UNIVERSITEIT GENT

FACULTEIT FARMACEUTISCHE WETENSCHAPPEN

Vakgroep Geneesmiddelenleer

Laboratorium voor Farmaceutische Technologie

Academiejaar 2009-2010

DEVELOPMENT OF SUSTAINED-RELEASE MULTIPLE UNIT DOSAGE FORMS VIA HOT-STAGE EXTRUSION

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Eerste Master in de Geneesmiddelenontwikkeling

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May 16, 2010

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First of all, I would like to thank professor Remon and professor Vervaet to give me the opportunity to learn about the work in the laboratory of Pharmaceutical Technology and to get a better insight in the industrial Pharmacy.

E eu gostaria de agradecer à Ana Almeida- minha mentora- por guiar-me, apoiar-me, e ajudar-me pacientemente durante meu período no laboratório, e a ler e corrigir minha tese. Seu entusiamo pelo trabalho, seu espírito encorajador, e sua ternura fizeram com que meu interesse pela pesquisa científica crescesse a cada dia.

Furthermore I want to thank professor De Beer and Lien Saerens for their support and their aid during the in-process control, to help me to interpret results and to correct that part of my thesis.

Finally I also want to thank the other PhD students, thesis students and staff to create a pleasant atmosphere at the laboratory.

Content

List with the used abbreviations

DSC: Differential Scanning Calorimetry

EVA: Ethylene Vinyl Acetate

HLB: Hydrophilic Lipophilic Balance

HME: Hot-Melt Extrusion

MI: Melt Index

MPT: Metoprolol Tartrate

PAT: Process Analytical Technology

PC: Principal Component

PE: Polyethylene

PEO: Polyethylene Oxide

Rpm: Rotations per minute

SEM: Scanning Electron Microscope

SS: Sorbitan Sesquioleate

T_g: Glass transition temperature

T_m: Melting temperature

VA: Vinyl Acetate

1. INTRODUCTION

1.1. CONTROLLED RELEASE FORMULATIONS

1.1.1. Controlled-release systems: general

Controlled drug delivery means that the release of the drug after administration is controlled. It occurs for example when a polymer is added to a drug. The drug release rate can be constant or cyclic over a long period, or it can be triggered by external events (*http://www.medicaldevicelink.com*).

Controlled release dosage forms offer several advantages: fewer and more effective doses - which results in improved patient compliance - , a more constant drug plasma level through zero-order release, a lower amount of drug necessary for the same effect, thus less side effects of the drug (*Huang & Brazel, 2001)*. The materials used must be biocompatible with body tissues during the prolonged contact, non-toxic and non-degradable. Some disadvantages of use of polymers comprise the higher cost in comparison with traditional formulations, the risk of dose dumping, the fact that they are rather unpredictable and that they have poor in-vitro in-vivo correlation. Therefore, the ideal drug delivery system has to be biocompatible, inert, comfortable for the user, non-toxic, safe from burst release, simple to administer, easy to make and free from impurities (*http://www.medicaldevicelink.com*).

When using a traditional formulation, the blood level of the drug rises after each administration to decrease then until the next administration. As some fluctuations are expected, it's necessary that the blood level of the drug remains between a maximum value – the toxic concentration – and a minimum value – below which the drug hasn't any further therapeutic effect -, the therapeutic window. It is the objective of a controlled-release formulation, to obtain a high blood level, within the therapeutic window, over a prolonged period. Figure 1.1. shows the drug levels in the blood with (a) a traditional formulation and (b) a controlled-release formulation (*http://www.medicaldevicelink.com*).

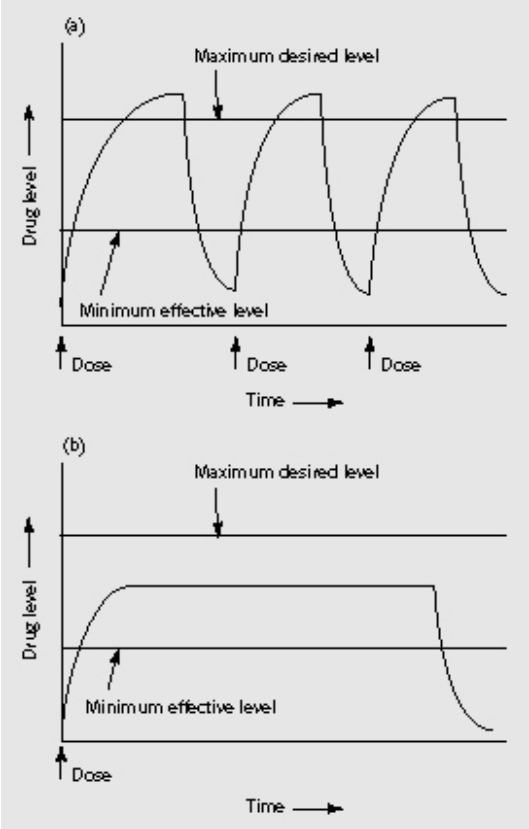


FIGURE 1.1. DRUG CONCENTRATION IN THE BLOOD AFTER (a) TRADITIONAL FORMULATION AND (b) CONTROLLED-RELEASE FORMULATION (*http://www.medicaldevicelink.com)*.

Controlled drug delivery formulations are getting more and more sophisticated. They are able to respond to changes in the biological environment, deliver drugs as a reaction on these changes and they can also deliver drug to very specific cell tissues. A lot of materials have been used to produce these formulations. Originally, the polymers used were intended for non-biological use in the plastic industry and they were selected for this aim based on their physical properties, e.g. poly(urethanes) for their good elasticity, poly(vinyl alcohol) for its hydrophilic properties and its strength, poly (vinyl pyrrolidone) to form suspensions. The material must be inert, free of impurities, good processable and have an appropriate physical structure for his use (*http://www.medicaldevicelink.com*).

1.1.2. Controlled-release mechanisms

Active pharmaceutical ingredients can be released from a controlled-release system by diffusion, degradation and swelling followed by diffusion. In this project, the release of the drug from the polymer matrix is via diffusion. Diffusion means that the drug diffuses through the polymer. This can happen via pores or between the polymer chains. Figure 1.2. shows the drug delivery from a matrix system in which a polymer and a drug are homogeneously mixed. The drug is dispersed into the matrix. As the release proceeds, the release rate slows down, because the layer the drug has to pass through has a larger diameter with time. Besides matrix systems, there are also reservoir systems. The formulation is then surrounded by a film or a membrane. The drug enters the membrane and exchanges with the surrounding fluid (*http://www.medicaldevicelink.com*).

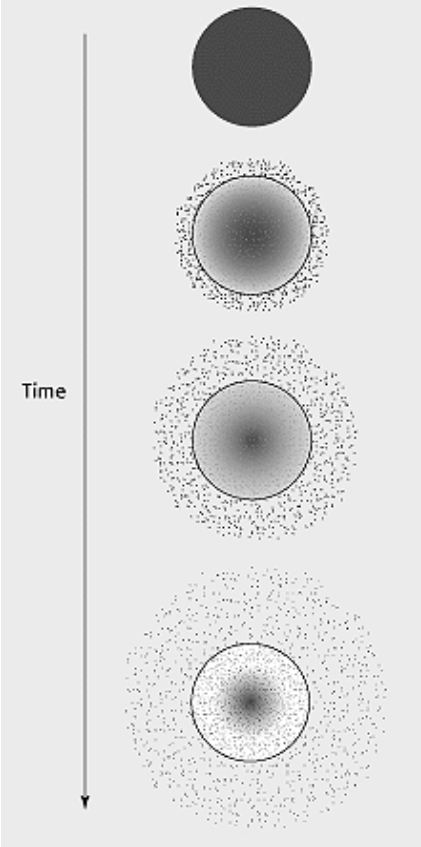


FIGURE 1.2.: DRUG DELIVERY FROM A MATRIX SYSTEM VIA DIFFUSION (*http://www.medicaldevicelink.com*).

Swelling-controlled release systems are dry; once administrated in the body, they absorb water or other body fluids and start to swell. As a result of this swelling, the drug is able to diffuse throughout the swollen network of the polymer. The swelling can be triggered by a change in the environment, like a change in the pH or ionic strength. This makes it for example possible to postpone the drug release until the upper small intestine is reached (*http://www.medicaldevicelink.com*). When a swelling agent is added to the polymer and drug, the drug release is characterized by 2 mechanisms: diffusion and swelling.

Sustained release, sustained action, prolonged action, extended action, depot and repeat action are terms used to classify controlled drug delivery systems (*www.pharmainfo.net*).

1.1.3. Sustained release

The goal of using sustained release formulations is to maintain an effective therapeutic concentration of the drug for an extended period of time. Especially drugs with a short half life are good candidates for this formulation. The rate of drug release equals the rate of drug elimination, thus ensuring that the drug concentration is within the therapeutic window for about 24 hours *(Kumar & Kumar, 2001)*. With these formulations, the initially high release rate seen with a traditional formulation is decreased and the decline period is slowed down (figure 1.3.) However, the limiting step is the drug diffusion out of the formulation that is influenced by the matrix pores, additives and the wettability of the formulation (*www.pharmainfo.net*).

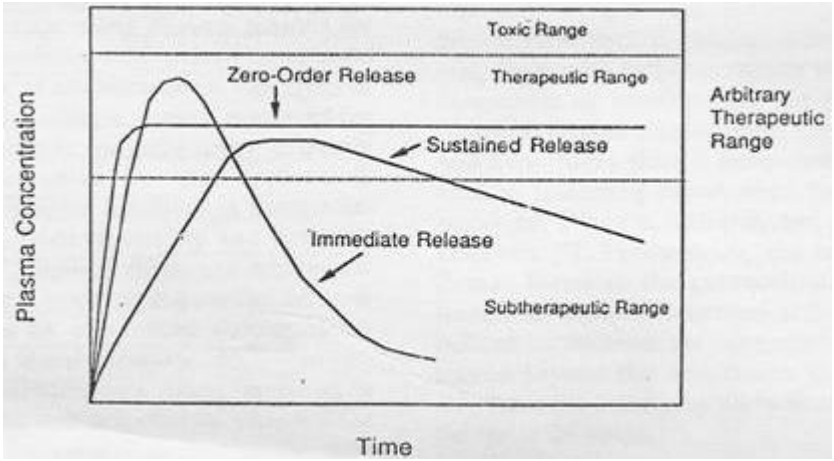


FIGURE 1.3.: PLASMA CONCENTRATION VERSUS TIME SHOWING DIFFERENCES BETWEEN ZERO-ORDER RELEASE, SUSTAINED RELEASE AND IMMEDIATE RELEASE *(www.pharmainfo.net)*

Sustained release dosage forms can be divided into monolithic formulations and multiple-unit dosage forms. There are a lot of interests in the multiple-unit dosage forms, thanks to their pharmacokinetic properties and flexibility: these particles are very small and are spread more uniformly in the intestinal tract; the gastric emptying and the feeding state don't have an influence on the spreading; and high local concentrations and dose dumping – seen with monolithic dosage forms – are avoided *(McGinity et al., 2007).*

A promising technique to produce these multiple-unit sustained release dosage forms is hot-melt extrusion.

1.2. SOLID DISPERSIONS AND SOLID SOLUTIONS

One of the biggest challenges today is to find a way to improve the solubility of poorly soluble compounds, since solubility is the key determinant for a good oral bioavailability. The Noyes-Whitney equation (1.1) shows us that the rate of dissolution depends on the solubility of the drug in the dissolution medium *(Leuner and Dressman, 2000).*

$$\frac{dC}{dt} = \frac{AD(Cs-C)}{h} \qquad (1.1)$$

$\frac{dC}{dt}$: rate of dissolution

A: surface area

D: diffusion coefficient

C_s: solubility in the dissolution medium adjacent to the solid surface

C: concentration in the bulk solution at time t

h: thickness of the dissolution layer adjacent to the solid surface

There are several options to improve the solubility or to adjust the release rate: reduction of the particle size or the thickness of the dissolution layer, adding surfactants, using salts, cyclodextrines, or soluble prodrugs. A promising option is to present the drug as a solid dispersion *(Leuner and Dressman, 2000).*

Solid dispersions refer to a group of solid products consisting of at least two different components, e.g. drug and polymer. The drug can be molecularly dispersed in the polymer, in amorphous form (clusters) or in crystalline form. Therefore, based on the polymer and drug molecular arrangement, different types of solid dispersions can be distinguished. Regarding pharmaceutical application, 3 sub-classifications have gained more importance: solid crystalline suspension, solid glassy suspension and solid glassy solution (also mentioned as solid solution) (Figure 1.4.) (table 1.1.) (*van Drooge et al, 2006).*

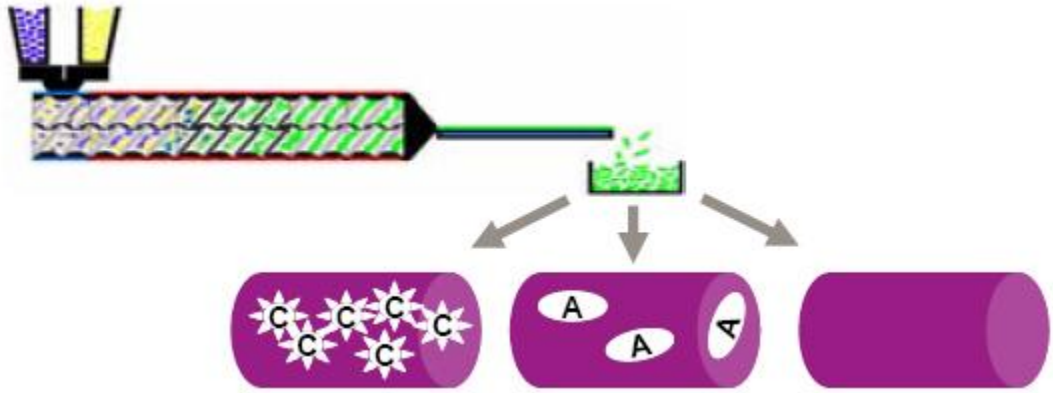


FIGURE 1.4.: .: SCHEMATIC REPRESENTATION OF THREE SUB-CLASSIFICATIONS OF SOLID DISPERSIONS. FROM THE LEFT TO THR RIGHT: SOLID CRYSTALLINE SUSPENSIO, SOLID GLASSY SUSPENSION AND GLASSY SOLUTION (*www.evonik.be*).

TABLE 1.1: CHARACTERISTICS OF THE SOLID DISPERSIONS (*www.evonik.be*)

Extrudate:	Solid crystalline suspension	Solid glassy suspension	Solid glassy solution
Polymer Phase	A[a]	A	A
Drug Phase	C[b]	A	A
Appearance	Opaque	Translucent	Translucent
A DSC will find	T_g [c] + F_p [d]	2 x T_g	1 x T_g

[a] A = Amorphous
[b] C = Crystalline
[c] T_g = Glass Transition
[d] F_p = melting peak

In a solid glassy solution, the drug is molecularly dispersed in the polymer phase, resulting in a single phase solid system. The drug and the polymer are both in the amorphous state and as a consequence there is only one T_g that can be distinguished on a DSC thermogram. In a solid glassy suspension, the drug still exists on an amorphous

form in the polymer. However, is not molecularly dispersed (there are no chemical interactions between drug and polymer) resulting in a two phase solid system. In this case, two T_g's can be distinguished on the DSC thermogram, confirming that there are still two distinct phases present in the extrudates. On a solid crystalline suspension, the drug is in the crystalline form, giving the extrudate an opaque appearance. On a DSC thermogram just one T_g is detected (polymer T_g) and one or more melting peaks, corresponding to the drug crystalline phase.

A solid glassy suspension is thermodynamically less stable than a solid crystalline suspension. For these reason the drug can recrystallize as a result of heat or humidity (*Goldberg et al., 1965).*

For poor water soluble drugs, solid dispersions (particularly solid glassy suspensions or solid glassy solutions) have several advantages: a particle size reduction; increasement of the surface area, resulting in increased dissolution rates, which turns out to an improved bioavailability; the wettability property of the drug is improved, leading to enhanced drug solubility; the drug particles get a higher degree of porosity, resulting in a higher dissolution rate (*Dhirendra et al., 2009*). In the case of highly water soluble drugs, a crystalline suspension (thermodynamically more stable) of the drug in a matrix created by a hydrophobic polymer, reduces drug release.

There are several ways to prepare a solid dispersion: the melting of excipients, the fusion method, spray drying, co-precipitation, co-evaporation, freeze-drying and co-milling *(Serajuddin, 1999).* In the hot melt method, to create a solid solution or a glassy suspension, the drug and the carrier are being melted at a temperature above the melting point of the drug and then cooled down. To create a crystalline suspension, the drug and the carrier are being melted at a temperature below the melting point of the drug and then cooled down. In the first two cases there are several disadvantages, such as the need for a very good miscibility of the drug and the carrier in the molten form, the risk of oxidation or evaporating of drug due to high process temperatures and the fact that separation can occur during cooling if the drug-matrix miscibility changes *(Leuner and Dressman, 2000).* Sometimes, the fusion method is referred to as the melt method. We can only do this if the starting materials are crystalline (*Dhirendra et al., 2009*). Due to these disadvantages, the solvent method became more popular. Drug and carrier are dissolved together in an appropriate solvent. The solvent is then being evaporated. This takes place at lower

temperatures, therefore avoiding thermal degradation of the components. A huge advantage was that polymers with high melting points could now be used as a carrier. These days, hot melt extrusion is one of the most used techniques *(Leuner and Dressman, 2000).*

1.3. HOT MELT EXTRUSION

1.3.1. General

Hot-melt extrusion (HME) is a known technique from the plastics and rubber industry. The inventor is Joseph Brama and it was first used for the production of lead pipes. In the mid-nineteenth century it was applied in the wire insulation polymer coating process (*Repka et al., 2006).*

These days, HME is used in the pharmaceutical industry to make homogenous formulations, e.g. granules, tablets, pellets, transdermal systems and transmucosal systems. There is only one machine needed, so the production of the extrudates is a continuous process. This means a decrease in time and costs and the possibility of automatisation. Furthermore, there isn't a big impact on the environmental, because it doesn't require the use of solvents, excluding as well the chance of hydrolysis. The aim of HME for the pharmaceutical industry is to form a solid dispersion - which increases the dissolution rate (increasing bioavailability), to mask the bad taste of some drugs or to control the drug release (sustained release systems) *(Chokshi et al., 2007)* During the HME process, raw material is mixed and compressed into a homogenous formulation with uniform density by putting it through a die under monitored conditions. An important condition is that the materials must be thermally stable at the working temperatures (*Repka et al., 2006).*

1.3.2. Process and equipment

There are two categories of extrusion processes: ram extrusion and screw extrusion. In ram extrusion, a ram (or a piston) generates high pressures, which replaces the material. The resulting extrudates have a very consistent diameter and the operating pressure is also good repeatable. The disadvantage of this technique is the limiting melting capacity, so there's no uniform temperature in the extrudates and as a result the extrudates are less homogeneous. In screw extrusion, there's a stainless screw rotating

inside a barrel that is heated and the materials are more intensely mixed (*Crowley et al., 2007*).

The HME equipment (figure 1.5.) contains a feeding system, an extruder with conveying, mixing and melting section, downstream auxiliary equipment for cooling, cutting and collecting, and other monitoring tools (*Radl S.,* 2009). The individual compounds of the extruder are a feeding hopper, a barrel, a screw driving unit, a screw, a die and a heating/cooling equipment. The screw is divided into three parts: first, the feeding section with a low pressure to allow consistent feeding and gentle mixing; second, the melting or compressing section with a higher pressure and more mixing and compression, with reduction of particle size, and third, the metering section to ensure a constant flow rate of the melt and a uniform thickness of the extrudate. The die is responsible for the shape of the final product. During the process, the temperature, screw speed, extrusion torque and pressure are monitored (*Repka et al., 2002).*

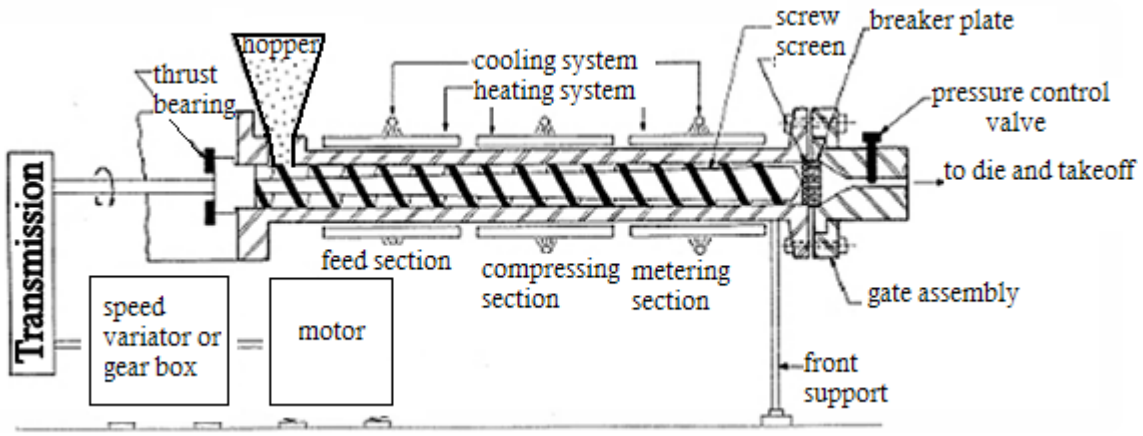


FIGURE 1.5.: SCHEMATIC DIAGRAM OF A SINGLE SCREW EXTRUDER (*Crowley et al., 2007)*

There are extruders with one single screw or extruders with two screws. Twin-screw extruders can be divided in co-rotating extruder (when the two screws rotate in the same direction) or counter-rotating extruder (when the two screws rotate in the opposite direction) (*Repka et al., 2002).* Counter-rotating twin screw extruders have some disadvantages: there's a risk that air is entrapped in the extrudate, there's a high pressure generated, the screw speed has a low maximum and there's a low output (*Crowley et al., 2007*). The screws can be non-intermeshing or intermeshing. When they are intermeshing, the extrudates are more conveyed and the residence time is shortened. There are different screw designs: forward-conveying elements, reverse-conveying

elements, kneading blocks and other designs to influence the degree of mixing (figure 1.6.) (*Shearer, 2000)*. It's easier to produce extrudates with a twin-screw extruder: the materials are more mixed and they come out faster (in the order of 5 to 10 minutes), so the time under high temperature is reduced. There's also a greater output and a reduction of particle size, which makes it possible that the material becomes dispersed or solved in the extrudate. On the other hand, single screw extruders are more simple and cost less *(Repka et al., 2002*).

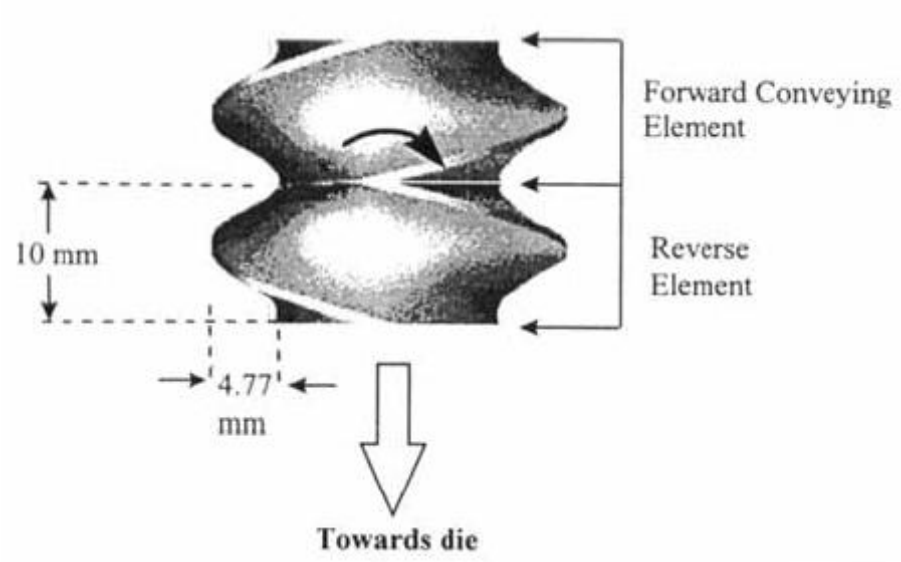


FIGURE 1.6.: SCREW GEOMETRY (*Chandrasekaran, 1997).*

In hot-melt extrusion, the powder blend of the materials is brought into the feeder and it is the rotating screw that makes sure that the blend is transferred through the heated barrel. The shearing effect of the rotating screws produces heat in the barrel, melting the materials together with the heat conducted from the heated barrel itself. In the end, the molten mass is pumped through the die. The process conditions (process temperature, screw speed, torque and pressure) depend on the properties of the materials that are used (chemical, physical en thermal stability) and the extruder design (*McGinity & Zhang, 2007*). The polymer should have a low glass transition temperature, because it has to be in the rubbery state under the process temperature to facilitate the extrusion. Polymers with a low viscosity and a high thermal conductivity are processed in a more efficient way (*Repka et al., 2002*).

1.3.3. Materials used in hot-melt extrusion

The formulations are a mixture of an active pharmaceutical ingredient and functional excipients. A functional excipient can be a matrix carrier, a bulking agent, a release modifying agent, an antioxidant, a swelling agent or other additives. The materials used in the process must be non-toxic and pure, and have a good thermal, physical and chemical stability. The process takes place at high temperature causing in certain cases degradation of the polymer and/or the drug. In order to avoid this, the stability can be increased by adding antioxidants, chelating agents and/or light absorbers *(Crowley et al., 2007).*

Another type of additives are plasticizers, they are responsible for lowering the glass transition temperature of a polymer. As a consequence when a plasticizer is incorporated, the processing temperature can be lowered. This reduces the advent of drug and/or carrier degradation and also makes the polymer more flexible *(McGinity & Zhang, 2007).*

Functional excipients can alter the porosity or increase the viscosity. A higher porosity increases the drug-release rate and a higher viscosity limits and reduces the initial burst release, often appearing with the matrix systems *(McGinity & Zhang, 2007).*

1.3.4. Advantages and disadvantages of hot-melt extrusion

The procedure of HME is simple, very efficient and continuous. There are no solvents or water needed: hydrolysis is avoided and there's no need to evaporate the solvent, this reduces the number of steps in the process. The product is a uniform dispersion of particles of reduced size, with an increased bioavailability. In the molten stage, the polymers can bind the drug and therefore act as a drug reservoir, so retarding the drug release *(Crowley et al., 2007).*

The disadvantages are the high processing temperature and the shear stress, which can have an influence on the polymer and drug stability during production and storaging. Another important disadvantage is the limited number of available polymers *(Breitenbach, 2002)* limiting the variety of possible formulations.

1.4. ETHYLENE VINYL ACETATE

1.4.1. Structure and synthesis

Ethylene vinyl acetate (EVA) is a thermoplastic semi-crystalline high molecular weight copolymer of polyethylene (PE) and vinyl acetate (VA). Ethylene and vinyl acetate can be free-radically copolymerized in different quantitative ratios using a peroxide catalyst, under high pressure (2000-3000 bar) and temperature (150-250°C) (figure 1.7.) (*Kolwert et al., 1989*).

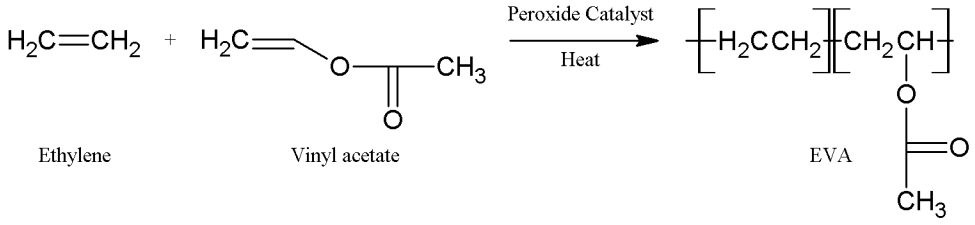


FIGURE 1.7.: SYNTHESIS OF EVA (*Shastri, 2002*).

Eva has many applications, such as footwear soles, medical gloves, wire coating, masks, babies' dummies, bottle teats and toys *(http://www.plastiquarian.com/eva.htm).*

1.4.2. Characteristics

EVA is non-degradable. This means that it can be removed completely when you want it to. EVA polymers are biocompatible, they don't cause adverse reactions and they have good rheological properties. The content of VA can be adapted to change the properties. When the percentage of VA is increased, the number of polar VA groups increases, the PE crystallinity decreases, the melting temperature reduces, the drug solubility increases, drug permeability increases, clarity increases and flexibility increases (*Van Laarhoven, 2005).* When the percent VA reaches 50%, the copolymer becomes totally amorphous. This results in important changes in the macroproperties of the extrudates; they have better impact strength.

The two most important parameters for EVA copolymers are the melt index (MI) and the percentage VA. The MI is an indication of the viscosity and the molecular weight (MW) of the polymer. A high MI means a low MW and a low viscosity (*www.dupont.com).* The chain structure determines the degree of crystallinity and also plays a role in the type of crystal that is formed. When the ethylene copolymers are

crystallised, ethylene segments with the same or similar length aggregate and form crystals. When the segments are long, they are similar to polyethylene and they form orthorhombic crystals. Orthorhombic crystals are thermodynamically stable. When the segments are shorter, monoclinic crystals are formed due to the influence of the other co-monomer unit. Increased co-monomer content results in an increase of the shorter ethylene chains; this increases the relative content of monoclinic crystals (*Zhang et al., 2002).* Besides the orthorhombic and monoclinic crystalline phases, there exist a third crystalline phase. This phase appears during storage at room temperature and melts at a temperature just above room temperature. This phase is the result of the secondary crystallization (*Wang et al., 2006*).

1.4.3. Toxicology

Adverse response to a formulation is the result of leachants. Leachants are components that hang out of the matrix. For systems based on EVA, it's possible to see unreacted vinyl acetate and low-molecular weight polyvinyl acetate. Polyvinyl alcohol, the degradation product of polyvinyl acetate, and polyvinyl acetate itself, are supposed to be non-toxic. Vinyl acetate is metabolised into acetaldehyde. This occurs rapidly in blood. Acetaldehyde is a carcinogen and teratogen. But the residual vinyl acetate can be removed easily via extraction of the polymer, so there is no problem. (*Shastri, 2002*).

1.5. METOPROLOL TARTRATE

1.5.1. Structure

Metoprolol tartrate (MPT) (figure 1.8.) is a white, crystalline and odourless powder. MPT is a β_1-selective antagonist. It is very water-soluble, and is soluble in alcohol, methylene chloride and chloroform. MPT is insoluble in ether (*http://chemicalland21.com*; *www.medicineonline.com*).

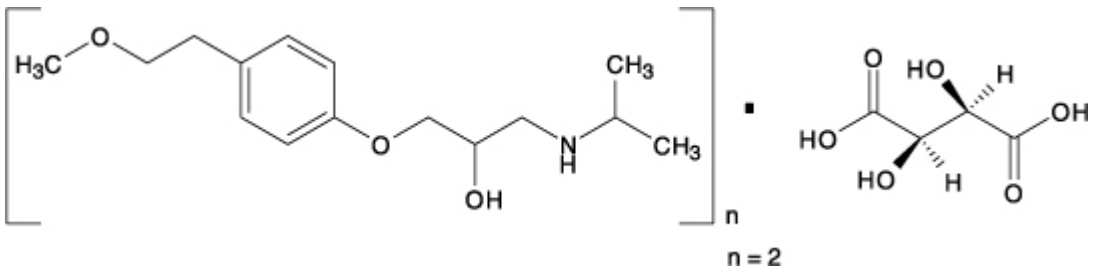


FIGURE 1.8.: STRUCTURE OF METROPROLOL TARTRATE (*www.medicineonline.com*)

1.5.2. Pharmacokinetics

MPT is quickly and almost completely absorbed following oral administration. The bioavailability is 40% to 50%, due to first pass metabolization. MPT crosses the placental barrier and the blood-brain barrier, and appears into breast milk. MPT is metabolised in the liver by CYP2D6 iso-enzymes. The rate of metabolization shows inter-individual differences due to genetic polymorphism. Poor metabolizers exhibit higher plasma concentrations. The elimination half-life of MPT is about 7 hours in poor metabolizers en 3 to 4 hours in extensive metabolizers. Plasma levels are variable. 12% of MPT is bound to serum albumin. A small amount (less than 5 percent) is recovered unchanged in the urine. The rest is metabolized; the metabolites are excreted by the kidneys in the urine (*www.medicineonline.com*; *www.rxlist.com*).

1.5.3. Pharmacodynamics

MPT is a cardioselective β_1-receptor blocking agent. It has no intrinsic sympathicomimetic activity. MPT is used in amounts lower than the amounts necessary to block β_2- receptors, located in the bronchial and vascular musculature. MPT blocks the adrenergic stimulation of the β_1-receptors; this results in a decrease in heart rate, heart contractility and cardiac output (*www.rxlist.com*). MPT also has an antihypertensive effect. MPT is widely used for the treatment of hypertension, angina pectoris, myocardial infarction, cardiac arrhythmias, hyperthyroidism, migraine headache, obesity, glaucoma, tremor… (*www.bcfi.be; www.medicineonline.com*).

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.

1.6.1. Hydrophilic polymers

Some hydrophilic polymers can 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 as they are getting solvated *(Maggi et al., 2001)*. Therefore, a hydrogel layer is formed, which regulates the water uptake and the drug release. Highly water-soluble

drugs are dissolved and are mainly released by diffusion, helped by a high drug concentration gradient. In case the drug is low 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 API 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 different 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 PEO with lower molecular weight is characterized by smaller crystals when compared with PEO with high molecular weight (smaller crystals melt at a lower temperature). The PEO stability in extrudates depends on the molecular weight of the polymer, the processing temperature, the screw speed and the storing conditions *(Zhang, 2002).*

1.6.2. Surfactants

To form a solid dispersion, as seen in 1.2., the drug and the matrix have to be compatible. If this isn't 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 (*Greenhalgh et al., 1999*).

A surfactant is amphiphilic: it consists of a hydrophilic part and a lipophilic part. Surfactants take place 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 hydrophile-lipophile balance (HLB) value is the hydrophilic/liphophilic balance. It's an indication of the water-solubility. The higher the HLB-value, the more water-soluble the surfactant. In this project, the effect of Tween 80 and Sorbitan Sesquioleate on the formation of the mini-matrices is being studied. The HLB-value of Sorbitan Sesquioleate is 3,7 , so Sorbitan Sesquioleate is rather hydrophobic. Tween80 has a higher HLB-value, it's more hydrophilic.

1.7. SCALE-UP PROCESS

The development of a new drug passes through different phases. At very early stages of clinical studies, less than 100 unit doses can be enough. As the product advances through the various stages, increasing supplies are needed, so the scale of manufacturing advances as well (*Ruegger et al., 2007*).

Scaling-up a process always holds a risk; the scale-up from the laboratory to the production scale can lead to changes in pharmaceutical characteristics. These changes are the result of differences in equipment and variations in raw materials. Scale-up processes can be difficult due to poor in-process controls or incorrect extrapolation from small-scale experiments. In practice, the initial transfer from laboratory scale to production scale is mostly empirical or a trial-and-error situation, instead of a systematic application of engineering principles (*Rekhi et al., 1996)*. There are different concerns, for example, which characteristics change?; can you predict the changes?; are the changes linear or non-linear?; do you know what is a critical parameter?; (*Ruegger et al., 2007*).

For a non continuous process, scale-up occurs in several steps, based on the weight: small-scale laboratory (0,5 to 2 kg), an intermediate step (5 to 10 kg), pilot scale (20 to 100 kg) and production scale, which ranges from 200 kg to greater than 1000 kg (*Ruegger et al., 2007*). A batch can be defined as a collective term for an amount of product that underwent the same treatment. *Laboratory scale batches* are the batches produced at the research and early development stage. Their size is 100 to 1000 times less than the production scale. These batches are used to support the formulation, development and the preclinical and/or clinical studies. Physicochemical results obtained from these batches help to evaluate and to define the critical product performance characteristics. *Pilot batches* are used in the process development or optimisation stage. They support stability studies and the preclinical and clinical evaluation; they foresee data that can predict the production scale product. The pilot batch size has to be at least

10% of the production scale batch. The pilot batch can be seen as the link between the process development on one hand and the industrial production of the product on the other hand. The production of pilot batches assures that the product and process will be able to be carried out on an industrial size. *Production-scale batches* are batches of similar size to those who will be produced during the commercial manufacturing of the product (*www.emea.europa.eu*).

During scale-up, batch sizes are increased and larger equipment is used. In the end, we want a process that is robust enough for routine commercial manufacturing processes. So scale-up is more than increasing the number of unit doses produced; it involves the transfer of knowledge and technology, obtained during the small-scale development of the product. The dosage form that will be ultimately transferred to production has to have a good bioavailability, be safe and be efficient. It also has to have an acceptable processing and production process. It's important to understand the critical versus non-critical parameters to have a successful scale-up (*Ruegger et al., 2007*).

For continuous processing, the conventional method to identify a batch is not applicable anymore. However, the FDA batch definition can also accommodate a continuous process as "batch" within the definition. It does not refer to the mode of manufacturing, but to a quantity of material. Hence, material manufactured within a specified time interval of a continuous process can be identified by a unique code (batch number) to allow tracking of the manufactured goods (*Vervaet, C. and Remon, J. P., 2010*).

As it was mentioned before, there are many advantages associated with this mode of production and the scale-up process is not an exception. A continuous process brings up less scale-up issues: increasing the production capacity does not require larger equipment (with a development, optimization, and validation phase at each scale), but only an extension of process time on the same equipment using the same process settings, providing enormous flexibility, and eliminating material and technology transfer. Given that a continuous process mainly operates under steady-state conditions, product of a given quality can be produced for any length of time (*Vervaet, C. and Remon, J. P., 2010*).

Nevertheless, the scale-up of HME is influenced by many factors. For example the temperature distribution in the die and the melt, the mechanical strength of the die and the distribution of the melt with the device, play an important role, especially in large-scale production systems (*Radl S., 2009).* The overall screw design is another important

parameter. Besides these factors, HME also requires a multiple powder feeder, a take-off cooling belt unit and a control panel to be scaled-up in size. Proper sizing of all components is a critical factor (*Ruegger et al., 2007*). When you extrude at a larger extruder, it is likely that the screw speed has to be increased to create a good torque. As a result from this, more shear rate is generated. This can increase the melting temperature with a decrease of molecular weight. The heat has to be removed to prevent overheating and degrading (*Giles, F. et al, 2005*).

In this project, the process is scaled-up form a laboratory mini-extruder (the powder weight used is 25g) to a larger extruder (the powder weight used is 200g). The extruder settings are adjusted to obtain good quality extrudates. The obtained extrudates are visually evaluated (to avoid shark skinning) and the dissolution profile compared. DSC runs were also performed in order to evaluate the physical state of the materials.

1.8. IN-PROCESS CONTROL

The manufacturing process should deliver formulations with a good performance and a very high, pre-defined quality. To make sure that this quality is achieved, the quality can be built-in. This is known as 'quality by design' (QbD). By doing this, final product testing can be avoided, reducing time and costs. The manufacturing process can be designed, analyzed and controlled by process analytical technology (PAT) via timely measurements of critical quality parameters of in-process materials. An important property for the stability – and further on the quality - of the final product in this case is the crystallization of the API. The crystal size distribution and polymorphic form can be controlled during extrusion by PAT. There are different non-invasive techniques. Off-line methods such as NMR and DSC do not measure continuously during the process. In this project, an in-line technique was used for the characterization of the crystals: Raman spectroscopy. In-line analysis is performed *in situ* inside chemical and physical processes. Besides off- and in-line measurements, there are also at- or on-line measurements; at-line means that you measure offline, but you do this immediately after producing the drug. On-line is when you re-route the process to do the measurements (*http://americanpharmaceuticalreview.com*).

Process measuring techniques such as Raman spectroscopy offer several advantages: they work at high speed, are very compact, foresee a good versatility, are

robust and consistent and have a high selectivity and sensitivity. Chemical and physical information is obtained (*El-Hagrasy A., 2005).*

Measurement and instrument precision and sensitivity are very important factors when selecting a measurement method. Robustness, repeatability and reproducibility are terms to describe this. The measurement is robust if it is both sensitive and precise. The instrumentation is robust if it operates reliably under the process conditions once the process is scaled up. The process is robust if the products reach the required specifications. Repeatability means that you consistently get the same result, when you work with the same parameters. The instrument needs to provide the same measurement results. If the measurement is precise and sensitive, accuracy is not a critical element. Very important is the batch-to-batch repeatability. Batch-to-batch repeatability indicates that the process operates in a robust region of the design space and that it can handle with random variability. The measurement and the process should also be reproducible. The results need to be consistent from one system to another. We want the same measurement at different scales and different locations (*http://blog.autochem.mt.com*).

In this work it was performed process monitoring with Raman spectroscopy and not in-process control. The process was just monitored, as there were no feedback and forward control loops implemented in the process. Furthermore the spectra's weren't used to make automatic actions or corrections. Process monitoring is used to predict product characteristics and to allow the adjustment of process parameters in order to obtain optimal results (*www.mpr.com*).

2. OBJECTIVE

The objective of this project is to produce a sustained release multiple-unit dosage form via a simple, flexible and continuous process: hot-melt extrusion. Ethylene vinyl acetate in powder form is used as a matrix former. The model drug used is a metoprolol salt, metoprolol tartrate. Polyethylene was added as swelling agents.

The in vitro release of metoprolol salt from extruded mini-matrices was investigated, as well as the physicochemical characteristics of the mini-matrices with differential scanning calorimetry (DSC) and scanning electron microscopy (SEM).

From all the produced formulations (made with the mini-extruder) it were chosen four that exhibited the best dissolution profile (higher drug release after 24 of dissolution experiments and closer to a zero-order release). These formulations were remade with the larger extruder. Parameters such as feeding rate, temperature and screw speed were adjusted to obtain a good quality extrudate and the properties of the extrudates were once again evaluated in order to compare the changes caused by the scale-up.

During extrusion it was also performed process monitoring with the help of a Raman probe.

3. MATERIALS AND METHODS

3.1. MATERIALS

Ethylene Vinyl Acetate (EVA) (Dupont, Geneva, Switzerland) (Figure 3.1. A) is used in a powder form, with a weight percent vinyl acetate of 40% and 28%. EVA is used as a hydrophobic matrix carrier. Metoprolol Tartrate (MPT) (10µm) (Esteve Quimica, Barcelona, Spain) (figure 3.1. B) is selected as a model drug. MTP is a non-plasticizing drug, with a melting point at 123°C. It is very water-soluble and it is well absorbed in the gastrointestinal tract.

To improve the release of MPT out of the EVA matrix, polyethylene oxide (PEO) is used in different molecular weights (1.10^5 (100K), 1.10^6 (1M) and 7.10^6 (7M)), respectively Sentry™ Polyox™ WSR N10, N12 and N303 (Dow Chemical Company, Midland, USA) (figure 3.2.A.). PEO is a thermoplastic, semi-crystalline homopolymer. It's water-soluble and has a melting range of 57-73°C.

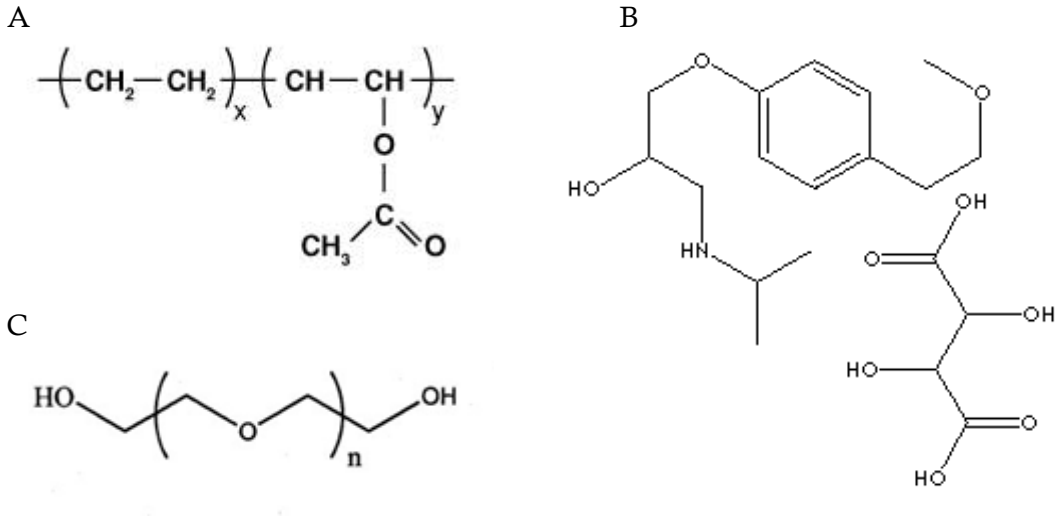


FIGURE 3.1.: STRUCTURES OF USED MATERIALS ETHYLENE VINYL ACETATE (A), METOPROLOL (B) AND POLYETHYLENE OXIDE (C) (*www.sigmaaldrich.com)*

3.2. METHODS

3.2.1. Preparation of tablets by hot-melt extrusion

Different amounts of EVA 28 and MPT with or without PEO - as can be seen in table 3.1 - were weighed and mixed with mortar and pestle until it was obtained a homogenous mixture. The physical mixtures were manually fed into the hopper and extruded at different temperatures (80°C, 90°C and 100°C), using an intermeshing co-rotating twin-screw mini-extruder (HAAKE MiniLab II Micro Compounder, Thermo Electron Corporation, Karlsruhe, Germany) (figure 3.2.). The screw speed was set at 60 rpm. The machine consists of a feeder, two Archimedean screws and a cylindrical die (2 mm diameter), which shapes the extrudates. After cooling down to room temperature, the extrudates are cut with surgical blades into mini-matrices of 2 mm length.

FIGURE 3.2.: HAAKE MINILAB II COMPOUNDER
(www.pharmaceuticalonline.com)

TABLE 3.1: COMPOSITION OF THE FORMULATIONS

Batch name	Polymer type	Drug	Polymer/drug ratio	PEO(%)			Extrusion temperature (°C)
				100K	1M	7M	
Influence of processing temperature							
0	EVA 28	MPT	1:1				80
1	EVA 28	MPT	1:1				90
2	EVA 28	MPT	1:1				100
Influence of addition of PEO							
3	EVA 28	MPT	5:4	10			90
4	EVA 28	MPT	5:4		10		90
5	EVA 28	MPT	7:5		5		90
6	EVA 28	MPT	2:1		10		90
7	EVA 28	MPT	7:5			5	90
8	EVA 28	MPT	2:1			10	90
9	EVA 40	MPT	1:1			5	90

Four batches (1-4) (table 3.2.) (with the best dissolution profile) were also extruded on a larger hot-melt extruder (Brabender, Eurolab 16, ThermoFisher Scientific, Duisburg, Germany). This is an intermeshing co-rotating twin screw extruder. The extrudates were extruded with a screw speed of 90 rpm or 110 rpm and a feeding rate of 0,450 kg/h or 0,500 kg/h. The temperature of the different zones varied between 90°C, 100°C, 110°C and 140°C.

TABLE 3.2: EXTRUDATES PRODUCED ON THE LARGER EXTRUDER

Batch name	Polymer type	Drug	Polymer/drug ratio	PEO 7M (%)	Screw speed rpm	Extrusion temperature (°C)
Influence of addition of PEO						
1	EVA 40	MPT	1:1	5	90	90
2	EVA 40	MPT	1:1	15	90	90
3	EVA 28	MPT	3:2	5	90	100
4	EVA 28	MPT	5:4	10	90	100
Batch name	**Polymer type**	**Drug**	**Polymer/drug ratio**		**Screw speed (rpm)**	**Extrusion temperature (°C)**
Influence of processing temperature and screw speed						
5	EVA 40	MPT	1:1		90	90
6	EVA 40	MPT	1:1		110	90
7	EVA 40	MPT	1:1		90	110
8	EVA 40	MPT	1:1		110	110
9	EVA 40	MPT	1:1		90	140
10	EVA 40	MPT	1:1		110	140

3.2.2. Extrudate characterization

The extrudates were visually inspected for surface defects. There was an evaluation of the deformation due to cutting and of the presence of cracks using a KH-7700 digital microscope (Hirox, Japan), with a high resolution zoom lens (MXG-10C model, using co-axial vertical lighting for high-level optical observation) and an OL-70 II objective lens with a magnification capacity of 70-700x. The imaging system had a 2.11 mega-pixel CCD sensor and a maximum pixel resolution of 30 mega-pixels (i.e. 6400 horizontal lines and 4800 vertical lines).

3.2.3. Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) was also used to visualize the surface morphology. Photomicrographs were taken with a field emission gun scanning electron microscope (type Quanta 200F, FEI, Eindhoven, Nederland). The pressure in the chamber was 100Pa and a large field detector (LFD) was used.

A conventional microscope uses light waves to create an image. A SEM uses a beam of high-energy electrons and obtains 2-dimensional images with a high resolution. Inside the microscope there has to be a vacuum to avoid interaction between the electrons and air molecules. The electron source produces a beam of electrons. A positive electrical potential accelerates the electrons towards the sample. The electron beam is focused into a monochromatic beam; this beam is then focused onto the sample. Due to interactions with the sample, the electron beam changes. This change is detected and transformed into an image. (*www.unl.edu*).

3.2.4. Raman Spectroscopy

Raman spectroscopy is a based on inelastic scattering of monochromatic light produced by a laser source. The sample molecules scatter photons from the incident laser light. The frequency of a small fraction of the scattered photons is changed (shift up or down), this is called the Raman effect. The frequency shift is a parameter for vibrational, rotational and other low frequency transitions in the sample molecules. The scattered light is collected by a lens and sent to the detector, resulting in a Raman spectrum (*www.piaction.com).* Raman spectroscopy is used in this project to investigate in-line the solid state and content of MPT in the extrudates during extrusion.

A RamanRxn 1 spectrometer (Kaiser Optical systems, Ann Arbor, USA) equipped with an air-cooled CCD detector (back-illuminated deep depletion design) and a Dynisco contact probe, which was implemented in the extrusion process stream (figure 3.3.). 10 spectra were collected from each batch during 5 minutes (i.e., every 30 seconds). The laser wavelength during the experiments was the 785 nm line from a 785 nm Invictus NIR diode laser. All spectra were recorded at a resolution of 4 cm^{-1} using a laser power of 400 mW and a laser light exposure time of 2 seconds. Data collection and analysis were done using the HoloGRAMS™ data collection software package, the HoloREACT™ data analysis software package and the Matlab® software package (version 6.5).SNV-preprocessing en PCA were done using SIMCA P+ (Umetrics, version 12.0.1.0).

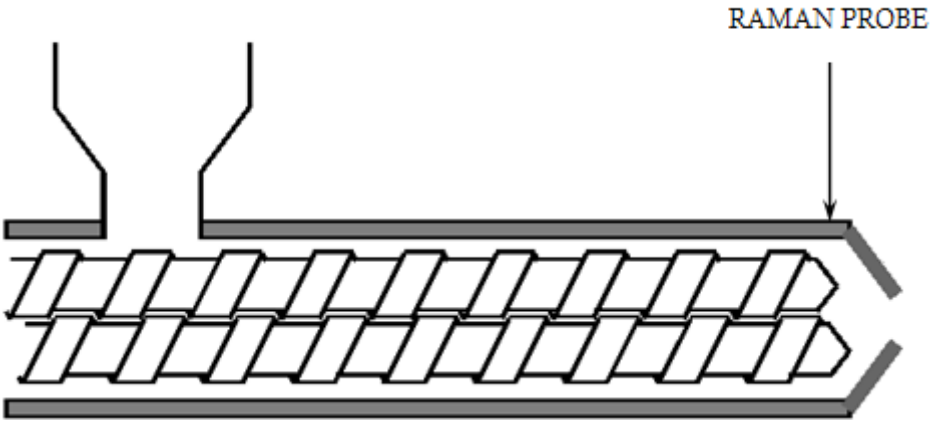


FIGURE 3.3.: RAMAN PROBE IMPLEMENTED IN THE EXTRUSION PROCESS STREAM (*www.polymerprocessing.com*)

3.2.5. Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) measures the energy needed to establish a nearly zero temperature difference between the sample and the reference material. The sample and the reference are subjected to identical temperature regimes; the heating or cooling down is controlled. DSC is used to study the thermal transitions of the polymer and the drug (*Schick, C., 2009).*

DSC can be divided into heat flux DSC and power compensation DSC (figure 3.4.). In heat flux DSC, there's one heater for both the reference and sample pan. In power compensation DSC, there is a microheater for the sample pan and another microheater for the reference pan.

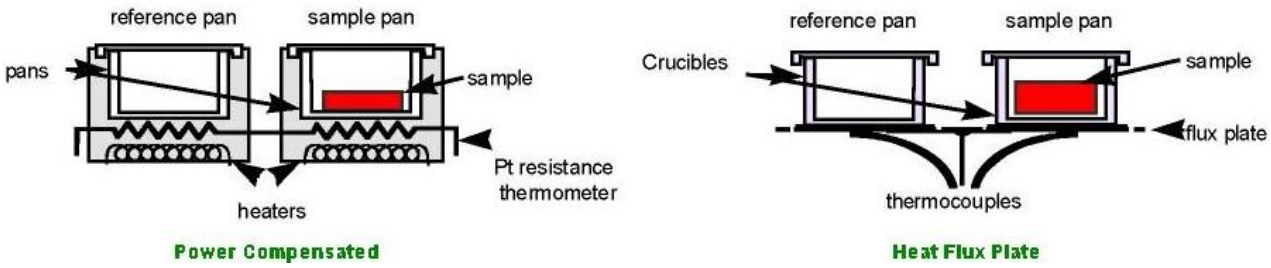


FIGURE 3.4.: POWER COMPENSATION AND HEAT FLUX DSC (*http://materials.npl.co.uk*)

M(DSC) measurements were carried out using a Q2000 Modulated DSC (TA, Instruments, Leatherhead, UK) equipped with a refrigerated cooling system. Dry nitrogen at a flow rate of 50ml/min was used to purge the DSC cell. Depending of the samples and the determined parameters (glass transition temperature (T_g), crystallization temperature (T_c), melting point (T_m) and heat of fusion (ΔH)), the experimental method

consisted of a single heating cycle (heating rate of 20ºC/min from -100 to 180ºC) or a 3-phase analysis with consecutive heating, cooling and heating cycles). All samples were analyzed in duplicate, except for the determination of T_g and ΔH where measurements were performed in triplicate. For MDSC it was used an amplitude of 0.3ºC, the period was 50 s and the underlying heating rate was 2ºC/min. The samples were evaluated according to the 3 cycle analysis (heating, cooling and heating) from -100 to 180ºC. All results were analyzed using the TA Instruments Universal Analysis 2000 software.

3.2.6. *In vitro* drug release

To determine the drug release in vitro, we use Apparatus 1 (baskets) on a VanKel VK 7010 Dissolution Tester (figure 3.5.) combined with a VK 8000 automatic sampling station (VanKel Industries, New Jersey, USA) The mini-matrices were weighed and placed by 8 in 6 vessels, containing 900 mL demineralised water as dissolution medium. The test was performed simultaneously in all dissolution vessels, without media displacement. The temperature was set at 37 ± 0,5°C. The rotational speed of the baskets was kept at 100 rpm. At specific time points (0.5, 1, 2, 4, 6, 8, 12, 16, 20, 24 hours) (without medium replacement), samples of 5 mL were retained and spectrophotometrically analyzed for MPT at 222 nm, by means of a Perkin-Elmer Lambda 12 UV–VIS double beam spectrophotometer (Zaventem, Belgium). Via linear regression using a calibration curve between 0 mg/mL and 0,03 mg/mL, the MPT content was determined. Each batch was evaluated in triplicate.

FIGURE 3.5.: VANKEL VK 7010 DISSOLUTION TESTER *(www.chemistry.nmsu.edu)*

4. RESULTS AND DISCUSSION

4.1. DRUG RELEASE FROM EVA MATRICES

Previous work showed that the extrusion of a high water soluble drug with EVA produced a sustained release formulation. However, 24h dissolution experiments were not enough to completely release the drug and in certain cases a first-order release was obtained instead of a zero-order release. Figure 4.1. shows the dissolution profiles of different types of EVA mixed with 50% drug. It was also assessed the addition of PEO 7M to the different EVA polymers (higher amounts of PEO 7M showed an increase of drug release). In this study, it was produced several extrudates (as described in 3.2.1) in order to understand the effect of PEO (with different molecular weights) on the particular case of EVA28.

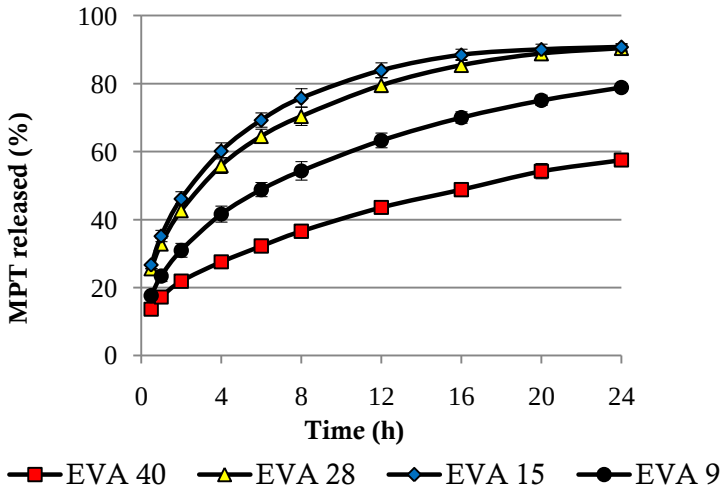


FIGURE 4.1. : DISSOLUTION PROFILES OF EVA/MPT 50/50

Concerning drug loading it was also seen that the concentration of the drug plays an important role in the change of the dissolution rate. Batches produced with 40, 50 or 60% of MPT resulted in good quality extrudates. Higher drug loading produced shark skinning extrudates and when a lower amount of MPT was added, just a small part of the drug was released after 24h of dissolution profile. Therefore, the produced batches only included 40 up to 60% of MPT.

4.1.1. Addition of PEO

When PEO 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 the 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.

PEO with a molecular weight of 1M was mixed in different percentages (5 and 10%) with EVA28 and MPT. The experiments (figure 4.2.) showed that a higher percentage of PEO yields a faster drug release, whereas the total amount released after 24h was not so affected. However, the batch with 5% of PEO 1M shows a release closer to a zero-order kinetic.

PEO is hydrophilic and it swells when mixed with water. As a result, a higher amount of PEO attracts more water to the matrix and increases the drug release (PEO will swell more). As the swollen PEO forms a bigger network the drug can diffuse to the surface through these channels and will be released. The results showed that 5% of PEO produces a better dissolution profile when compared with 10% of PEO. Similar amount of drug was released after 24h of dissolution experiments for both concentrations (around 85-90%).

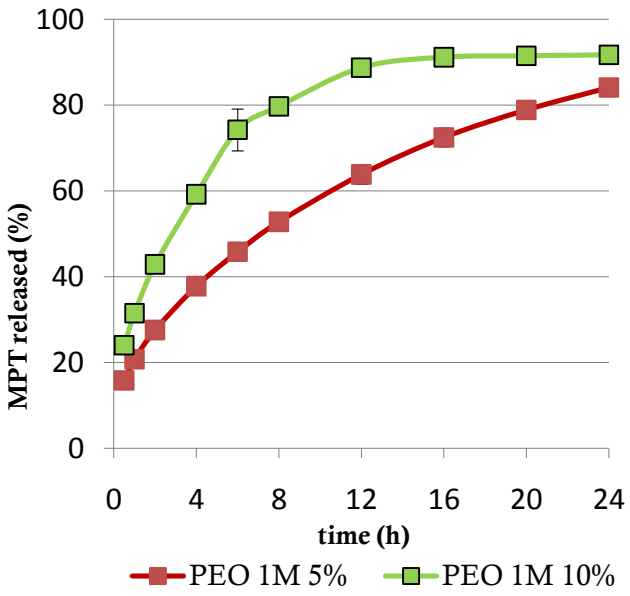


FIGURE 4.2.: DRUG RELEASE PROFILE OF MATRICES PRODUCED WITH EVA28/MPT/PEO 1M, 55/40/5, w/w/w (BATCH 5), EVA28/MPT/PEO 1M, 50/40/10, w/w/w (BATCH 6)

Figure 4.2. also tells us that MPT is released in a biphasic profile. First, a fast release is observed – burst release -, followed by a slower release. The burst release is related with the drug closer to the tablet surface while the slower part corresponds to the drug closer to the inner part of the matrix Therefore, by adding PEO as drug release modifying excipient, the elastic matrix structure stretches due to the swelling properties of PEO 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.

4.1.1.1. Influence of the molecular weight

For 10% of PEO the different molecular weights seem to affect drug release on a similar way. A maximum of 90% of drug is released after 24h of dissolution experiments. However, PEO 100K (lower viscosity polymer) shows a faster release during the first 12h, when compared with PEO 1M and 7M (higher viscosity polymers) (figure 4.3.).

In literature (*Maggi et al., 2002; Prodduturi et al., 2005*), it has been mentioned that when using a higher molecular weight PEO, the rate of drug release slows down. This can be related with the fact that a higher molecular weight PEO has a longer chain and has a higher viscosity reducing drug release. However, in the case of elastic matrices like EVA, a higher viscosity seems not to be always a negative factor for drug release. Due to

this viscosity, the polymer gets more entangled and the matrix swells more, increasing pore size and releasing more drug. However, if the matrix has a limited elasticity, a stronger gel is formed, reducing the pathway for drug release. As a consequence, the drug release rate is reduced.

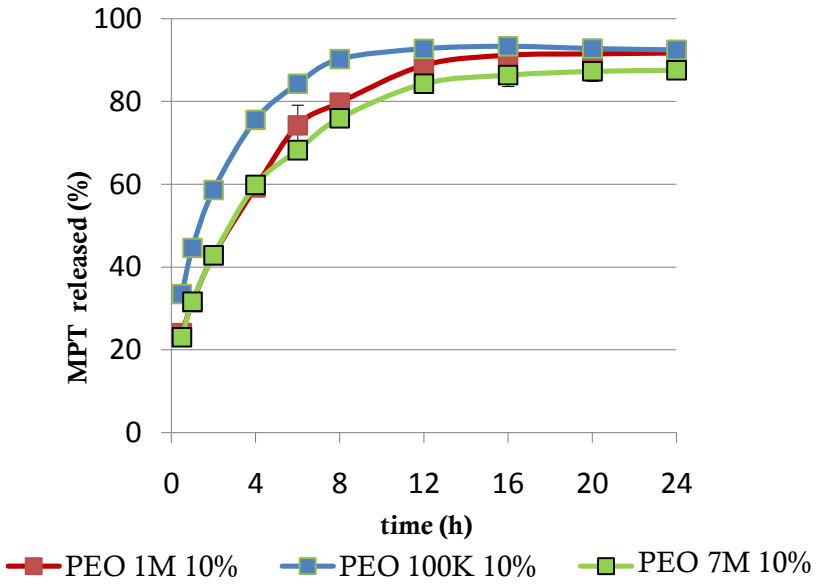


FIGURE 4.3.: INFLUENCE OF THE MOLECULAR WEIGHT OF PEO ON THE DISSOLUTION RATE OF EVA28/MPT/PEO, 50/40/10, w/w/w (BATCH 3, 4, 7)

4.1.1.2. Influence of the concentration of EVA

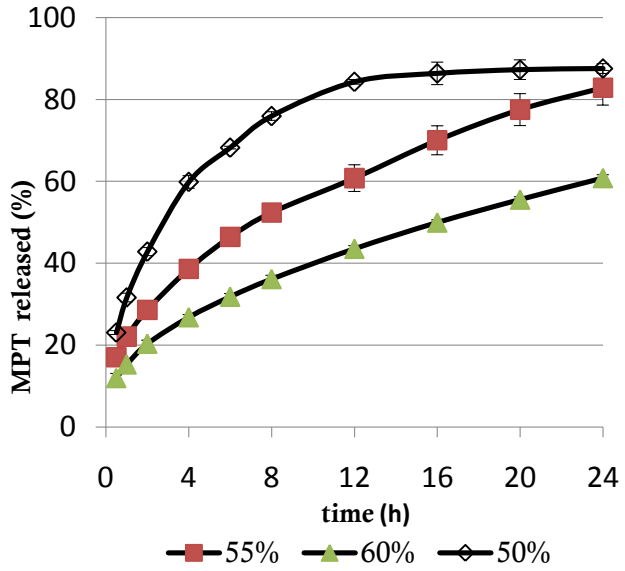


FIGURE 4.4.: INFLUENCE OF THE CONCENTRATION OF EVA28 ON THE DISSOLUTION PROFILE AND DISSOLUTION RATE OF MPT (EVA28/MPT/PEO7M, 55/40/5, w/w/w EVA28/MPT/PEO7M, 60/30/10, w/w/w and EVA28/MPT/PEO7M, 50/40/10, w/w/w)

Figure 4.4. shows that the amount of EVA28 used in the formulation plays a major role on the dissolution profile of the drug. The formulation with 50% of EVA28 registered a higher burst release and a higher dissolution rate. For 60% of EVA28 the drug release is only limited to 60% (24 hours). As EVA is a hydrophobic matrix, a higher amount of polymer reduces the water uptake, reducing the dissolution of drug in the water and its diffusion through the matrix. Although with 55% of EVA28, a better release was achieved (zero order kinetic), still it was never possible to reach 100% of drug release after 24 hour (85% released).

4.1.1.3. Influence of process 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 EVA28 (T_m EVA28 = ±74°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 2 phase system (crystalline drug embedded in a semi-crystalline polymer), were processed at a temperature below the melting point of the drug (T_m MPT = ±122°C).

A formulation containing the same amount of EVA28 and MPT (1:1, batch 0,1 and 2) was extruded at 80°C, 90°C and 100°C to evaluate the effect of temperature on the dissolution profile.

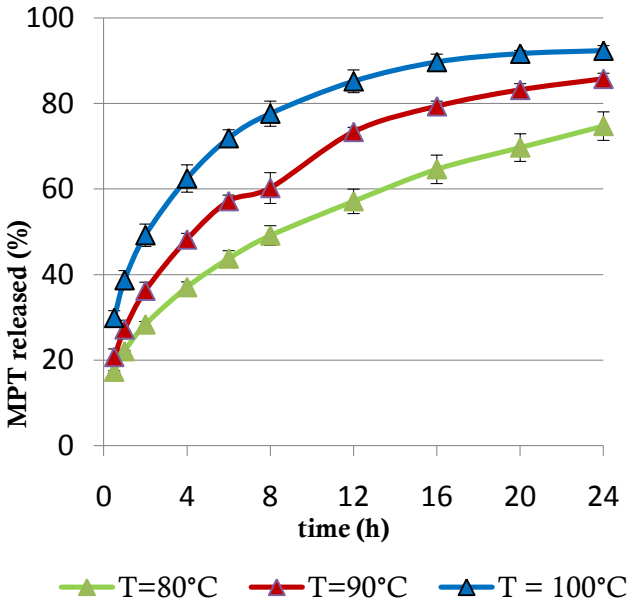


FIGURE 4.5.: INFLUENCE OF THE PROCESS TEMPERATURE ON THE DISSOLUTION PROFILE OF EVA 28/MPT, 50/50, w/w

We can see from figure 4.5. that the higher the process temperature is, the higher the release rate and the total amount of drug released after 24 hour are. At 80°C, the drug release is limited to 75% (after 24 hour of dissolution experiments). However, when the extrusion occurs at 100°C, a higher burst effect and the highest amount of drug released is registered. According to the results, it can be concluded that the optimal extrusion temperature is 90°C (lower burst release when compared with the matrices extruded at 100°C and a similar amount of drug is released after 24h).

4.1.2. Up-scaling

The study of EVA as a carrier for sustained released formulations by means of hot-melt extrusion has been performed with the help of a HAAKE MiniLab compounder. This lab-scale extruder has the advantage of being able to extrude small sample volumes being a powerful tool for quick analysis. Performing the same test with a standard lab extruder would take much longer. Therefore, a complete screen of different mixtures (EVA polymers, a highly water soluble drug and other additives), was performed on the MiniLAb extruder in order to find a good proportion (for a sustained-release formulation) between the different materials and extruder settings (temperature and screw speed).

As mentioned in the introduction, the *Laboratory scale batches* objective is to support the formulation and development (*www.emea.europa.eu*). Hence, the physicochemical results obtained from these batches help to evaluate and to define the critical product performance characteristics as the final goal is to obtain a process that is robust enough for routine commercial manufacturing processes (*Ruegger et al., 2007*).

For these reasons, it were chosen four formulations (manufactured in the MiniLab extruder): two including EVA40 (studied in previous work) (figure 4.6.) and two other ones produced with EVA28, that showed the most promising sustained-release formulations (maximum drug released after 12 and 24h) (table 4.1.).

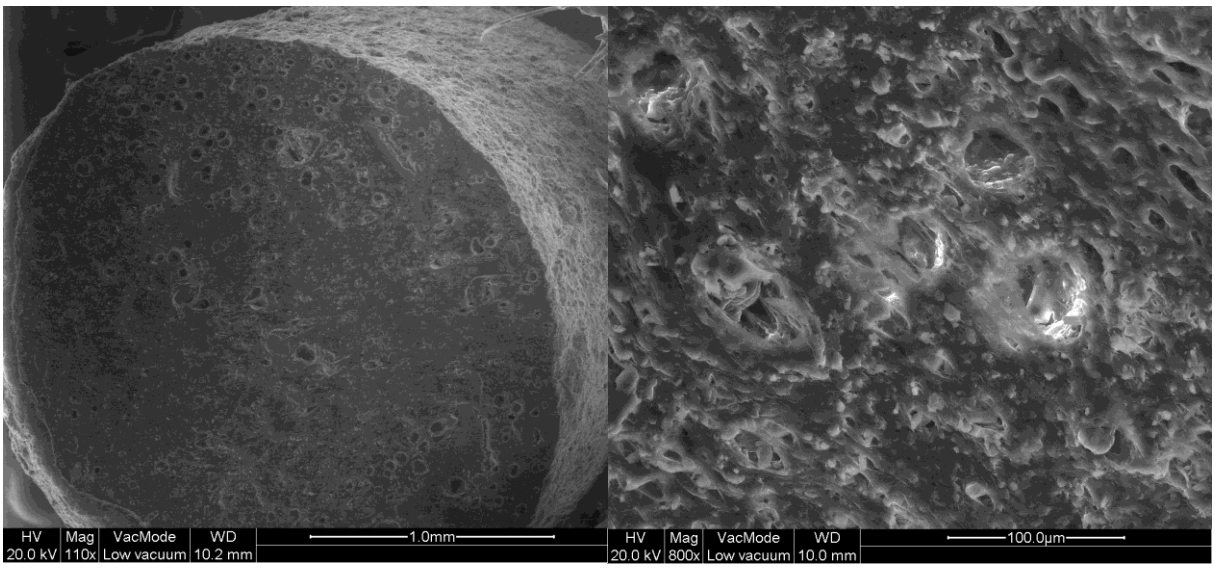
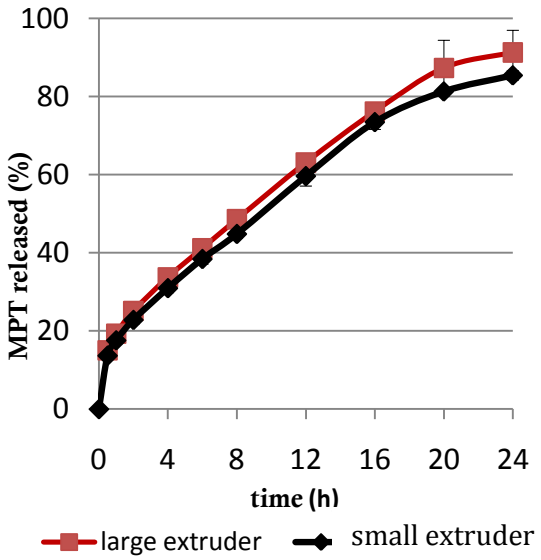


FIGURE 4.6. SEM IMAGE OF A MINI TABLET OF EVA40/MPT/PEO7M, 47,5/47,5/5, w/w/w, PRODUCED IN THE MINILAB EXTRUDER

TABLE 4.1. FORMULATIONS CHOSEN TO PRODUCE ON THE LARGER EXTRUDER

Formulation	(w/w/w)
EVA40/MPT/PEO7M	47,5/47,5/5
	42,5/42,5/15
EVA28/MPT/PEO7M	55/40/5
	50/40/10

These four batches were afterwards extruded on a large extruder and the dissolution profiles compared.



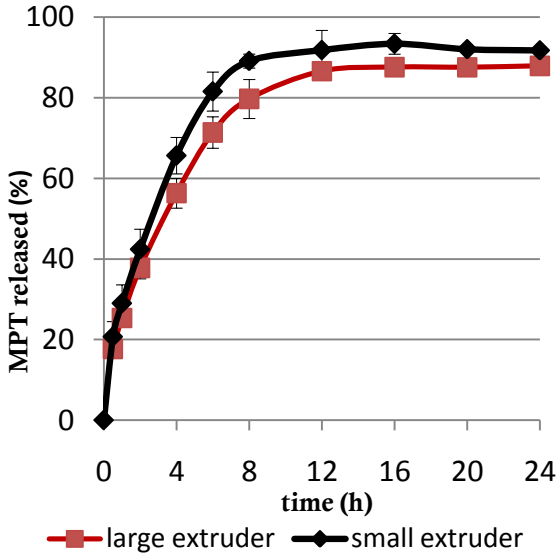
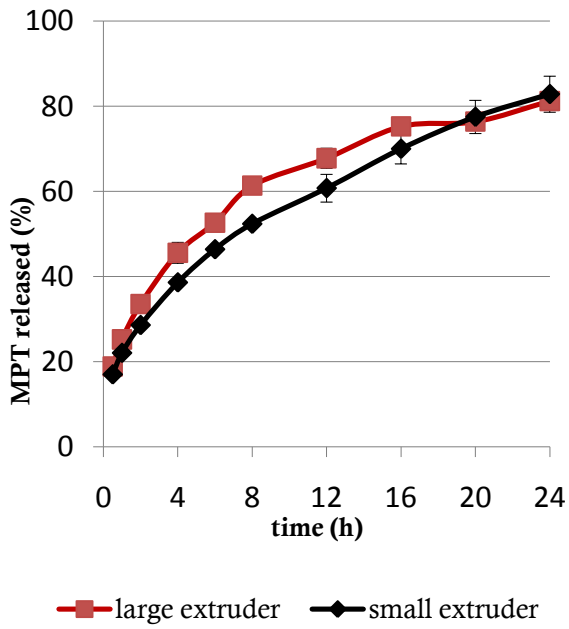


FIGURE 4.7.: EVA40/MPT/PEO7M, 47,5/47,5/5

FIGURE 4.8.: EVA40/MPT/PEO7M, 42,5/42,5/15



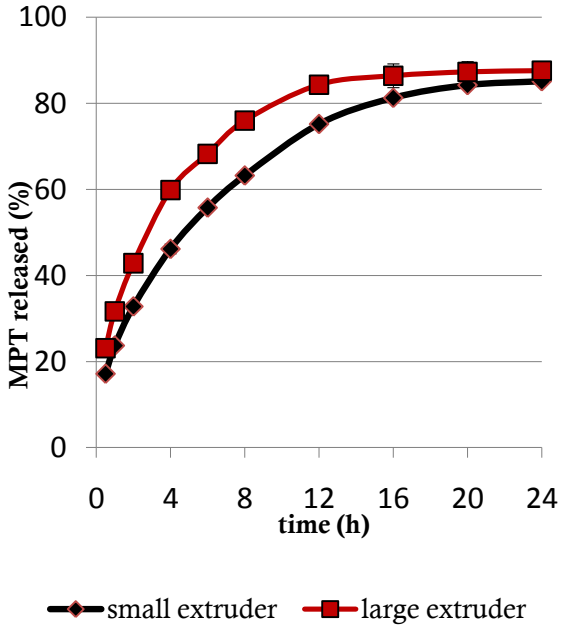


FIGURE 4.9.: EVA28/MPT/PEO7M, 55/40/5

FIGURE 4.10.: EVA28/MPT/PEO7M, 50/40/10

Comparing with the small extruder, these formulations were extruded at the same temperature of 90ºC, However to obtain better quality extrudates the temperature in the die was increased up to 100ºC. Furthermore, the screw speed had to be adjusted to 90rpm, whereas in the small extruder a 60rpm was sufficient to extrude the mixture. This increase is directly related with the fact that the materials were no longer manually fed. Instead, a gravimetric feeder was supplying the extruder with the premixed formulation. As it was necessary to find a good balance between the feeding rate and the screw speed (too much material fed would create accumulation of the powder in the first zone of the

extruder or too less would not allow a continuous extrusion) the feeding rate was adjusted at 0,450kg/h).

The four figures (4.7, 4.8, 4.9 and 4.10) show that the dissolution profiles of the formulations made on the large extruder, are similar with the dissolution profile of the formulations made on the small extruder. Nevertheless, the diameter of the die in the small extruder was 2mm, while on the larger extruder a 3mm diameter was used. Hence, no differences in terms of dissolution profile were registered. Further experiments will be performed with a 2mm diameter, to better understand these observations.

4.1.2.1. Reproducibility

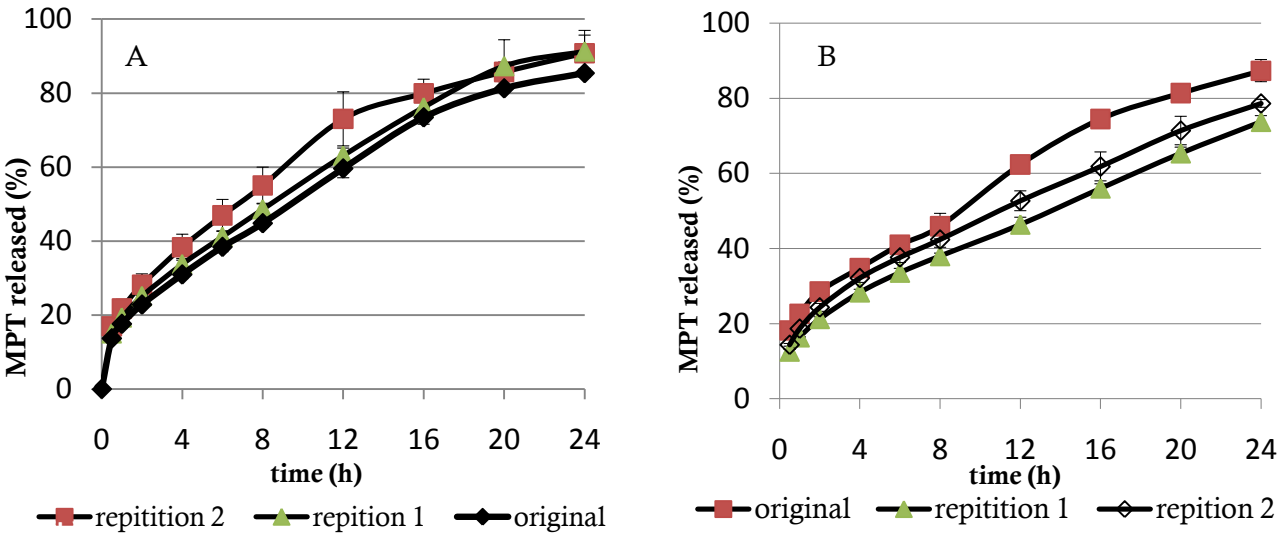


FIGURE 4.11.: REPRODUCIBILITY TEST ON SMALL EXTRUDER (A) AND LARGER EXTRUDER (B)

The reproducibility test with the small extruder (figure 4.11.(A)) shows that the dissolution tests performed at different time points, give the same result. So we can conclude that the results are reproducible. When compared with the larger extruder, figure 4.11.(B) shows similar results with an additional small increase in variability. Both extruders proved to produce reproducible batches, although further experiments should be performed with the larger extruder, (e. g. larger extrusion periods) to improve the homogeneity of the batches.

4.2. THERMAL ANALYSIS: DSC

4.2.1. Comparison large and small extruder

The thermal characteristics of EVA polymers, MPT and other additives were already investigated in previous studies. DSC results showed that EVA polymers contained 2 types of crystals with exception of EVA40 (where 3 types were identified) and a T_g ranging form -28 to -25°C. MPT was in the crystalline form with a melting peak (T_m) at 123ºC and PEO showed semicrystalline properties with a T_g around -67ºC and a melting peak at 65ºC. After extrusion at 90ºC the extrudates thermogram registered no shift on EVA T_g, and the T_m of the crystalline form of MPT was detected at the same temperature when compared with the pure form. Regarding EVA and PEO T_m a small shift was detected. However, due to the fact that the T_m signal of both components overlay and the amount of PEO was very low (5%) it is difficult to clearly understand in this thermograms if the shift is significant or not. Furthermore, when a material is mixed with other substances (e.g. PEO mixed with MPT or EVA) and not on the pure form, the melting peaks tend to be broader exhibiting a lower melt onset temperature.

Figure 4.12. shows that for the case of EVA28/MPT/PEO7M, 55/40/5, w/w/w, after extrusion with the larger extruder, no differences in the physical state of the materials were registered. The same conclusions were obtained for the other batches (graphics not shown).

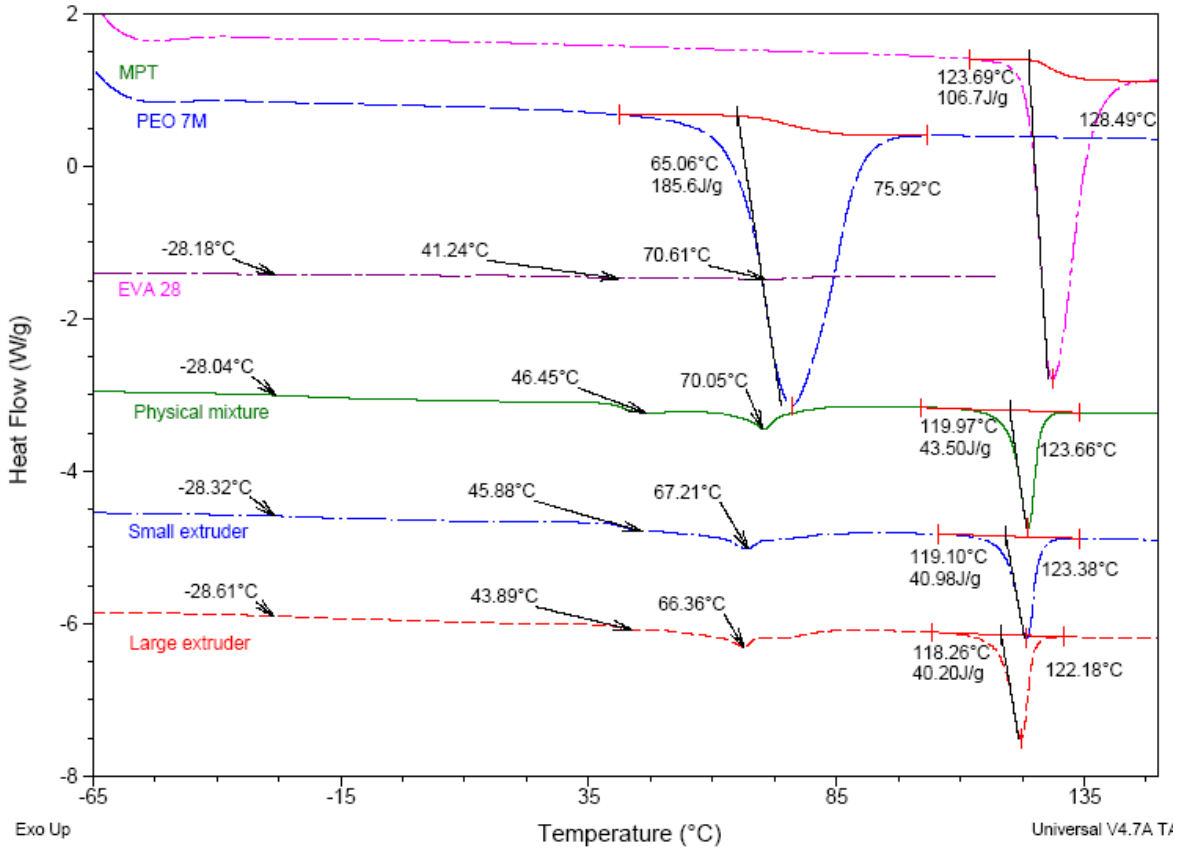


FIGURE 4.12.: THERMOGRAM OF EVA28/MPT/PEO7M, 55/40/5, w/w/w AS A PHYSICAL MIXTURE AND AS EXTRUDATE

4.2.2. Influence of the addition of surfactants to EVA polymers

In order to evaluate influence of the addition of surfactants on the polymer processability, in previous studies surfactants (Sorbitan sesquioleate (SS; HLB = 3.7) and Tween 80 (Polysorbate 80; HLB = 15)) 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 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 gave bad quality extrudates while for 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 bad processability.

This work 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 (data not shown in this thesis). The increase of release rate depended on the type of surfactant, concentration and VA content.

Therefore, in order to verify the possible plasticizing effect of SS and Tween 80 in the different types of EVA, further thermoanalysis (DSC) were performed to confirm these changes.

4.2.2.1. Addition of Tween 80

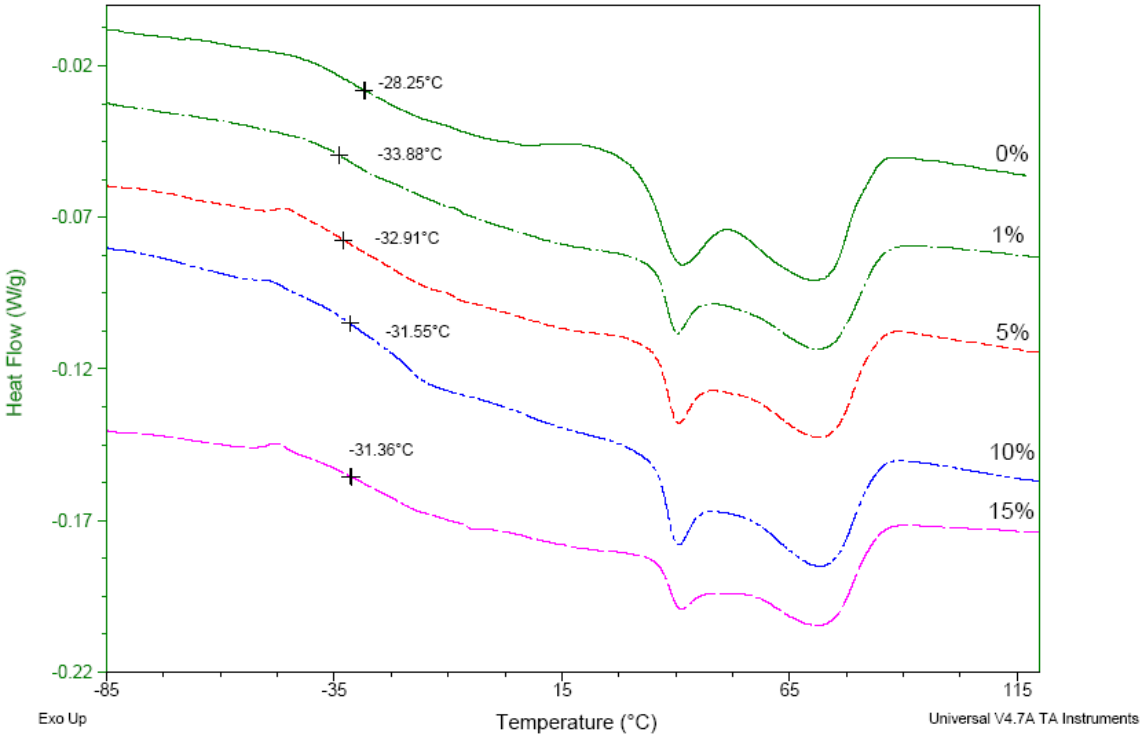
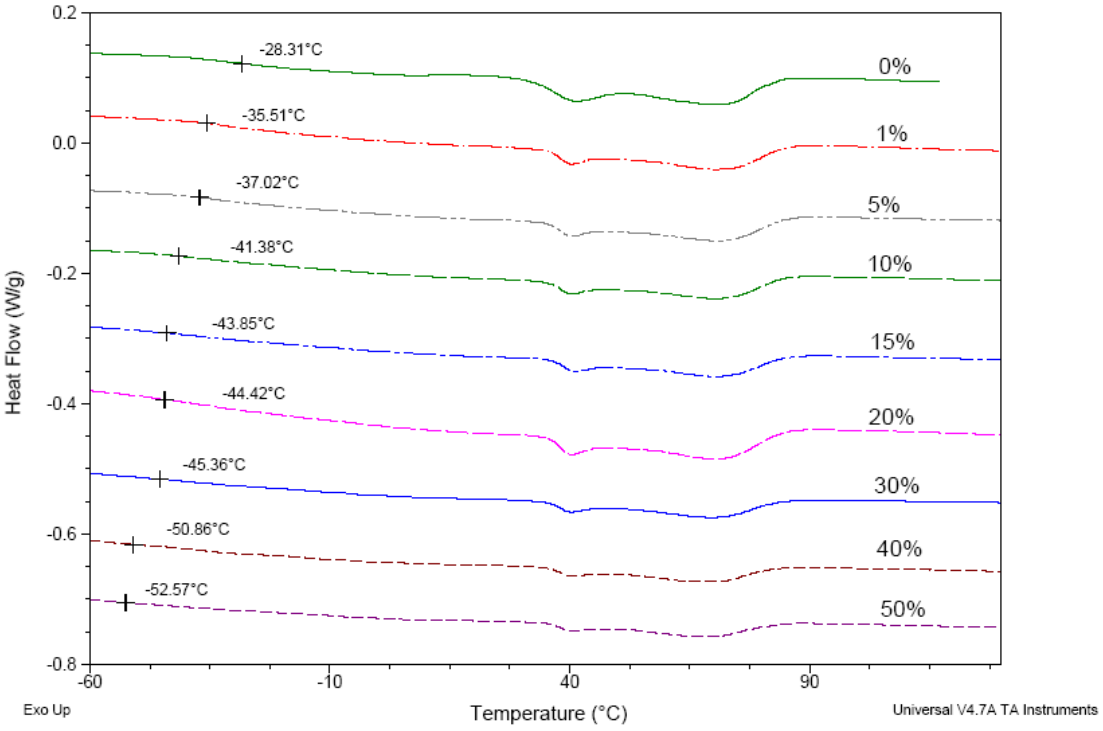


FIGURE 4.13.: THERMOGRAM OF EVA28 AND TWEEN80 IN DIFFERENT CONCENTRATIONS (0-15%)

As it can be seen on figure 4.13., being Tween80 a hydrophilic surfactant and EVA a hydrophobic polymer it was not detected a shift in T_g when it was added increasing concentrations of Tween 80. For EVA40 and EVA15 nothing happens either. It can be concluded that the addition of Tween80 does not plasticizes EVA polymers, not improving the processability of EVA polymers.

4.2.2.2. Addition of Sorbitan Sesquioleate



GRAPHIC 4.14.: THERMOGRAM OF EVA28 + SORBITAN SESQUIOLEATE IN DIFFERENT PERCENTAGES (0-50%)

Sorbitan Sesquioleate with an HLB value of 3 is a quite hydrophobic surfactant. When it was added an increasing amount of Sorbitan Sesquioleate to EVA28, it was registered a shift on EVA T_g to the left. This indicates that Sorbitan Sesquioleate has plasticized the polymer. For this reason it was easier to extrude the formulation with the surfactant. The same effect was seen for EVA40 and EVA15 when adding increasing amounts of Sorbitan Sesquioleate (graphics not shown).

These observations proved that the addition of SS to EVA polymers improved the processability, whereas Tween80 did not affect positively the extrusion. Tween80 increased in fact the residence time of the mixture in the extruder and as a consequence bad quality extrudates were obtained.

4.3. PROCESS MONITORING

4.3.1. Raman Spectroscopy

4.3.1.1. Analysis of in-line collected Raman spectra

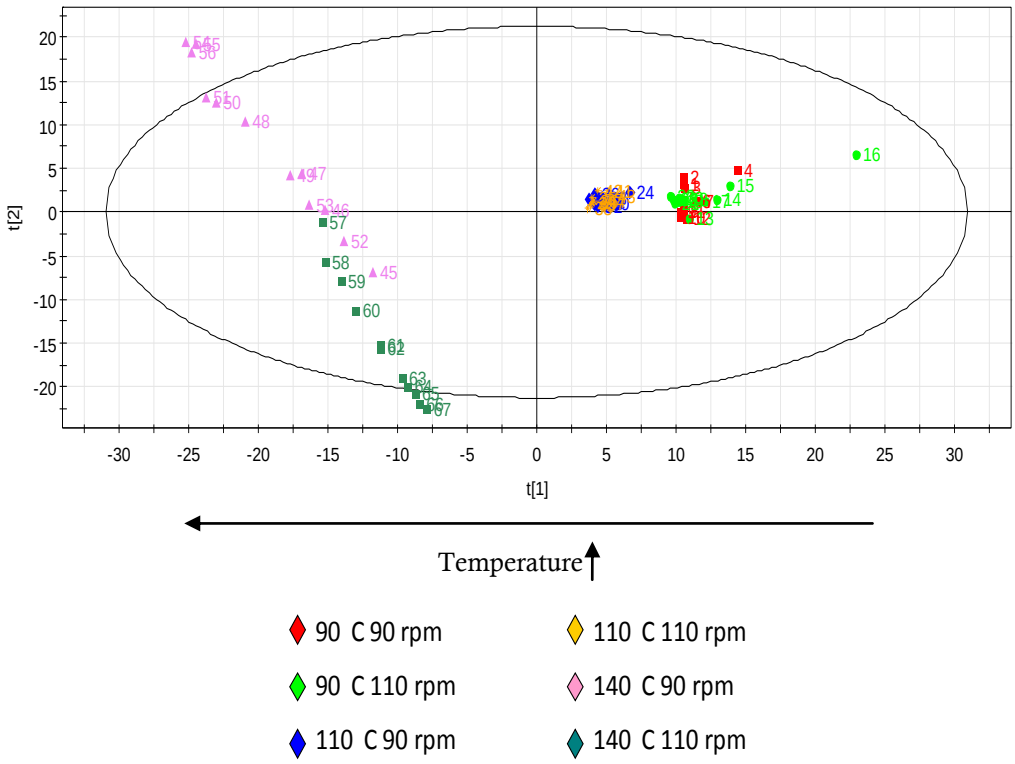


FIGURE 4.15.: PC 1 VERSUS PC 2 SCORES PLOT OF THE IN-LINE COLLECTED RAMAN SPECTRA COLLECTED AT DIFFERENT PROCESS CONDITIONS (TEMPERATURE: 90°C, 110°C and 140°C; SCREW SPEED: 90 rpm and 110 rpm)

Figure 4.15. shows the principal component (PC) 1 versus PC 2 scores plot obtained after principal component analysis of the in-line collected Raman spectra of EVA40/MPT 50/50 at the different examined temperatures (90, 110 and 140 °C) and screw speed conditions (90 and 110 rpm). Each dot in the scores plot represents one in-line collected Raman spectrum. The spectra of the extrudates produced at 90°C and at 110°C are clearly clustered, while the spectra collected at 140°C are more spread. PC 1 represents the variation in the Raman spectra (see 4.3.1.2.) due to the applied process temperature. PC 2 represents the variation in the Raman spectra (see 4.3.1.2.) detected by the Raman probe. At 140°C, the polymer-drug mixtures are totally melted and just drop out of the barrel instead of coming out in a continuous and uniform way (at 90 and 110 °C), resulting in score variation along PC 2 for the Raman spectra collected at 140 °C.

4.3.1.2. Influence of the process temperature and the screw speed on the in-line collected Raman spectra.

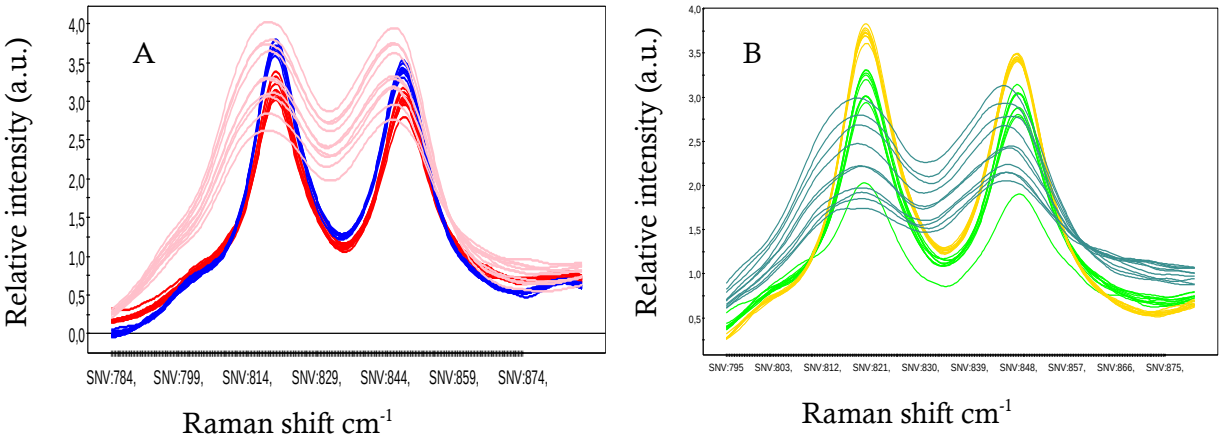


FIGURE 4.16.: IN-LINE RAMAN SPECTRA (785 – 875 cm^{-1}) COLLECTED DURING EXTRUSION AT 90 RPM (A) AND 110 RPM (B)

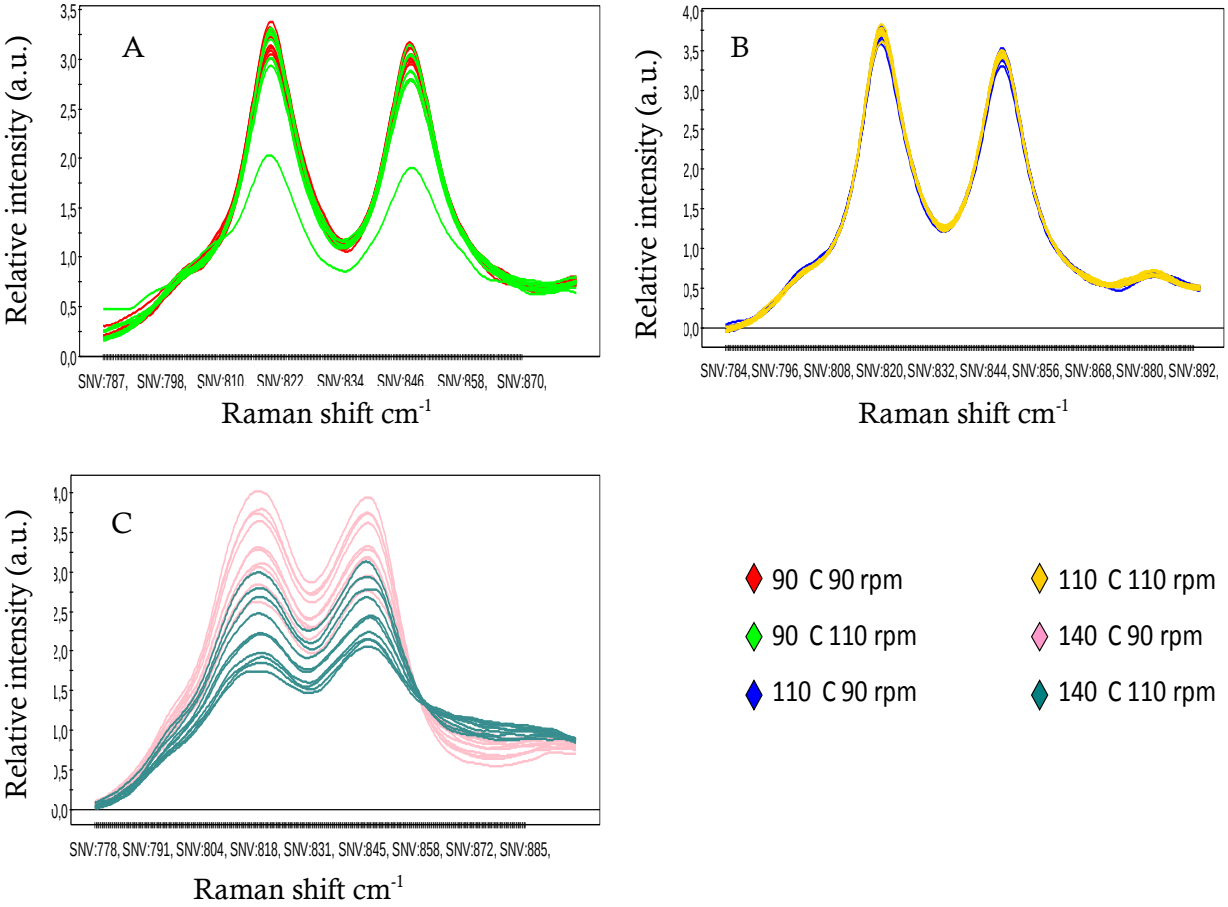


FIGURE 4.17.: IN-LINE RAMAN SPECTRA (785 – 875 cm^{-1}) COLLECTED DURING EXTRUSION AT 90°C (A), 110°C (B) AND 140°C (C)

Figure 4.17 C shows that extrudates (♦ and ♦) produced at 140° (at different screw speeds, 90 and 110rpm, respectively) have broad and flattened bands (first peak: 810-835 cm^{-1} to 804-832 cm^{-1}), indicating amorphicity. When produced at lower temperatures (90 and 110°C), the extrudates show sharp bands, indicating crystallinity. Figure 4.16. shows that the screw speed has an influence on the crystallinity: a higher screw speed (B) results in more flattened bands. Looking at extrudate ♦ and ♦, a larger variation can be seen in the spectra collected during production at 110 rpm (♦) compared to 90 rpm (♦). This could be due to the fact that a higher screw speed reveals more shear stress and this conducts more heat through the barrel, the drug is melted more and less particles stay in the crystalline form. We can see that the spectra from the extrudates produced at 140°C are higher in intensity. This is because of the applied temperature. The intensity of Raman peaks in spectra is temperature dependent.

4.3.1.3. Polymer and drug interactions

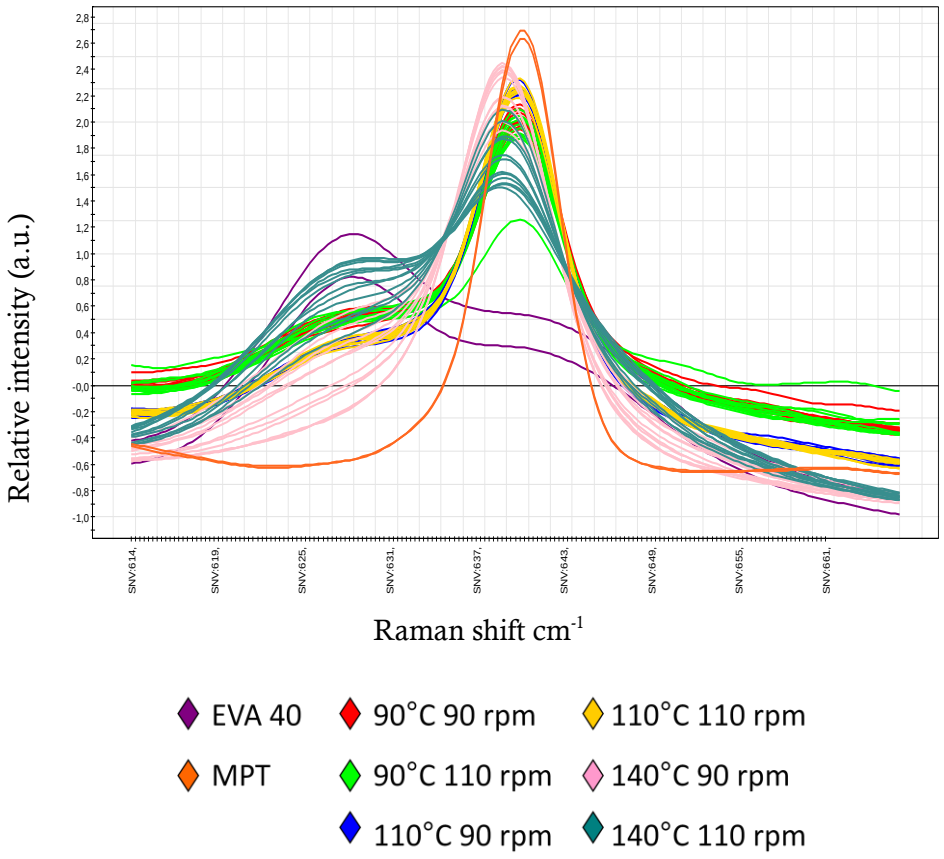


FIGURE 4.18.: IN-LINE RAMAN SPECTRA OF EVA40/MPT, 50/50, w/w AND PURE MPT (614-665 cm^{-1}) COLLECTED AT DIFFERENT TEMPERATURES (90, 110 AND 140°C) AND DIFFERENT SCREW SPEEDS (90 AND 110 RPM) DURING EXTRUSION

Figure 4.18. shows a peak shift from 641 cm^{-1} (crystalline) to 639 cm^{-1} (amorphous) between the pure spectrum of MPT and the spectrum of the EVA40/MPT (1:1). This finding indicates a possible interaction between MPT and EVA40. As the shift is small the possible interactions is very limited. The chemical structure of polymer and drug show a carbonyl group and an amino group, respectively (figure 4.19.). The 2 chemical groups are responsible for the possible interaction between the drug and the polymer.

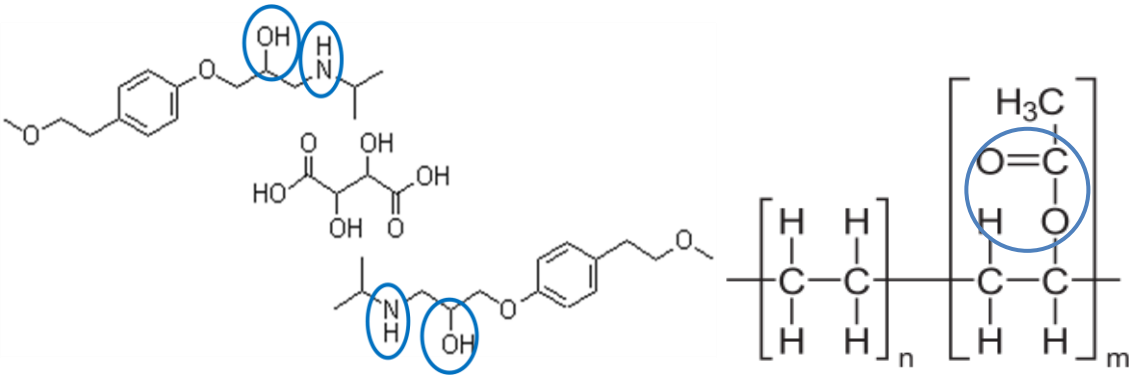


FIGURE 4.19.: REACTIVE GROUPS, THE AMINOGROUP OF MPT (A) REACTS WITH THE CARBONYLGROUP OF EVA 40 (B) (*www.sigmaaldrich.com*)

5. CONCLUSION

In the first part of this thesis, it was investigated the influence of the addition of different amounts of PEO and distinct molecular weights (100K, 1M and 7M) to EVA28. The results with 5% PEO and equal amounts of EVA and MPT (1:1) showed that a zero-order release kinetic was achieved. However, the maximum drug released after 24h was limited to 85-90%. It was never reached 100% of drug released. This indicates that a small part of drug is entrapped in the inner part of the mini tablet not being able to be released.

Subsequently the influence of the molecular weight of PEO was verified. The results indicated that PEO with a higher molecular weight (7M) when compared with 100K tends to decrease the drug release rate during the first 12h of the experiment. It can be concluded that the high viscosity of the polymer delays the contact of the drug with the dissolution medium. On the other hand the amount of EVA28 in the formulation proved to be a main factor to modulate the release of the model drug.

To complete a previous study of the influence of the addition of surfactants to EVA matrices, a DSC study was performed. Sorbitan sesquioleate proved to have a plasticizer effect on EVA, whereas tween80 did not affect the T_g of the polymer. It can be concluded that the addition of sorbitan sesquioleate has a favorable effect on the processability of the polymer, confirming previous observations.

It was also studied the drug release profiles, reproducibility and process parameters during up-scaling. In the end thermal analysis was performed in order to evaluate the physical state of the different materials. Thermal analysis of the pure components, the physical mixture and the extrudates produced on the small extruder and on the large extruder, were compared. The extrudates produced on the larger extruder showed no differences when compared with the ones manufactured on the small extruder and the physical mixture. There were no changes in glass transition temperature, melting temperature and heat of fusion. Therefore, the materials formed a stable solid crystalline suspension. Dissolution results showed that the release profiles of extrudates produced on the larger extruder are similar to those of the extrudates produced at the small extruder. As it were used dies with different diameters (2mm in the MiniLab extruder and 3mm on the larger extruder), further experiments should be conducted in order to investigate the

influence of the extrudates diameter on the release profile. Reproducibility testing showed that extrudates produced on the small and large extruder are reproducible.

It can be concluded that the scale-up of the process had no influence on the properties of the extrudates. However, some of the extruder settings needed to be adapted, mainly the screw speed (from 60 to 90 rpm) and the feeding rate (from manually to 0,450 kg/h).

In-line measurements with Raman spectroscopy seem to indicate that there is an interaction happening between EVA and MPT. This possible reaction of the aminogroups of MPT with the carbonylgroups of EVA, resulted in a peak shift in the Raman spectra. The spectra also showed clearly whether the drug was in the crystalline or amorphous state when the temperature or the screw speed was modified. Raman spectroscopy in-line proved to be a good tool to monitor the extrusion process.

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