions were analyzed in the reversing heat flow while melting peaks were analyzed in the total heat flow signal or non-reverse heat flow (in case of overlapping signals).

Table 3.2. Samples analyzed by (M)DSC technique. EX: Extruded Samples, PM: Physical Mixture

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Composition</th>
<th>Extrusion Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pure EVA9</td>
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</tr>
<tr>
<td>2</td>
<td>Pure EVA15</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>Pure EVA28</td>
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</tr>
<tr>
<td>7</td>
<td>EX EVA40/MPT 50/50 (w/w)</td>
<td>90</td>
</tr>
</tbody>
</table>

3.2.7. In vitro drug release

Drug release from the mini-matrices 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). After being weighed, the mini-tablets (8 tablets of ±2mm length) were placed in the dissolution medium (consisting of 900 mL demineralized water). The temperature of the medium was set for 37 ± 0.5°C, while the rotational speed of the baskets was set at 100 rpm. Samples of 5 ml were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h (without medium replacement) and spectrophotometrically analyzed for MPF, MPS and MPT at 222 nm by means of a Shimadzu UV-1650 PC UV–VIS double beam spectrophotometer (Shimadzu Benelux, Antwerp, Belgium). The drug salt content in the samples was determined by linear regression using calibration curves (see figure 3.2.). Each batch was evaluated in triplicate.
3. MATERIAL AND METHODS

3.2.8. X-ray tomography

The internal 3D-structure of the mini-matrices (total porosity, maximum opening and equivalent diameter) was evaluated by means of X-ray tomography.

Total porosity is defined by the amount of small spaces or voids within a solid material and expressed as the percentage of the volume of a material’s pore, to its total volume. Equivalent diameter and maximum opening are the diameter of a sphere with the same volume and the diameter of biggest sphere that can be inscribed in the pore, respectively.

Mini-matrices containing EVA9, 15, 28 and 40 in combination with 50% MPT, were scanned before and after 24h dissolution testing with the high resolution micro-CT scanner of the Ghent University Centre for X-ray Tomography (www.UGCT.ugent.be). The EVA40 matrices (with and without the addition of 5% PEO) were evaluated before and after 24h and 72h dissolution testing. The system is composed of a Feinfocus X-ray tube with Tungsten transmission target and beryllium exit window, a Micos high precision airbearing rotation stage and a Varian Paxscan 2520V a-Si flat panel detector. The tube was operated at 70 kV, which results in the detection of details as small as 2 µm. During the scans the sample was rotated over 360° in 0.36° steps, with radiographic images recorded at every step. The detector consists of a CsI screen with 2000 x 1600 pixels of 127 µm and was operated in non-binning mode with an exposure time of 2 s. The source-to-object distance was approximately 15 mm and the source-to-detector distance was 890 mm in order to obtain a voxel pitch.
around 2 µm. The 1000 shadow images were processed and reconstructed to 1500 cross-sectional images of 1100 x 1100 pixels with Octopus software. Additional reconstructions using the Modified Bronnikov Algorithm (MBA) and the Bronnikov Aided Correction (BAC) were performed, to reduce the phase artifacts.

Image analysis on the BAC data was done with the in-house developed software package Morpho+. In a first step, the whole tablet was segmented based on greyscale. Application of a series of operations made it possible to set the tablet, including the pores, as a volume of interest. This results in a geometry-independent analysis and allows analyzing the whole tablet instead of a single region. In a second step, only the air inside the tablet was segmented, thus visualising the pores. Based on this segmentation, the partial porosity through the object, the equivalent diameter and the maximum inscribed sphere of the pores were calculated. The pore distribution was visualized in Volume Graphics VGStudioMax 1.2.1., based on the maximum inscribed sphere.

As the voxel pitch was about 2 µm, pores with a smaller diameter were not visible on the CT scans. However, they do affect the reconstructed image by reducing the density inside that voxel. This is called the “partial volume effect”, making the results less reliable for small pores.
4. RESULTS AND DISCUSSION

4.1. DIFFERENT EVA GRADES

4.1.1. Influence of the vinyl acetate content on the release properties

Matrices containing 50% MPT and 50% EVA (with variable VA contents: 9, 15, 28 and 40%) were manufactured by HME. A different extrusion temperature was required for the different EVA grades (containing 50% MPT) to obtain extrudates with sufficient quality. EVA40 and EVA28 were extruded at a process temperature of ±90°C, while EVA15 and EVA9 required a minimum extrusion temperature of about 110°C to acquire extrudates with a smooth surface. The drug release profile of the different matrices is shown in figure 4.1.

![Drug release profile from matrices containing 50% MPT and 50% EVA](image)

Figure 4.1. Drug release profile from matrices containing 50% MPT and 50% EVA (with variable VA contents: 9, 15, 28 and 40).

The release from 50% MPT matrices followed zero-order kinetics for EVA40, but was limited to 58% after 24h. In contrast, EVA28 and 15 showed the fastest release (91% MPT after 24h), whereas 79% MPT was released after 24h in case of EVA9.

As mentioned in the introduction, when the VA content increases the overall rigidity of the polymer chain decreases and consequently the polymer becomes more rubbery and permeable. As the molecular distances within the polymer crystals are normally smaller than the molecular size of drug to be released the diffusion process of the drug molecules takes place in the amorphous regions. Therefore an increase of the drug release rate is normally observed (Tallury et al., 2007). This conclusion is not consistent with the drug release profile for the different EVA grades above. Drug release after 24h from EVA28 was found to be
considerably higher than EVA40, despite the fact that EVA40 has a higher VA content. The unexpected result indicated that other parameter besides crystallinity was affecting drug release from EVA matrices.

4.1.2. **Thermal behaviour and crystallinity**

In this project the crystallinity determination of the different EVA grades was performed by XRD and DSC. Figure 4.2. shows the X-ray diffraction (XRD) patterns for EVA40, 28, 15 and 9. The crystallinity parts give narrow diffraction peaks and the amorphous parts give a very broad peak. As the VA content decreases, the degree of crystallinity of EVA increases and, therefore, a more sharpen peak is observed for EVA9. The XRD patterns show an increase in the intensity of the peaks when the VA content decreases.

![Figure 4.2. XRD patterns of EVA9, EVA15, EVA28 and EVA40.](image)

Thermal investigation by DSC of the different EVA grades resulted in distinct thermograms (see figure 4.3. and table 4.1.). As stated by Salyer & Kenyon (1971) crystallinity of EVA is reduced in proportion to the molar concentration of comonomer. The decrease in crystallinity with increasing amount of VA is reflected in a lower melt temperature along with a lower heat of fusion (energy needed to change from ordered solid to disordered liquid state). The percentage crystallinity ($X_c$) of the different EVA grades was evaluated from the heat of fusion using the following equation (1):

$$X_c(\%) = \frac{\Delta H_m}{\Delta H_m^0} \times 100$$  

(1)
where $\Delta H_m$ is the heat of fusion measured from the DSC thermogram, and $\Delta H^\circ_m$ the heat of fusion of 100% crystalline polyethylene (277.1 J/g) (Shi et al., 2008). EVA40 showed the lowest crystallinity (13.7%) coupled with the lowest heat of fusion (38.0 J/g) and melt temperature (42.8 °C). At low VA content a higher percent crystallinity was observed (e.g. EVA9: $X_c = 33.1\%$).

Table 4.1. General and thermal properties for the different EVA grades.

<table>
<thead>
<tr>
<th>Polymer type</th>
<th>VA (%)</th>
<th>$M_w$</th>
<th>$T_g$ (°C)</th>
<th>Melt onset temperature (°C)</th>
<th>$T_m$ (°C)</th>
<th>$\Delta H_m$ (J/g)</th>
<th>Crystallinity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA40</td>
<td>40</td>
<td>64900</td>
<td>-28.8</td>
<td>34.7</td>
<td>42.8</td>
<td>38.0</td>
<td>13.7</td>
</tr>
<tr>
<td>EVA28</td>
<td>28</td>
<td>101600</td>
<td>-28.5</td>
<td>40.0</td>
<td>74.0</td>
<td>47.2</td>
<td>17.1</td>
</tr>
<tr>
<td>EVA15</td>
<td>15</td>
<td>151200</td>
<td>-25.2</td>
<td>70.0</td>
<td>91.0</td>
<td>81.4</td>
<td>29.4</td>
</tr>
<tr>
<td>EVA9</td>
<td>9</td>
<td>578200</td>
<td>-26.3</td>
<td>80.1</td>
<td>98.5</td>
<td>91.8</td>
<td>33.1</td>
</tr>
</tbody>
</table>

DSC experiments demonstrated that EVA40 had three crystalline forms. Figure 4.4. shows the DSC thermogram of pure EVA40 where three melting peaks (A, B and C) were observed. This is in accordance with the conclusions earlier written down by Wang et al. (2006). However, at a lower VA content only 2 polymorphs were visualized (which were present in similar proportions in case of EVA 28) (see figure 4.3.). In the case of EVA40 the melting endotherm can be described on the one hand by the onset melting temperature, the
temperature where the transition starts to deviate from the baseline, and on the other by the extrapolated onset melting temperature (34.7°C), the temperature at the intersection of the extrapolated baseline prior to the transition with the extrapolated leading edge of the transition. The broadness of the peak defines the purity of the crystalline phase undergoing melting, with less pure and less perfect smaller crystals melting first followed by melting of the purer larger crystals (Clas et al., 1999). Both the onset melting temperature as the extrapolated onset melting temperature (34.7°C) are situated below 37.5°C. This indicates that the crystalline phase of EVA40 starts to melt below body temperature.

Figure 4.4. Heat flow signal and the first derivative (with respect to time) of the heat flow signal of pure EVA40, with A: \( T_{m,1} \); B: \( T_{m,2} \) and C: \( T_{m,3} \).

From table 4.1. and the first heating curves of the different EVA grades in figure 4.5., it can be found that the glass transition temperature of the different types of EVA was similar. Since the \( T_g \) is about -27.2°C, the different EVA grades are in a more flexible, rubbery state at room temperature. However, the specific heat capacity change (\( \Delta C_p \)) during glass transition increases as the VA content increases. This can be explained in the following way: the amorphous phase of EVA consists of an interfacial (rigid; less mobile) and a melt-like (mobile) amorphous phase (Wang et al., 2006). The free movement behavior of amorphous segments during the glass transition contributes the change of the specific heat. When some amorphous segments are locked (less mobile) between the crystalline chains or do not contribute to the glass transition change, the change of heat capacity will be reduced (Li &
Curran, 2006). Consequently, it could be expected that EVA copolymer with higher VA content have a lower rigid amorphous content and therefore are more flexible.

According to these thermoanalysis, the incorporation of vinyl acetate co-monomer units into a polyethylene backbone chain has 3 main critical effects: (a) reduced crystallinity, (b) reduced melting point and (c) higher polymer flexibility. This is in accordance with the conclusions earlier written down by Salyer & Kenyon, (1971).

![Figure 4.5. First heating curves of the different EVA grades.](image)

### 4.1.3. Determination of molecular weight and particle size

Determination of the weight-average molecular weight ($M_w$) of the different EVA grades was performed by means of GPC and the mean particle size diameters of EVA powders were determined by laser diffraction. The molecular weights are given in table 4.1.

The $M_w$ correlates to melt rheological and mechanical properties of polymers. These are critical parameters for polymer processing. From table 4.1, it can be concluded that as the VA content of the different types of EVA decreases the $M_w$ increases. Melt viscosity depends on $M_w$ and the MFI is inversely proportional to melt viscosity. Consequently, when the VA content decreases the melt viscosity increases and the MFI is reduced. As mentioned before, different extrusion temperatures were required for the different EVA grades (containing 50% MPT) to obtain extrudates with smooth surfaces (without sharkskin). In order to avoid sharkskin extrudates for EVA15 and 9 it was necessary to raise the extrusion temperature up
to ±110°C. Therefore it was obtained a reduction in polymer melt viscosity and an enhancement in melt flow.

The median particle size of the different types of EVA were similar (±430µm), with the exception of EVA40 (D(\(\nu\),0.5) = 586.51µm).

4.1.4. Matrix porosity

Porosity is a measure of the void spaces (pores) in a solid material, and a fraction of the volume of voids over the total volume as a percentage between 0 and 100%. Matrices porosity was evaluated by means of X-ray tomography and SEM before and after 24h of dissolution experiments and for the particular case of EVA40 a 72h dissolution experiment was performed.

Figure 4.6. SEM images of EVA28-based minitablets (containing 50% MPT): (A) General SEM image of a minitablet before dissolution; (B) General SEM image of a minitablet after 24h dissolution; (C) Zoomed SEM image of a pore before dissolution and (D) Zoomed SEM image of a pore after 24h dissolution.
The release mechanism of MPT by EVA is suggested to occur as follows: Water penetrates in the insoluble EVA matrix through the pores and dissolves the dispersed MPT powder particles. The powder particles, once dissolved, leave behind additional pores in the polymer matrix. In figure 4.6. SEM images are shown of EVA28 based minitablets (containing 50% MPT) before and after 24h dissolution. More in detail, the presence and absence of drug particles in the polymer pores respectively before (figure 4.6.C) and after 24h dissolution (figure 4.6.D) was observed. The dissolved drug molecules can diffuse out through the pores (existing before dissolution) and the created interconnecting pores during dissolution. It is the high tortuosity of the pores and the degree of retardation caused by restricted spaces or channels between connected pores that cause the prolonged release of MPT (Hsu & Langer, 1985).

Table 4.2. depicts the matrix porosities and mean equivalent pore diameters before and after dissolution for the different types of EVA. The tomography results indicate an increase of porosity after drug being released for EVA9, 15 and 28. The largest increase in porosity including an MPT release after 24h of 91% was observed for EVA15. By contrast EVA40 showed a decrease in porosity after 24 and 72h dissolution experiments. EVA40 turns out to reduce the porosity during the release of MPT. Consequently only 58% MPT was released after 24h. The mean equivalent pore diameter remained almost the same for the different EVA grades. On the basis of dissolution experiments a higher change in porosity after dissolution should be expected. Since the powder particles, once dissolved, leave behind additional pores in the polymer matrix, a higher increase in porosity would appear. The reduced change in porosity indicates an elastic rearrangement of EVA during dissolution. As the drug particles support the elastic matrix before dissolution, it seems that an elastic rearrangement of the matrix occurs after drug release, reducing the pores size.

<table>
<thead>
<tr>
<th></th>
<th>EVA 40</th>
<th>EVA 28</th>
<th>EVA 15</th>
<th>EVA 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total porosity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before dissolution</td>
<td>7.21</td>
<td>5.21</td>
<td>8.93</td>
<td>7.68</td>
</tr>
<tr>
<td>After dissolution</td>
<td>6.54 (1.02*)</td>
<td>8.35</td>
<td>12.90</td>
<td>9.53</td>
</tr>
<tr>
<td>∆ porosity</td>
<td>-0.67 (-6.19*)</td>
<td>3.14</td>
<td>3.97</td>
<td>1.85</td>
</tr>
<tr>
<td>Mean equivalent pore diameter (µm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before dissolution</td>
<td>25.3±12.5</td>
<td>30.2±14.9</td>
<td>51.0±24.1</td>
<td>55.2±32.6</td>
</tr>
<tr>
<td>After dissolution</td>
<td>27.0±21.8 (26.1±14.6*)</td>
<td>29.6±17.0</td>
<td>30.1±22.7</td>
<td>33.7±28.4</td>
</tr>
</tbody>
</table>
The decrease in porosity of EVA40 based matrices during dissolution seems to be dependent on following factors: (i) when the drug is released from the elastic polymer, the matrix collapse and as a result the structure suffers an elastic rearrangement due to the rubbery state of EVA; (ii) the onset melting temperature as well as the extrapolated onset temperature (34.7°C) of EVA40 are situated below the applied dissolution bath temperature (±37.5°C). As a consequence EVA40 starts partially to melt during dissolution. SEM images (from previous work) of EVA40 based matrices (containing 50% MPT) before and after 24h dissolution are shown in figure 4.7. The SEM images demonstrate a change on the matrix shape (figure 4.7.B). Further investigation of the polymer surface showed distinct polymer blobs (encircled in red) corresponding to the pure polymer form of EVA40.

![Figure 4.7](image)

**Figure 4.7.** SEM images of EVA40 based minitablets (containing 50% MPT): (A) General SEM image of a minitablet before dissolution; (B) General SEM image of a minitablet after 24h dissolution; (C) and (D) Zoomed SEM image of the polymer surface after 24h dissolution.
The collapse of the EVA40 matrices was also macroscopically observed as the volume of these matrices significantly \( n = 10, \ P < 0.001 \) decreased by 24\%, in contrast the change in volume of EVA28 matrices that was limited to 6.2\% \( n = 10, \) not statistically significant.

4.2. **DRUG LOADING**

Minitablets with different polymer/drug ratios (50/50, 60/40 and 80/20 w/w) were manufactured. The extrusion process was performed at a temperature of about 90°C. The addition of different amounts of MPT yielded extrudates with different qualities and drug release profiles. Up to 50\% MPT load the EVA40 extrudates had a smooth surface, while at 60\% drug content the matrices showed severe surface defects (shark skinning). Figure 4.8. shows the release profile of MPT from EVA40 based minitablets as a function of drug loading. An increase of drug loading results in a higher drug release, after 24h of dissolution experiments. It is also registered a higher initial (burst) release in the first hour. At a drug polymer/drug ratio of 50/50 w/w, 58\% MPT was released after 24h, while at lower loadings, in particular 40\% and 20\% MPT, the release was limited to 36\% and 8\%, respectively.

![Figure 4.8.](image)

**Figure 4.8. Drug release profile from EVA40 based minitablets as a function of drug loading.**

At low loadings a substantial fraction of the drug appears to be entrapped inside the matrix, not being able to be released during the dissolution experiments. MPT is embedded in the polymer matrix surrounding the pores, supporting the matrix structure. As the the minitablets are characterized by a matrix with interconnected or isolated pores, only the drug particles situated at or near the surface of the matrix are able to be released. At high drug loading, the drug particles created more pores (as they occupy more space in the matrix) and as a consequence a more extensive pore network was formed. This permits the drug molecules to escape from the polymer matrix contributing for a higher release.
4. RESULTS AND DISCUSSION

4.3. METOPROLOL SALTS: TARTRATE, SUCCINATE AND FUMARATE

Solubility of the drug can influence the drug dissolution rate. When the solubility of the drug decreases, drug diffusion is lowered. Therefore, the dissolution profiles of minitablets containing three different dicarboxylic acid salts of metoprolol (tartrate, fumarate and succinate) were analyzed (see figure 4.9.). The solubility in water of MPF, MPS and MPT is respectively ± 435, ± 200 and > 700 mg/mL (Ragnarsson et al., 1987). Smooth extrudates containing 50/50 EVA40/metoprolol salt w/w were extruded at a process temperature of 90°C. It was also determined the melting points of the different salts by DSC: ± 151°C, ± 139°C and ± 123°C for MPF, MPS and MPT, respectively.

According to the drug release profile it can be concluded that the highest amount of drug released after 24h was obtained for matrices containing 50% MPT, corresponding to the salt with the highest solubility. However, for MPF and MPS the drug release profile was very similar. These results seem to indicate that EVA matrix is playing an important role on drug release.

![Figure 4.9. Drug release profile from EVA40 based minitablets containing 50% MPF, MPS and MPT.](image)

4.4. INFLUENCE OF EXTRUSION TEMPERATURE

During extrusion several parameters need to be controlled in order to achieve an extrudate with sufficient quality. The extrusion temperature is chosen depending on the melting point \( T_m \) of the drug and carrier. Normally its value is higher than the polymer \( T_m \) because if the process temperature is too close to the melting point of EVA40 \( T_m \text{EVA40} = ± 47°C \), the melt viscosity will be too high (www.dupont.com, 2009). If the process is too far above the melting point, the polymer might degrade (a maximum processing temperature of ± 230°C was established in previous
TGA experiments). To obtain a stable solid dispersion (thermodynamically stable) and good quality extrudates, matrices with a two-phase system (crystalline drug embedded in a semi-crystalline polymer), were processed at a temperature below the melting point of the drug ($T_{m\text{ MPT}} = \pm 122^\circ\text{C}$).

Matrices containing EVA40/MPT (50/50, w/w) were manufactured at different extrusion temperatures (60°C, 80°C, 90°C, 100°C and 120°C). At these temperatures smooth surface extrudates were obtained with the exception of 120°C where glassy sticky extrudates were produced. The glassy extrudates indicated that MPT was most likely in the amorphous stage. However, besides the bad quality extrudates, after a few hours recrystallization of the drug was visible as the extrudate acquired a white colour, typical for crystalline forms. In figure 4.10, it can be seen the influence of processing temperatures on drug release from EVA40 hot-melt extruded mini-matrices (EVA40/MPT w/w 50/50).

![Figure 4.10. The influence of processing temperatures (given in the figure) on the drug releases from EVA40 hot-melt extruded mini-matrices; drug loading 50% w/w.](image)

From the dissolution profile above it can be concluded that the MPT release from hot-melt extruded mini-matrices increased with increasing extrusion temperature. However, the difference seems not to be significant from 80 up to 100°C (about 60% of drug released after 24h) while for an extrusion temperature of $\pm 60^\circ\text{C}$ the release rate was considerably lower (40% of drug released).

4.5. **INFLUENCE OF THE ADDITION OF POLYETHYLENE OXIDE**

The release from 50% MPT matrices followed zero-order kinetics for EVA40, but was limited to 58% after 24h. In contrast, EVA28 and 15 showed the fastest release (91% MPT after 24h), whereas 79% MPT was released after 24h in case of EVA9. In order to obtain a
sustained release formulation with almost all MPT released after 24h (one dose for daily oral intake) it was added PEO (7M) as an hydrophilic excipient. With this third component it was expected to increase the drug release as more water would be taken up by the matrices.

4.5.1. Processability

The addition of different amounts of PEO (7M) to the MPT-EVA blends affected strongly the HME processability. Shark skinning, discoloration and/or degradation were taken into account. Table 4.3. depicts the physical appearance of the extrudates for the different drug-polymer-PEO blends. EVA40 and EVA28 were extruded at a process temperature of ±90°C, while for EVA15 and EVA9 an extrusion temperature of about 110°C was required. The melting point of PEO (7M) is around 70°C and as the extrudates were produced at 90°C the polymer melted during the extrusion process. The addition of 5% PEO (7M) required a reduction in drug loading from 50% to 40% MPT to obtain smooth surface extrudates for the four types of EVA. Only for EVA40 smooth surface extrudates were obtained at a drug load of 50%. For a concentration of 10% PEO (7M), smooth surface extrudates were obtained for EVA40 and EVA28 (containing 40% MPT). For EVA15 and 9 a reduction in drug loading from 40% to 30% MPT was necessary to avoid shark skin extrudates. In these cases, a grey discoloration of the extrudates occurred, probably due to polymer degradation as the residence time inside the extruder was higher and the mixture showed difficulties to pass through the extruder chamber and the die.

During extrusion the polymer melt sticks to the screws in constant rotation and is dragged along with it (drag flow). However the die restricts melt flow which results in an increased pressure in the extruder behind the die. Because of the die not all the ‘dragged’ material is extruded and the pressure in the extruder ‘head’ increases. In any channel with a pressure difference, flow is made be from the high pressure end to low pressure (pressure flow), leading to mixing in the channel. The total amount of material extruded can be defined as the difference between the drag flow (the forward stream) and pressure flow (the backward stream) (www.plastics-elearning.com, 2009). When the difference in backward and forward stream decreases, the amount of material extruded is reduced with an increased residence time of the material in the extruder. As a consequence the material is mixed more extensively and exposed for a longer time to heat (by friction and the heated barrel). As a result a grey discoloration and/or degradation of the material may occur.
Table 4.3. Composition, process temperature and physical appearance of the extrudates.

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Polymer type</th>
<th>Polymer/drug ratio</th>
<th>PEO (7M) (%)</th>
<th>Extrusion temperature (°C)</th>
<th>Physical appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EVA40</td>
<td>1:1</td>
<td>5</td>
<td>90</td>
<td>White, smooth</td>
</tr>
<tr>
<td>2</td>
<td>EVA28</td>
<td>1:1</td>
<td>5</td>
<td>90</td>
<td>White, shark skin</td>
</tr>
<tr>
<td>3</td>
<td>EVA15</td>
<td>1:1</td>
<td>5</td>
<td>110</td>
<td>White, shark skin</td>
</tr>
<tr>
<td>4</td>
<td>EVA9</td>
<td>1:1</td>
<td>5</td>
<td>110</td>
<td>White, shark skin</td>
</tr>
<tr>
<td>5</td>
<td>EVA40</td>
<td>6:4</td>
<td>5</td>
<td>90</td>
<td>White, smooth</td>
</tr>
<tr>
<td>6</td>
<td>EVA28</td>
<td>6:4</td>
<td>5</td>
<td>90</td>
<td>White, smooth</td>
</tr>
<tr>
<td>7</td>
<td>EVA15</td>
<td>6:4</td>
<td>5</td>
<td>110</td>
<td>White, smooth</td>
</tr>
<tr>
<td>8</td>
<td>EVA9</td>
<td>6:4</td>
<td>5</td>
<td>110</td>
<td>Light grey, smooth</td>
</tr>
<tr>
<td>9</td>
<td>EVA40</td>
<td>1:1</td>
<td>10</td>
<td>90</td>
<td>White, shark skin</td>
</tr>
<tr>
<td>10</td>
<td>EVA40</td>
<td>6:4</td>
<td>10</td>
<td>90</td>
<td>White, smooth</td>
</tr>
<tr>
<td>11</td>
<td>EVA28</td>
<td>6:4</td>
<td>10</td>
<td>90</td>
<td>White, smooth</td>
</tr>
<tr>
<td>12</td>
<td>EVA15</td>
<td>6:4</td>
<td>10</td>
<td>110</td>
<td>White, shark skin</td>
</tr>
<tr>
<td>13</td>
<td>EVA9</td>
<td>6:4</td>
<td>10</td>
<td>110</td>
<td>White, shark skin</td>
</tr>
<tr>
<td>14</td>
<td>EVA15</td>
<td>7:3</td>
<td>10</td>
<td>110</td>
<td>Grey, smooth</td>
</tr>
<tr>
<td>15</td>
<td>EVA9</td>
<td>7:3</td>
<td>10</td>
<td>110</td>
<td>Grey, smooth</td>
</tr>
</tbody>
</table>

4.5.2. **In vitro release**

4.5.2.1. **General**

When PEO (7M) is exposed to the dissolution medium (i.e. water), the polymer may undergo a relaxation process so that the polymer chains become more flexible and the matrix swells. This allows the entrapped drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrices, polymer dissolution is also another important mechanism that can modulate the drug delivery rate. However, EVA is not water soluble, so this variable is not taken into account. On the contrary, PEO dissolves in the dissolution medium. For PEO it is found that the swelling of the polymer rather than the dissolution of the polymer is the governing factor for drug release (Wu et al., 2005).

In this project the matrices are made up of a hydrophobic EVA matrix with the hydrophilic PEO polymer as additive. Consequently, a complex release mechanism is
expected, depending on factors as swelling, diffusion, dissolution of the hydrophilic PEO in combination with the hydrophobic EVA matrix properties.

4.5.2.2. Polyethylene oxide (7M) content

In figure 4.11, the drug release profiles of EVA40 and EVA28 based matrices containing 40% MPT with different amounts of PEO (7M) (0, 5 and 10%) are shown. From the dissolution profile of both EVA40 and 28 it can be concluded that an increase of PEO (7M) yields a faster drug release. A higher initial (burst) release and a higher amount of MPT released after 24h is observed as the amount of PEO (7M) rises. For EVA40 zero-order kinetics were obtained after 1h release.

![Figure 4.11. Drug release profiles of EVA40 and EVA28-based matrices containing 40% MPT with increasing amounts of PEO (7M) (0, 5 and 10%).](image)

By adding PEO (7M) as drug release modifying excipient, the elastic matrix structure stretches due to the swelling properties of PEO (7M) and the inner core of the matrices becomes more exposed to the dissolution medium. Because the permeability of the matrices increases, a higher amount of drug is released. The drug release occurs via drug diffusion through the micro-capillary network formed after dissolution of MPT in the mini-tablet.

The degree of stretching depends on the elasticity of the polymer matrix. The contribution of the swelling agent to the increase in drug release rate, is expected to be considerably higher for an elastic matrix than for a rigid matrix, as it will be more affected by the swelling agent. For EVA40 based matrices (containing 40% MPT) the addition of increasing concentrations of PEO (7M), 0, 5 and 10%, resulted in 36%, 52% and 85% MPT released, respectively (after 24h), whereas for EVA28 based matrices, a smaller increase in
MPT release rate was observed, (57%, 65% and 78%, respectively). This means that PEO (7M) has a greater effect on the MPT release rate for EVA 40-matrices (more elastic structure) compared with EVA 28-matrices (less elastic).

The in vitro drug release profiles of EVA15 and EVA9 based matrices containing 40% MPT with increasing amounts of PEO (7M) (0 and 5%) are shown in figure 4.12. In contrast to EVA 40 and 28, the addition of 5% PEO to EVA15 or EVA9 resulted in a decrease of MPT released during dissolution experiments. For EVA15, the amount of MPT released after 24h decreased from 70 to 38%, when added 5% PEO. For EVA9 the amount of drug released after 24h decreased from 54% to 31%. It can be concluded that for EVA15 and 9 the addition of PEO had a negative effect on drug release rate. Since EVA15 and 9 have lower elasticity, higher crystallinity and higher rigidity, the swelling properties of PEO (7M) did not influence the matrix structure. The structure was not stretched and the inner core remained unexposed to the dissolution medium. As the water penetrates into the pores, PEO (7M) starts to dissolve and a highly viscous gel is formed. As there was no stretching of the matrix the permeation of the dissolution medium and the diffusion of dissolved MPT through the PEO phase becomes more difficult. Therefore, the highly viscous PEO phase worked as a barrier for the dissolution of MPT, decreasing the release rate of MPT.

4.5.2.3. Different EVA grades with the addition of PEO

The release profiles of the different EVA grades after the addition of 5 and 10% of PEO (7M), were compared and are shown in figure 4.13. In the presence of 5% PEO, the highest drug release rate is observed for EVA 28, followed by EVA 40 and almost no
difference was detected for EVA15 and EVA9 (the lowest release). However, by adding 10% of PEO a shift on drug release rate happens and a similar amount of MPT is released after 24h for EVA40 and EVA28.

It can be concluded that the drug release from the EVA matrices is dependent on the VA content of the polymer. A higher VA content increases the polymer flexibility as it was proved before with DSC (section 4.1.2). For EVA28 and 40 the addition of PEO (7M) resulted in an increase in drug release rate. While for polymers with a lower VA content, EVA15 and 9, adding PEO (7M) caused a decrease in the release rate. The increase in release rate for EVA40 and 28 was affected by the amount of PEO (7M) (higher the concentration PEO (7M), higher the drug released). However, with the addition of 5% PEO (7M) the highest drug release rate was observed for the less elastic EVA28. By adding 10% PEO (7M) drug release rate of EVA28 and the more elastic EVA40 were similar. These results suggested that the collapse of the EVA40 matrix was reduced by the swelling agent by improving the matrix structure as it gives it some support. Nevertheless PEO (7M) molecules dissolve and diffuse through the pores out of the matrix during dissolution. However, when a critical amount of drug and swelling agent left the EVA40 matrix system, again a collapse occurs.

To confirm the occurrence of this collapse the porosity of an EVA40 matrix (containing 50% MPT) with the addition of 5% PEO was evaluated by means of X-ray tomography before and after 24h and 72h of dissolution experiments. After 24h and 72h of dissolution a change in porosity of +0.74% and -1.09%, respectively, was registered. Therefore, during the first 24h of dissolution experiments the porosity increased slightly
mainly due to some dissolved drug crystals. Afterwards the decrease in porosity occurred as a consequence of an elastic reorganization of the matrix, followed by a partial melting of the polymer (results confirmed previously by DSC). However, when compared with matrices without PEO (7M), the decrease in porosity is lower.

4.6. INFLUENCE OF THE ADDITION OF SURFACTANTS

The specific objectives of this part of the study were to investigate the properties of 2 surfactants on the processability of the blends (drug-polymer-surfactant) during hot-melt extrusion (possible plasticizing effect) and on the dissolution enhancement of MPT from the extruded matrices. Surfactants with different HLB-values were chosen: sorbitan sesquioleate (SS; HLB = 3.7) and Tween 80 (Polysorbate 80; HLB = 15).

As mentioned in the introduction the amphiphilic character is responsible for different functions/behaviours of the surfactants. They are able to reduce the surface tension of water and thus lead to better wetting of the hydrophobic matrix. Moreover, surfactants have the ability to lower melt viscosity and increase drug solubility and homogeneity in the polymer matrices. When surfactants lower the $T_g$, a change in crystallinity of the carrier polymer occurs. Since drug diffusivity is dependent on the grade of crystallinity of EVA drug release will not only change as a result of a change in wettability.

4.6.1. Processability

4.6.1.1. Polymer-surfactant blend

In order to evaluate influence of the addition of surfactants on the polymer processability surfactants were added in increasing amounts (1, 5, 10, 15, 20, 30, 40 and 50%) to the different types of EVA. An extrusion temperature of ± 90°C and ± 110°C was applied for EVA40 and 28 and EVA15 and 9, respectively, to obtain extrudates with sufficient quality. For EVA40 and 28 increasing amounts of SS created smooth and more flexible extrudates when compared with pure EVA processed at the same temperature. For EVA15 and 9 no notable change in flexibility was observed, but a grey discoloration of the extrudates occurred at 15 and 10% SS, respectively. A further increase in amount of SS to EVA9 resulted in extrudates with undulated surfaces while for EVA15 the extrudates remained smooth. Pictures of extrudates of EVA40 and 9 with increasing amounts of SS are shown in figure 4.14.
The addition of increasing amounts of Tween 80 to the different types of EVA showed no notable change in flexibility of the extrudates. Only for EVA40 smooth surface extrudates were obtained. The remaining types of EVA gave shark skinning extrudates starting from 5% Tween 80. Grey extrudates were obtained at concentrations of 5% for EVA28 and 15, and 1% Tween 80 for EVA9.

As the amount surfactant increased, loss of surfactant occurred during extrusion. Table 4.4. shows the minimum concentrations of surfactant that resulted on considerable loss of surfactant for the different types of EVA. The loss of surfactant during processing is explained by the low mixability of the polymer with the surfactant (Tween 80) or the maximum amount of surfactant that is able to be mixed with EVA (polymer saturation). Since the extrudates can be considered as solid solutions, the solubility of the surfactant in the molten state of the polymer is limited.

Table 4.4. Concentrations of surfactants for the different types of EVA resulting in loss of surfactant.

<table>
<thead>
<tr>
<th>Polymer type</th>
<th>Surfactant loss at SS (%)</th>
<th>Tween 80 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVA40</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>EVA28</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>EVA15</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>EVA9</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

4.6.1.2. Polymer-surfactant-drug blend

Minitablets of EVA with a different VA-content (9, 15, 28 and 40%), distinct drug loading (40 and 50%) and increasing amounts of surfactant (0.5, 1 and 4%) were produced. The processability varied according to the different VA grades in the polymer. The addition of increasing amounts of surfactant (SS as well as Tween 80) gave smooth surface extrudates for EVA40 and 28 at both drug loadings. For EVA9 the addition of SS yielded extrudates of a poor quality. When 1% SS was added to the formulation with a drug loading of 40 and 50%,
grey extrudates were obtained. A reduction in drug loading down to 20% did not eliminate the grey color. The production of these extrudates required an increased residence time of the drug-polymer-surfactant blend. Because EVA9 gave bad quality extrudates, no dissolution experiments were performed. In case of EVA15 a maximum concentration of 1% SS could be used in order to avoid shark skinning extrudates. The influence of the addition of Tween 80 to drug-polymer blends based on EVA15 and 9 was not investigated due to the bad processability as mentioned in 4.6.1.1.

In order to verify the possible plasticizing effect of SS and Tween 80 in the different types of EVA, a shift in $T_g$ and/or a reduction in melting peak is normally observed. Further thermoanalysis (DSC) will have to be performed to confirm these changes.

4.6.2. **In vitro release**

4.6.2.1. **Addition of sorbitan sesquioleate**

In figure 4.15, the drug release profiles for EVA-based matrices (with the exception of EVA9) containing 40 and 50% MPT including 1% SS are shown. The dashed lines depict the release profiles of EVA matrices without the addition of surfactant.

The results showed that the drug release was increased by the addition of SS, besides the influence of drug loading. The higher the drug loading the higher the initial burst effect and the higher the amount of MPT released after 24h. The highest release rate was observed for matrices based on EVA15 which released 91% of the drug after 8h when 1% SS was added. However, it should be noted that the release profiles of EVA28 with and without surfactant are similar showing no influence on the MPT dissolution profile.

![Figure 4.15. Drug release profiles of matrices based on EVA40, 28 and 15 containing 50% (left) and 40% MPT (right) with and without the addition of 1% SS.](image-url)
Since surfactants reduce the surface tension of water, the release rate increased by better wetting of the hydrophobic matrix. By decreasing the surface tension of the dissolution medium, the surfactant allowed a more rapid and possibly more complete penetration into the matrix. As mentioned previously the addition of SS increased the flexibility of the extrudates. This finding suggests a possible plasticizing effect of SS on the EVA copolymers. In addition the enhancement in drug release rate could also result from a change in permeability of drug or an increase in matrix porosity (Cho et al., 2007).

One should take into account the fact MPT particles can dissolve in the liquid surfactant (Tween 80, hydrophilic in character) and by consequence a change in drug crystallinity may occur. Therefore, an enhancement in drug release rate can be expected.

In figure 4.16. the drug release profiles of EVA40 and EVA28 based matrices containing 50% MPT with increasing amounts of SS (0, 0.5, 1 and 4%) are shown. For matrices based on EVA28, MPT release is not affected by the addition of SS. This finding was observed for both drug loadings confirming the previous observations (no influence of SS for EVA28). From the dissolution profile of EVA40 it can be concluded that an increase of SS yields a faster drug release. A higher initial release and a higher amount of MPT released after 24h is observed. For 40% drug load the same trend was observed (data not showed). The higher the surfactant content the higher the increase in wettability of the hydrophobic matrix. Anew an increasing plasticizing effect with increasing amount of surfactant could change matrix porosity and drug permeability, resulting in a drug release rate alteration.

Figure 4.16. Drug release profiles of matrices based on EVA40 (right) and EVA28 (left) containing 50% MPT with increasing amounts of SS (0, 0.5%, 1 and 4%)
4.6.2.2. **Addition of Tween 80**

Since in case of EVA15 and 9 the quality of the extrudates was insufficient, dissolution experiments were just performed for EVA40 and 28. For both EVA grades minitablets containing 40% and 50% MPT with increasing amounts of Tween 80 (0, 0.5, 1 and 4%) were manufactured at an extrusion temperature of ± 90°C. The drug release profile of EVA28-based matrices containing 40% MPT with increasing amounts of Tween 80 (0, 0.5, 1 and 4%) is shown in figure 4.17. When the concentration of Tween 80 increases a higher initial burst effect and a higher amount of drug released after 24h is observed. The same trend was noted for matrices with a 50% drug load. EVA40-based matrices presented similar behaviour for both drug loadings (data not shown). Since no change in flexibility was noted for extrudates with increasing amounts of Tween 80, the observations seem to indicate that there was no plasticizing effect on EVA40 and 28. By consequence the enhancement in drug release rate is mainly caused by an increase in wettability of the hydrophobic matrices.

Therefore, it can be said that the increase of release rate depends on the type of surfactant, its concentration and VA content.

![Figure 4.17. Dissolution profile of EVA28-based matrices containing 40% MPT with increasing amounts of Tween 80 (0, 0.5, 1 and 4%).](image-url)
5. CONCLUSION

The main purpose of this study was the development of a sustained multiple-unit dosage form based on EVA, containing metoprolol salts as model drugs. In order to modulate drug release and to obtain a sustained release with a maximum drug released after 24h and an acceptable processability by HME, the influence of several variables was investigated. These variables include VA content, drug loading, extrusion temperature, drug salt, swelling agents and surfactants.

EVA shows various properties with varying the VA content. The properties of the EVA are caused by the crystallinity of the EVA which can be controlled by the VA content. The crystallinity of EVA with the VA content is important to understand the thermal and release properties of EVA. In this project EVA40, 28, 15 and 9 were investigated. Different process temperatures were required for the different EVA grades to obtain extrudates with smooth surfaces (without sharkskin).

Determination of the degree of crystallinity by DSC and XRD confirmed a decrease in crystallinity with increasing VA content. According to literature an increased drug permeability and consequently an increased drug release rate was expected for matrices with a higher VA content. Nevertheless the drug release profiles of matrices based on the different types of EVA were inconsistent with this theory. Drug release after 24h for EVA28 was found to be considerably higher than for EVA40. Evaluation of matrix porosity by X-ray tomography before and after dissolution showed a distinct decrease in porosity for EVA40 matrices. Moreover thermoanalysis revealed a partial melting of EVA40 during dissolution. As a result the decrease in drug release rate occurred as a result of an elastic reorganization of the matrix combined with a partial melting of the polymer during dissolution. These results indicated that besides crystallinity, the elasticity and melting temperature of EVA play an important role in the drug release behavior.

Beside the VA content, the influence of drug loading, drug salt and extrusion temperature on in vitro drug release rate by EVA40 matrices were studied. For a higher drug loading a higher drug release rate was observed. The addition of different amounts of MPT yielded extrudates with different qualities. The dissolution profiles of minitablets containing three different salts of metoprolol (tartrate, fumarate and succinate) were also analyzed. The highest amount of drug released after 24h was obtained for matrices containing MPT, corresponding to the salt with the highest solubility. For less soluble salts, in decreasing order
MPF and MPS, the drug release profile was very similar. Likewise the effect of extrusion temperature on drug release rate was examined. Increasing extrusion temperature (from 60°C up to 100°C) resulted in an increased MPT release from hot-melt extruded mini-matrices.

The release of the drug from 50% MPT matrices followed zero-order kinetics for EVA40, but was limited (58% after 24h). In contrast, EVA28 and 15 showed the fastest release (91% MPT after 24h), whereas 79% MPT was released after 24h in case of EVA9. In order to obtain a sustained release formulation with almost all MPT released after 24h (one dose for daily oral intake) it was added PEO (7M) as a hydrophilic excipient.

The addition of different amounts of PEO (7M) to the MPT-EVA blends affected strongly the HME processability and drug release behavior. Dependent on VA content a reduction in drug loading was required in order to obtain smooth surface extrudates. Drug release was affected positively and negatively by the addition of PEO (7M). For EVA40 based matrices (containing 40% MPT) the addition of increasing concentrations of PEO (7M), 0, 5 and 10%, resulted in 36%, 52% and 85% MPT released, respectively, whereas for EVA28 based matrices a smaller increase was observed. For EVA40 zero-order kinetics were obtained after 1h release. The contribution of the swelling agent to the increase in drug release rate is expected to be considerably higher for an elastic matrix than for a rigid matrix, as it will be more affected by the swelling agent. For EVA15 and 9 the addition of PEO had a negative effect on drug release rate. Since EVA15 and 9 have lower elasticity, the swelling properties of PEO (7M) did not influence the matrix structure. As there was no stretching of the matrix the permeation of the dissolution medium and the diffusion of dissolved MPT through the PEO phase becomes more difficult. Therefore, the highly viscous PEO phase worked as a barrier for the dissolution of MPT, decreasing the release rate of MPT. By adding 10% PEO (7M) drug release rate of EVA28 and the more elastic EVA40 were similar. These results suggested that the elastic reorganization of the EVA40 matrix was reduced by the swelling agent by improving the matrix structure as it gives to it some support. Determination of the porosity of an EVA40 matrix (containing 50% MPT) with the addition of 5% PEO before and after dissolution confirmed this suggestion.

The final part of the study was to investigate the properties of two surfactants (sorbitan sesquioleate (HLB = 3.7) and Tween 80 (HLB = 15)) on the processability of the blends (drug-polymer-surfactant) during hot-melt extrusion process (possible plasticizing effect) and on the dissolution enhancement of MPT from the extruded matrices.
In order to evaluate influence of the addition of surfactants on the polymer processability surfactants were added in increasing amounts (1 up to 50%) to the different types of EVA. For EVA40 and 28 increasing amounts of SS created smooth and more flexible extrudates when compared with pure EVA processed at the same temperature. For EVA15 and 9 no notable change in flexibility was observed. Moreover the addition of Tween 80 to the different types of EVA showed no change in flexibility. Minitablets of EVA with a different VA-content, distinct drug loading (40 and 50%) and increasing amounts of surfactant (0.5, 1 and 4%) were produced. The addition of increasing amounts of surfactant gave smooth surface extrudates for EVA40 and 28 at both drug loadings. For EVA9 the addition of SS gave bad quality extrudates while for EVA15 a maximum concentration of 1% SS could be used. The influence of the addition of Tween 80 to drug-polymer blends based on EVA15 and 9 was not investigated due to bad processability.

Dissolution experiments for EVA40 and 15 showed that the drug release was increased by the addition of SS. An increase of SS yielded a faster drug release, at both drug loadings. For EVA28, the addition of SS had no influence on the MPT dissolution profile. The release rate increased by better wetting of the hydrophobic matrix. As the addition of SS increased the flexibility of the extrudates, a possible plasticizing effect could change permeability of the drug or increase the matrix porosity resulting in an increased drug release.

The addition of Tween 80 resulted in an increase in drug release for EVA40 and 28. This enhancement in drug release was observed at both drug loadings. Since no change in flexibility was noted for extrudates with increasing amounts of Tween 80, the observations seem to indicate that there was no plasticizing effect on EVA40 and 28. By consequence the enhancement in drug release rate was mainly caused by an increase in wettability of the hydrophobic matrices.

The present work has showed that surfactants can be used to enhance the release rate of MPT from EVA matrices. However, they are not able to produce the zero-order release pattern for MPT matrices. The increase of release rate depends on the type of surfactant, concentration and VA content. In order to verify the possible plasticizing effect of SS and Tween 80 in the different types of EVA further thermoanalysis (DSC) will have to be performed to confirm these changes.
6. REFERENCES


6. REFERENCES


