Manufacturing of matrix tablets by combining countercharged poly(meth)acrylate polymers to provide sustained release of highly soluble drugs

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Table of contents

Abbreviations

A	cross sectional area of the polymer film [cm^2]
c	concentration of the drug [mol/cm^3]
c_0	total concentration of the drug in the matrix [mol/cm^3]
c_s	saturation concentration of the drug [mol/cm^3]
CAP	captopril
d'	characteristic particle size [mm]
D	diffusion coefficient of the drug in the polymer [cm^2/s]
DAB	Deutsches Arzneibuch
De	Deborah's number
DIP	diprophylline
DILT	diltiazem HCl
DS	dry substance
DSC	differential scanning calorimetry
E	EUDRAGIT® E PO
EL	EUDRAGIT® E PO:EUDRAGIT® L 100-55 (1:4)
e.g.	exempli gratia
FS	EUDRAGIT® FS 30 D
G*	complex shear modulus [Pa]
h	height of the tablet curvature [mm]
H	height of the tablet band [mm]
HPC	hydroxypropyl cellulose
HPLC	high performance liquid chromatography
HPMC	hydroxypropyl methyl-cellulose
IPEC	interpolyelectrolyte complex
J	molar flux of drug [mol/cm^2s]
k	dissolution velocity constant [l/s]
L	length of the die from capillary viscosimeter [mm]
LOD	loss on drying
M_t	amount of drug released at a certain time t [kg]
M_∞	total amount of drug released [kg]
MC	methyl cellulose
^{n}	diffusional exponent
n	number of experiments, sample size
Na CMC	sodium carboxymethyl cellulose
^{13}C-NMR	solid state nuclear magnetic resonance carbon 13
Ph. Eur.	European Pharmacopoeia
Q	amount of drug released at a time t [mol/cm^2]
r	radius [mm]
R^2	coefficient of determination
RS	EUDRAGIT® RS 30 D
SD	standard deviation
SEM	scanning electron microscopy
SF	standard formulation
SLS	sodium lauryl sulphate
S_w	"Swelling interface" number
t	time [s]
T_g	glass transition temperature [ºC]
TEC	triethyl citrate
TGA	thermogravimetry analysis
USP	United States Pharmacopeia

UV	ultraviolet
z	length diffusion path [cm]
α	angle [º]
δ	sample thickness [cm]
ΔP	difference in pressure [Pa]
ε	porosity of the matrix
η	dynamic viscosity [Pa·s]
η^*	complex shear viscosity [Pa·s]
ν	velocity of the swelling interface [cm/s]
θ	diffusion time [s]
λ	relaxation time [s]
ρ_{tapped}	tapped density [g/ml]
ρ_{bulk}	bulk density [g/ml]
τ	tortuosity of the pores
Φ	laminar stationary flow [mm^3/s]
ω	angular frequency of oscillation [s^{-1}]

1 Introduction

1.1 Tablet: definition and types

According to the USP, tablets are defined as solid dosage forms containing medicinal substances with or without suitable diluents (USP 31 NF 26 2008). Within this definition, tablets can be classified in different types depending on the formulation and the manufacturing process (compressed, molded, coated, dragée, lozenge, chewable, buccal, sublingual, effervescent, etc…). The most commonly used tablets are compressed tablets. In this case, the tablets are prepared by the application of high pressure to a powder or granules using steel punches and dies.

Tablets can be also classified in three major groups depending on their release behavior: immediate release, where the drug is immediately released after ingestion; delayed-release, where the drug is released after a lag time to avoid a possible destruction or inactivation of the drug in the gastric fluid as well as irritation of the gastric mucosa. The third group corresponds to the sustained release tablets, where the drug is released over an extended period of time. The present study will focus on sustained release tablets.

Sustained release tablets are divided into multiparticle and monolithic tablets (Bauer et al. 2006). In multiparticle tablets several units (crystals, particles, granules, pellets) are embedded maintaining their physical and chemical properties. Multiparticle tablets disintegrate in contact with biological fluids releasing the units with intact properties. The monolithic tablets can either be coated with an inert polymer that releases the drug through diffusion or be matrix tablets, where the drug is embedded in a sponge-like structure and released through different mechanisms (Ritschel et al. 2002).

The release of a drug through a polymer can usually be described by Fick's laws of diffusion.

Fick's first law, is shown in equation (1.1):

$$J_1 = -D_{12}\frac{\partial c}{\partial z} \qquad (1.1)$$

J_1 = *molar flux of drug [mol/cm^{2}s]*

D_{12} = *diffusion coefficient of the drug in the polymer [cm^2/s]*

∂c = *concentration of the drug [mol/cm^3]*

∂z = *length diffusion path [cm]*

This equation is normally used for the description of reservoir-type, diffusion-controlled systems at steady-state diffusion and release. To determine the variation of the drug concentration in the medium with time, Fick's second law is used (equation 1.2):

$$\frac{\partial c_1}{\partial t} = D_{12} \frac{\partial^2 c_1}{\partial z^2} \qquad (1.2)$$

∂c = *concentration of the drug [mol/cm^3]*

∂t = *time [s]*

D_{12} = *diffusion coefficient of the drug in the polymer [cm^2/s]*

∂z = *length diffusion path [cm]*

A simple equation (equation 1.3) was presented by Ritger and Peppas (Ritger et al. 1987) to describe the release behavior from controlled release polymeric devices. The exponent *n* represents the diffusional exponent and depending on its value defines one or other release mechanism.

$$\frac{M_t}{M_\infty} = kt^n \qquad (1.3)$$

M_t = *amount of drug released at a certain time t [kg]*

M_∞ = *total amount of drug released [kg]*

k = *dissolution velocity constant [1/s]*

t = *time [s]*

n = *diffusional exponent*

The values for the diffusional exponent differ depending on the geometry of the system (Peppas 1985; Ritger et al. 1987; Lindner et al. 1996) as shown below (Table 1)

Table 1 Diffusional exponent and mechanism of diffusional release from various non-swellable controlled release systems

Diffusional exponent *n*			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.50	0.45	0.43	Fickian diffusion
0.50<n<1.00	0.45<n<0.89	0.43<n<0.85	Anomalous (non Fickian) transport
1.00	0.89	0.85	Zero-order release: erosion or relaxation control

There are three main mechanisms to classify controlled release systems (Langer et al. 1983). These mechanisms are shown in Table 2. The mechanisms written in bold letters are those directly related with this study.

Table 2 Classification of controlled release systems by mechanisms

Diffusion controlled
Reservoirs (membranes)
Matrices (monoliths)
Chemically controlled
Erosion
Pendant chain
Solvent activated
Osmotic pressure
Swelling

1.1.1 Diffusion controlled: reservoirs (membranes)

The membrane diffusion controlled systems are the most widely used. The diffusion of the drug takes place through the thin layer that separates the core of the drug from the media. This layer remains intact along the complete gastro intestinal (GI) tract and controls the release by diffusion of the drug through the layer (Bauer 1998).

1.1.2 Diffusion controlled: matrices (monoliths)

The matrices can be classified into systems where the drug is dissolved, into systems where the drug is dispersed or into porous matrix systems.

In the case where the drug is dissolved in the polymer, the drug release is controlled by the solubility of the drug in the polymer. The controlled release mechanism can be explained by Fick's second diffusion law (equation 1.2).

When the drug is dispersed, the release is controlled by the dissolution of the drug (Narasimhan 2000). The kinetic release can be explained with the equation (1.4):

$$Q = A\sqrt{Dc_s \cdot (2c_0 - c_s) \cdot t} \qquad (1.4)$$

Q = *amount of drug released at a certain time t [mol/cm^2]*

A = *cross sectional area of the polymer film [cm^2]*

D = *diffusion coefficient of the drug in the polymer [cm^2/s]*

c_0 = *total concentration of the drug in the matrix [mol/cm^3]*

c_s = *saturation concentration of the drug [mol/cm^3]*

t = *time [s]*

The same equation can be used to explain the release of the drug through the pores of a matrix system, considering the porosity and tortuosity of the structure, as described in equation (1.5):

$$Q = \sqrt{D\frac{\varepsilon}{\tau}(2c_0 - \varepsilon \cdot c_s)c_s \cdot t} \qquad (1.5)$$

Q = *amount of drug released at a certain time t [mol/cm^2]*

D = *diffusion coefficient of the drug in the liquid in the pores [cm^2/s]*

ε = *porosity of the matrix*

τ = *tortuosity from the pores*

c_0 = *total concentration of the drug in the matrix [mol/cm^3]*

c_s = *saturation concentration of the drug [mol/cm^3]*

t = *time [s]*

1.1.3 Chemically controlled: erosion

The erosion type of controlled release system can be used in both reservoirs and matrices. The release from the reservoirs is dependent upon the permeability and thickness of the layer. These variables will define the release.

The release from matrices is controlled by a combination of diffusion and erosion. The erosion can be homogeneous or heterogeneous. When the erosion is taking place in the entire matrix structure the erosion is homogeneous; when the erosion starts on the surface of the polymer matrix it is heterogeneous.

1.1.4 Chemically controlled: pendant chain

This kind of controlled release is not as extensively used as are the cases described before. The drug is chemically bonded to the polymer and is released through an enzymatic or hydrolytic reaction that separates the drug from the polymer structure.

1.1.5 Solvent activated: osmotic pressure

The release of the drug is controlled by the tablet structure (OROS= Osmotic Release Oral System). The tablet is made of a drug containing core where the drug is embedded, and a semi permeable membrane with an orifice. The solvent diffuses through the membrane, the volume of medium dissolves the drug and an equal volume of dissolved drug is released through the orifice (Conley 2006).

1.1.6 Solvent activated: swelling

This controlled release mechanism takes place in polymeric systems where the drug is dissolved or dispersed in the polymer. The moment the system comes in contact with the medium, the polymer swells, lowering its glass transition temperature and the polymer allows the drug to dissolve. It is possible to recognize two main interfaces. The first separates the glassy state from the rubbery state (swelling interface) moving inwards to the center of the core, and the other separates the rubbery state from the medium (polymer interface) moving outwards. In the last case the polymer normally dissolves (Langer et al. 1983).

Between the glassy and the rubbery state a macromolecular relaxation takes place. This relaxation affects the drug diffusion through the polymer, giving Fickian or non-Fickian diffusion (Colombo 1993).

The transport of the drug through the polymer can be controlled by the macromolecular relaxation or by the diffusion of the drug through the rubbery polymer. The Deborah number, described in the equation (1.6), is used to characterize this transport:

$$De = \frac{\lambda}{\theta} \qquad (1.6)$$

De =*Deborah number*

λ = *Relaxation time [s]*

θ = *Diffusion time [s]*

When the Deborah number is greater than 1, the transport is completely relaxation-controlled. A number lower than 1 means the transport is completely diffusion-controlled. When the value is close to 1 an anomalous diffusion behavior takes place, because the relaxation and diffusion time are similar (Vrentas et al. 1975).

To determine if the release of the drug follows zero-order release or Fickian diffusion, the swelling interface number, described in the equation (1.7), is used:

$$Sw = \frac{v\delta(t)}{D} \qquad (1.7)$$

Sw = *"Swelling interface" number*

v = *velocity of the swelling interface [cm/s]*

δ = *sample thickness [cm]*

t = *time [s]*

D = *diffusion coefficient of the drug in the polymer [cm^2/s]*

When the *Sw* is lower than 1, a zero-order release can be expected. A *Sw* greater than 1 means Fickian diffusion.

This overview provides necessary knowledge of the different possible release mechanisms required to discuss the topic of this investigation, manufacturing of matrix tablets to provide

sustained release of highly soluble by combining countercharged poly(meth)acrylic polymers. The next point to discuss is the variety of excipients that can be used to build a matrix.

1.2 Excipients used to build a matrix

Matrix formulations are commonly chosen for controlled release due to the several advantages they offer. The manufacturing of these tablets does not require special equipment. In several cases, the drug release velocity depends on the matrix structure and not on other factors like intestine motility, electrolyte concentration of the medium or pH. Compared to coated tablets, matrix tablets are more robust. Coated tablets are also more likely to lead to a dose dumping effect if the film is not properly formed or is physically damaged post manufacture (Ritschel et al. 2002).

The excipients used to build a matrix can be classified by their chemical structure and by their properties as hydrophilic, inert, lipidic, biodegradable and resin matrices (Gandhi et al. 1999).

1.2.1 Hydrophilic (Cellulose ethers and esters)

These excipients are the most widely option to use for matrix tablets to provide sustained release. These polymers are semisynthetic products obtained by alkylation of cellulose. The differences between the various types reside in the different degree of substitution and degree of polymerization varying also the total molecular weight (Figure 1), and therefore their release characteristics. The release is based on swelling process leading to a gel layer formation (Vueba et al. 2005).

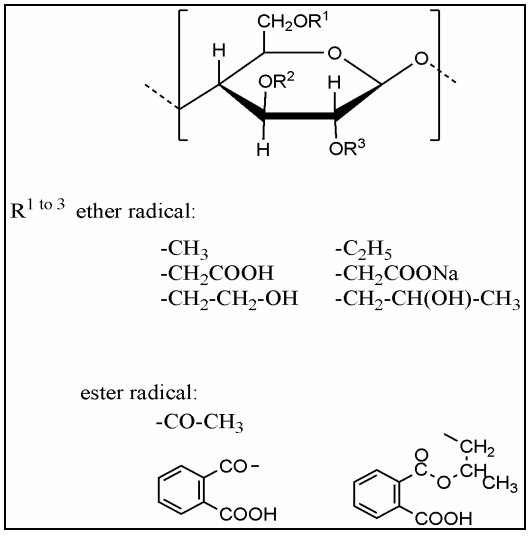


Figure 1 Structures of cellulose esters and ethers

1.2.2 Inert poly(meth)acrylates polymers

Inert poly(meth)acrylates are pH independent insoluble polymers. These kind of polymers are normally recommended as matrix formers among the poly(meth)acrylates. pH-dependent poly(meth)acrylates can also be used as matrix formers (Gallardo 2007). An example of such pH-dependent polymers are anionic poly(meth)acrylates with a solubility above pH= 6 for EUDRAGIT® L 100 and above pH=7 for EUDRAGIT® S 100 and EUDRAGIT® FS 30 D.

These polymers are synthesized by radical polymerization. The polymers differ in the monomers chosen for their synthesis. Poly(meth)acrylates can be classified based on their active groups. These active groups can be cationic, anionic or neutral, as shown below (Figure 2).

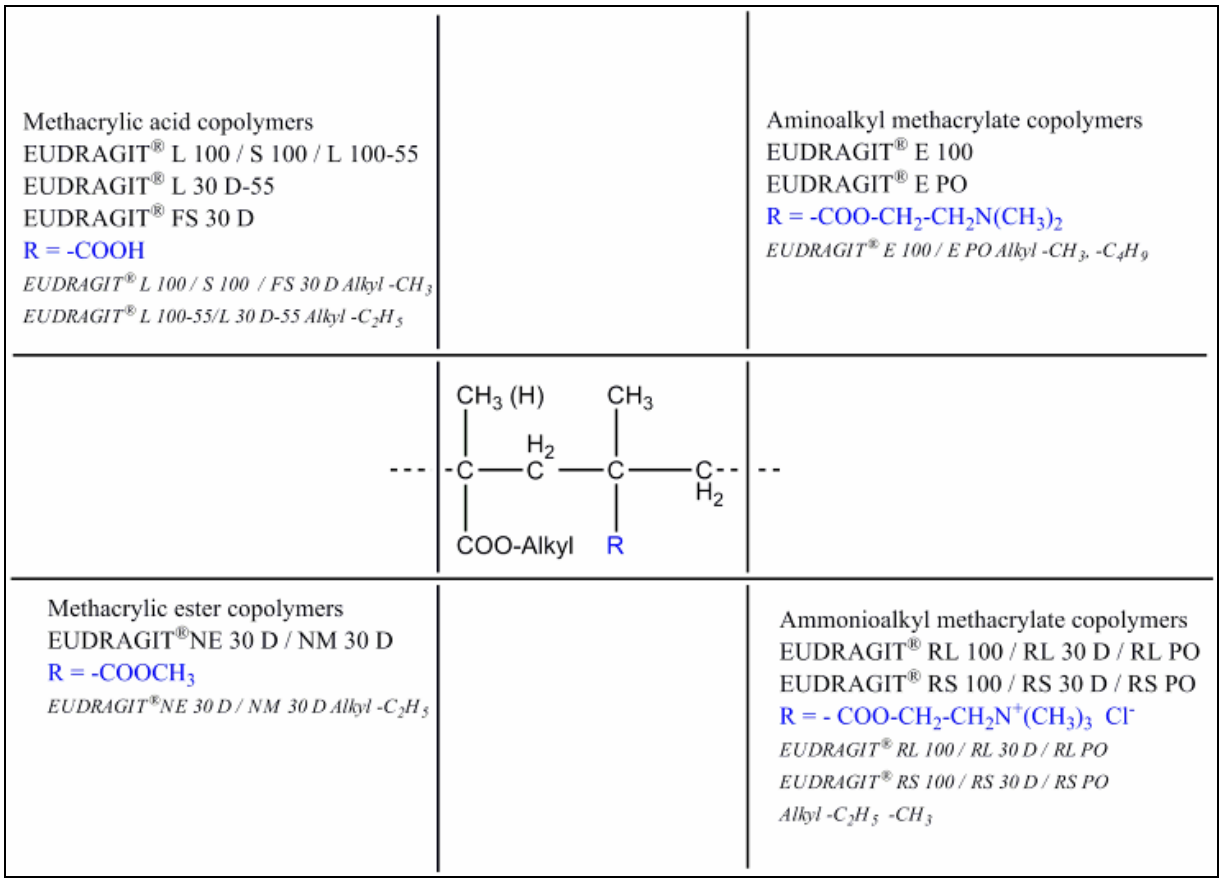


Figure 2 Structure of poly(meth)acrylates

The response of these polymers to different pH values differs depending on the monomers that constitute the polymer. The different behaviors are described in Table 3.

Table 3 Solubility values of poly(meth)acrylates

Group	Behavior
Methacrylic acid copolymers	Gastroresistant or enteric. Soluble above pH 5.5, pH 6.0 or pH 7.0
Methacrylic ester copolymers	Insoluble and permeable
Aminoalkyl methacrylate copolymers	Gastrosoluble. Soluble below pH 5.0 and permeable above
Ammonioalkyl methacrylate copolymers	Insoluble. Variable permeability

Inert matrices release the drug from the matrix structure by diffusion through pores. When anionic pH-dependent poly(meth)acrylates are chosen as matrix formers, the release is the result of a combination of diffusion through the pores and erosion of the matrix structure (Gallardo 2007).

1.2.3 Lipidic

Waxes and lipids are non swellable lipophilic excipients that can be used as matrix formers (Özyazici et al. 2006). Their hydrophobic character makes them suitable for sustained release applications. They have advantages such as inertness against other materials, ease of manufacturing with high reproducibility and low production costs. The physical characteristics of these lipids or waxes depend upon their structure (length of the chain, number of double bonds) changing their fusion point or their capability to be digested.

1.2.4 Biodegradable

These polymers are based on polylactic and polyglycolic acids. Their main advantage is their biodegradation which can take up to over a year. There are different routes of synthesis such as step growth polymerization of lactic acid enantiomers and/or glycolic acid, postcondensation of macromonomers, and ring opening polymerization of 1,4-dioxane-2,5-diones. The release mechanism is based on a combination of diffusion, chemical reaction and erosion of the structure (Brannon-Peppas 2000).

1.2.5 Resin matrices

Resin matrices provide a sustained release by building a chemical bond with the drug. Ion exchange resins are crosslinked, water insoluble polymers carrying ionizable functional groups. These functional groups can react with cationic or anionic drugs.

Combinations of HPMC with ion exchange resins (sodium polystyrene sulfonate, Amberlite® IRP 69 and cholestyramine resin, Duolite® ATP 143) were manufactured using anionic and cationic drugs (Sriwongjanya et al. 1998). A stronger sustained release was observed when HPMC was used in combination with ion exchange resins than with the resins alone, due to the interaction between the drug and resin. The release was extremely low when the tablets were tested only in demineralised water because of the absence of ions that could replace the drug.

1.3 Combination of polymers for sustained release matrix formulations

The combination of polymers to manufacture matrix tablets has been a research topic for decades. The purpose of the combinations was to modulate the drug release. The combination of polymers can show additive or synergistic effects on the release retardation (Varma 2004).

The classification of these combinations has been structured in two main groups: combination of cellulose-based polymers and combinations of poly(meth)acrylates.

1.3.1 Combination with cellulose-based polymers

The release of drug from hydrophilic matrices depends on three different factors, as described in Figure 3. It shows the eroding front of the tablet (circles), swelling front (squares) and the diffusion front (triangles) (Colombo et al. 1999; Colombo et al. 2000).

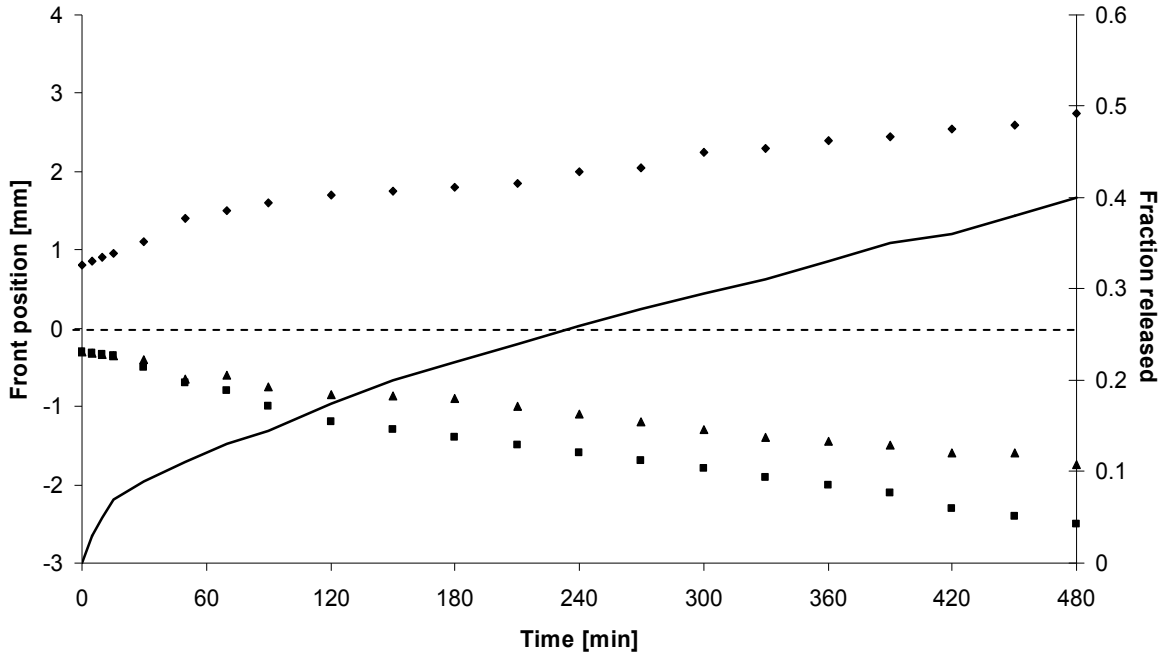


Figure 3 Representation of the three different front, erosion (circles), swelling (squares) and diffusion (triangles) compared with the release of inbuflomedil pyridoxalphosphate tablets in a hydroxypropyl methyl cellulose matrix (Colombo et al. 1999; Colombo et al. 2000)

Considering these factors, the delivery kinetics depend on the drug gradient in the gel layer, and therefore the drug concentration and thickness of the gel layer control the drug flux. Most studies focus on controlling the thickness of the gel layer to adapt the release. Combination of polymers has shown an influence on this aspect.

The viscosity of a matrix tablet made from a combination of non ionic and ionic cellulose based polymers is influenced by different factors (Walker et al. 1982). It is possible to detect a synergism in the viscosity values of ionic and non ionic polymer combinations. This synergism is the result of a cross-linking promoted by the carboxyl group from Na CMC with hydrogen bonding. The degree of this synergism depends on several properties from the non ionic polymers, such as degree of substitution and the alkyl substituent content, the nature of the alkyl substituent and the chain length.

Ibuprofen matrix tablets combining HPMC K4M, MC, Na CMC and HPC were prepared to investigate their influence on the release and on the swelling behavior (Nerurkar et al. 2005). All the polymers where combined in different ratios with HPMC K4M. The combinations of HPMC K4M with MC or HPC resulted in burst effects, which could be explained by the degree of substitution of these two polymers. HPC and MC are less hydrophilic than HPMC

K4M. This difference reduces the water absorption and therefore reduces the swelling front. On the other hand, when the polymer combined was anionic, Na CMC, the reaction with the non ionic HPMC K4M led to a synergism in the viscosity. The formation of hydrogen bonds between Na CMC and the hydroxyl groups from HPMC K4M increases the viscosity and thus stabilizes the gel layer providing a stronger sustained release.

Several analytical techniques can be used to obtain more information about possible interaction among different polymers. An example is the use of differential scanning calorimetry. The tests were performed on ibuprofen matrix tablets with HPMC K100M, HPC, MC25 in different combinations to detect possible interaction between drug and polymers (Vueba et al. 2006). Ternary combination of ibuprofen/MC25/HPMC K100M and ibuprofen/HPC/HPMC K100M showed a shift on the excipients signal, that could be explained as drug:polymer and polymer:polymer interactions that modulate the hydration/dehydration processes. Nevertheless, these interactions were not strong enough to be detected by Raman spectroscopy.

1.3.2 Combination of poly(meth)acrylates

This research focused on the combination of poly(meth)acrylate, even if the investigations on these combinations are not so extended, compared for example to the combinations on cellulose-based polymers (Gallardo et al. 2008). Neutral (EUDRAGIT® NE 30 D) and cationic poly(meth)acrylates with a chloride anion (EUDRAGIT® RS and EUDRAGIT® RL) are described as inert polymers used as matrix formers. Also pH-dependent poly(meth)acrylates of anionic character have been used as matrix formers. The combination of these polymers is mainly additive because no interactions between polymers take place (Rabasco et al. 1991). The processes most widely used to combine poly(meth)acrylate for the production of matrix tablets are direct compression and wet granulation (aqueous and organic). Direct compression is the most widely used process because of its easiness and saving of time and costs. Direct compression is also used to avoid possible ionic interaction between the polymers during the process resulting in a possible coagulation of the polymer mixture. But even direct compression shows a synergic effect on the sustained release (Cameron et al. 1987). The sustained release properties in 0.1 N HCl of theophylline matrix tablets with 15% polymer content of a combination of EUDRAGIT® RS PM with EUDRAGIT® L 100 1 to 1 (w/w) were stronger than the release profile of the same formulation with the pure polymers.

When the combination of the polymers is manufactured by wet granulation, the organic granulation is the most widely used. It is not the most recommended due to the environmental problems associated with the solvents used. The polymers are soluble in organic solvents such as isopropanol and acetone, improving their distribution and therefore a stronger sustained release (Figure 4).

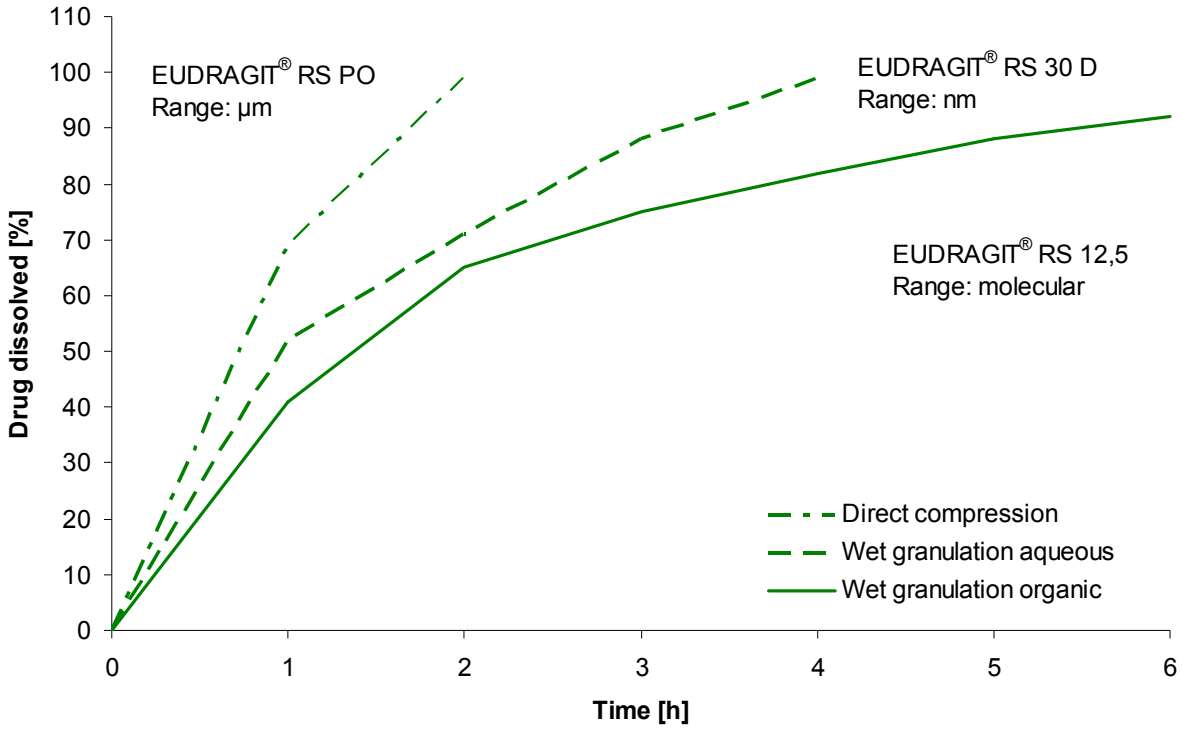


Figure 4 Difference on the release profile of diprophylline matrix tablet with 10% polymer content, depending on the process chosen and the grade of the poly(meth)acrylate (Petereit 1994)

To explain the property of the poly(meth)acrylates a study involving the manufacturing of Carteolol HCl matrix tablets was performed (Fernandez-Arevalo et al. 1993). 50% of EUDRAGIT® RS 100 was used to prepare the matrices. To granulate the drug with the filler and the polymer two methods were chosen. One used an organic mixture of isopropanol acetone 6:4 and the other method used EUDRAGIT® L 12.5% (organic solution with 12.5% EUDRAGIT® L 100 polymer content). The manufactured tablets with the polymer combination showed a stronger sustained release.

These results showed that the polymer combination results in an additive effect of the polymer properties. But not only organic granulations are chosen to perform a wet granulation. Lately the importance of safety and environmental awareness has changed the way to proceed. Dispersions with partial neutralization of poly(meth)acrylates are also a

possibility to improve the distribution and retard effect of these polymers (Pharma polymers 2008). In two studies combinations of EUDRAGIT® E 100 or EUDRAGIT® E PO with EUDRAGIT® L 100 or EUDRAGIT® L 100-55 adjusting the dispersions to a same pH value were done (pH 5.5 in the case of EUDRAGIT® L 100-55 and pH 6.0 in the case of EUDRAGIT® L 100) (Moustafine et al. 2005; Moustafine et al. 2006). The obtained interpolyelectrolyte complexes (IPEC) were compressed by direct compression with 33% of ibuprofen as model drug. No interaction was found between the drug and the IPEC and a stronger sustained release than with an inert polymer such as EUDRAGIT® RS was found along 2 hours in 0.1 N HCl followed by 2 hours in 6.8 phosphate buffer.

1.4 Manufacture processes for matrix tablets

The processes used to manufacture matrix tablets can be classified into four major groups: direct compression, dry granulation with compression, hot melt extrusion and wet granulation with compression.

1.4.1 Direct compression

This process has been used since 1950 especially in process development. The drug and the excipients used to make a compressible mass are mixed and then compressed into tablets.

The advantages are the simplicity of the procedure saving a lot of steps compared to other processes, and it is cheap and fast. Furthermore this process is recommended for formulations containing drugs that could be affected by humidity or temperature for increasing their stability. The absence of water in the process leads to better stability results compared to a wet granulation process. Another advantage is from the point of view of documentation. The reduced amount of equipments involved in a process like this reduces validations and other related documentation.

Although the process has extensive advantages, there are some disadvantages. One of the most important disadvantages that could affect the process is bad flow properties and compressibility of some drugs. The difference in the particle size of the different components of the formulation can lead to a segregation of the mixture (Cooper et al. 1972). This is one of the factors that can directly affect the release profile of the drug (Velasco et al. 1999).

The equipments used for this process are a mixer that mixes all the excipients with the drug and a tabletting machine. The tabletting machine can be eccentric or rotary. In the eccentric

the feeder moves back and forward over the die plate to fill the die where the punches make the tablet. This machine is convenient to compress small batches where the amount of powder mixture is low. The inconvenience is the segregation of the powder produced with the feeder movement over the die. The low speed in the case of compressing greater amounts of powder is a problem. These problems can be solved with a rotary compression machine. The dies are filled by gravity from the static feeder reducing the risk of segregation and to a higher compression velocity.

1.4.2 Dry granulation

Dry granulation is a process where the powder mixture is compacted by a compaction process and followed by a milling process. The process is characterized by a lower energy and cost requirement and shorter procedure time compared to wet granulation. It is used for those drugs and excipients that are sensitive to humidity and/or heating. Furthermore the elaboration of granules by compaction, and afterwards compression, increases the disintegration time of the produced tablets. Also the percentage of fines produced during granulation can be high. If the percentage exceeds 10-15% a repetition of the compaction is necessary (Patel et al. 2006).

The compact can be produce with an eccentric compression machine with punches of a diameter greater than 20 mm or a roller compactor as shown below (Figure 5).

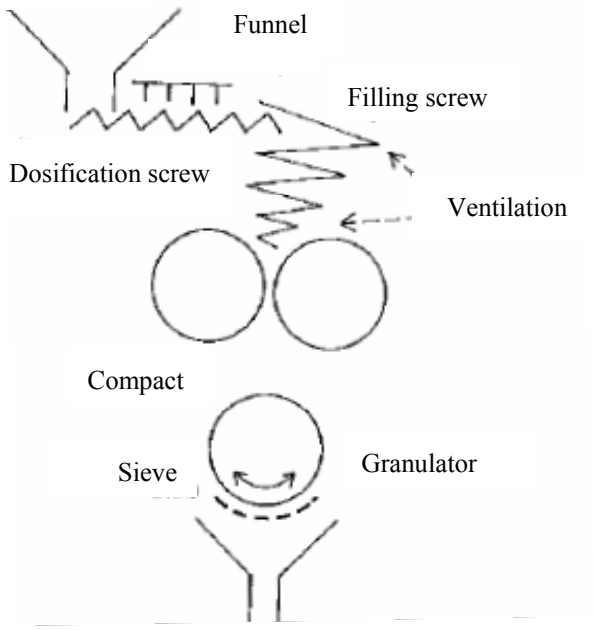


Figure 5 Scheme of a compactor (Ritschel et al. 2002)

1.4.3 Melt extrusion

In melt extrusion, drug and excipients are melted together and forced through an orifice or die producing a product called extrudate. One advantage is the absence of water, especially when working with hydrophilic substances. The absence of organic solvents avoids explosion risks and causes fewer environmental problems. The easiness of the process makes it suitable for manufacturing of sustained release forms (Zhang et al. 1999; Crowley et al. 2007; Repka et al. 2007). One main factor providing sustained release properties is the high density of the extrudate. Since this is a thermal process, the drying step involved in a wet granulation is also deleted saving time and costs. A disadvantage of the process is the impossibility of using thermosensitive drugs.

The equipment used in this process is an extruder and it could be vertical or horizontal. Based on the screws it can be a single or twin screw. In the case of a twin screw extruder they can be also divided in corrotating or counterrrotating. The extruder has several barrels that can be heated independently. The mixing efficiency of an extruder is an advantage, having dispersive and distributive mixing properties. The screws can be segmented and by using different elements like kneading or mixing element the mixing properties of the extruder can be defined (Breitenbach 2002). Therefore, a homogeneous product results from this process. A limitation to the process could be a high viscosity of the excipients causing a high torque value and high shear stress. Using plasticizers in the formulation can lower the viscosity and therefore improve the process.

1.4.4 Wet granulation

This process is the most widely used even if it requires higher amount of energy or costs. The drug and the excipients get in contact with a liquid (demineralised water or organic solvent) with the aim of obtaining a homogeneous wet mass (Huang et al. 2003). This mass is passed through a sieve to obtain granules. The flowability of the powder mixture improves with this process. The particle size and the distribution of the different components are homogeneous in each granule avoiding segregation. It is recommended that the liquid added to the powder mixture will not exceed 30% of the powder mixture for the traditional kneading granulation, although is possible to use higher percentage. This increases the process time and makes the process more complicated (Ritschel et al. 2002).

Binders used during wet granulation can be, among others, cellulose derivates, starches, polysaccharides and synthetic polymers. These binders are added after approximately 2

minutes of mixing. The binding liquid can be added at once or in several steps. After the binding liquid is added, the wet mass can be sieved to obtain wet granules or it can be dried and then granulated. The drying process can take place on a tray in a drying oven, fluid bed, vacuum or microwaves devices (Giry et al. 2006). The equipments used to perform a wet granulation are fluid bed or high shear mixer. In the fluid bed the powder mix is continually flowing while the binder is sprayed. The binder can be added with a top, tangential or bottom spray gun. The high shear mixer is a container with a mixer and a chopper keeping the powder mixture in continuous movement. The binder can be simply poured into the powder mixer or sprayed. The main function of the chopper is to homogenize the granule sizes in the case they start to agglomerate. In addition, it distributes the binder more homogeneously in the powder mixture.

During the granulation of a powder mixture in a high shear mixer five different phases exist depending on the degree of humidity of the powder (Leuenberger et al. 1989):

- Phase I, the fluid starts to be adsorbed to the surface of the particles, but the adhesion and cohesion forces are not strong enough
- Phase II, isolated fluid bridges are formed at the points where the particles are in contact. Beginning of capillarity forces.
- Phase III, enhancement of the fluid bridges through the entire powder mass.
- Phase IV, filling of remaining pores with liquid.
- Phase V, over wetting of the powder leading to a suspension. The process has to stop before this phase starts.

The phases can be detected by measuring the energy needed from the machine to move the wet mass, as shown below (Figure 6).

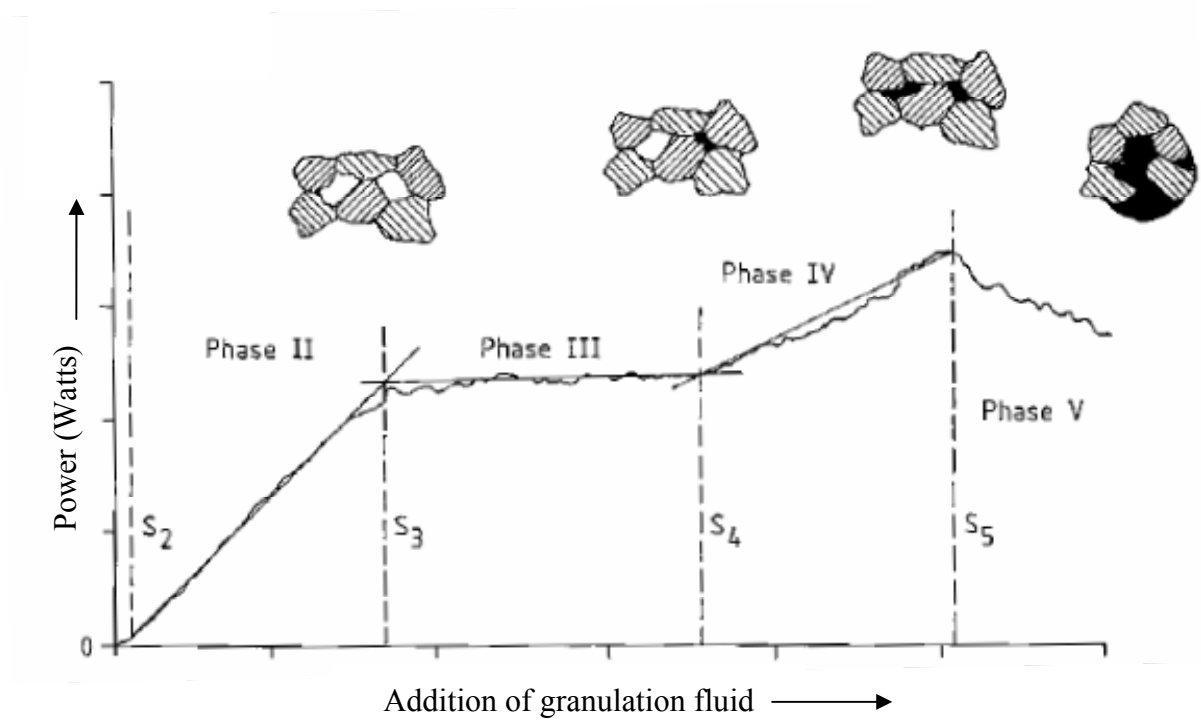


Figure 6 Representation of the energy needed in the different phases of a wet granulation process (Leuenberger et al. 1989)

1.5 Summary

Matrix tablets are one of the most widely used options to provide sustained release properties. The reasons are the ease and low manufacturing costs of the process, especially if the tablets are produced using a direct compression process. Also the variability of the manufacturing processes like direct compression, compaction, wet granulations or melt extrusion, can provide sustained release properties for different drugs that are sensitive under certain conditions like humidity or high temperatures.

Cellulose-based or poly(meth)acrylate polymer are widely used as excipients to build matrix tablets. Combination of excipients to modulate the release of a drug is an extended field of investigation. But the combination of countercharged polymers, especially poly(meth)acrylate, has not been investigated extendedly.

Therefore this work focused on the understanding of the reaction that takes place between the countercharged poly(meth)acrylate, and on the application of the interaction in the manufacturing of matrix tablets to provide sustained release of highly soluble drugs.

2 Aim of the study

The aim of the study is to provide a strong sustained release of highly soluble drugs through the combination of a cationic poly(meth)acrylate polymer, such as EUDRAGIT® E PO with different anionic poly(meth)acrylate polymers, such as EUDRAGIT® L 100-55, EUDRAGIT® L 100, EUDRAGIT® S 100 and EUDRAGIT® FS.

Inert or anionic poly(meth)acrylates are usually used as matrix formers due to their insolubility in different pH values as is the case of inert polymers, or because of their solubility above high pH values as is the case of the anionic polymers. Polymer combinations are used to modulate the release profile of the drugs and provide different sustained release profiles through addition or synergism of the combined polymers. These combinations have been widely used for the cellulose-based polymer but not for poly(meth)acrylates. The main poly(meth)acrylate combinations are based on mixture between inert poly(meth)acrylates or inert with anionic poly(meth)acrylates. Countercharged poly(meth)acrylate are immiscible leading to coagulation. The reaction between two countercharged pH-dependent poly(meth)acrylate could provide a base to manufacture matrix tablets with a different sustained release compared with other polymers.

Analytical methods such as gravimetry analysis, Fourier-transform infrared spectroscopy, differential scanning calorimetry, thermogravimetric analysis or viscosimetry analyses between others were performed to characterize the properties of the combination of the countercharged poly(meth)acrylates.

Two processes were used to compare the differences of the sustained release of the manufactured matrix tablets using the poly(meth)acrylate combination. One was a wet granulation with a high shear mixer and the other was melt extrusion. The influence of highly soluble drugs with different ionic characters (diprophylline, diltiazem HCl and captopril), the different processes and other excipients were tested.

3 Results and discussion

3.1 Characterization of methacrylic copolymer combinations

3.1.1 Sediment

3.1.1.1 Preparation of the polymer solutions

EUDRAGIT® polymers are commercially available in three different grades (powder or granules, aqueous dispersion or organic solution). The name of the polymer is directly linked to the grade: "PO" e.g. EUDRAGIT® E PO stands for the micronized powder grade. The number 100 as in EUDRAGIT® L 100 stands for powder or EUDRAGIT® E 100 stands for granules. The dispersions containing 30% solid are described with "30 D". And 12.5% in the name refers to the organic solution with 12.5% polymer. Since EUDRAGIT® FS 30D is commercialized only as aqueous dispersion an experimental polymer in powder grade Preparation 4155 F (EUDRAGIT® FS) was used in these trials.

For the preparation of the organic solutions in this trial, powder grade polymers were dissolved in organic solutions of isopropanol/acetone 60/40 (w/w). The following polymers were chosen for the trial (Table 4):

Table 4 List of polymers used for the combinations

Polymer	Percentage of monomers with active groups	Character
EUDRAGIT® E PO	50	Cationic
EUDRAGIT® L 100-55	50	Anionic
EUDRAGIT® L 100	50	Anionic
EUDRAGIT® S 100	33	Anionic
EUDRAGIT® FS	10	Anionic

In aqueous dispersions polymers are presented in latex particles at a nanometer scale whereas in a polymer solution, the particles exist at a molecular level. The organic solvents were selected as all polymers are fully dissolved in this medium enhancing interaction between

polymers. The selected solvents are the same used for the commercialized organic solutions of these polymers (Pharma polymers 2005).

Preparation of low concentrations solutions (point 6.2.1.1.1) was performed to avoid inappropriate distribution of the polymers. When the polymers are combined at higher concentrations, the interaction between the polymers solutions could take place only at the contact surface. This partial reaction could lead to an insufficient distribution of the two polymers in the combination. An example for this possible hypothesis can be seen in Figure 7.

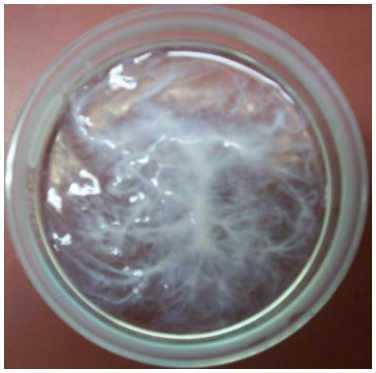


Figure 7 Example of insufficient distribution of a mixture between two high concentrated (10%) organic solutions of poly(meth)acrylate polymers

By reducing the concentration the reaction between the polymers still takes place and the distribution is homogeneous. The final polymer concentration of all combinations was 1.6 g in 500 ml solvent.

3.1.1.2 Mixture in the Schmizo reactor

A Schmizo reactor is a glass reactor with an integral cooling/heating jacket connected to a water bath where the temperature can be controlled. The reactor has a lid with several openings: one opening for the propeller and two small ones for the burettes used to add the polymer solutions. Lid and reactor are closed and sealed with a rubber ring avoiding a possible evaporation of the solvent. The parameters used for the different combinations such as rotation speed of the propeller, temperature, the molar ratios in which the polymers were combined, volumes and orders of addition are described in the experimental section (point 6.2.1.1.1). Scheme of the Schmizo reactor is described in Figure 8.

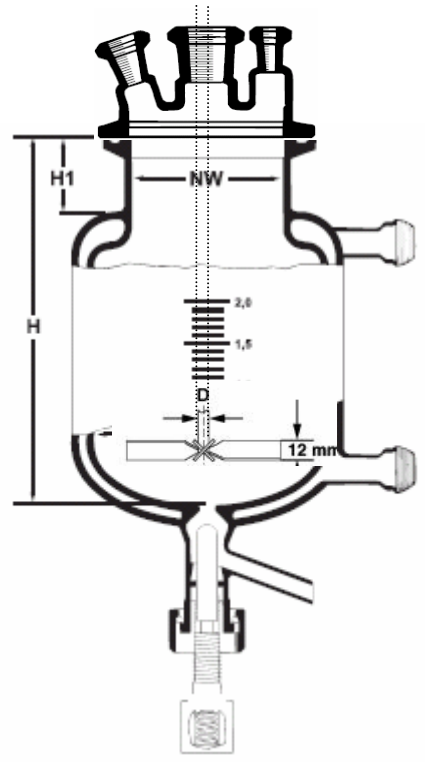


Figure 8 Scheme of Schmizo reactor with lid and scheme of the used propeller

Turbidity appeared in the reactor within the first minute that the polymers came into contact. The white turbidity was produced by precipitated particles resulting from the reaction of the anionic and cationic polymers. Depending on the particle size of the precipitate more or less sediment occurred. When the particles were larger, the sedimentation of the precipitate was easier and therefore the turbidity of the supernatant decreased and vice versa.

The properties of the sediment changed depending on the combined polymers. The softness of the sediment changed depending on the anionic polymer used in the combination. The difference in the softness is caused by the different T_g values of the anionic polymers. T_gs of all polymers are described in the experimental section (point 6.1.1)

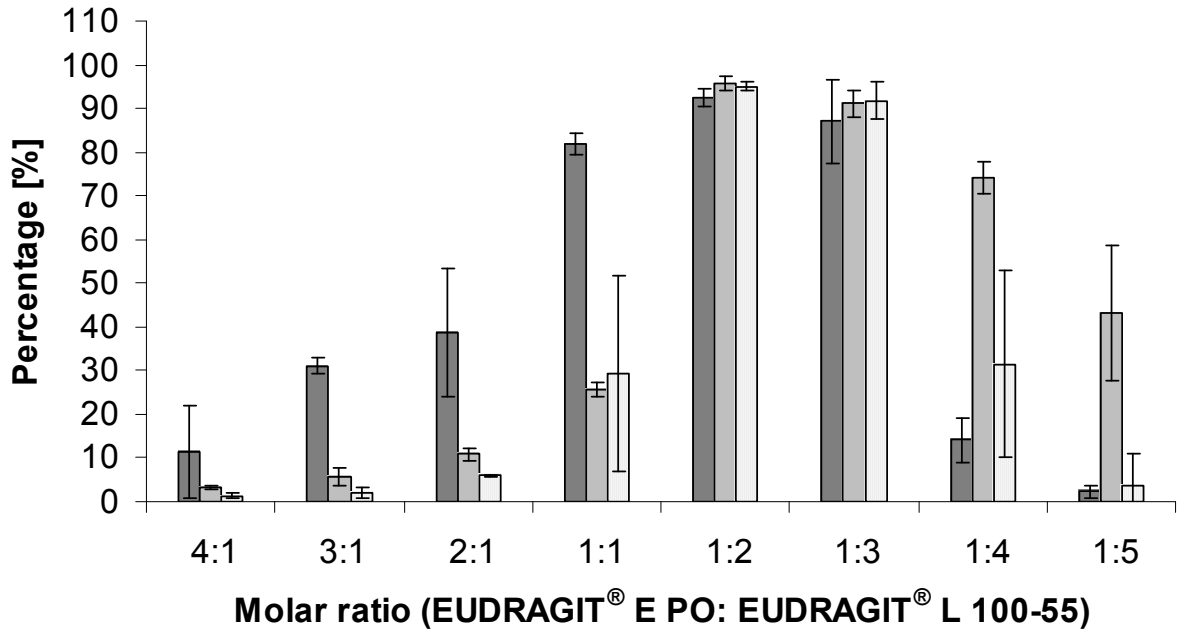
The T_gs of the anionic polymers are high, forming a brittle sediment, except EUDRAGIT® FS where the T_g value is approximately 50ºC. In this case the sediment was rubber-like.

3.1.1.3 Gravimetric results and statistical interpretation

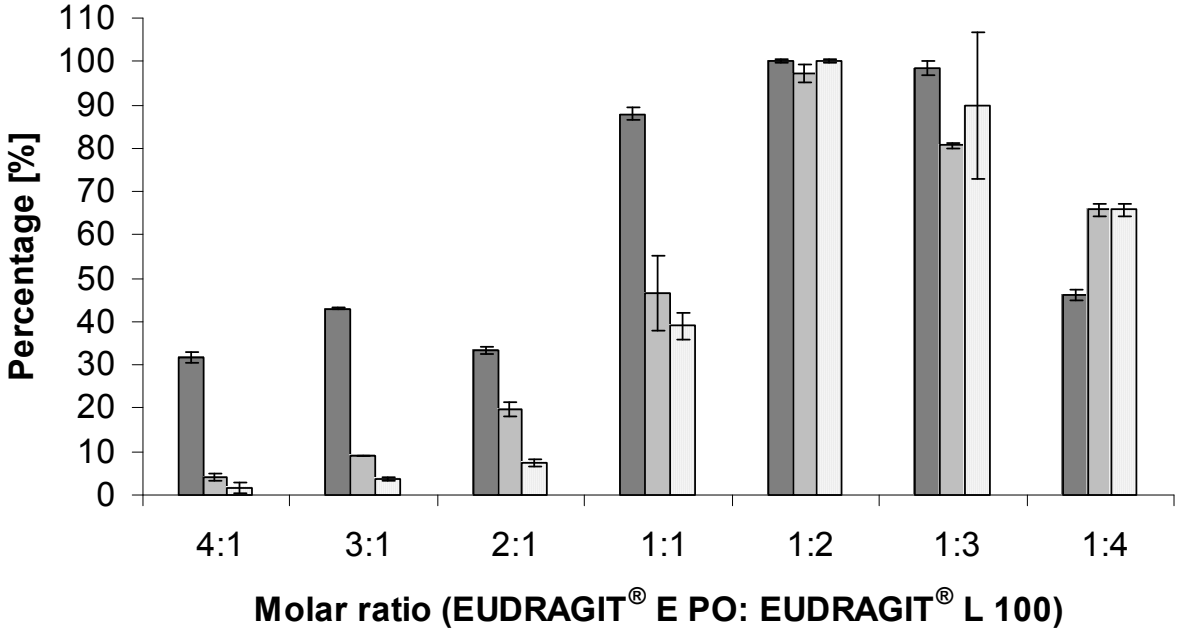
The aim of the gravimetric trials was the determination of the factors affecting the formation and amount of sediment. The evaluated factors were:

- Influence of the percentage of carboxylic groups in the anionic polymers combined with EUDRAGIT® E PO
- Influence of the molar ratio
- Influence of the order of addition. Cationic polymer over anionic polymer, anionic polymer over cationic polymer or both polymers added at the same time
- Influence of the weight of each polymer in the different combinations, independent of the molar ratio

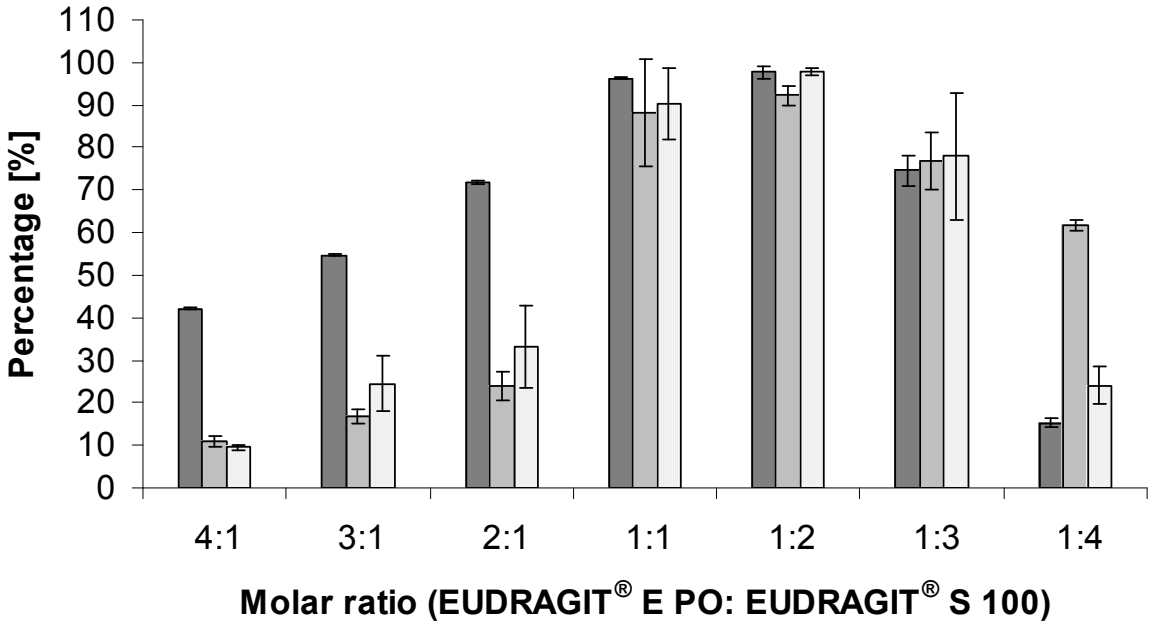
In Figure 9 the gravimetric results representing the percentage of sediment versus the molar ratio of the different anionic polymers are shown.



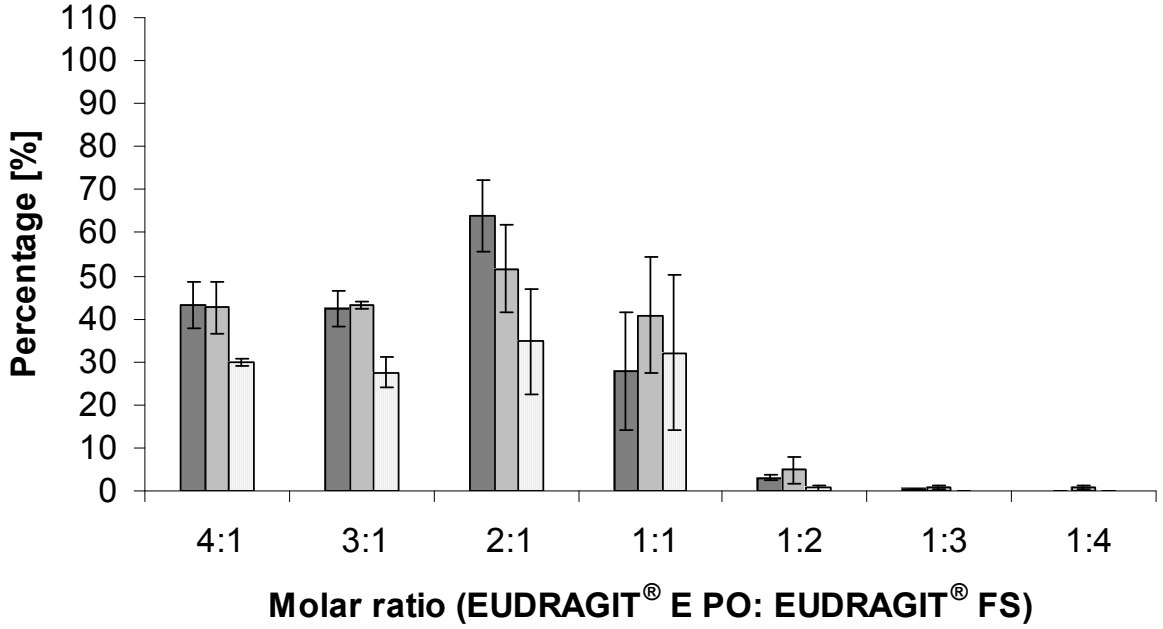
a)


Percentage [%]
110
100
90
80
70
60
50
40
30
20
10
0
4:1
3:1
2:1
1:1
1:2
1:3
1:4
Molar ratio (EUDRAGIT® E PO: EUDRAGIT® L 100)

b)


Percentage [%]
110
100
90
80
70
60
50
40
30
20
10
0
4:1
3:1
2:1
1:1
1:2
1:3
1:4
Molar ratio (EUDRAGIT® E PO: EUDRAGIT® S 100)

c)



d)

Figure 9 Results of the gravimetric trials performed for the combinations of EUDRAGIT® E PO with different anionic poly(meth)acrylates. (n=3). Addition of EUDRAGIT® E PO over anionic polymers(dark grey columns), addition of anionic over EUDRAGIT® E PO (black diagonal striped columns) and addition of both polymers simultaneously (black pointed columns). a) Combinations EUDRAGIT® E PO with EUDRAGIT® L 100-55, b) combinations EUDRAGIT® E PO with EUDRAGIT® L 100, c) combinations EUDRAGIT® E PO with EUDRAGIT® S 100, d) combinations EUDRAGIT® E PO with EUDRAGIT® FS

In all figures a maximum of sediment is observed. Only for the combination with EUDRAGIT® FS the maximum sediment collected does not reach the total amount of polymer. This polymer has the lowest amount of active groups (10% carboxylic groups) from all the anionic polymers used. It is possible to assume that a low percentage of active groups reduces the chances to react with a countercharged polymer, thus reducing the amount of sediment collected. The other anionic polymers (33% and 50% active groups) have more chances to react with the countercharged polymer and therefore, approximately 100% of sediment was produced.

The position of the maximum of sediment collected is different depending on the anionic polymer used in the combination. The anionic polymers differ in the amount of active groups, and therefore in the acidic value. A higher acidic value means a higher amount of active groups and vice versa. The active groups of the cationic polymer are determined by the alkali value. Molar ratios of the combinations were calculated based on the acidic value of the anionic polymers and the alkali value of the cationic polymer (point 6.2.1.1.1).

At the molar ratio where the difference in the weight of the combined polymers was tthe lowest, the maximum of collected sediment appeared. For the combination wit EUDRAGIT® E PO and EUDRAGIT® S 100 the similarity in weight was obtained at a molar ratio of 1:1 (difference in weight: 0.058 g), whereas for EUDRAGIT® L 100 and EUDRAGIT® L100-55 the difference in weight was the lowest (difference in weight: 0.070 g) at a molar ratio of 1:2.

The similarity on the polymer weight reduces the chances to have free polymer chains dissolved that do not react, leading to the highest amount of sediment. In these combinations the variability on the amount of sediment collected was not affected by the order of addition of the polymers.

For EUDRAGIT® FS the similarity in weight was obtained at a ratio of 3:1 (difference in weight: 0.074 g). Nevertheless the highest amount of sediment was obtained at the ratio 2:1. The difference in the amount of sediment, compared to the other anionic polymer is that, with these combinations a 100% sediment was not achieved. As the percentage of active groups in EUDRAGIT® FS is the lowest, the chance of reacting with EUDRAGIT® E PO is decreased. This leads to the lowest amount of collected sediment compared to the other combinations and to high standard deviation values.

On both sides of the maximum, the amount of collected sediment varied as the molar ratio changed.

The variability on the amount of sediment was affected by the order of addition. In all cases (Figure 9 a-d), on the left side of the maximum where the fraction of EUDRAGIT® E PO is higher than the fraction of the anionic polymer, a higher percentage of sediment was obtained when EUDRAGIT® E PO was added over anionic polymers. These values can be explained by the higher reactivity of EUDRAGIT® E PO due to its structure (Vollmert 1982). The longer side chain of this polymer provides a higher movement and flexibility to interact with the anionic polymers. The differences in the structure are shown below (Figure 10).

On the right side of the maximum where the amount of anionic polymer exceeded the amount of EUDRAGIT® E PO the differences in the polymer concentrations in the reactor and the burette competes with the high reactivity of EUDRAGIT® E PO. When a drop of the anionic polymer solution from the burette had a higher concentration than the EUDRAGIT® E PO solution in the reactor, the reaction between the polymers took place mainly on the contact surface. This led to insufficient and rough distribution of the polymers, and to a formation of larger precipitated particles. These larger particles improved the sedimentation process

increasing the percentage of sediment collected. To confirm this hypothesis, an additional combination for EUDRAGIT® E PO: EUDRAGIT® L 100-55 was performed. The molar ratio was 1:5 and the concentration of the anionic polymer added into the reactor was greater than the concentration of EUDRAGIT® E PO in the reactor. This additional combination followed the same trend shown in the previous combinations and led to higher percentage of sediment compared to the sediment obtained following other order of addition.

The gravimetric values have high standard deviations caused by the irregular dropping of the polymers from the burette. The feeding rate was set at 1.6 ml/min, but in some cases the conditions changed adding the polymer solution with a faster or slower feeding rate.

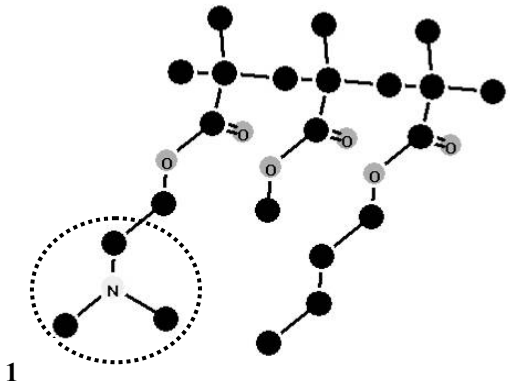
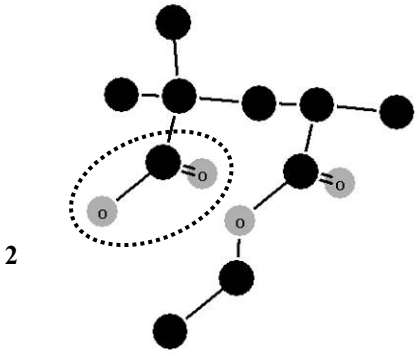
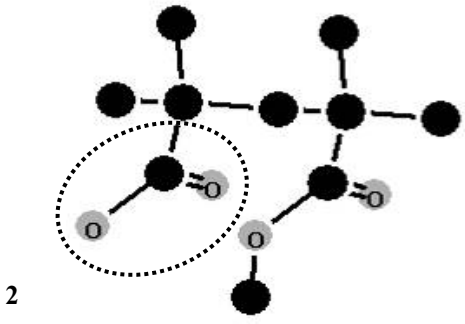
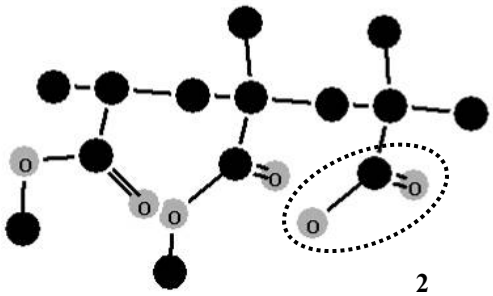
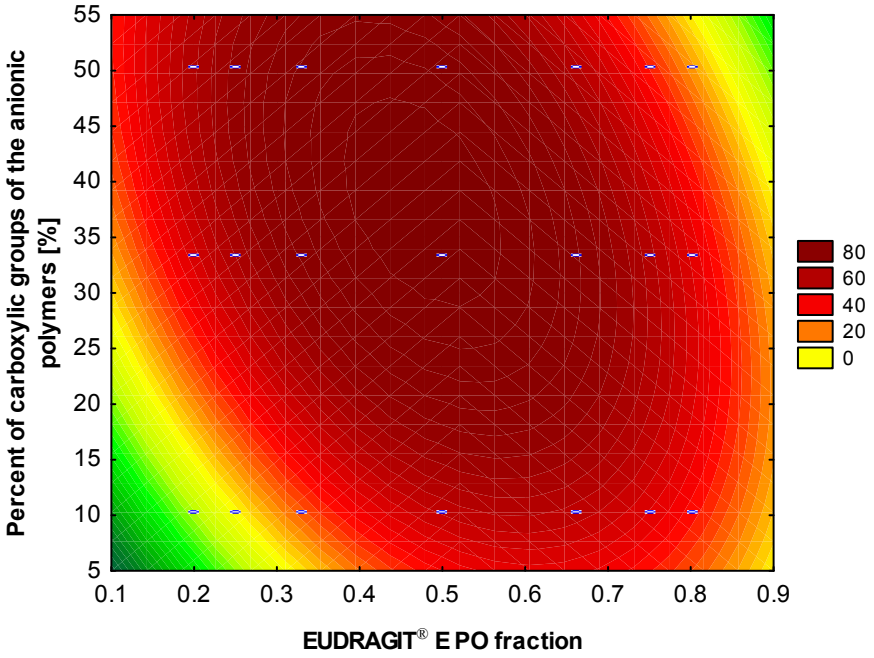
	
EUDRAGIT® E PO	EUDRAGIT® L 100-55
	
EUDRAGIT® L 100 / S 100*	EUDRAGIT® FS

*Figure 10 Structure of polymers. Higher reactivity of EUDRAGIT® E PO due to the greater length of the side chain [1]dimethylaminoethyl group, [2]carboxylic group. * The structure of EUDRAGIT® S 100 is similar to EUDRAGIT® L 100 differing only in the frequency of the carboxylic groups: (1:2) for the first one and (1:1) for the second one*

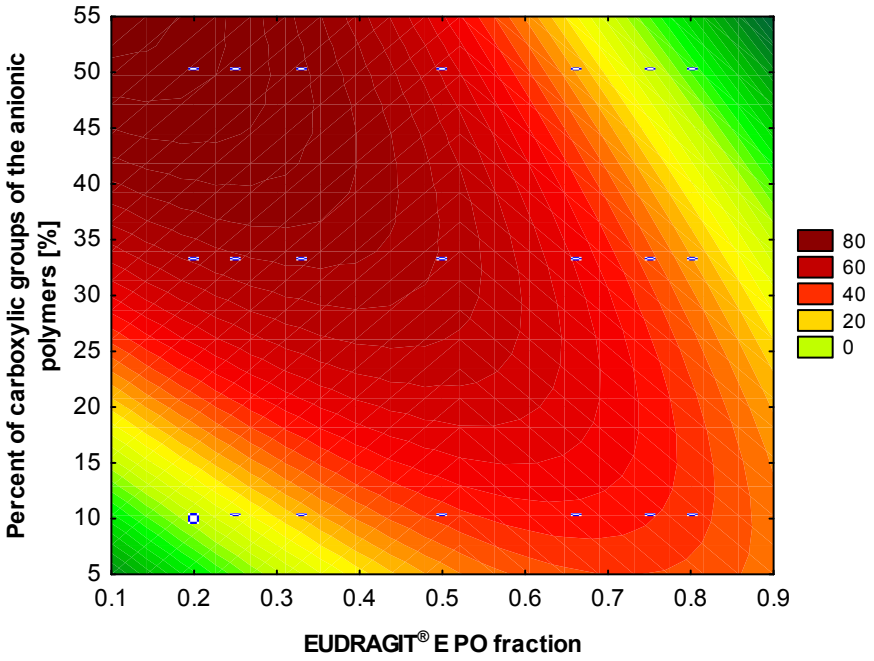
The gravimetric results were statistically analyzed. A central composite design was chosen to analyze the relation between the percentage of EUDRAGIT® E PO in the combinations, the percentage of carboxylic groups in the anionic polymers and the amount of sediment.

a)



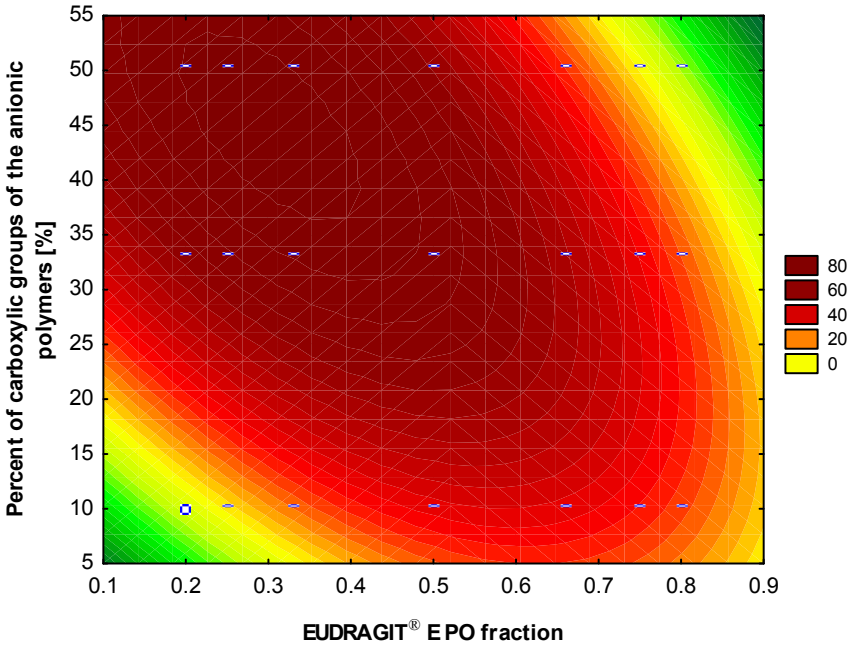
$z=-176.78+643.66x-509.57x^2+6.07y-0.05y^2-4.17xy$

b)



$z=-100.66+331.22x-210.04x^2+5.72y-0.04y^2-5.66xy$

c)



$$z=-125.73+410.84x-308.96x^2+6.15y-0.05y^2-4.99xy$$

Figure 11 Results from the central composite design performed on the gravimetric results to define the influence of the percentage of carboxylic groups in the anionic polymers and the EUDRAGIT® E PO fraction on the percentage of sediment. a) Results from the combinations where EUDRAGIT® E PO was added over the anionic polymers, b) results from the combinations where the anionic polymers were added over EUDRAGIT® E PO, c) results from the combinations where both polymers were added simultaneously. Model equation z=percentage of sediment [%], y=percentage of carboxylic groups of the anionic polymers [%], x=EUDRAGIT® E PO fraction

The statistical study showed the different trends on the sediment formation influenced by the different order of addition (Figure 11 a-c). Due to the large standard deviations obtained in some of the combinations, the results of the coefficient of determination were not close to 1 (Table 5).

Table 5 Results of r-square for the different combinations

	Addition of EUDRAGIT® E PO over anionic polymers	**Addition of anionic polymers over EUDRAGIT® E PO**	**Addition of both polymers simultaneously**
r-square	0.71	0.82	0.72

In the figures below, the significance of the different factors on the percentage of sediment is represented, depending on the order of addition.

EUDRAGIT® E PO fraction (L) had no significant effect on the sediment amount, whereas other factors showed a significant effect. The quadratic value of EUDRAGIT® E PO fraction (Q) value showed a slightly higher significance than the interaction between the (1) EUDRAGIT® E PO fraction and the (2) percentage of carboxylic groups of the anionic polymers (1Lby2L) (Figure 12).

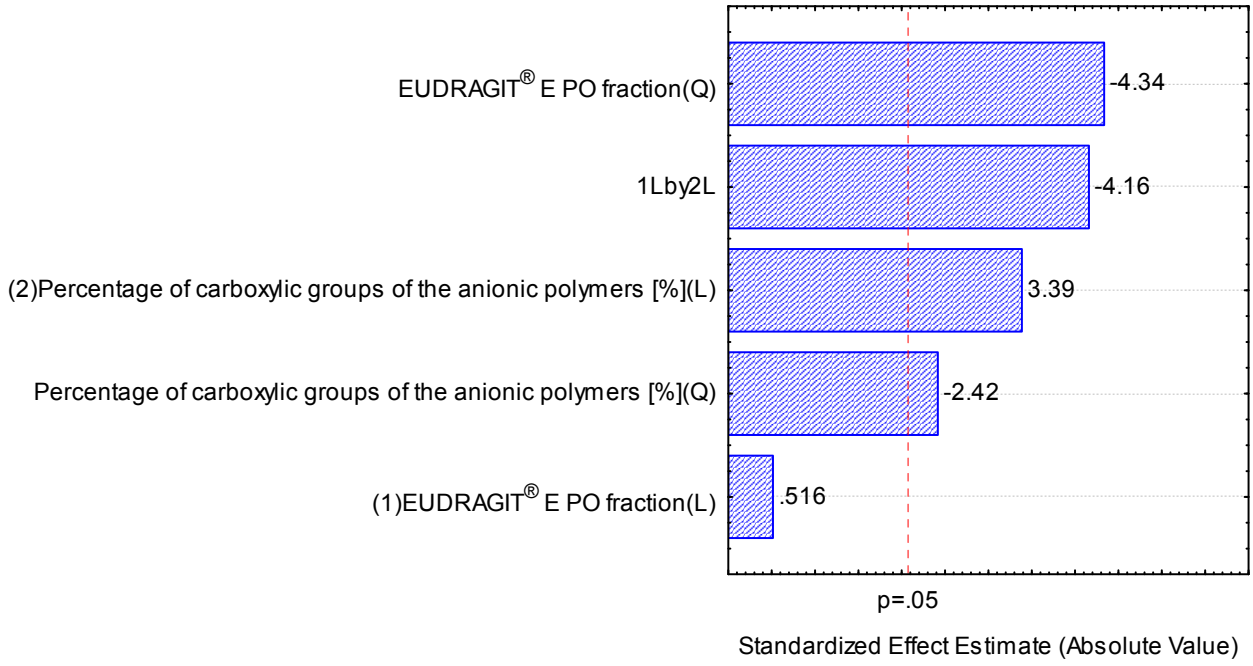


Figure 12 Significance of the different factors on the percentage of sediment. Combinations where EUDRAGIT® E PO was added over the anionic polymers

In Figure 13 and Figure 14, all factors showed significance on the sediment formation. The interaction between (1) EUDRAGIT® E PO fraction and the (2) percentage of carboxylic groups of the anionic polymers (1Lby2L) showed the most significant influence compared to the individual factors.

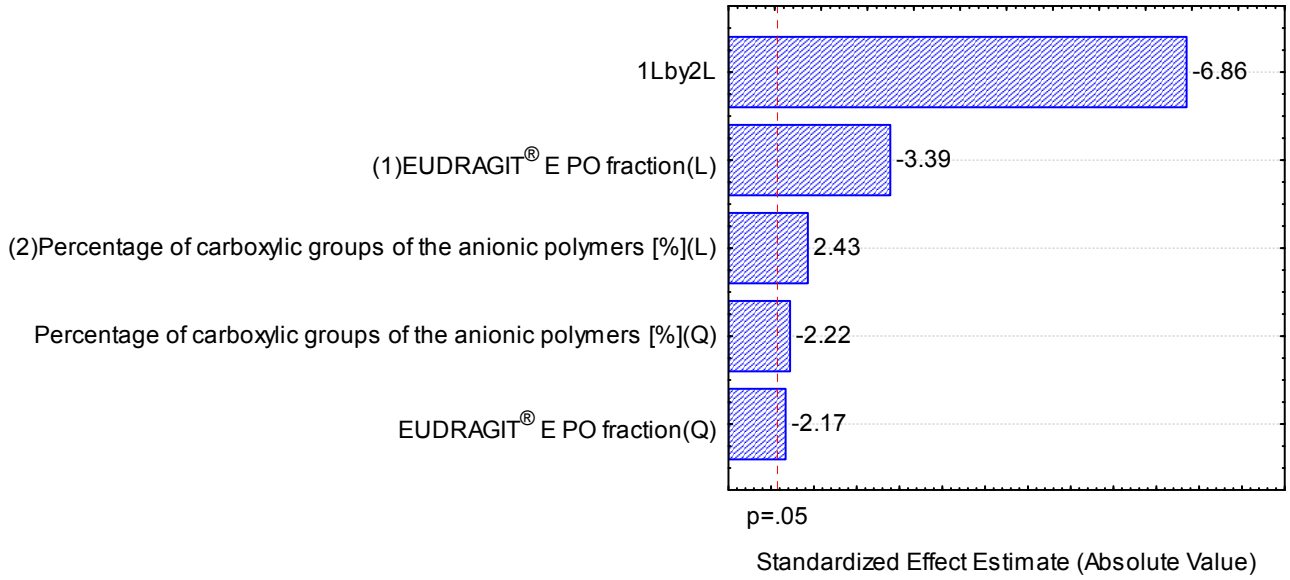


Figure 13 Significance of the different factors on the percentage of sediment. Combinations where the anionic polymers were added over EUDRAGIT® E PO

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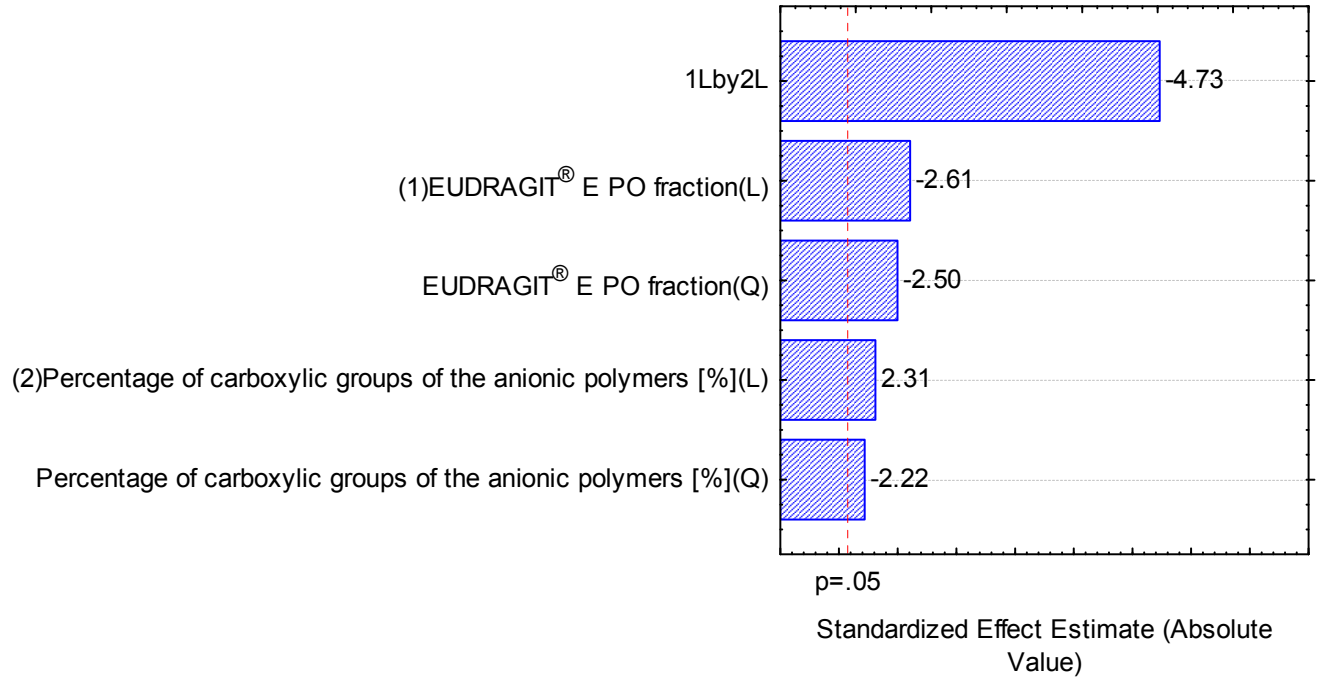


Figure 14 Significance of the different factors on the percentage of sediment. Combinations where the anionic polymers and EUDRAGIT® E PO were added simultaneously.

After analyzing statistically the data it can be concluded that the sediment formation was affected by the order of polymer addition. The interaction between the two factors, (1) EUDRAGIT® E PO fraction and (2) percentage of carboxylic groups of the anionic polymers (1Lby2L), was in all three cases one of the most significant factors on the sediment formation. The influence of the individual factors was significant but at a lower level.

Similar studies used a combination of countercharged poly(meth)acrylate (Moustafine et al. 2005; Moustafine et al. 2006). The polymers were dissolved in solvents and then diluted with demineralized water up to a certain pH value for both polymers. A similar precipitate formation was obtained when the polymers were mixed. Using different analytical methods the precipitate was identified as an interpolyelectrolyte complex (IPEC).

The following analytical methods were performed to confirm and describe the characteristics of the precipitate as an IPEC.

3.1.1.4 Titration

Once the factors influencing the amount of sediment were known, the next step was the determination of the sediment composition. For this method new combinations were prepared. The total volume of solvent and amount of polymer in the combinations were increased to achieve enough amount of sediment to analyze as described in point 6.3.2.7.

The polymer combinations focused only on EUDRAGIT® E PO and EUDRAGIT® L 100-55. The reason is the highest content of carboxylic groups enhancing the chance to react with EUDRAGIT® E PO and therefore probably leading to the strongest sustained release effect. Both polymers were chosen for the manufacturing of matrix tablets in a later step. The total amount in the combinations, volume of solvent and concentration are described in experimental section (point 5.3.2.6). The analysis was performed on those combinations close to the maximum found in the gravimetric study, 1:1, 1:2, 1:3 where the percentage of sediment collected was the greatest. To evaluate the composition of sediments far away from the maximum, only two ratios 3:1 and 1:5 were chosen. All the combinations were prepared in the same way, by adding EUDRAGIT® E PO over EUDRAGIT® L 100-55. Only in the case of the 1:5 combination, EUDRAGIT® L 100-55 was added over EUDRAGIT® E PO, to achieve the maximum percentage of sediment for this combination.

The determination of the acidic value (point 6.3.2.7) was intended to perform, to compare these values with the alkali values. For the method, another solvent, pyridine, was used to dissolve the sediment, as the sediment was not soluble in the original solvent described in the

method (isopropanol:water 60:40). The change in the method affected the determination of the acidic value providing erroneous data. In the case of the alkali value, the solvents described in the method (point 6.3.2.7) could dissolve the sediment and therefore, the parameters of the validated method were not changed.

To calculate the amount of EUDRAGIT® E PO in the sediment, the equation (3.1) was used:

$$\text{EUDRAGIT® E PO in sediment} = \frac{AV_{titration} \times weight_{sediment}}{AV_{Batch}} \qquad (3.1)$$

where:

$AV_{titration}$ is the alkali value of the sediment [mg KOH/g dry substance]

AV_{Batch} is the alkali value of the polymer batch used [mg KOH/g dry substance]

Once the amount of EUDRAGIT® E PO in the sediment was determined, the value was compared with the weighed amount of EUDRAGIT® E PO for each combination. Considering the weighed amount of EUDRAGIT® E PO as 100% the percentage of EUDRAGIT® E PO in the sediment can be calculated (Table 35, Appendix)

After obtaining this value the amount of EUDRAGIT® L 100-55 can be calculated by subtracting the amount of EUDRAGIT® E PO in sediment from the total sediment amount.

These results indicate that the amount of EUDRAGIT® E PO in the sediment was lower than the amount weighed to prepare the combinations. Only in the combination with lower amount of EUDRAGIT® E PO, the percentage in the sediment was greater than theoretical value (Figure 15).

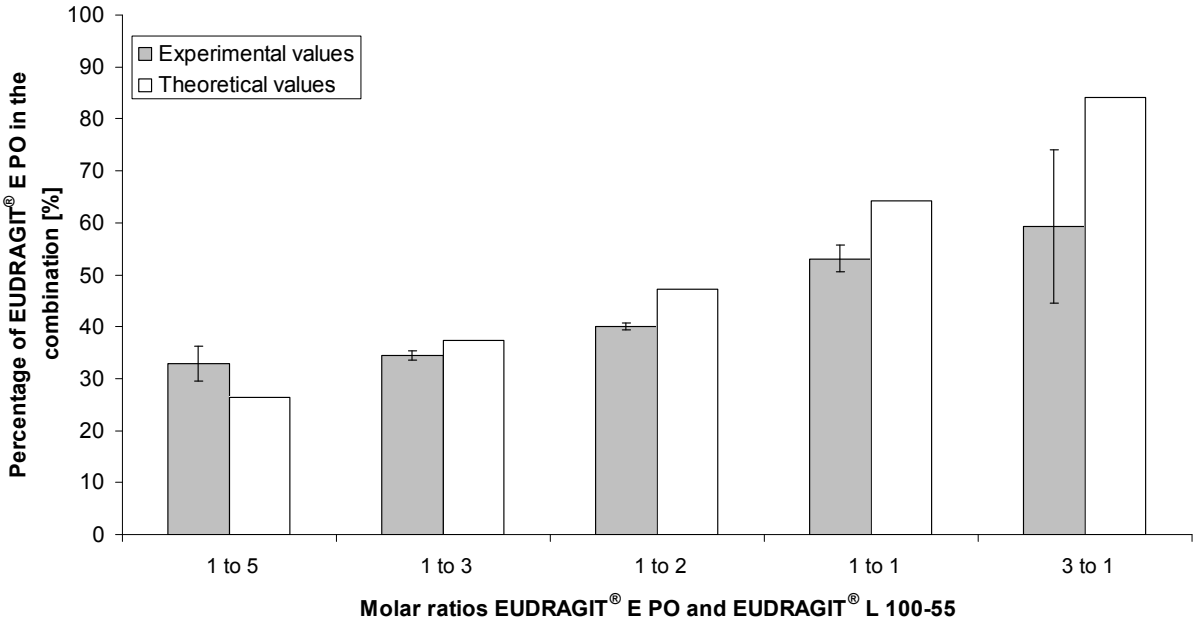


Figure 15 Representation of the theoretical and experimental percentage of EUDRAGIT® E PO calculated from the titration values (n=3)

The titration results confirm that the percentage of EUDRAGIT® E PO found in the sediment was directly affected by the molar ratio. The trend is similar to the theoretical values meaning that when there was a higher amount of EUDRAGIT® E PO in the combination, there will be more EUDRAGIT® E PO in the sediment. Differences between the theoretical and the experimental percentages were observed. The results demonstrate that when EUDRAGIT® E PO was added at the lowest fraction the need of anionic polymer chains to form the sediment was much lower than for the other ratios where the percentage of EUDRAGIT® E PO was greater.

This trial was useful to understand the composition of the sediment, but the standard deviations observed in some combinations, especially in the combination with molar ratio 3:1, did not show a good reproducibility in the measurements. Therefore the next analytical method was chosen to confirm the sediments composition.

3.1.1.5 Nitrogen content analysis (Kjedahl method)

The determination of the nitrogen content of the samples was performed to confirm the values obtained from the titration trials. Combinations of EUDRAGIT® E PO with EUDRAGIT® L 100-55 with molar ratios from 4:1 to 1:4 were tested with the Kjedahl method (point 6.3.2.2). The experimental values are represented as grey bars in Figure 16.

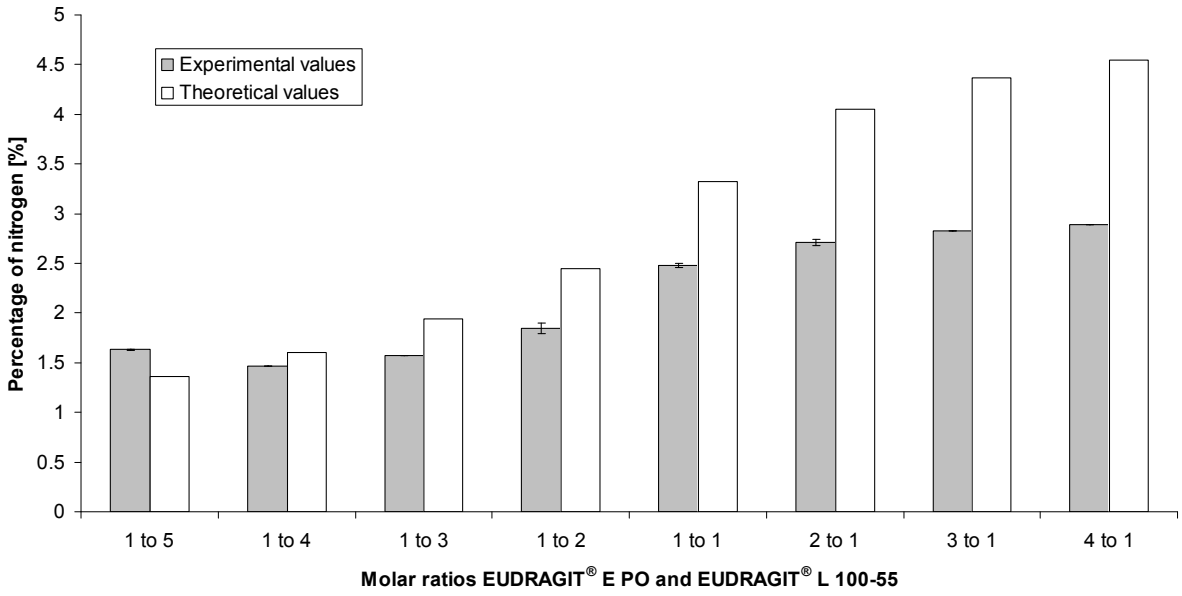


Figure 16 Comparison of the percentage of nitrogen content in the different combinations. White columns with stripes represent the percentage of nitrogen calculated from the amount of polymers used for the combinations and the grey columns represent the percentage of nitrogen obtained from the nitrogen content analysis by the Kjedahl method. Those values without error bars correspond to a unique value because the amount of sample was too low. Values with error bars (n=2)

The theoretical percentage of nitrogen in pure EUDRAGIT® E PO was calculated (equation (3.2):

$$\%\ Nitrogen = \frac{atomic\ weight\ nitrogen}{Sum\ atomic\ weight\ atoms\ in\ monomer} \times 100 \qquad (3.2)$$

For EUDRAGIT® E PO the percentage of nitrogen was 5.18%. Knowing the amount of EUDRAGIT® E PO weighed in the different combinations, the theoretical weight of nitrogen can be determined.

Knowing the theoretical weight of nitrogen and the total weight of the combination (1.6 grams), the percentage of nitrogen in the combination could be determined. These values were compared to the values obtained by the Kjedahl method (Table 36, Appendix). The trend that these values showed was close to the trend of the titration values previously obtained.

3.1.1.6 Fourier transform spectroscopy (FT-IR)

The trials were performed to detect the possible interaction between the two polymers (point 6.3.1.2). The interaction occurs between the carboxylic group from EUDRAGIT® L 100-55 and the dimethylaminoethyl group of EUDRAGIT® E PO forming a carboxylate group.

First, the pure polymers were analyzed to determine the position of the important signals. Depending on the atoms and the kind of bonds, signals appear at different wavelength values. Between 4000 cm^{-1} and 3200 cm^{-1} the signals from single bond between hydrogen and heteroatoms appear. From 3200 cm^{-1} to 2800 cm^{-1} is observed the signals from the single bond between carbon and hydrogen. Triple bonds are detected between 2300 cm^{-1} and 2100 cm^{-1}. And between 1800 cm^{-1} and 1500 cm^{-1} the signals from double bonds are observed.

The carboxylic signal is detected at a wavelength of 1750 cm^{-1}, and the dimethylaminoethyl group at a wavelength of 2800 cm^{-1}. The following figure (Figure 17) shows the signals of the active groups from the pure polymers and also the signals corresponding to the sediment.

In the sediment spectrum, the signals from the pure polymers disappeared and a new signal corresponding to the carboxylate appeared at a wavelength close to 1600 cm^{-1}.

This method was successful to detect and characterize the interaction between the two polymers.

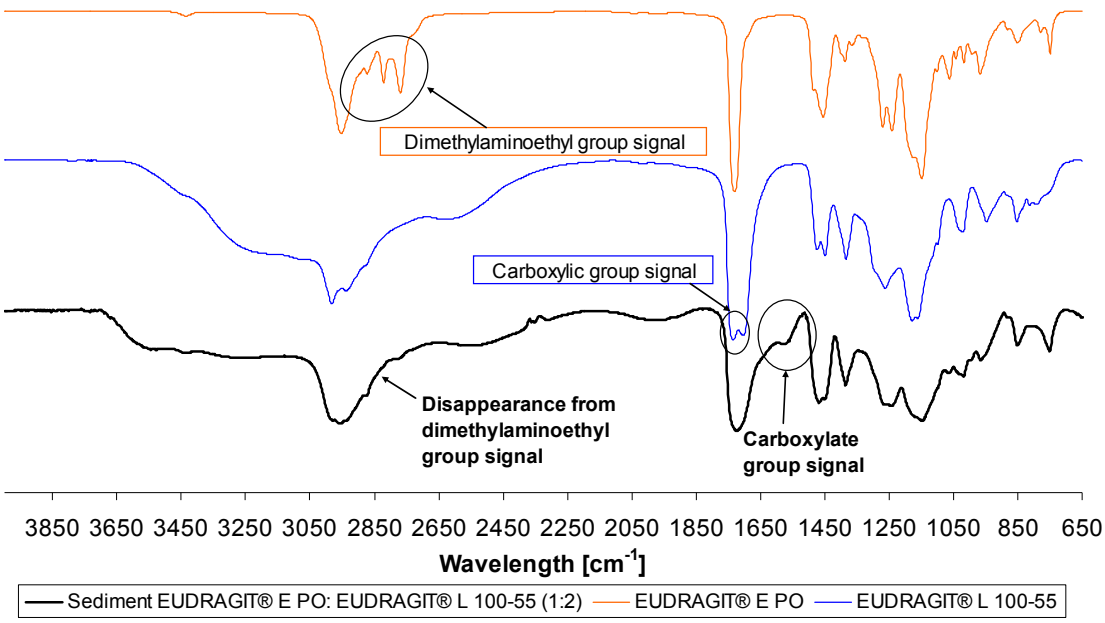


Figure 17 IR spectrum from the sediment resulting from the combination of EUDRAGIT® E PO and EUDRAGIT® L 100-55 in a 1:2 molar ratio. The circles marks the disappearance of the dimethylaminoethyl and carboxylic group signals, and the appearance of a new signal resulting from the ionic interaction between the polymers, the carboxylate group

3.1.1.7 Proton nuclear magnetic resonance analysis (^{1}H-NMR)

This technique was used to make a quantitative determination of the polymers that formed the sediment. The trial is described in point 6.3.2.5.

The results of EUDRAGIT® E PO percentage in sediment, theoretical and experimental, are shown in Table 6.

The results confirmed the values previously obtained from other analytical techniques (points 3.1.1.4 and 3.1.1.5). The percentage of EUDRAGIT® E PO in sediment was lower than the percentage of EUDRAGIT® E PO weighed at the beginning. The high reactivity of EUDRAGIT® E PO was the reason for the decrease of the percentage.

Table 6 Experimental and theoretical percentages of EUDRAGIT® E PO in the sediments obtained by combining EUDRAGIT® E PO with EUDRAGIT® L 100-55, EUDRAGIT® L 100, EUDRAGIT® S 100 and EUDRAGIT® FS in different orders of addition

Sample	EUDRAGIT® E PO theoretical [%]	EUDRAGIT® E PO experimental [%]
EUDRAGIT® E PO over EUDRAGIT® L 100-55 (1:2)	47	43
EUDRAGIT® L 100-55 over EUDRAGIT® E PO (1:2)	47	46
Addition of the polymers simultaneously	47	46
EUDRAGIT® E PO over EUDRAGIT® L 100 (1:2)	47	43
EUDRAGIT® L 100 over EUDRAGIT® E PO (1:2)	47	48
Addition of the polymers simultaneously	47	45
EUDRAGIT® E PO over EUDRAGIT® S 100 (1:1)	52	48
EUDRAGIT® S 100 over EUDRAGIT® E PO (1:1)	52	47
Addition of the polymers simultaneously	52	47
EUDRAGIT® E PO over EUDRAGIT® FS (2:1)	42	38
EUDRAGIT® FS over EUDRAGIT® E PO (2:1)	42	38
Addition of the polymers simultaneously	42	38

3.1.1.8 Differential scanning calorimetry (DSC)

This method is widely used to determine the glass transition temperature (T_g) of materials (Craig et al. 1999). With this method the T_g of pure polymers or blends formed among two polymer can be detected. When two polymers are miscible, the resulting complex should show only one T_g (Zheng et al. 2003) instead of showing the two original T_gs.

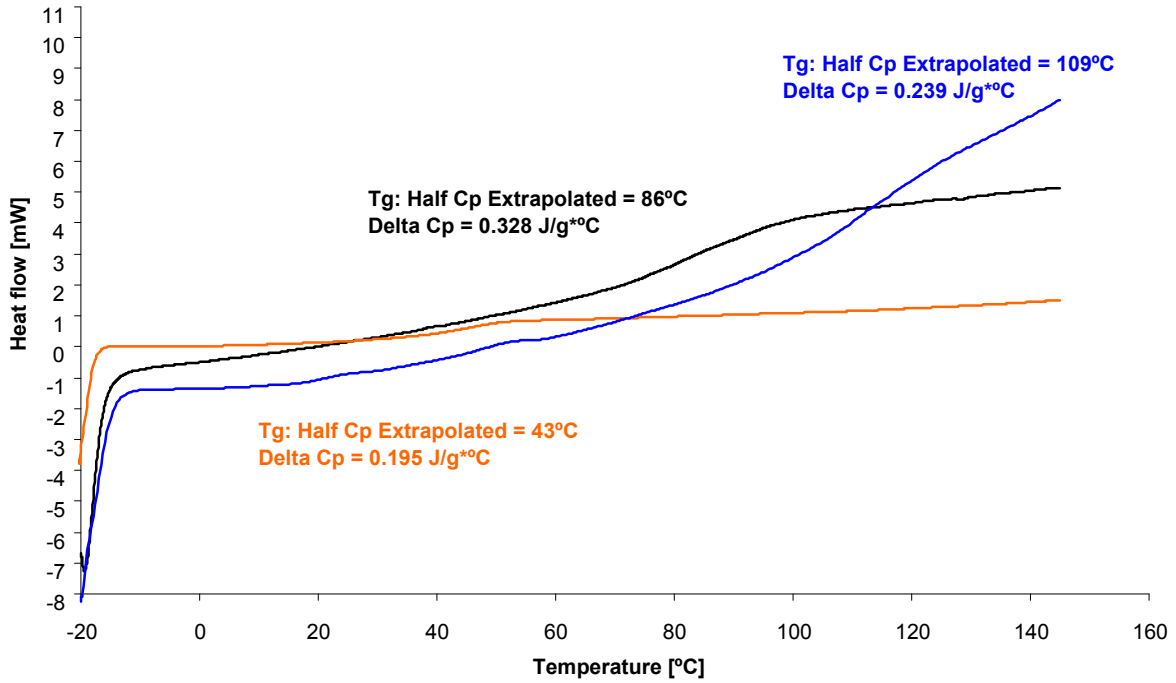


Figure 18 Example of DSC diagram of EUDRAGIT® E PO (orange), EUDRAGIT® L 100-55 (blue) and sediment resulting from the combination between EUDRAGIT® E PO and EUDRAGIT® L 100-55 with a molar ratio of 1:2 (black).

In this method, the order of addition of the polymers was important to evaluate.

Table 7 T_g values of the sediment of EUDRAGIT® E PO with the different anionic polymers mixed following different orders of addition

DSC	EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:2)	EUDRAGIT® E PO: EUDRAGIT® L 100 (1:2)	EUDRAGIT® E PO: EUDRAGIT® S 100 (1:1)	EUDRAGIT® E PO: EUDRAGIT® FS (2:1)
Cationic over anionic	86	116	108	39
Anionic over cationic	99	115	143	40
Simultaneous addition	101	115	86	46

When two amorphous polymers are mixed and a reaction between them occurs, their chains are connected in different points forming a net structure. The T_g value for this structure has to be greater than the T_g values of the pure polymers due to the less flexibility of the polymer combination (Elias 2003). In Figure 18 the T_g value of the mixture is between the T_g values of the pure polymers, meaning that even having this net structure, the flexibility is not reduced. This value can be explained by two factors. First, the solvents used for the mixture were

acetone and isopropanol, which could act as plasticizer, especially isopropanol. Isopropanol is extremely complicated to eliminate from a system, even when drying under vacuum. Secondly the amount of point where the two polymers react with each other are extremely low giving more flexibility to the polymer chains in the sediment.

The T_g of a polymer blend can be calculated using the Gordon-Taylor equation (Schellenberg et al. 1994; Schneider 1997) presented below (equation (3. 3).

$$T_g = \frac{(w_1 T_{g1} + K w_2 T_{g2})}{w_1 + K w_2} \qquad K \approx \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \qquad (3.\ 3)$$

where:

T_g= glass transition temperature from the blend [K]

w_i= weight fraction of the components

T_{gi}= glass transition temperature of the components [K]

K= parameter

ρ_i= density of the components [g/ml]

subscript 2 corresponds to the component with the higher T_g

Knowing the Tg and weight fraction of the components and that the density value of the poly(meth)acrylate is approximately 1.11 g/ml the theoretical value of T_g of the blend can be calculated.

Table 8 Theoretical values of T_g of the blends between EUDRAGIT® E PO and different anionic polymers mixed following different orders of addition. Calculation based on the polymer fraction values obtained with ^{1}H-NMR.

DSC	EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:2)	EUDRAGIT® E PO: EUDRAGIT® L 100 (1:2)	EUDRAGIT® E PO: EUDRAGIT® S 100 (1:1)	EUDRAGIT® E PO: EUDRAGIT® FS (2:1)
Cationic over anionic	81.4	101.7	96.0	46.9
Anionic over cationic	79.3	96.0	97.1	46.9
Simultaneous addition	79.3	99.4	97.1	46.9

All T_g values obtained from DSC measurements were higher than the theoretical values calculated with the Gordon-Taylor equation. Only the blends with EUDRAGIT® FS showed a lower experimental T_g value than the theoretical value.

The combination of these polymers does not show additivity of the components properties as is assumed in the Gordon-Taylor equation (Schneider 1997). The polymers react with each other building an IPEC. The lower values of the combinations with EUDRAGIT® FS can be explained with the low T_g from the anionic polymer and its low percentage of active groups reducing the chances to react with EUDRAGIT® E PO and therefore increasing the flexibility of the resulting IPEC.

3.1.1.9 Thermal gravimetric analysis (TGA)

This method was performed to determine the stability of the sediments at different temperatures (Price et al. 2000). The determination of the temperature where the first mass loss occurs was the aim of these trials. The mass loss can correspond to a decomposition of the product when the temperature increases.

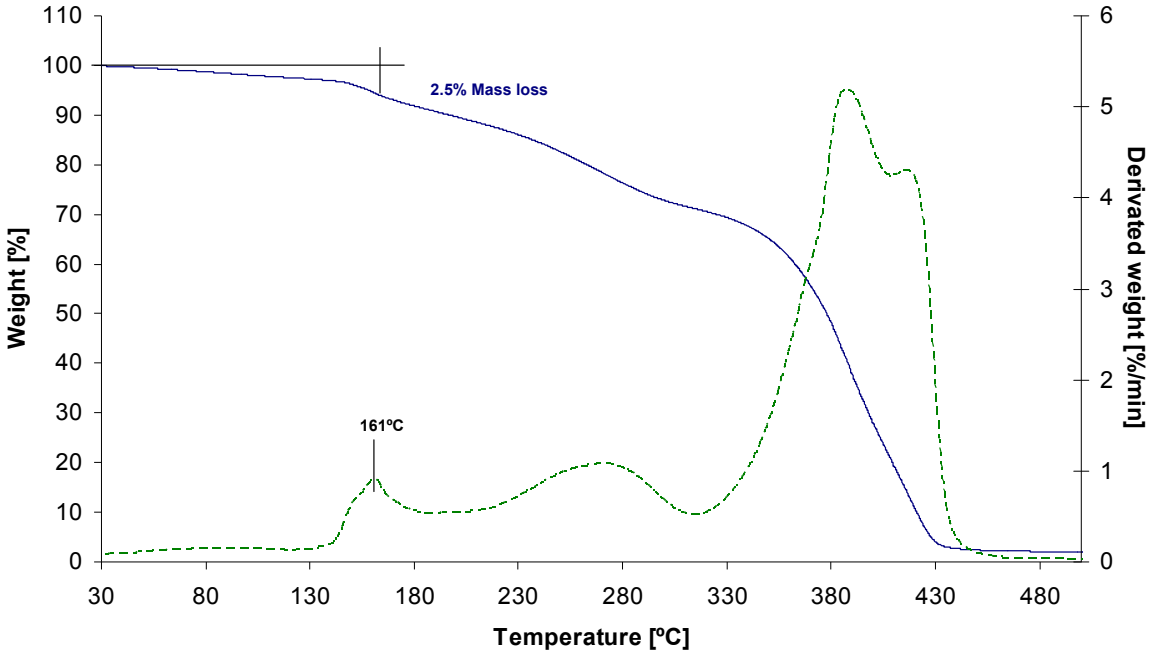


Figure 19 TGA diagram of sediment from the combination EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:2) molar ratio. The first mass loss was detected at a temperature of 161°C

The samples tested were the same as in the DSC trials (point 3.1.1.7). In all cases, the measurements followed similar patterns, having a first mass loss between 2 and 8% (Figure 19). The temperatures, where the mass losses occurred are listed below (Table 9):

Table 9 Results of the TGA experiments, temperature where the mass loss occur, measured on the sediments of EUDRAGIT® E PO with the different anionic polymers mixed following different orders of addition

TGA	EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:2)	EUDRAGIT® E PO: EUDRAGIT® L 100 (1:2)	EUDRAGIT® E PO: EUDRAGIT® S 100 (1:1)	EUDRAGIT® E PO: EUDRAGIT® FS (2:1)
Cationic over anionic	157ºC	158ºC	156ºC	137ºC
Anionic over cationic	161ºC	158ºC	162ºC	137ºC
Added simultaneously	165ºC	157ºC	149ºC	168ºC

The temperature where the mass loss took place was determined, but the reason for the mass loss was not identified. It can be concluded that these polymer combinations can be used in processes where heating is involved as long as the temperature does not reach the decomposition temperature of the polymers (Table 18) e.g. in melt extrusion.

3.1.1.10 Mass spectroscopy

Mass spectroscopy was performed to evaluate the components of the sediment that change with the temperature.

10 mg of sample was heated in a defined temperature interval from 20ºC up to 190ºC (Figure 20).

After 2 minutes of heating a peak with a value of relative abundance close to 100% could be observed corresponding to the first mass loss of the sample previously tested in the thermogravimetry analysis. This peak corresponds to the remaining isopropanol in the sample.

The mass loss was not caused by a decomposition of the sediment, but by residual isopropanol in the sediment, meaning that the complex is even more stable at high temperatures than expected from the TGA measurements.

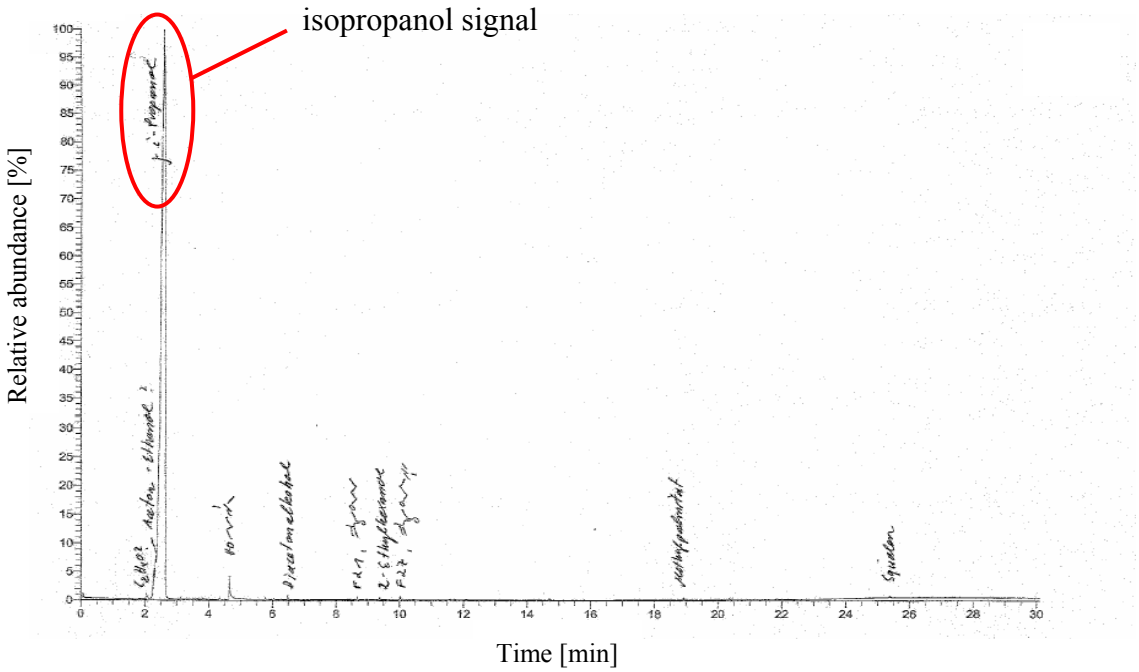


Figure 20 Detection of isopropanol signal using mass spectroscopy of EUDRAGIT® E PO with EUDRAGIT® L 100-55 combined at a molar ratio 1:2. Heating interval from 20°C to 190°C

3.1.1.11 Solid state nuclear magnetic resonance analysis (^{13}C-NMR)

^{13}C-NMR was used to confirm and detect the reaction between the two polymers. Combinations of EUDRAGIT® E PO with EUDRAGIT® L 100-55 were tested. The method could detect the displacement of the dimethylaminoethyl group in 2 ppm (Figure 21). This displacement is characteristic for the protonization of the nitrogen, that could result from the possible interaction between the dimethylaminoethyl group of EUDRAGIT® E PO and the carboxylic group of EUDRAGIT® L 100-55 (Kalinowski et al. 1984). Other combinations did not show any differences between a physical mixture of the polymers and the complex because of the low percentage of carboxylic groups content in the other anionic polymers.

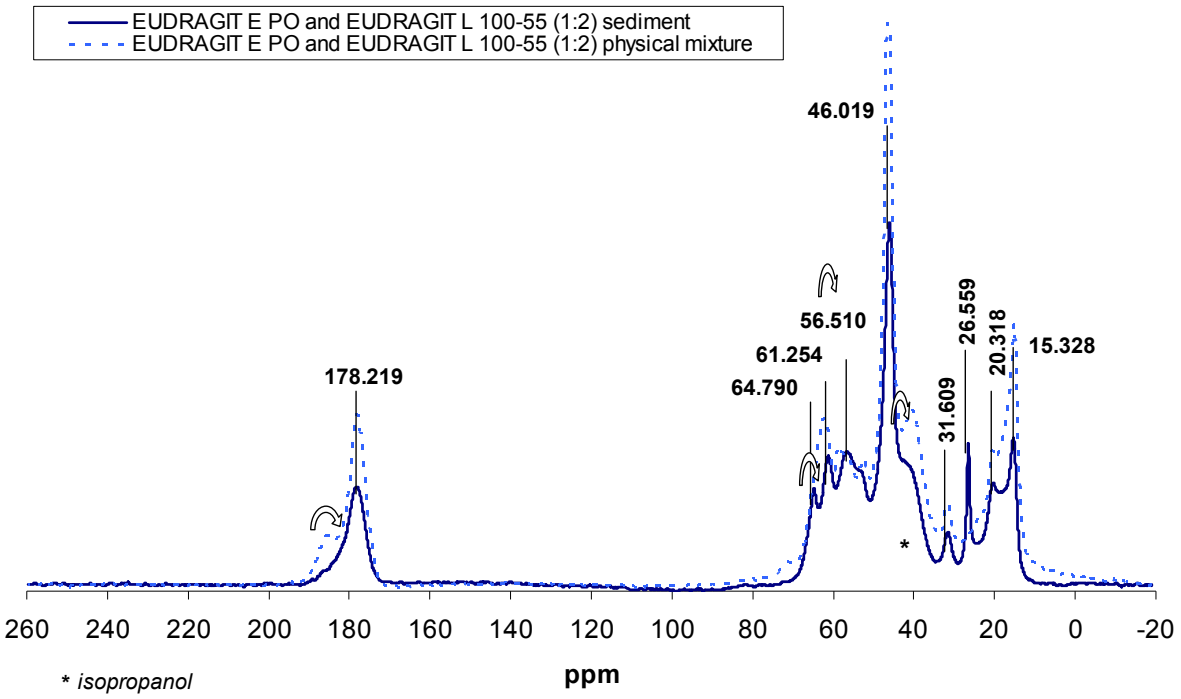


Figure 21 ^{13}C-NMR diagram of the 1:2 molar ratio sediment and a physical mixture with the same molar ratio

3.1.2 Supernatant

The supernatants from the combinations had different grades of turbidity inversely proportional depending on the amount of sediment collected. For these trials, the molar ratios from 1:4 to 4:1 of EUDRAGIT® E PO added over EUDRAGIT® L 100-55 were produced. The sediment was centrifuged and the supernatants were analyzed.

For the laser diffraction analysis, the supernatants were diluted with the original solvent mixture of isopropanol/acetone (60/40) (w/w) down to a concentration below 10%.

The results showed in almost all combinations similar mean values of particle size, below 0.5 micron (Figure 22 and Figure 23).

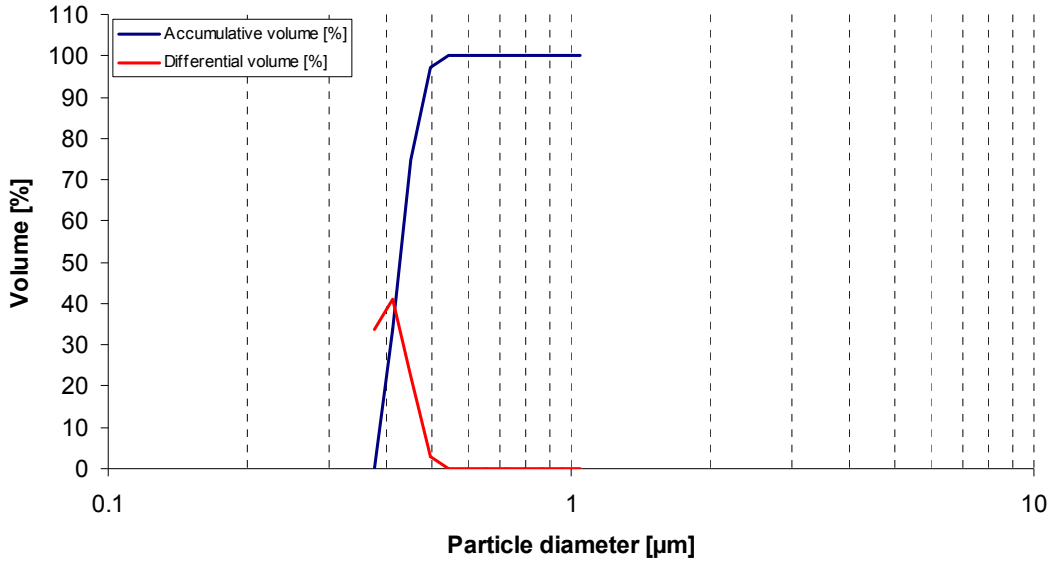


Figure 22 Representation of the percentage of accumulative and differential volume from the EUDRAGIT® E PO with EUDRAGIT® L 100-55 (1:2) supernatant

The only combination showing another profile was the 1:3 molar ratio. Here, from the moment that the combination was made and centrifuged until it was measured the next day, new sediment was formed. Although the combination was filtered with filter paper the separation was not as good as with the centrifugation, resulting in another shape of the profile.

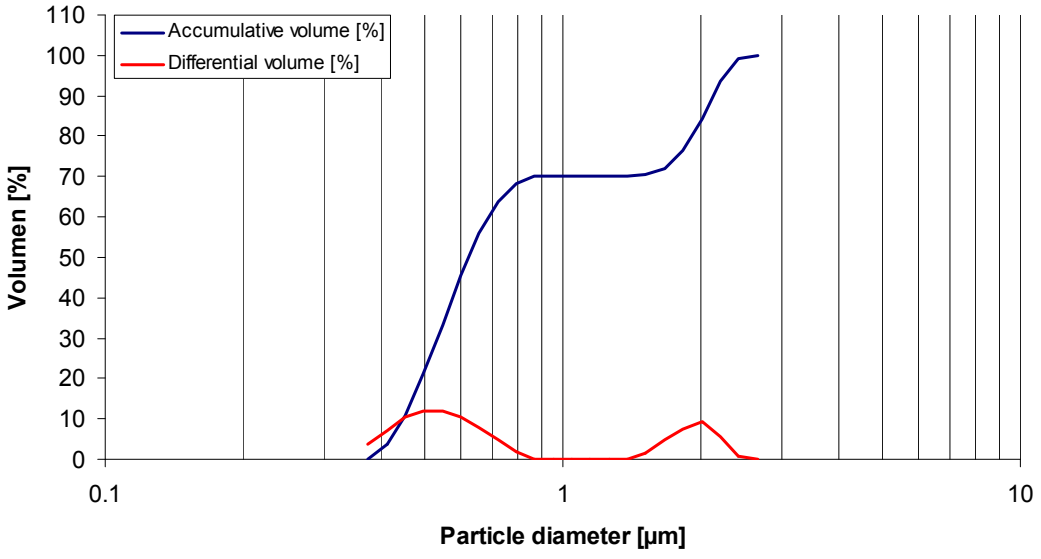


Figure 23 Representation of the percentage of accumulative and differential volume from the EUDRAGIT® E PO with EUDRAGIT® L 100-55 (1:3) supernatant. The new formation of sediment during the night led to a different profile.

The values for the particle diameter are listed below (Table 10):

Table 10 Particle diameter of the different combinations: mean value with standard deviation

	4 to 1	**3 to 1**	**2 to 1**	**1 to 1**	**1 to 2**	**1 to 3**	**1 to 4**
Mean value [µm] / SD	0.444 / 0.041	0.442 / 0.041	0.429 / 0.032	0.432 / 0.034	0.430 / 0.033	1.000 / 0.684	0.485 / 0.063

Almost all the samples still have precipitate in the supernatant with size equal or below 0.5 µm meaning that the centrifugation process could not separate these precipitate particles that remained suspended. All combinations formed a sediment formation. The amount of sediment varied with the particle size of the precipitates, leading to the differences in the results on the gravimetric trials.

The equipment used to measure the particle size can measure in two different modules: a module with minimum particle size detection below 0.4 µm used for aqueous dispersions. The other module measures organic solutions with a minimum particle size detection of 0.4 µm. Since the samples were prepared in isopropanol acetone mixtures, the lowest value detected was 0.4 µm.

3.1.3 Summary

The combination of countercharged polymethacrylic polymers formed a precipitate resulting from the ionic reaction between the dimethylaminoethyl group from EUDRAGIT® E PO and the carboxylic groups from the different anionic polymers. The precipitate is insoluble in the organic solvents used and resulting in more or less amount of sediment depending on the combination ratio. The amount of sediment was directly affected by the molar ratio of the combination, by the order of addition of the polymers and by the percentage of carboxylic groups of the anionic polymers. These different factors influence directly the particle size of the precipitate. When the size of the particles was larger than 0.5 µm, it was possible to separate the precipitate by centrifuging the sample. If it was smaller, the precipitate remained suspended in the organic solvent leading to more or less turbidity of the supernatant.

The composition of the sediment was directly affected by the molar ratio of the combinations. When the fraction of EUDRAGIT® E PO in the combination was low the proportion of this polymer in the sediment was greater than in the original proportion. The opposite occured

when the fraction of EUDRAGIT® E PO increases. The reactivity of EUDRAGIT® E PO was greater when its proportion in the combination was the lowest.

Fourier transform spectroscopy, DSC and ^{13}C-NMR were used to detect the ionic interaction between the two polymers and define the sediment as an IPEC. The first method showed a clear signal of carboxylate, resulting from the interaction between the two polymers. The miscibility of the two polymers was detected with the presence of a unique T_g in the DSC trials, as the T_g was found between the two T_g values of the pure polymers. This value could explain the hypothesis of the low percentage of points of interactions between the polymers giving the sediment flexibility. ^{13}C-NMR also confirmed the interaction, but only in the combination with EUDRAGIT® E PO and EUDRAGIT® L 100-55. In other combinations where the anionic polymers had a lower percentage of carboxylic groups the detection of interactions was not possible.

These IPECs also demonstrated their thermostability in the thermogravimetry trials. The first mass loss was detected at quite high temperatures making the use of the combination of these polymers at high temperatures possible, like in a melt extrusion process. The main mass loss was caused by the isopropanol still embedded in the dried sediments from the IPECs.

The use of IPEC as sustained release systems for drug release is known (Karnachi et al. 1996; Mitrevej et al. 2001; Moustafine et al. 2005; Moustafine et al. 2006; Moustafine et al. 2008). Therefore the next step after the characterization of the IPEC is the use of this complex in the manufacturing of matrix tablets with highly soluble drug using different processes. The first trials were developed with a neutral drug to avoid possible interactions with the drug that could influence the release profile.

3.2 Wet granulation with high shear mixer

3.2.1 Process description

The wet granulation was performed with two different methods, fluid bed and high shear mixer. The granulation process in fluid bed was not successful. The amount of inlet air that dried the wet mass did not make the granules formation possible. In the end, the product was a mixture of all components of the formulation (drug+filler) with the polymers but not bound in granules. Therefore the use of the high shear mixer was selected. With this process the process time and the humidity increased, making the reaction between the polymers easier leading to a granule formation. The drug and excipients can be homogeneously mixed with the help of a granulation liquid, in this case polymer dispersion (Ritschel et al. 2002).

For these trials a model drug, diprophylline, and filler, EMCOMPRESS® were selected. Diprophylline was chosen due to its high solubility (point 6.1.2) and because of its neutral character. The neutral drug was chosen to avoid possible interactions between the polymers and drug causing a change in the release profile. Once the sustained release properties of the IPEC are investigated with diprophylline, granulations with other drugs having other ionic character can be performed to evaluate possible interactions between IPEC and drug.

EMCOMPRESS® was selected as filler due to its good binding and flow properties. It is non hygroscopic and is practically insoluble in water, but soluble in diluted acids (Schmidt et al. 1993; Schlack et al. 2001).

The polymers selected for the granulations were EUDRAGIT® E PO and EUDRAGIT® L 100-55 (powder grade) or EUDRAGIT® L 30 D-55 (aqueous dispersion) depending on the trials performed. These polymers were selected for the reasons previously described (point 3.1.1.4).

The aim was to perform aqueous granulations avoiding the use of organic solvents due to the environmental problems related to organic solvents. The trials were performed following always the same pattern. First, the cationic polymer was added via an opening in the lid of the mixer. Then the anionic polymer was added the same way. The order of addition showed an influence on the sustained release properties.

3.2.2 Preliminary trial

The first set of trials was performed to evaluate the differences in the release profile when using pure polymers or IPEC using the simplest formulations, dispersing the polymers only in water. EUDRAGIT® E PO was combined with EUDRAGIT® L 100-55 in different molar ratios from 1:4 to 4:1. Beside these combinations, matrix tablets with pure polymers and with EUDRAGIT® RS PO were manufactured. The polymer dispersions had 30% polymer content and the percentage of polymer applied to the dry powder (diprophylline + EMCOMPRESS®) was 16.7% (Table 11).

The wet mass was granulated after the mixing process and dried at 40ºC during 24 hours. The granules were mixed with magnesium stearate and compressed in the eccentric tabletting machine. All tablets were compressed with the same compression force (10 kN). The characteristics from drying, mixing and tabletting are described in the experimental section (point 6.2.2). The dissolution from the tablets was first tested for 2 hours in acidic media, followed by 6 hours in phosphate buffer 6.8 (Figure 24).

Table 11 Formulations for the trials in high shear mixer. The ratios of the combinations correspond to the molar ratios of EUDRAGIT® E PO to EUDRAGIT® L 100-55

	EUDRAGIT® E PO	EUDRAGIT® L 100-55	EUDRAGIT® RS PO	Combination 4:1	Combination 3:1	Combination 2:1	Combination 1:1	Combination 1:2	Combination 1:3	Combination 1:4	Percentage [%]
Diprophylline [g]	175	175	175	175	175	175	175	175	175	175	29.2
Emcompress® [g]	325	325	325	325	325	325	325	325	325	325	54.1
EUDRAGIT® E PO [g]	100			87.7	84.3	78.1	64.1	47.2	37.3	30.9	16.7
EUDRAGIT® L 100-55 [g]		100		12.3	15.7	21.9	35.9	52.8	62.7	69.1	
EUDRAGIT® RS PO [g]			100								
Water [g]	233.3	233.3	233.3	233.3	233.3	233.3	233.3	233.3	233.3	233.3	---

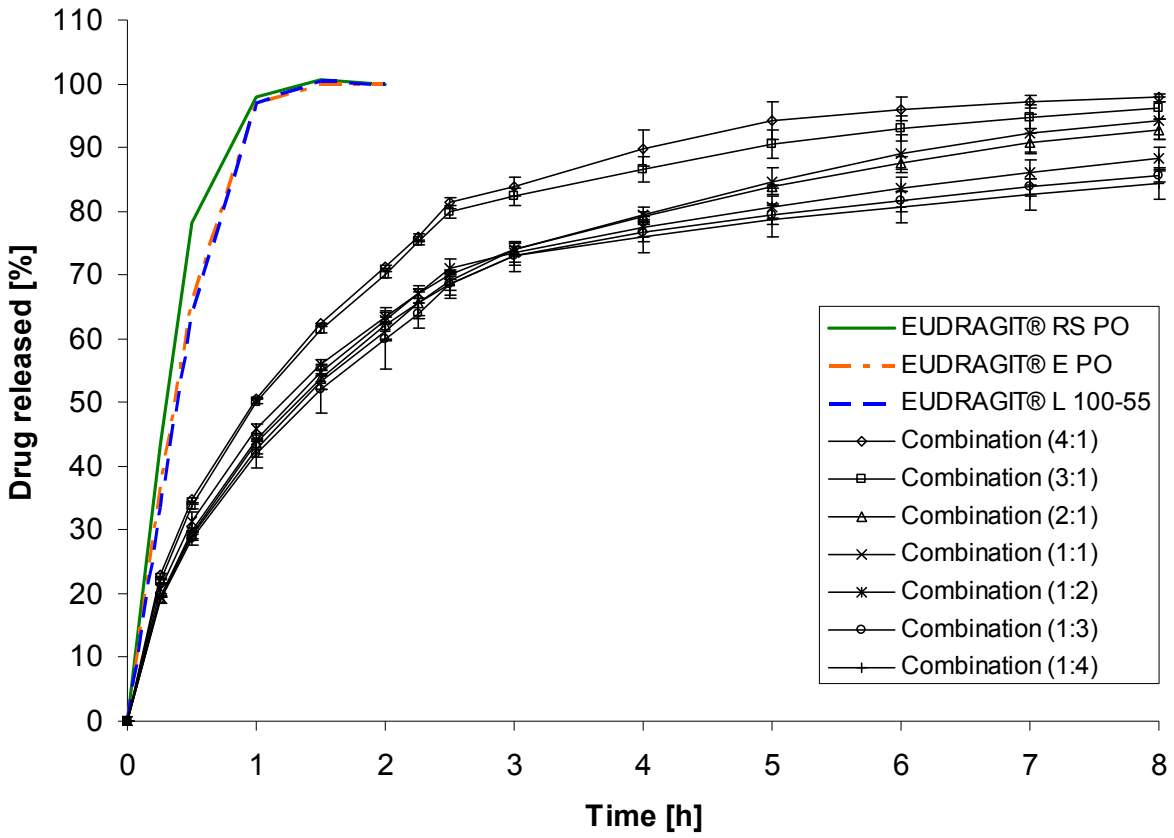


Figure 24 Release profile of Diprophylline matrix tablets in 700 ml of 0.1 N HCl for the first two hours followed by 6 hours in phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Test Apparatus II, 50 rpm. Nominal weight 500 mg. Diameter 12 mm. Curvature radius 25 mm. Compression force 10 kN. (n=3)

The tablets containing only pure polymers disintegrated within the first 2 hours releasing the total amount of drug. Only when using a combination of polymers a sustained release profile over 8 hours was achieved. The interaction between the two polymers forming the IPEC reduces the chance of burst effect, shown in the samples with only one polymer. The release in acidic medium was fast, but when the pH of the medium increases to 6.8 the tablets swelled producing a stronger sustained release. The swelling effect of the IPEC showed the hydrophilic character of the active groups that did not interact to form the IPEC. These active groups are sensitive to erosion in acidic medium and sensitive to swelling in phosphate buffer pH 6.8 (de la Torre et al. 2003; Moustafine et al. 2005; Moustafine et al. 2006). The phosphate and sodium ions from the buffer could interact with the free active groups from the polymers accelerating the IPEC formation increasing the stability of the structure. The pH change had an influence on the release mechanism. The release profile in 0.1 N HCl followed a first order release kinetic, while the release in 6.8 seems to be closer to a zero-order release

kinetic. The clear difference in the release profile when varying the pH, could be due to a high percentage of free active groups of EUDRAGIT® E PO not interacting with carboxylic groups from the anionic polymers. Since the dimethylaminoethyl groups have a higher reactivity than the carboxylic groups, they are more sensitive to the pH variations than the carboxylic groups from the anionic polymers.

The release profile from the different molar ratios from the IPEC showed an increase on the sustained release as the EUDRAGIT® L 100-55 fraction increased. These differences are clearer seen on the release of the combinations with 4:1 and 3:1 molar ratio. Here the release was more rapid compared to the other combinations. The higher content of EUDRAGIT® E PO in the IPEC makes these combinations more sensitive to erosion in acidic medium accelerating the release of the drug. The release in 0.1 N HCl was over 10% faster than with the rest of the combinations. In pH 6.8, the differences were directly related to the percentage of EUDRAGIT® L 100-55 in the combination. The higher the percentage, the slower is the release. EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:4) showed the slowest release from all the combinations.

These results showed that the interaction between these polymers can provide a stronger sustained release than the pure polymers or even a matrix former such as EUDRAGIT® RS PO, when they are only dispersed in water (Fukuda et al. 2006).

The next step was to change the formulations to provide a stronger release profile. Parameters like particle size from the polymers, used plasticizers, variation of the drug filler fraction, polymer applied, polymer combination or temperature were evaluated in the trial plan. The aim of the trial plan was to define which parameters are significant to provide a strong sustained release.

3.2.3 Trial plan: results and statistical interpretation

The trial plan was performed using diprophylline as model drug and EMCOMPRESS® as filler. The polymer formulations were changed for the trial plan to improve the sustained release. The aqueous dispersion from EUDRAGIT® L 100-55 (EUDRAGIT® L 30D-55) was used because particle sizes of the polymer are smaller improving the polymer distribution in the mass (Figure 4). The aqueous dispersion was mixed with triethyl citrate (TEC) as plasticizer. The addition of a plasticizer reduces the T_g and the minimum film-forming temperature (MFT), increasing the elasticity and adhesiveness of the polymer leading to an

increase of the breaking resistance of the tablets. This property could increase the sustained release of the matrix tablets (Rey et al. 2000).

EUDRAGIT® E PO was prepared following a recommended standard formulation (SF) to obtain a colloidal solution (Pharma polymers 2008). The formulation consists of a mixture of the polymer with 10% sodium lauryl sulfate and 15% stearic acid based on the polymer dry substance. The maximum polymer content in this case had to be reduced down to 18% because of the high viscosity of the colloidal solution.

A 2^4 statistical study was developed. The factors evaluated in this study are the temperature used in the process, the amount of polymer applied, the polymer combination (EUDRAGIT® E PO fraction) and the amount of diprophylline in the formulation in relation to EMCOMPRESS® (diprophylline fraction). The details of these factors are listed in the experimental section (point 6.2.2.7). The aim of the trial plan was to determine the reproducibility of the trials and observe the significance of the factors described above that could affect the release profile.

The statistical study is composed of 16 (2^4) trials plus 3 central points to evaluate the reproducibility of the data. The factor values are listed in Table 12.

Table 12 Values of the different factors tested from the granulations performed for the statistical plan

Trial number	Temperature [ºC]	Polymer content [%]	EUDRAGIT® E PO fraction	Diprophylline fraction
1	40	20.00	0.20	0.35
2	40	20.00	0.20	0.55
3	***50***	***18.35***	***0.50***	***0.45***
4	60	20.00	0.67	0.55
5	60	16.70	0.67	0.55
6	40	16.70	0.67	0.35
7	60	20.00	0.20	0.35
8	60	20.00	0.67	0.35
9	40	16.70	0.20	0.35
10	***50***	***18.35***	***0.50***	***0.45***
11	60	16.70	0.67	0.35
12	40	20.00	0.67	0.55
13	40	20.00	0.67	0.35
14	40	16.70	0.20	0.55
15	60	16.70	0.20	0.55
16	60	20.00	0.20	0.55
17	40	16.70	0.67	0.55
18	60	16.70	0.20	0.35
19	***50***	***18.35***	***0.50***	***0.45***

3.2.3.1 Analysis of the granules

After the mixing and granulation processes described in the experimental section (point 6.2.2.3) the granules obtained were dried in a drying oven. The analyses performed on the granules were water content, particle size distribution, compressibility and determination of the mean particle size (d'). The summary of all the analysis is described in the appendix (Table 37, Appendix).

The water content was determined after drying until a constant mass value was achieved. The great differences in the loss on drying (LOD) values were statistically analyzed (2^4 statistical study). None of the independent variables or the combination between them showed a significant influence. The coefficient of determination was 0.53.

A possible explanation for the variability in the results can be the low capacity of the drying oven. The high number of batches to dry at the same time and so frequently, possibly had an influence on the air humidity inside the drying oven reducing the capacity to eliminate the remaining water of the batches, especially between the batches 6 and 19.

The particle sizes distribution was analyzed according to Rosin, Rammler, Sperling and Bennet (RRSB). The mass fraction versus the sieve sizes were represented in a double logarithmic grid (RRSB grid) DIN 66145 (De Souza et al. 2000). This representation gives a straight line allowing calculating the charactersitic particle size corresponding to the 63.2% of the mass fraction ($d'=1-e^{-1}$). The granules size for tabletting or capsule filling are normally in the interval between 300 and 800 μm (Serno et al. 2007).

The graph with the particle sizes distribution is represented in Figure 25.

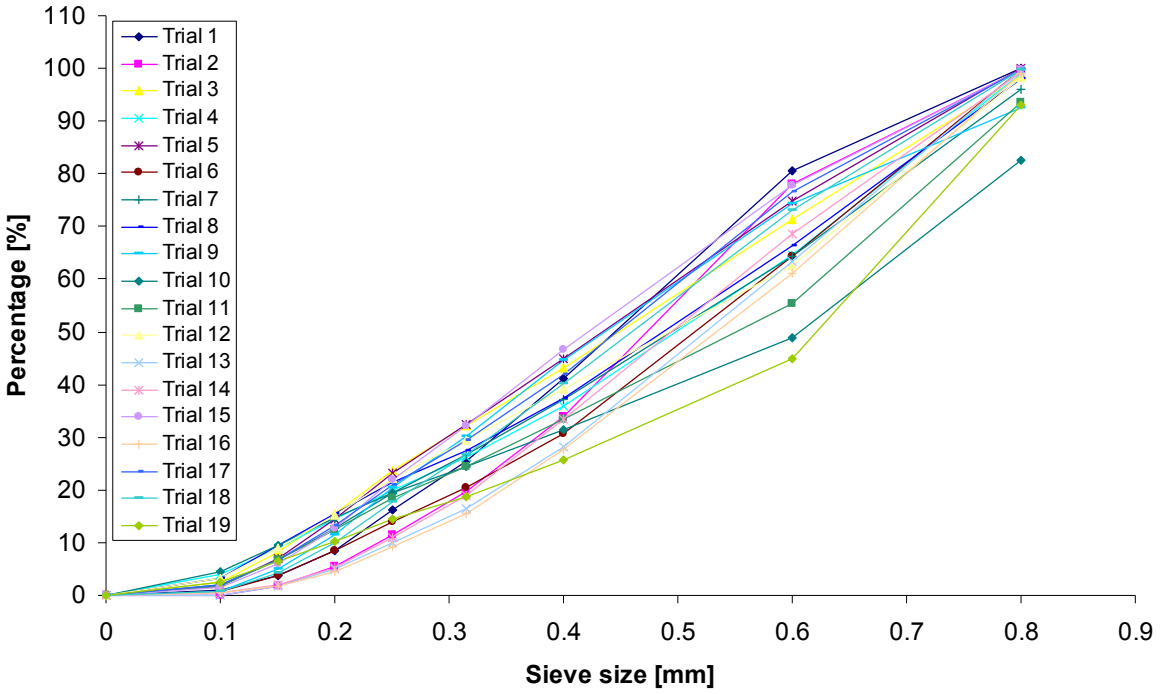


Figure 25 Particle size distribution of the 19 batches manufactured for the statistical trial plan

The d' value for all the batches was within the interval between 300 and 800 µm, meaning that the granules from all the batches were suitable for tabletting. The great differences in the particle size, especially observed in the 600 µm fraction were statistically analyzed. None of the independent variables or the combination of them showed a significant influence on the particle size. The coefficient of determination was 0.25. This random variability on the values can be the result of the differences in the process time and the drying during the mixing process.

The bulk density was the poured density and the tapped density after the tapping process. The Hausner factor is a measure for the flowability/compressibility of powders and should be close to 1. Preferably granules should have a Hausner factor lower than 1.16 for preparing tablets (Serno et al. 2007).

The results showed optimal flow properties in all batches (Table 37). The results were also statistically analyzed and none of the factors of the trial plan had a significant influence on the result. The coefficient of determination was 0.44.

3.2.3.2 Compression

3.2.3.2.1 Equipment

All the batches were mixed with magnesium stearate. Then the mixture was compressed using an eccentric machine. Description of weight, dimensions and compression force is described in the experimental section (point 6.2.2.6).

Different characteristics from the produced tablets were evaluated. These characteristics were breaking resistance, height, weight, density and release profile.

3.2.3.2.2 Tablet breaking resistance, weight and height

The method used to obtain the values is described in the experimental section (point 6.3.4).

The breaking resistance values are listed in the appendix (Table 38, Appendix). The values were statistically analyzed to observe a significance influence of the factors on the breaking resistance.

Figure 26 shows the significance of EUDRAGIT® E PO fraction, the diprophylline fraction and the combination of the polymer content with EUDRAGIT® E PO on the breaking resistance of the tablets. The first two factors are more significant than the third.

Since the EUDRAGIT® E PO colloidal solutions applied was more diluted than the EUDRAGIT® L 30D-55 it acted as binding material but also dissolved partially the drug. This partial dissolution helped the adhesion between the particles, forming harder granules (Bauer et al. 2006). This effect was stronger when the fraction of diprophylline increased.

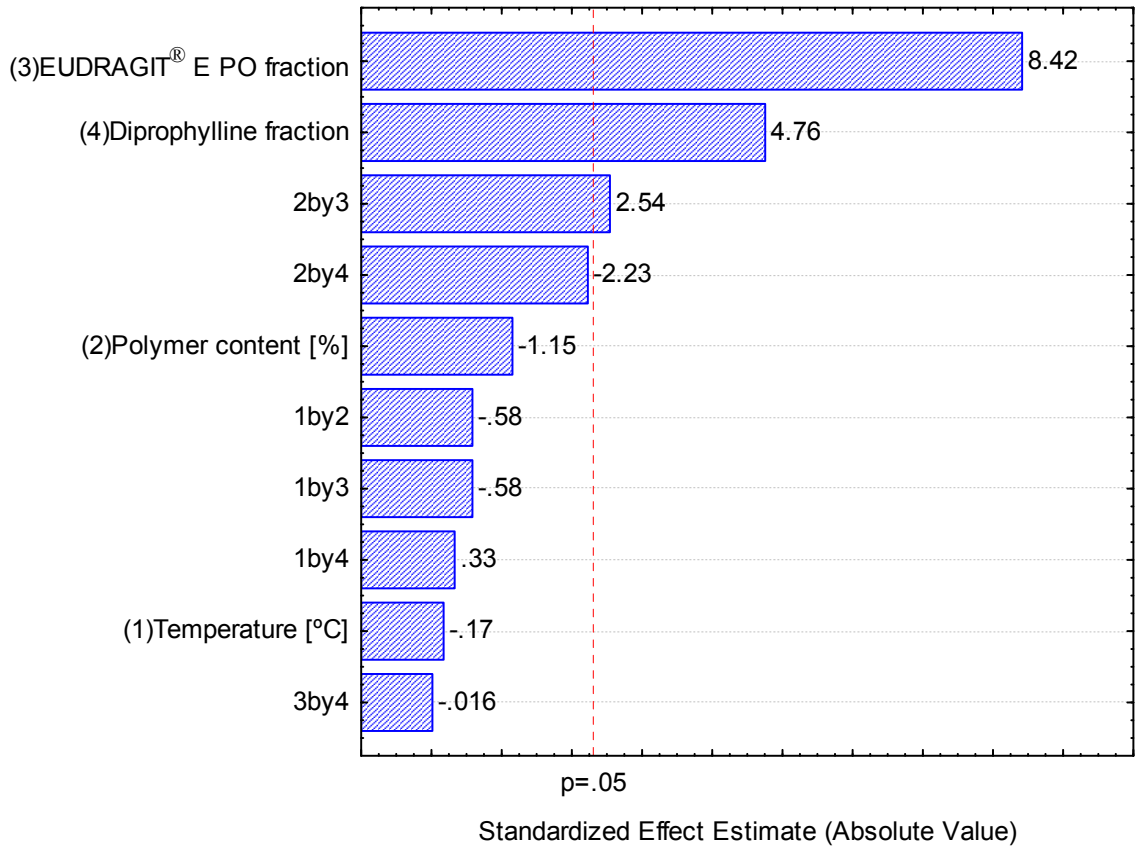
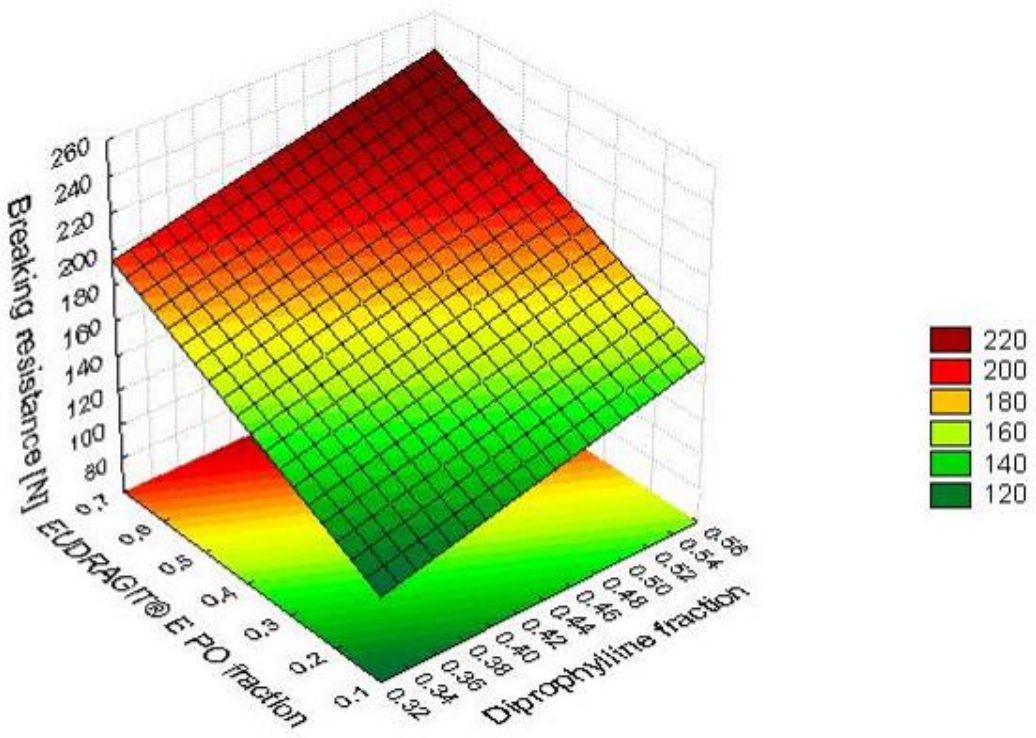


Figure 26 Significance of the different factors on the breaking resistance of the matrix tablets manufactured from the trial plan

A surface plot with the two significant factors is shown in Figure 27. Since the other two factors, polymer content and temperature, did not show a significant influence on the breaking resistance of the tablets, they were fixed with their mean values tested in this statistical study (18.35% polymer content and 50ºC temperature). The coefficient of determination was 0.93.



z=-265.778+(2.340*w)+(16.988*v)+(-284.980*x)+(1103.714*y)+(-0.140*917.5)+
(-0.984*w*x)+(1.313*w*y)+(25.951*v*x)+(-53.409*v*y)+(-2.660*x*y)

z=-265.778+(2.340*50)+(16.988*18.35)+(-284.980*x)+(1103.714*y)+(-0.140*917.5)+
(-0.984*50*x)+(1.313*50*y)+(25.951*18.35*x)+(-53.409*18.35*y)+(-2.660*x*y)

z=43.50+142.02x+189.31y-2.66xy

Figure 27 Response surface plot and model equation representing the influence of the EUDRAGIT® E PO and diprophylline fraction on the breaking resistance of the matrix tablets. The other two factors are fixed with their central values v= polymer content (18.35%) and w= temperature (50ºC). z= breaking resistance value; y= EUDRAGIT® E PO fraction; x= diprophylline fraction; xy= interaction from EUDRAGIT® E PO fraction and diprophylline fraction

The same statistical analysis was performed for the weight values (Table 39, Appendix). None of the factors had a significant influence on the result. The coefficient of determination was 0.56.

3.2.3.2.3 Tablet density

This value was calculated based on the weight and the geometry of the tablet. The values used were the previous values from multicheck results (Table 39, Appendix) and the dimensions from the punch (12 mm diameter and 25 mm curvature radius).

The density values (Table 40, Appendix) were statistically analyzed to observe which factor has a significant influence on the density of the tablets. The polymer content and especially the diprophylline fraction showed to be significant. The less amount of diprophylline was, the higher was the density. EMCOMPRESS® is an excipient with a high density (2.89 g/ml) (Schüssele et al. 2003; Rowe et al. 2006) therefore, those batches with a higher fraction of EMCOMPRESS® in the formulation showed higher density values and vice versa. The polymer content was significant. Those formulations with less amount of polymer showed a higher percentage of fines, increasing the value of the tablet density (Bauer et al. 2006).

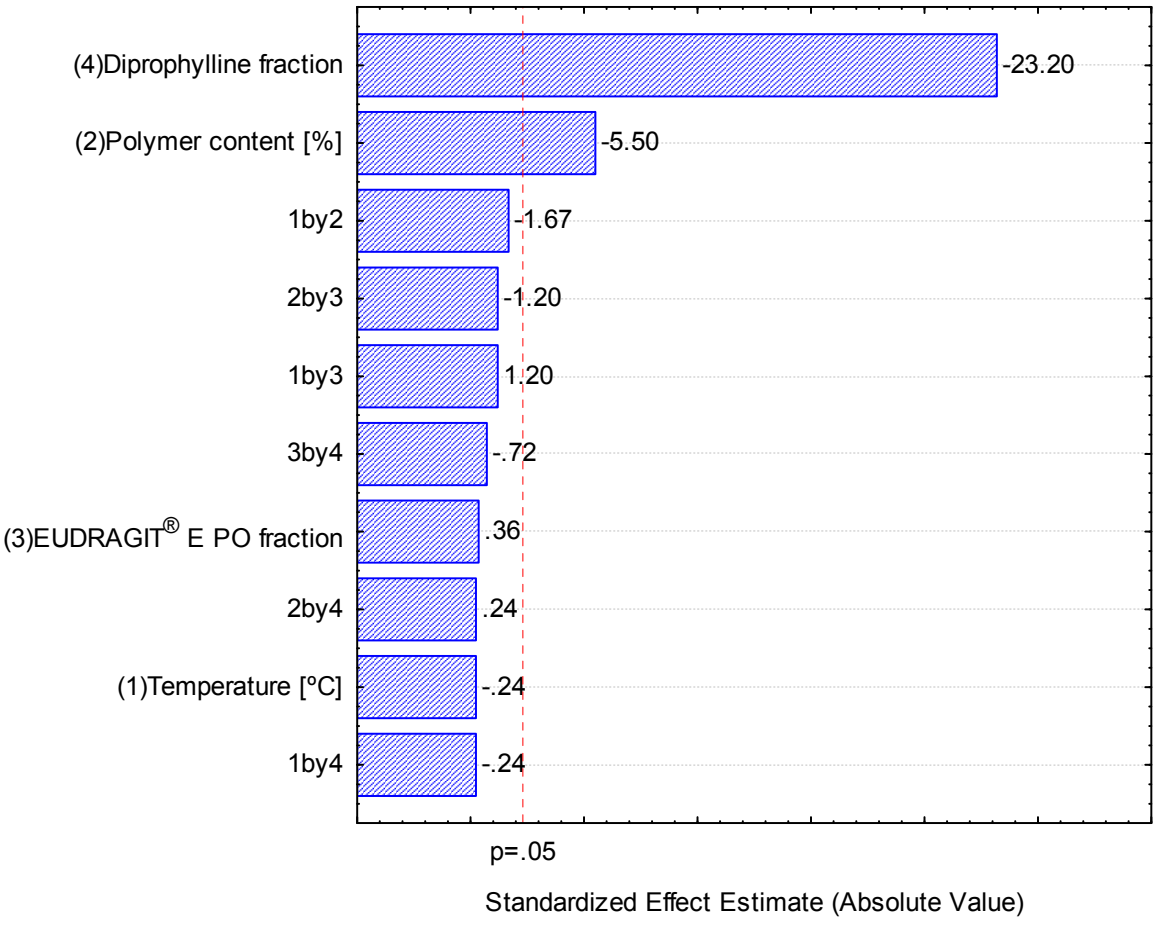
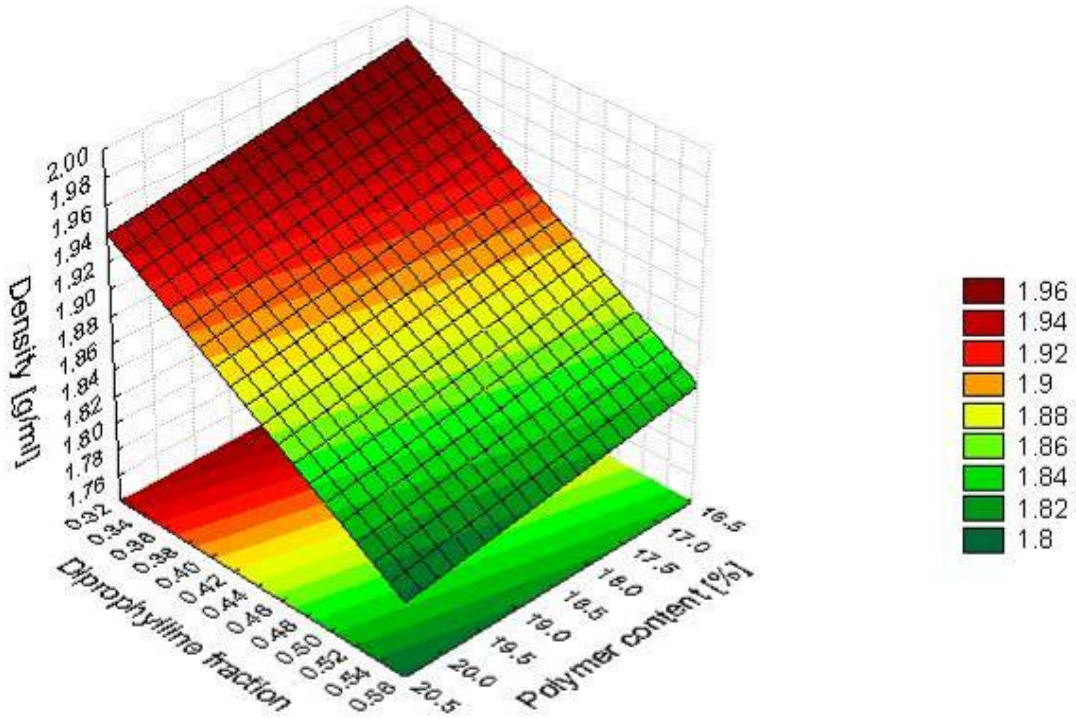


Figure 28 Significance of the different factors on the density of the matrix tablets manufactured from the trial plan.

The response of the two factors previously discussed can be seen in the surface plot in Figure 29. The coefficient of determination was 0.99



Z=2.037477+(0.004506*w)+(0.006347*x)+(0.121270*v)+(-0.609800*y)+
(-0.000265*w*x)+(0.001330*v*w)+(-0.000625*w*y)+(-0.008059*v*x)+(0.003788*xy)+(-0.079787*v*y)

Z=2.037477+(0.004506*50)+(0.006347*x)+(0.121270*0.5)+(-0.609800*y)+
(-0.000265*50x)+(0.001330*25)+(-0.000625*50y)+(-0.008059*0.5x)+(0.003788*xy)+(-0.079787*0.5y)

z=2.36-0.011x-0.68y+0.003788xy

Figure 29 Response surface plot and model equation representing the influence of the diprophylline fraction and polymer content on the density of the matrix tablets. The other two factors are fixed with their central values v=EUDRAGIT® E PO fraction (0.50) and w= temperature (50ºC). z= density value; y= diprophylline fraction; x= polymer content percentage; xy= interaction from polymer content percentage and diprophylline fraction

3.2.3.3 Dissolution test

The dependent variable was the percentage of drug dissolved after 2 hours. The values are described in the appendix (Table 41, Appendix).The different release profiles are shown in Figure 30.

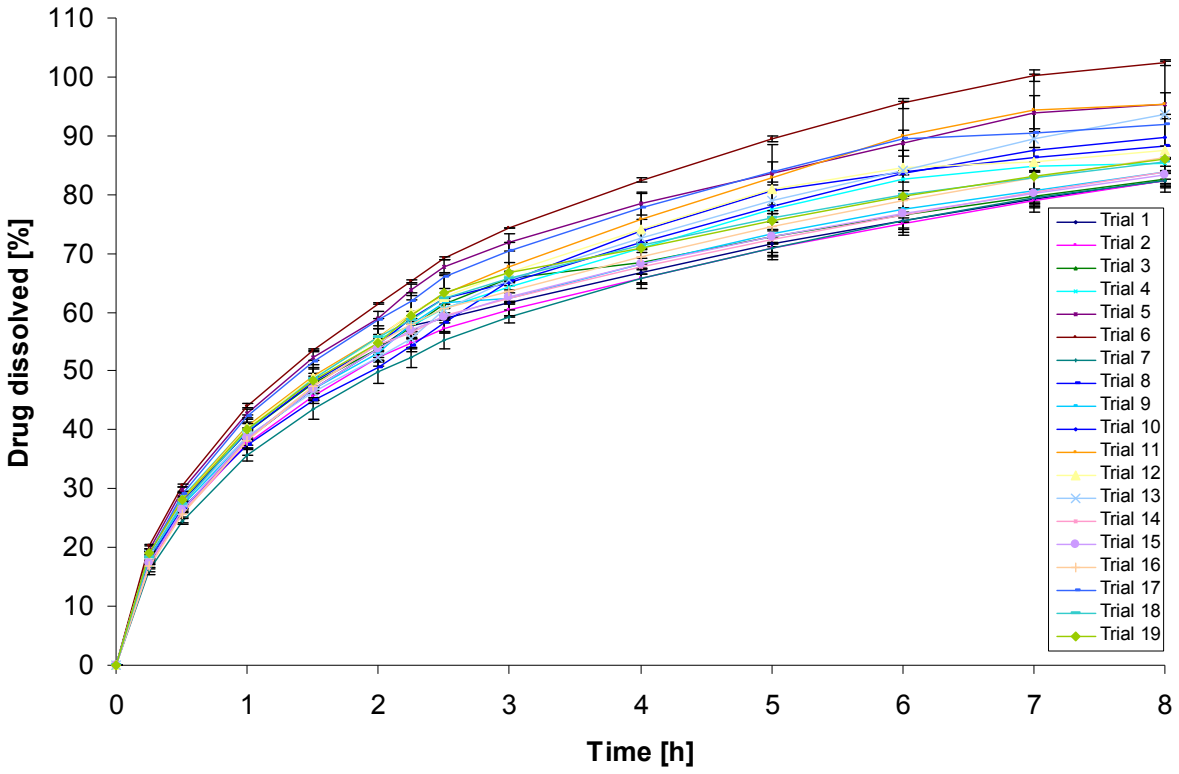


Figure 30 Release profile of all the diprophylline matrix tablets from the trial plan. Dissolution test performed in 700 ml of 0.1 N HCl the first two hours followed by phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Test Apparatus II, 50 rpm. Nominal weight 500 mg. Diameter 12 mm. Curvature radius 25 mm. Compression force 10 kN. (n=3)

The differences in the release profile after 2 hours were within 11% of drug dissolved, even though 4 variables were varied in the trial plan. The data was statistically analyzed to observe the significance of the factors on the drug released after 2 hours (Figure 31).

The analysis showed mainly the polymer content showed significance. When the polymer content increased the sustained release was stronger. At a lower polymer level, EUDRAGIT® E PO fraction, the combination of polymer content with the diprophylline fraction, and the combination of the temperature with the diprophylline fraction were significant. The increase of EUDRAGIT® E PO or diprophylline fraction accelerated the release of the drug. The hydrophilic character of EUDRAGIT® E PO previously described (point 3.2.2), can make the

matrix sensitive to erosion in acidic medium. The high solubility of the drug enhanced its dissolution when the diprophylline fraction was increased.

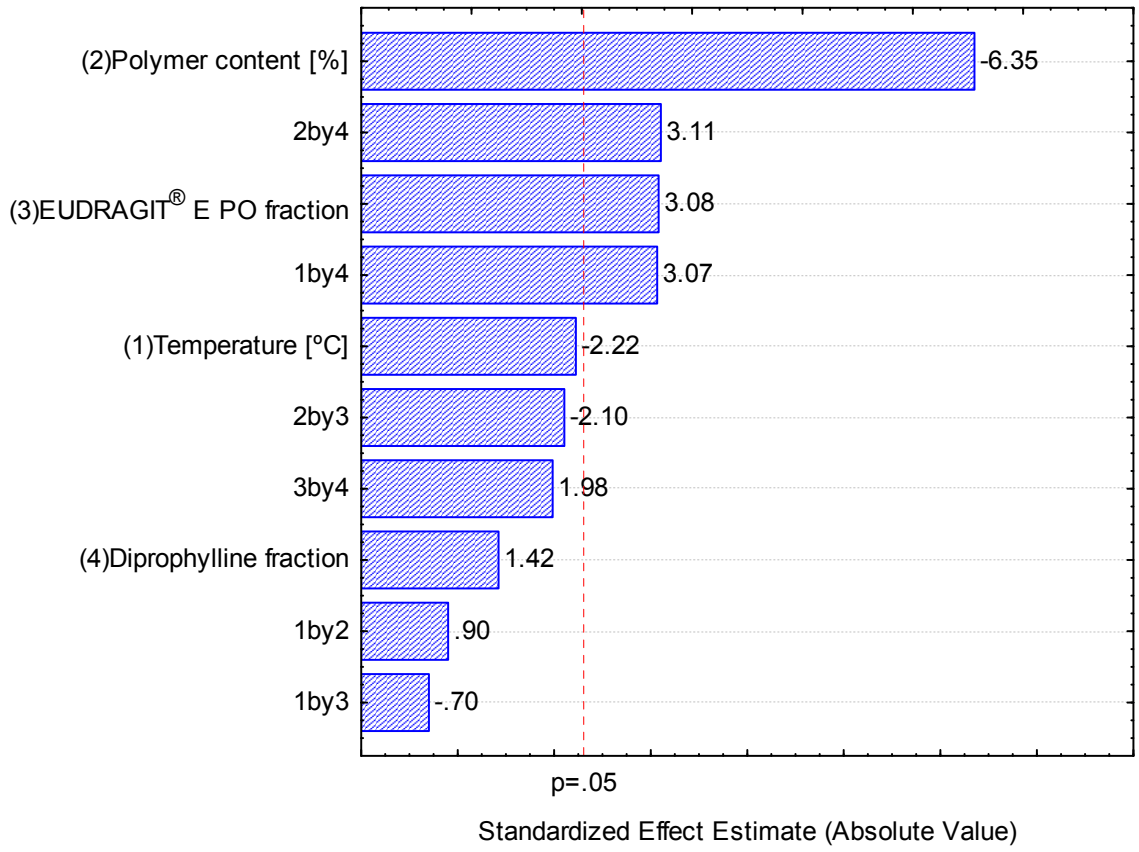
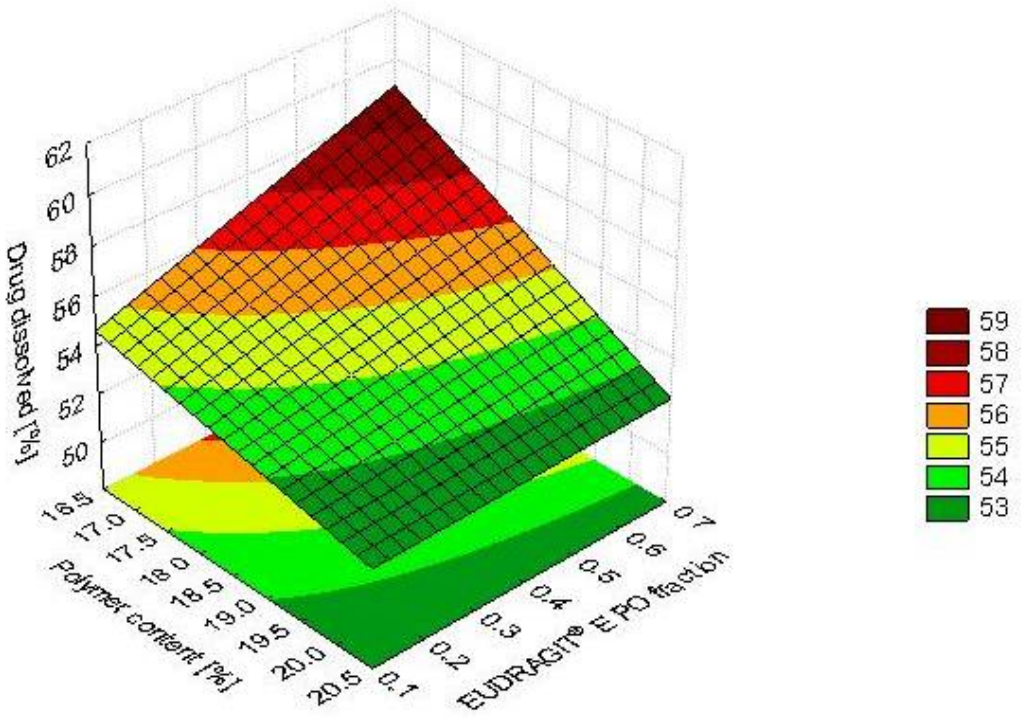


Figure 31 Significance of the different factors on the release of diprophylline after 2 hours of dissolution of the matrix tablets manufactured from the trial plan

EUDRAGIT® E PO and polymer content were chosen as factors fixing the other two factors to their center point values, in this case the temperature at 50ºC and the diprophylline ratio at 0.45 (Figure 32). The coefficient of determination was 0.91. From the surface plot the stronger influence of the polymer content on the sustained release of the tablets can clearly be observed.



z=151.783+(-0.772*v)+(-3.959*y)+(27.928*x)+(-162.565*w)+(0.017*v*y)+(-0.093*v*x)+(0.956*v*w)+(-1.692*x*y)+(5.871*w*y)+(26.330*w*x)

z=151.783+(-0.772*50)+(-3.959*y)+(27.928*x)+(-162.565*0.45)+(0.017*50*y)+(-0.093*50*x)+(0.956*22.5)+(-1.692*x*y)+(5.871*0.45*y)+(26.330*0.45*x)

z=61.54+35.13x-0.47y-1.692xy

Figure 32 Response surface plot and model equation representing the influence of the polymer content and the EUDRAGIT® E PO fraction on the percentage of drug dissolved after 2 hours in 0.1 N HCl. Fixed factors: v= temperature (50ºC) and w= diprophylline ratio (0.45). z= percentage of drug dissolved after 2 hours; y= polymer content percentage; x= EUDRAGIT® E PO fraction; xy= interaction from EUDRAGIT® E PO fraction and polymer content percentage

The results from the trial plan showed a low variability on the sustained release of the drug after two hours in dissolution. A reason for the low variability can be the high percentage of EMCOMPRESS® in the formulation.

This excipient is suitable for the matrix formation, improves the flowability of the granules but is soluble in acidic medium. The presence of this excipient in the formulation could have a great influence on reducing the sustained release effect, especially in the first two hours of dissolution.

The next trials were focused on the influence of EMCOMPRESS® on the release of diprophylline.

3.3 Granulation with different amount of polymer

3.3.1 Preliminary trials

For the preliminary trials, diprophylline was chosen as model drug. The formulation of the tablets was changed. After observing the low variability on the release profile in the trial plan, EMCOMPRESS® was removed. It was also assumed that the presence of stearic acid in the EUDRAGIT® E PO standard formulation could compete with EUDRAGIT® L 30 D-55 reducing the chances to form the IPEC. Therefore stearic acid was also removed.

Four different formulations were tested, where these two excipients were systematically included/excluded from the formulation (Table 13). All the formulations were mixed with 20% EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) 1:4 molar ratio. This polymer combination provided the slowest release profile of the trial plan (point 3.2.3.3).

Table 13 Variation of the excipients including or excluding EMCOMPRESS® and stearic acid based on the formulation that provided the slowest release profile in the trial plan. The variation of the excipients changed the drug content. PF=preliminary formulation

	EMCOMPRESS® [%]	**Stearic acid [%]**	**Drug content [%]**
PF 1			80.7
PF 2		15	80.7
PF 3	54		28.2
PF 4	54	15	28.2

Only the drug content should have a great influence on the release profile, but even an increase of drug content over 50% showed only a variation of 10% on the release profile (Figure 33).

The formulation without stearic acid and EMCOMPRESS® showed a faster release than the other formulations. The results showed that the IPEC formation was not affected by the presence of stearic acid.

To keep the formulation as simple as possible, the combination without stearic acid and EMCOMPRESS® was selected. The differences in the release profile were within 10% and

the reduction of the polymer volume (without stearic acid, EUDRAGIT® E PO can be prepared as a suspension containing 30% polymer) improved the granulation time.

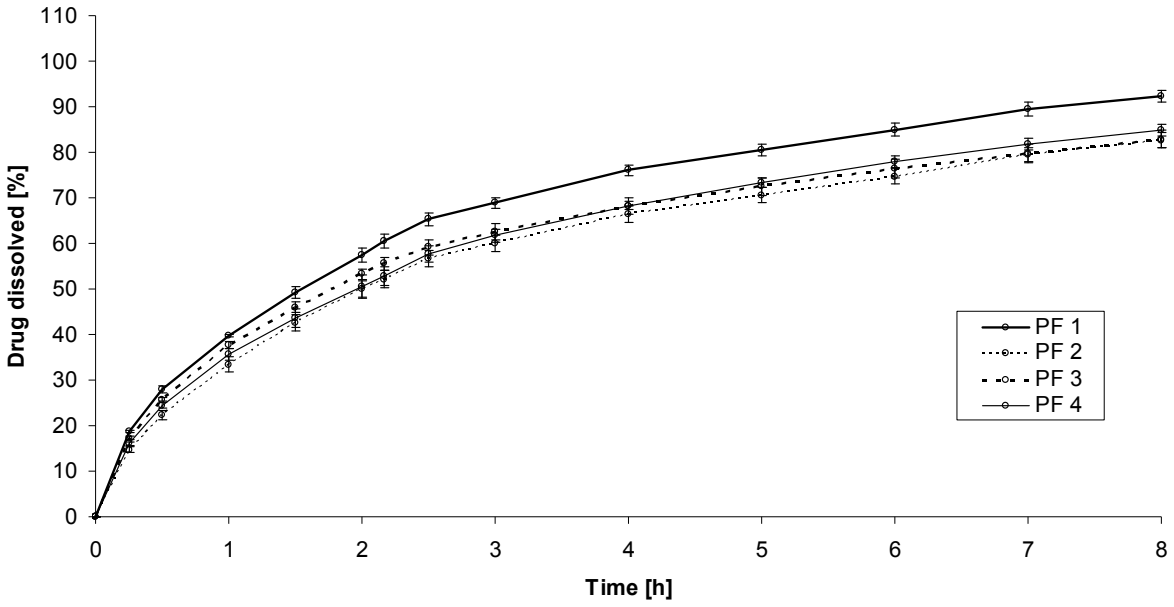


Figure 33 Release profile of diprophylline matrix tablets. Influence on the sustained release of diprophylline depending on the use of Emcompress® and/or stearic acid. Dissolution test performed in 700 ml of 0.1 N HCl the first two hours followed by phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Test Apparatus II, 50 rpm. (n=3)

The next parameter to determine was the polymer content needed to provide sustained release.

3.3.2 Granulation with different polymer percentage

Diprophylline was chosen again as model drug and the polymer combination selected in the previous point was used. The granulations were performed using 5%, 10%, 15%, 20% and 50% of polymer. The same trials were performed with EUDRAGIT® RS 30 D (inert poly(meth)acrylate used as matrix former) to compare the variation on the release profile. The formulations are described in Table 14.

Table 14 Description of the formulations varying polymer content. Dip= diprophylline; EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); RS= EUDRAGIT® RS 30 D; DS=dry substance; the number in the formulation name represents the percentage of polymer applied

	Diprophylline [g]	**EUDRAGIT® E PO [g]**	**EUDRAGIT® L 100-55 DS [g]**	**TEC [g]**	**EUDRAGIT® RS 30 D DS [g]**
DipEL5	498.75	8.10	18.15	3.63	
DipEL10	495.00	16.98	38.02	7.60	
DipEL15	488.75	26.62	59.63	11.93	
DipEL20	480.00	37.04	82.96	16.59	
DipEL50	375.00	115.74	259.26	51.85	
DipRS5	498.75				26.25
DipRS10	495.00				55.00
DipRS15	488.75				86.25
DipRS20	480.00				120.00
DipRS50	375.00				375.00

3.3.2.1 Analysis of the granules

LOD of the granules was measured after drying overnight, as well as the flowability and compressibility properties. The d' determination was performed in the same way as described in the first wet granulation (point 3.2.3). All the results are described in the appendix (Table 42, Appendix).

The particle size distribution represented in Figure 34 and Figure 35 showed an increase of the granules size when the percentage of polymer increased. At a low polymer percentage, the amount of polymer was not sufficient to form the granules.

In the formulations with EUDRAGIT® RS 30 D the same trend was observed, but the granulations with 20% and 50% polymer content showed higher percentage of fines than the granulation with 15% polymer content. The process time for the granulations with 20% and 50% polymer content was twice longer compared to the previous granulations. This increase in process time could possibly lead to a partial dissolution of the drug, as seen before in point

3.2.3.2.2 resulting in a harder mass. During the granulation the mass would produce a higher percentage of fines during the granulation caused by the oscillation sieve.

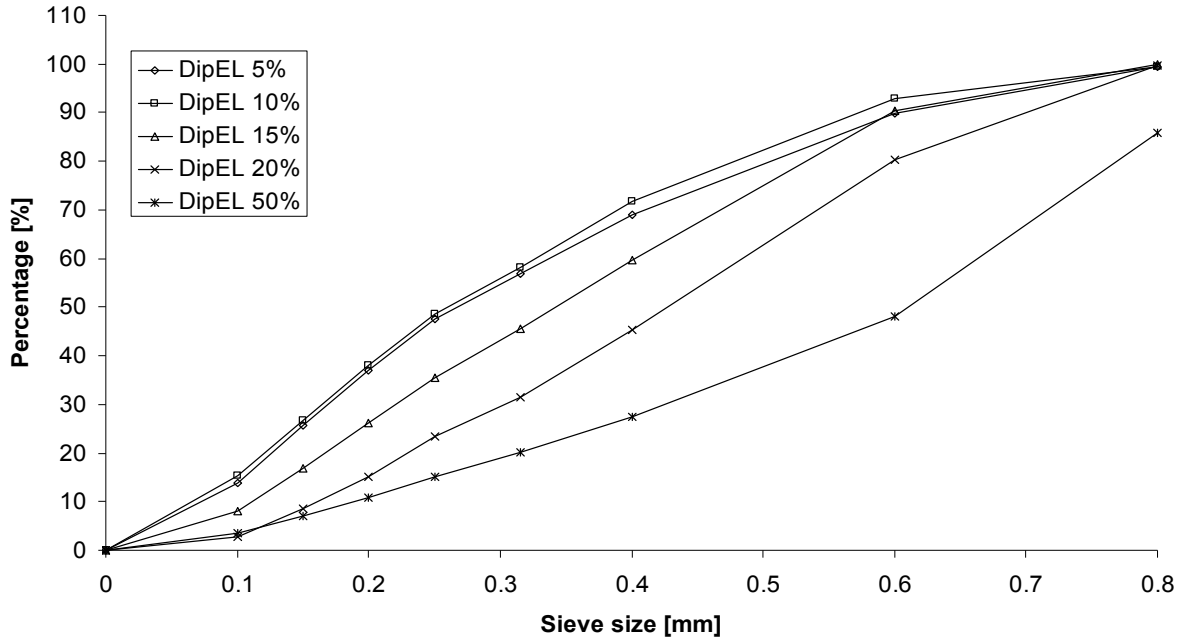


Figure 34 Particle size distribution of diprophylline granulated with different percentages of EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4). Dip= diprophylline; EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4)

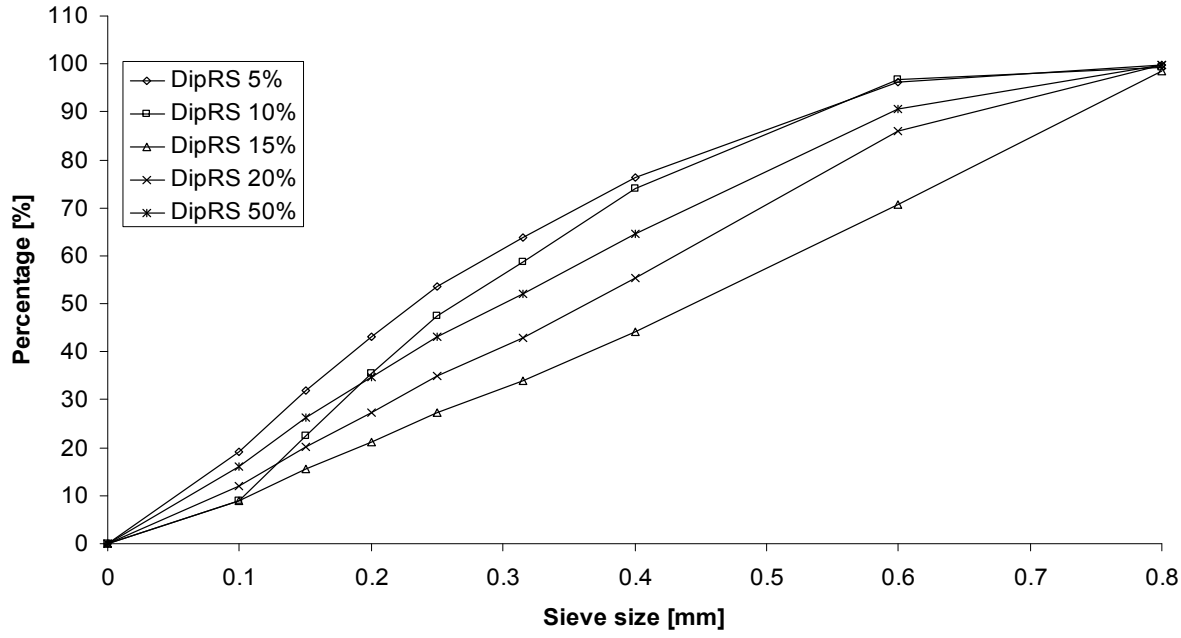


Figure 35 Particle size distribution of diprophylline granulated with different percentages of EUDRAGIT® RS 30 D Dip= diprophylline; RS= EUDRAGIT® RS 30 D

The compressibility and d' values of the granules with EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4) and EUDRAGIT® RS 30 D were analyzed to observe a trend between these values and the percentage of polymer applied. Only for the granules produced with EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4) showed an increase in the value (Figure 36).

The compressibility values of all batches was similar with values between 1.21 and 1.12 making the granules suitable for compression (Serno et al. 2007).

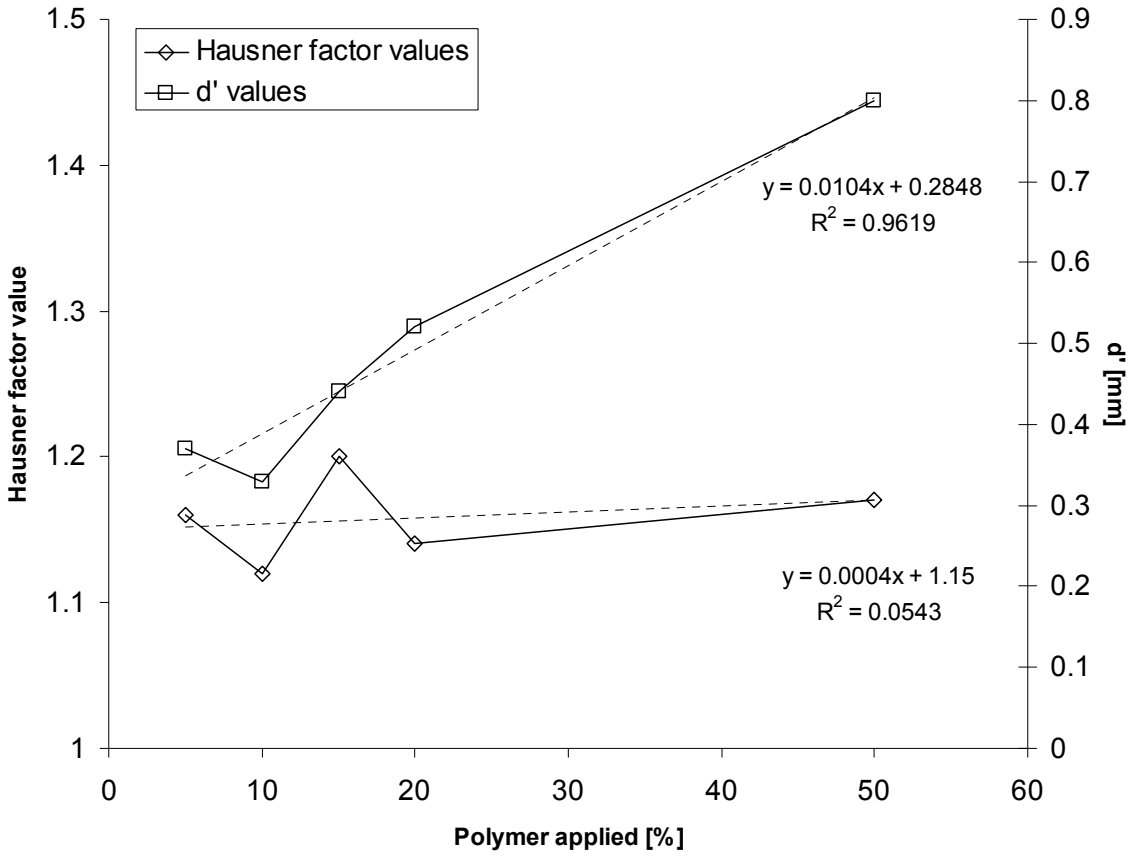


Figure 36 Representation of the compressibility values with the values of d' for the diprophylline granules with different percentages of EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4)

The increase in process time described at the beginning of this point showed a direct influence on the d' values represented in Figure 37.

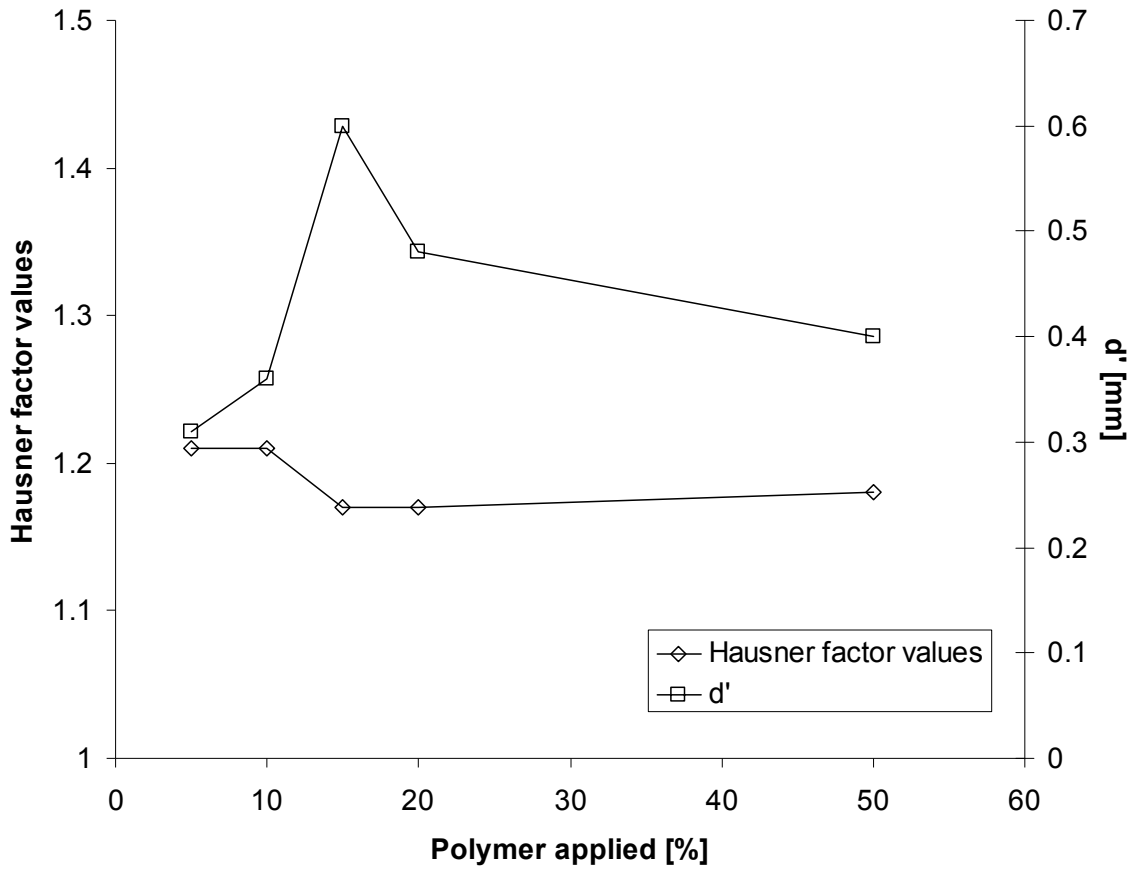


Figure 37 Representation of the compressibility values with the values of d' for the diprophylline granules with different percentages of EUDRAGIT® RS 30 D

3.3.2.2 Compression

3.3.2.2.1 Equipment

The compression was performed under the same conditions as described previously in the point 3.2.3.2.1.The same tablet properties were evaluated.

3.3.2.2.2 Tablet breaking resistance, weight and height

The method used to obtain these values is described in the experimental section (point 6.3.4).

The breaking resistance values are listed in the appendix (Table 43, Appendix). These values were analyzed to observe a possible significance of the applied polymer on the breaking resistance. As the polymer percentage increased the results showed a decreasing trend of the values but with a low coefficient of determination due to the high variability (Figure 38).

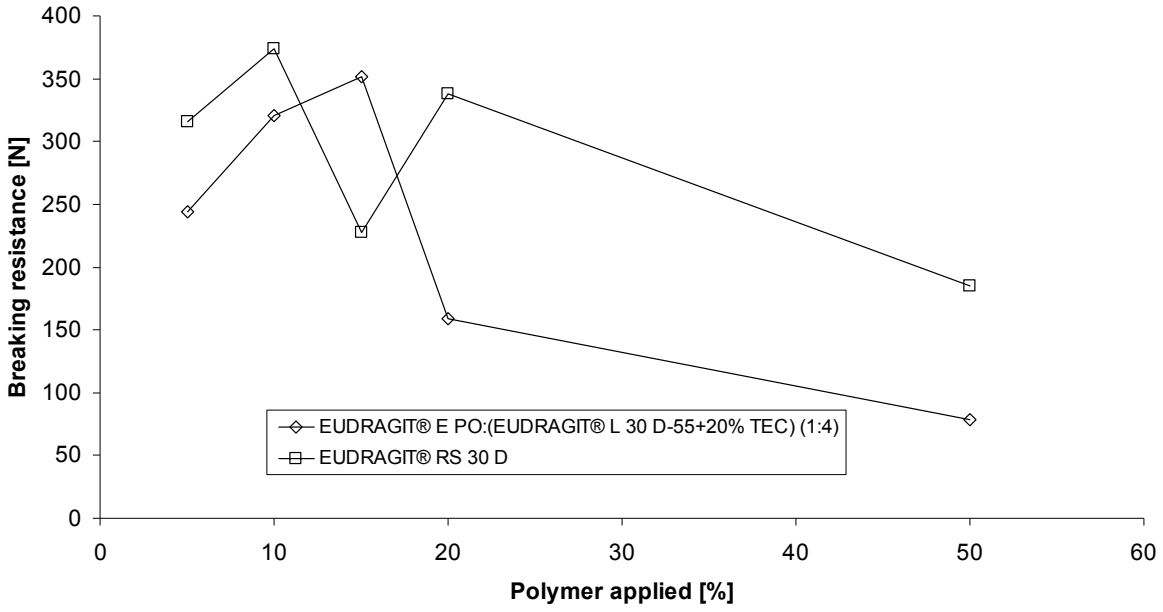


Figure 38 Representation of the breaking resistance values from the diprophylline tablets with different percentages of polymer applied. Rhombus= EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); squares= EUDRAGIT® RS 30 D

3.3.2.2.3 Tablet density

The density value was calculated based on the weight and the geometry of the tablet. The weight values used are described in Table 43, Appendix and the dimensions from the punch were 12 mm diameter and 25 mm curvature radius.

The density values (Table 43, Appendix) were analyzed to observe a possible significance of the polymer applied on the density of the tablets.

Since EMCOMPRESS® was not in the formulation, the density of the tablets decreased (Figure 39). The variation in the density values was affected by the amount of polymer

applied. The values for the IPEC and for EUDRAGIT® RS 30 D showed an increase as the polymer applied increased (especially with EUDRAGIT® RS 30 D). The values were related to the d' values. When the percentage of fines in a mixture is greater, the tablet has a greater elastic behavior during compression (Ritschel et al. 2002) reducing the density of the tablets.

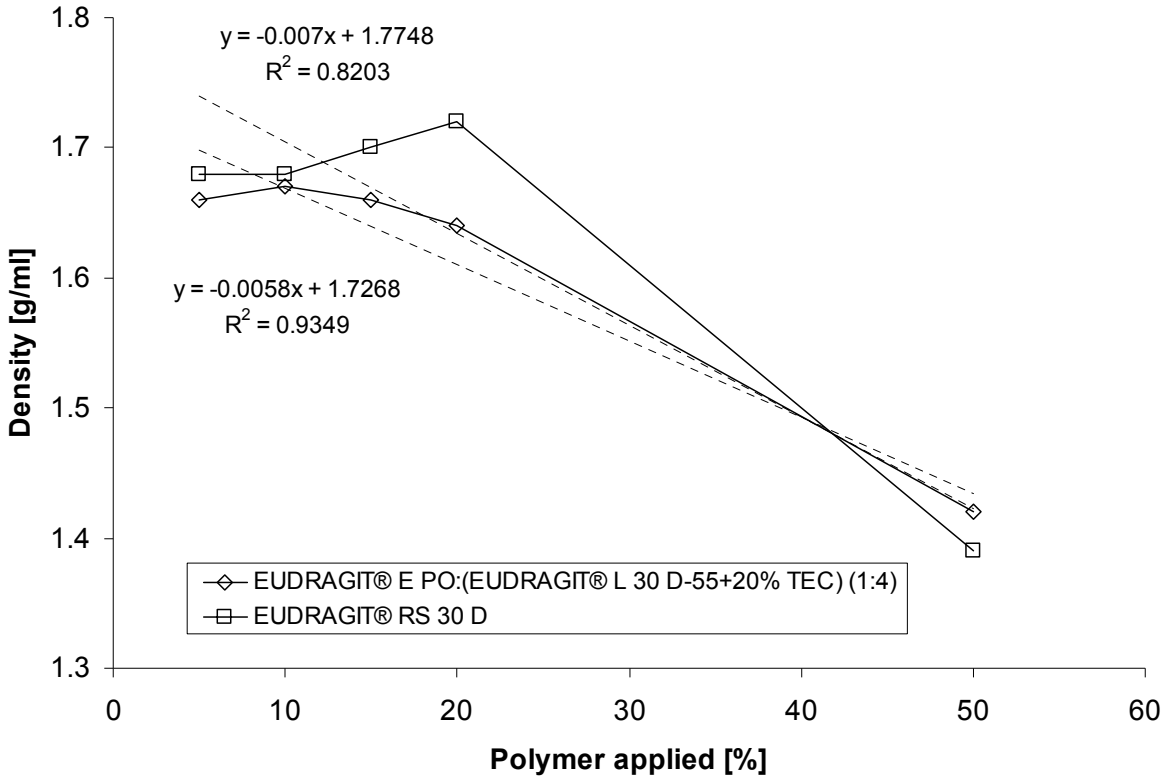


Figure 39 Representation of the density values from the diprophylline tablets with different percentages of polymer applied. Rhombus= EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); squares= EUDRAGIT® RS 30 D

3.3.2.3 Dissolution test

The tablets were tested in the dissolution test along 8 hours combining 2 hours in acidic medium and 6 hours in pH 6.8 medium. These tests were performed to observe which percentage of polymer was necessary to build a matrix structure and to provide sustained release of the drug. The release profiles are represented in Figure 40 and Figure 41.

In both cases the formulations with only 5% polymer applied did not show sustained release. They disintegrated within the first hour of dissolution. The same happened to the formulation with 10% IPEC but not in the case of EUDRAGIT® RS 30 D. The difference on the release profile can be the result of the higher breaking resistance that the tablets showed with 10% EUDRAGIT® RS 30 D compared to the tablets with 10% of IPEC.

The faster release can be also explained with the percolation theory (Leuenberger et al. 1987; Caraballo et al. 1993). The particle size from EUDRAGIT® RS 30 D was smaller compared to the IPEC. Since the particles were smaller, the formation of an infinite cluster of this polymer is easier avoiding disintegration of the tablet. This effect combined with the hydrophilic character from EUDRAGIT® E PO in the IPEC explained previously (point 3.2.2) were responsible for the faster release of the drug using the IPEC compared to EUDRAGIT® RS 30 D.

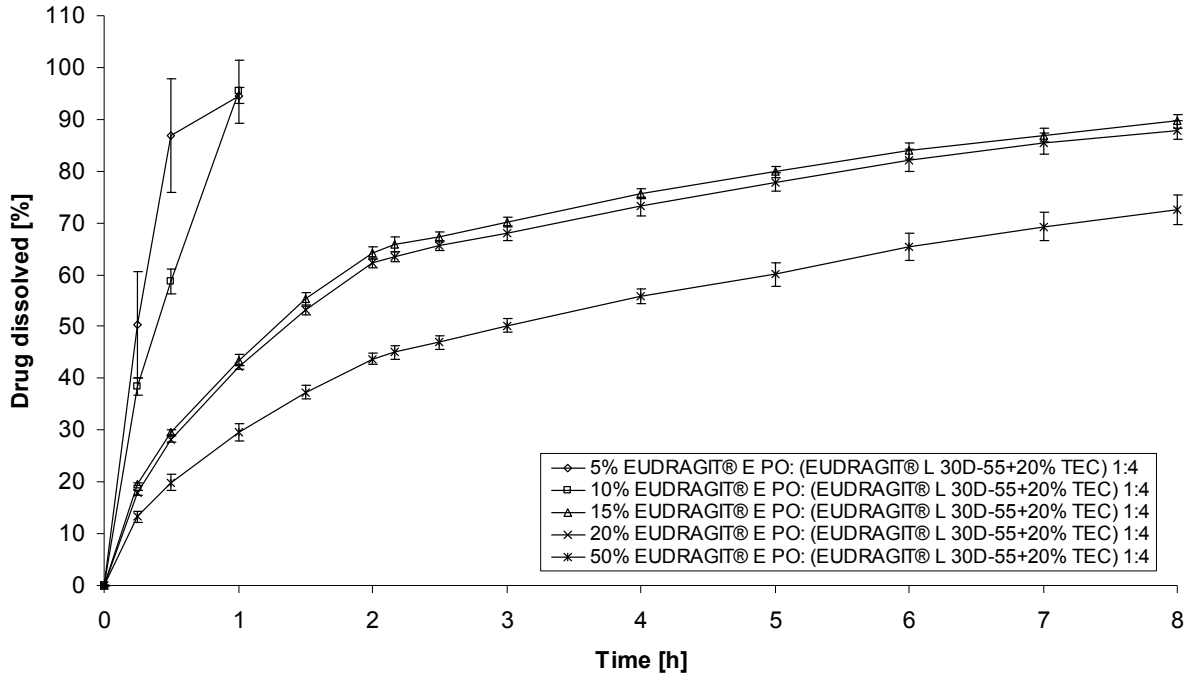


Figure 40 Release profile of Diprophylline matrix tablets in 700 ml of 0.1 N HCl the first two hours followed by 6 hours in phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Comparison of the effect of polymer content on the sustained release effect. Test Apparatus II, 50 rpm. Nominal weight 500 mg. Diameter 12 mm. Curvature radius 25 mm. Compression force 10 kN. (n=3)

The same hypothesis could explain the slight differences between the formulations with 15% and 20% polymer applied in both cases (Millán et al. 1998; Caraballo et al. 1999). With 15% polymer was enough to obtain an infinitive cluster of insoluble polymer. The increase of polymer content to 20% did not show a stronger sustained release.

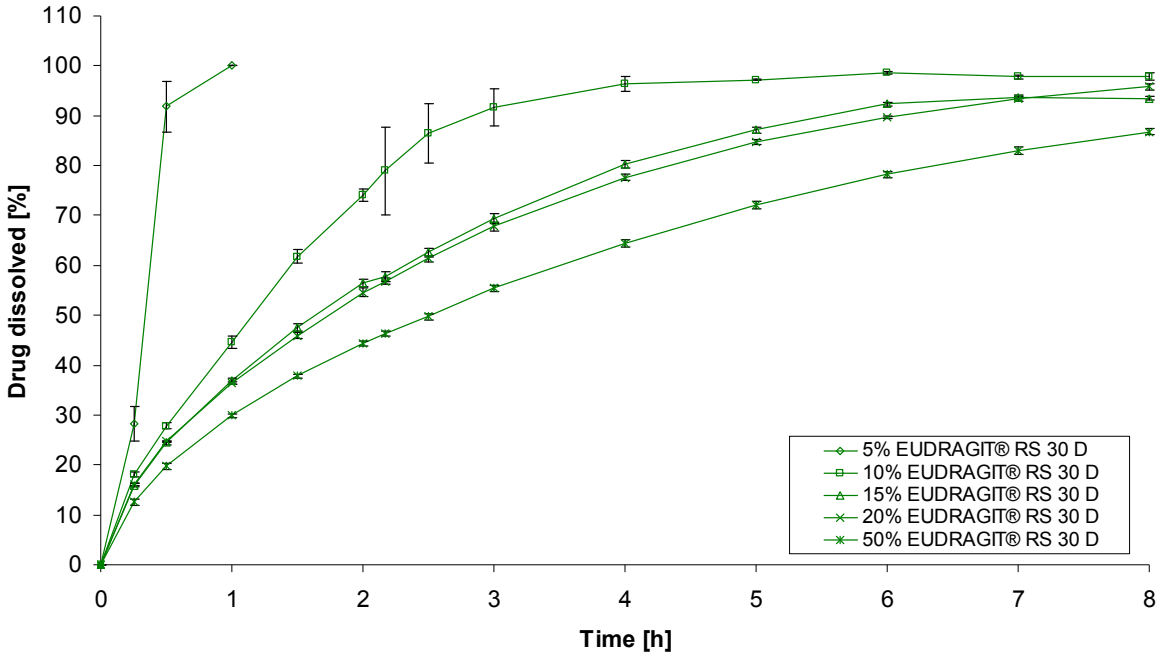


Figure 41 Release profile of Diprophylline matrix tablets in 700 ml of 0.1 N HCl the first two hours followed by 6 hours in phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Comparison of the effect of polymer content on the sustained release effect. Test Apparatus II, 50 rpm. Nominal weight 500 mg. Diameter 12 mm. Curvature radius 25 mm. Compression force 10 kN. (n=3)

Since a similar release profile was achieved with 15% and 20% polymer applied, the lower percentage was selected because the process time was shorter. Therefore, the polymer content selected for formulations with other drugs of different ionic character was 15%.

3.3.2.4 Scanning electron microscopy (SEM)

This analysis was performed as described in point 6.3.1.4 to observe the influence of the media in the IPEC structure. The formulation was made with EMCOMPRESS® and a polymer combination 1:4 molar ratio EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC). The pictures in showed the structure of the tablet before and after the dissolution test.

The picture after the dissolution test showed a sponge-like structure built from the polymer combination, which was not possible to recognize in the picture before the dissolution test.

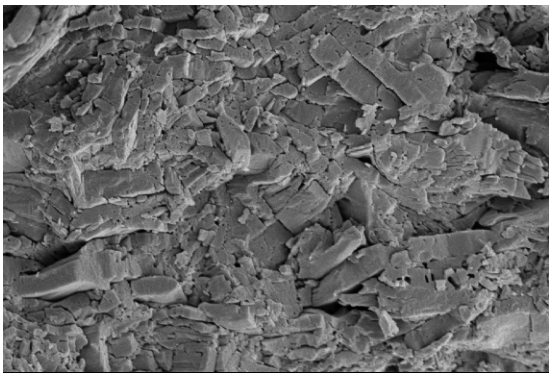
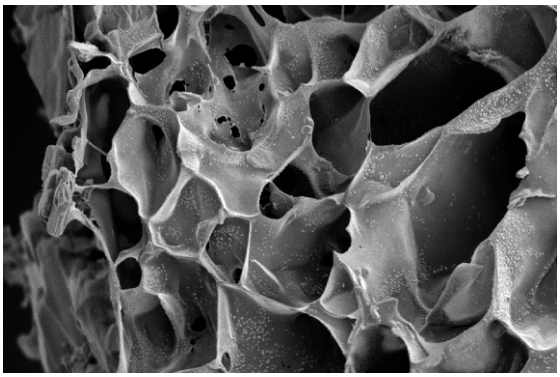
Before dissolution test	After dissolution test
	

Figure 42 SEM pictures from matrix tablets manufactured with diprophylline, x2000 magnification

3.4 Granulation of anionic and cationic drugs.

The drugs selected for these trials were captopril (anionic) and diltiazem HCl (cationic). Both drugs are highly soluble. The aim of the trials was to observe a possible interaction between IPEC and the drug that could lead to a stronger sustained release.

Table 15 Description of the formulation with different polymers and different drugs. Dilt= diltiazem HCl; Cap= captopril; EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); RS= EUDRAGIT® RS 30 D; FS= EUDRAGIT® FS 30 D; E= EUDRAGIT® E PO; DS=dry substance; the number in the formulation name represents the percentage of polymer applied.

	Diprophylline [g]	**EUDRAGIT® E PO [g]**	**EUDRAGIT® L 100-55 DS [g]**	**TEC [g]**	**EUDRAGIT® FS 30 D DS [g]**	**EUDRAGIT® FS 30 D DS [g]**
DiltEL15	495.00	16.98	38.02	7.60		
DiltRS15	498.75					26.25
DiltFS15	498.75				26.25	
DiltE15	498.75	26.25				
CapEL15	495.00	16.98	38.02	7.60		
CapRS15	498.75					26.25
CapFS15	498.75				26.25	
CapE15	498.75	26.25				

3.4.1.1 Analysis of the granules

The granulation of captopril with EUDRAGIT® E PO lead to an interaction between drug and polymer resulting in a plastic mass impossible to granulate. Therefore, no granules or tablets were manufactured for this batch. LOD, flowability and compressibility properties were tested. The d' values were determined in the same way as described in the first wet granulation (point 3.2.3). All the results are described in the appendix (Table 14, Appendix).

The particle size distribution represented in Figure 43 and Figure 44 showed an increase in the percentage of fines for the batches granulated with the IPEC (for both drugs) and the granulation of diltiazem HCl with EUDRAGIT® FS 30 D. The higher percentage of fine can be explained with the partial dissolution of the drug, as seen before in point 3.2.3.2.2.

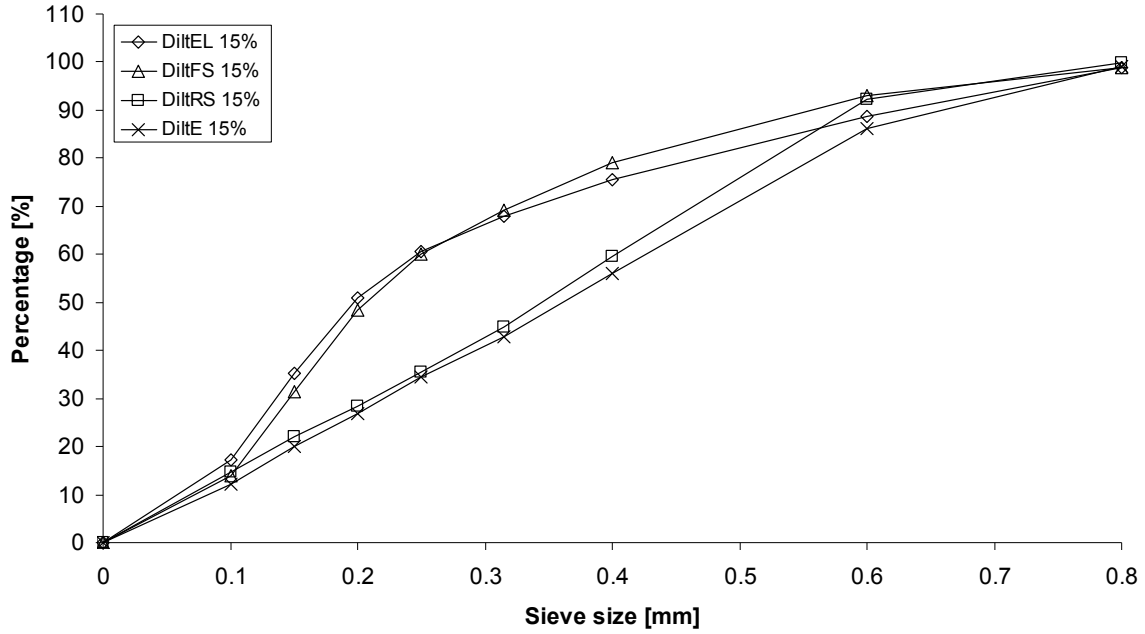


Figure 43 Particle size distribution of diltiazem HCl granulated with different polymers. Dilt= diltiazem HCl; EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); FS= EUDRAGIT® FS 30 D; RS= EUDRAGIT® RS 30 D; E= EUDRAGIT® E PO; the number in the formulation name represents the percentage of polymer applied

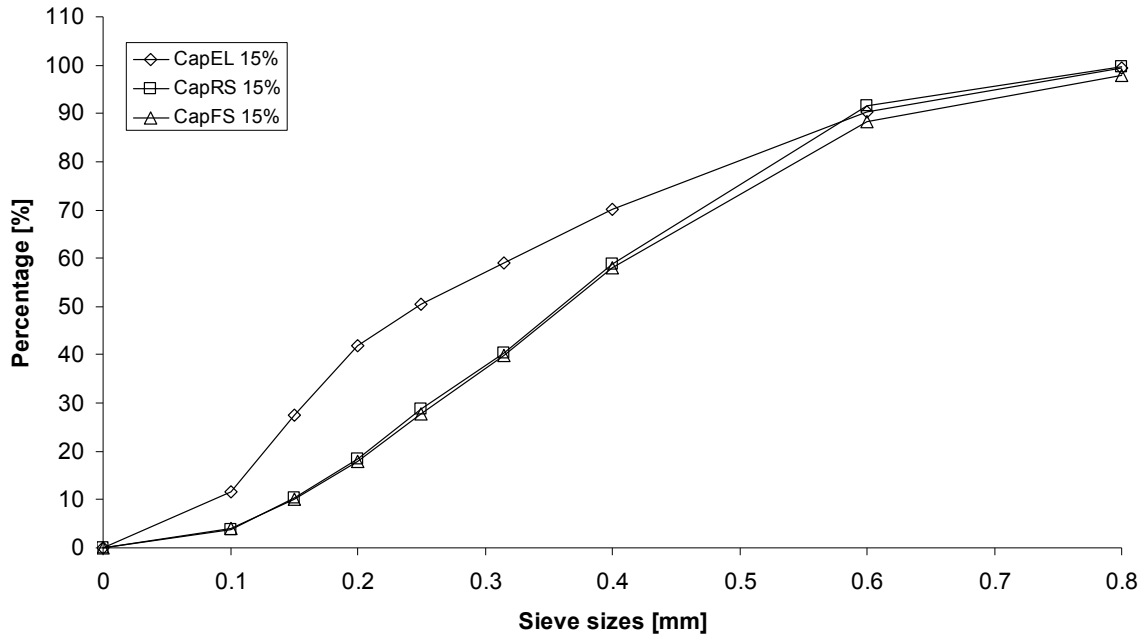


Figure 44 Particle size distribution of captopril granulated with different polymers. Cap= captopril; EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); FS= EUDRAGIT® FS 30 D; RS= EUDRAGIT® RS 30 D; the number in the formulation name represents the percentage of polymer applied

The partial dissolution of the drug can be influenced by the different ionic character of the polymers. Diltiazem HCl as cationic drug can react with the carboxylic groups from EUDRAGIT® L 30 D-55 or from EUDRAGIT® FS 30 D in the IPEC. The low percentage of active groups in EUDRAGIT® RS 30 D (approximately 5%) was not enough to react with the anionic drug (captopril) leading to its partial dissolution. In the other examples, the hydrophilic character from EUDRAGIT® E PO and its high reactivity made the interaction with the drug easier and therefore the percentage of fines increased.

3.4.2 Compression

3.4.2.1 Equipment

The compression was performed under the same conditions as described previously in the point 3.2.3.2.1.The same tablet properties were evaluated.

3.4.2.2 Tablet breaking resistance, weight and height

The method used to obtain these values is described in the experimental section (point 6.3.4).

The breaking resistance values are listed in the appendix Table 45. These values were represented to observe an influence of the polymers on the breaking resistance.

Both drugs showed an increase when granulated with EUDRAGIT® FS 30 D in Figure 45. The softness of the polymer can be an explanation for the increase in the breaking resistance. The softness can increase the plastic behavior of the tablet leading to an increase of the breaking resistance (Ritschel et al. 2002).

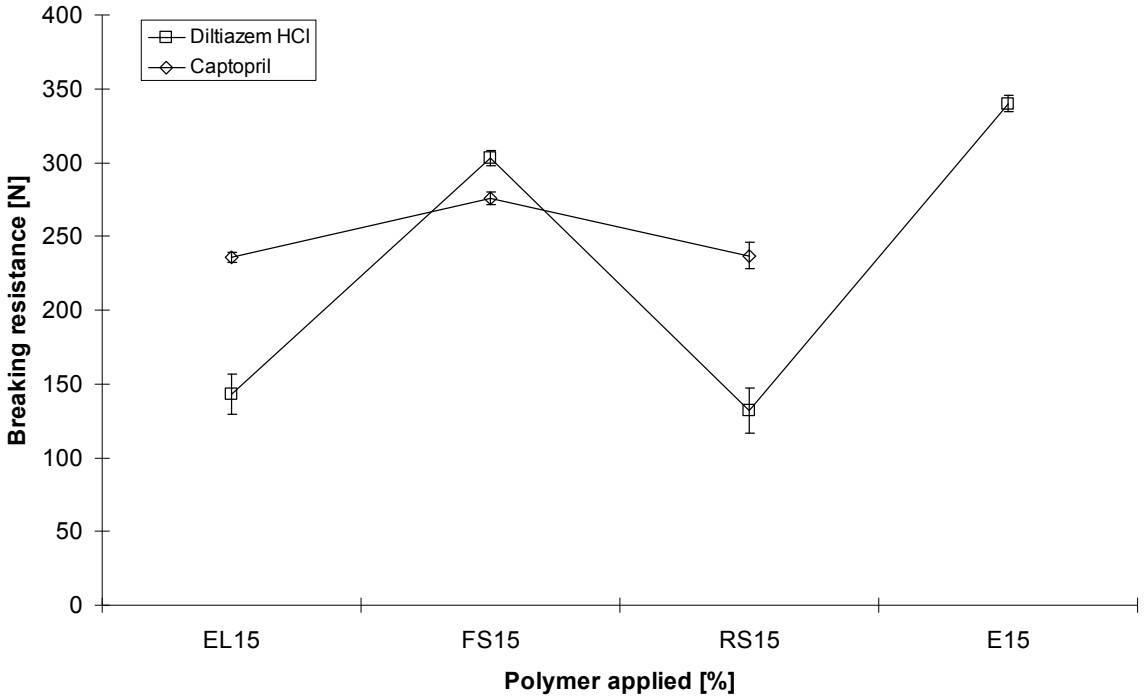


Figure 45 Breaking resistance values from the diltiazem HCl and captopril tablets with different polymers. Black rhombus= captopril; black squares= diltiazem HCl; EL= EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); FS= EUDRAGIT® FS 30 D; RS= EUDRAGIT® RS 30 D; E= EUDRAGIT® E PO; the number in the formulation name represents the percentage of polymer applied

3.4.2.3 Tablet density

The density value was calculated based on the weight and the geometry of the tablet. The weight values used are described in Table 45 in the appendix and the dimensions from the punch were 12 mm diameter and 25 mm curvature radius.

The density values were analyzed to observe a possible significance of the polymer applied on the density of the tablets.

Even the low variability of the density values, the density of the tablets that used the IPEC for the granulation were the lowest. The free volume (space between polymer chains) present in a combination of polymers is higher than the free volume of a pure polymer (Schneider 1997).

The increase of the free volume reduces the density of the tablets. Therefore the IPEC density values were lower than the values from the pure polymers.

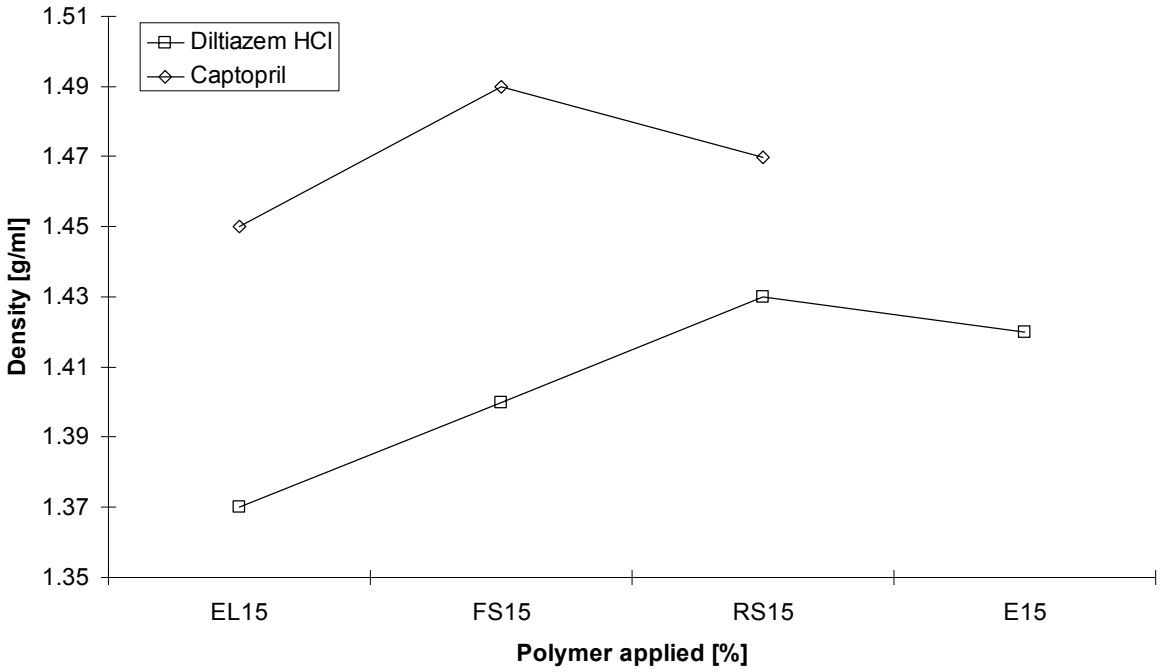


Figure 46 Density values from the diltiazem HCl and captopril tablets with different polymers applied. Rhombus= captopril; Squares= diltiazem HCl; EL= EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); FS= EUDRAGIT® FS 30 D; RS= EUDRAGIT® RS 30 D; E= EUDRAGIT® E PO; the number in the formulation name represents the percentage of polymer applied

3.4.3 Dissolution test

3.4.3.1 Release in 0.1 N HCl and phosphate buffer pH=6.8

Captopril and diltiazem HCl tablets were tested under these conditions. The formulations used were 15% IPEC, EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4), with 15% EUDRAGIT® FS 30 D, with 15% EUDRAGIT® RS 30 D and with 15% EUDRAGIT® E PO (only for diltiazem HCl due to the reaction between captopril and EUDRAGIT® E PO). The release profiles from captopril and diltiazem HCl matrix tablets are described in Figure 47 and Figure 48.

Captopril showed the same release profile for the different polymers used. The absence of variability on the release profile confirms the absence of interaction between drug and polymer. The only interaction took place with EUDRAGIT® E PO during granulation, but the manufacturing of tablets was not possible.

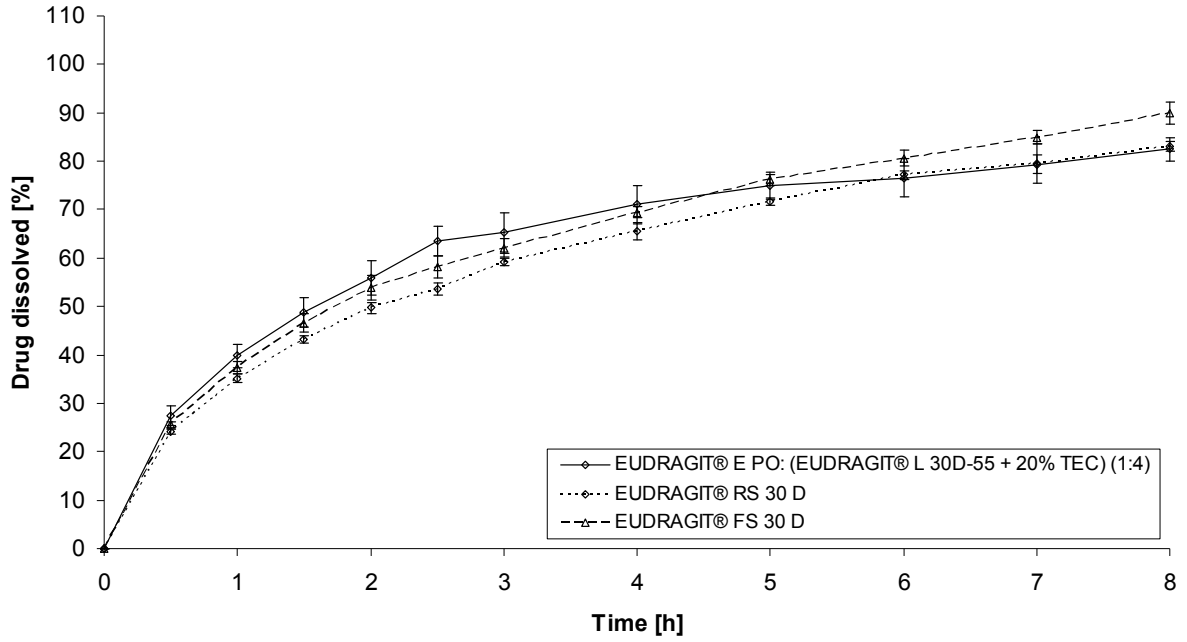


Figure 47 Release profile of captopril matrix tablets in 700 ml of 0.1 N HCl the first two hours followed by 6 hours in phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Comparison of the effect of different polymers on the sustained release effect. Test Apparatus II, 50 rpm. Nominal weight 500 mg. Diameter 12 mm. Curvature radius 25 mm. Compression force 10 kN. (n=3)

Diltiazem HCl matrix tablets did not show sustained release due to the higher solubility of the drug compared with the other model drugs (point 6.1.2.). Only in the case of EUDRAGIT® RS 30D the tablet did not disintegrate, providing sustained release (Figure 48). The other tablets disintegrated within the first 30 minutes of dissolution.

EUDRAGIT® E PO is soluble in pH below 6 therefore the disintegration in this example is expected. The drug release from IPEC was sensitive in acidic medium in previous trial accelerating the release. The hydrophilic character of EUDRAGIT® E PO, combined with the low density values of the IPEC matrix tablets and the high solubility of the diltiazem HCl accelerated the erosion of the structure leading to disintegration. EUDRAGIT® FS 30 D is insoluble below pH 7.0, but in this example disintegrated within 30 minutes in acidic medium. The only difference to EUDRAGIT® RS 30D is the presence of carboxylic groups. Possibly an interaction with the cationic character of the drug can lead to a salt formation with the polymer leading to its solubilization.

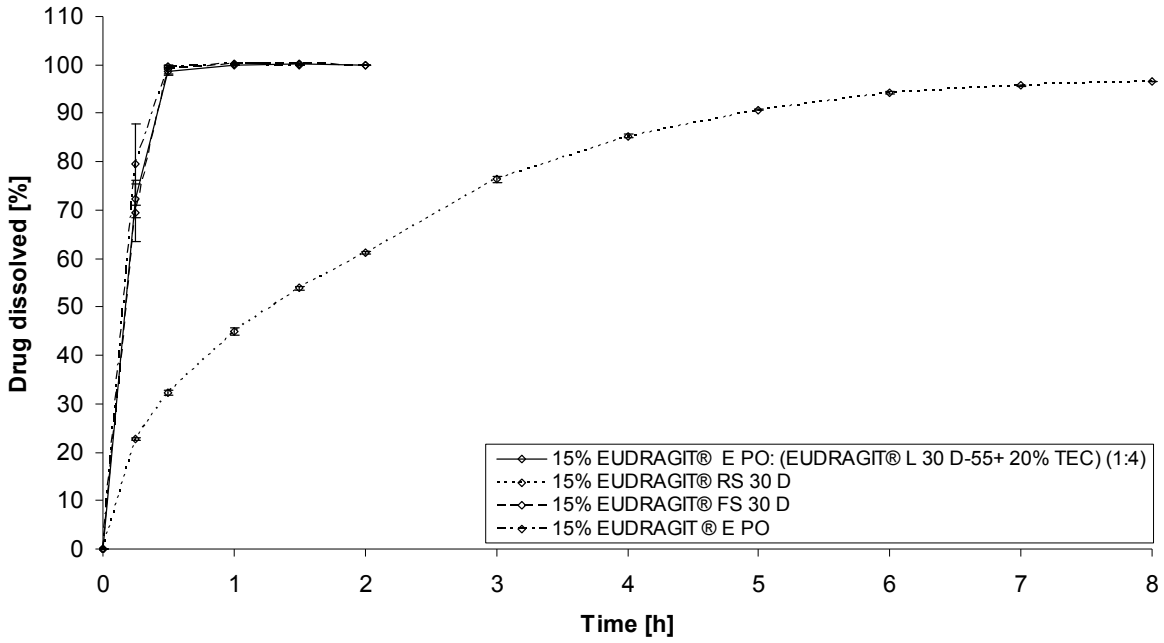


Figure 48 Release profile of diltiazem matrix tablets in 700 ml of 0.1 N HCl the first two hours and then in phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Comparison of the effect of different polymers on the sustained release effect. Test Apparatus II, 50 rpm. Nominal weight 500 mg. Diameter 12 mm. Curvature radius 25 mm. Compression force 10 kN. (n=3)

3.4.3.2 Release only in phosphate buffer pH=6.8

Since the release of diprophylline in pH 6.8 was slower with IPEC than with EUDRAGIT® RS 30 D, both formulations were tested only in phosphate buffer 6.8 for diprophylline and diltiazem HCl. The results are described in Figure 49 and Figure 50. With diprophylline the release from the IPEC was slower than with EUDRAGIT® RS 30D. The swelling effect of the IPEC in phosphate buffer led to a gel-formation providing partial sealing of the surface of the tablet leading to stronger sustained release properties.

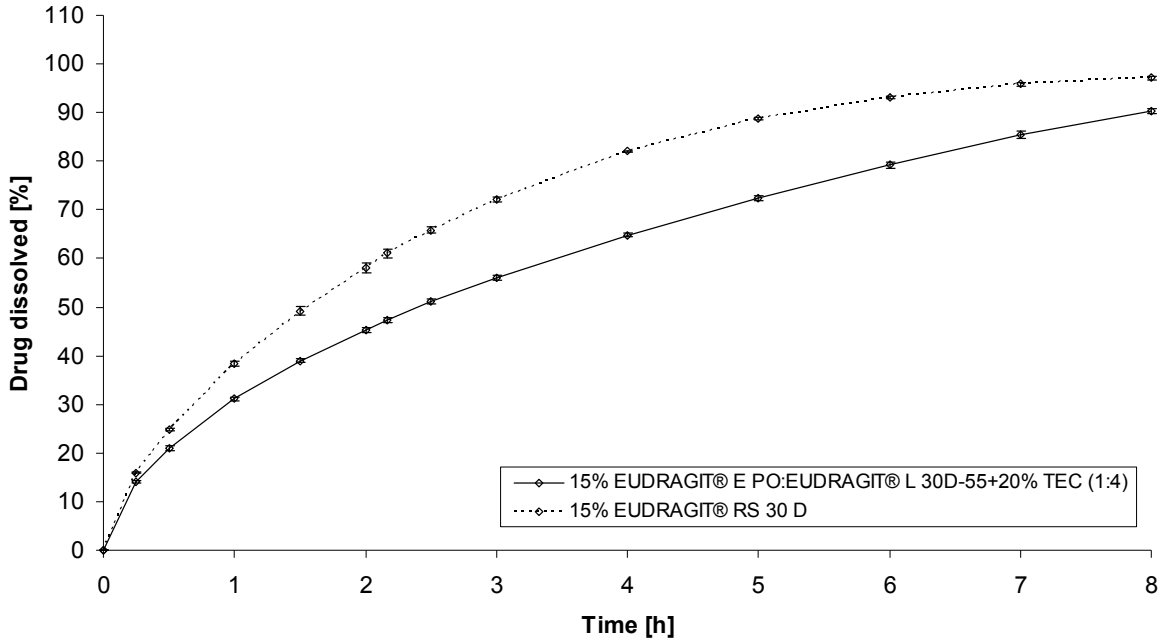


Figure 49 Release profile of diprophylline matrix tablets in 914 ml of 0.1 N HCl+214 ml of $Na_3PO_4 \cdot 12H_2O$. Comparison of the effect of different polymers on the sustained release effect. Test Apparatus II, 50 rpm. Nominal weight 500 mg. Diameter 12 mm. Curvature radius 25 mm. Compression force 10 kN. (n=3)

The release of diltiazem tablets in phosphate buffer did not avoid the disintegration of the tablet manufactured with the IPEC. The tablet disintegrated within an hour.

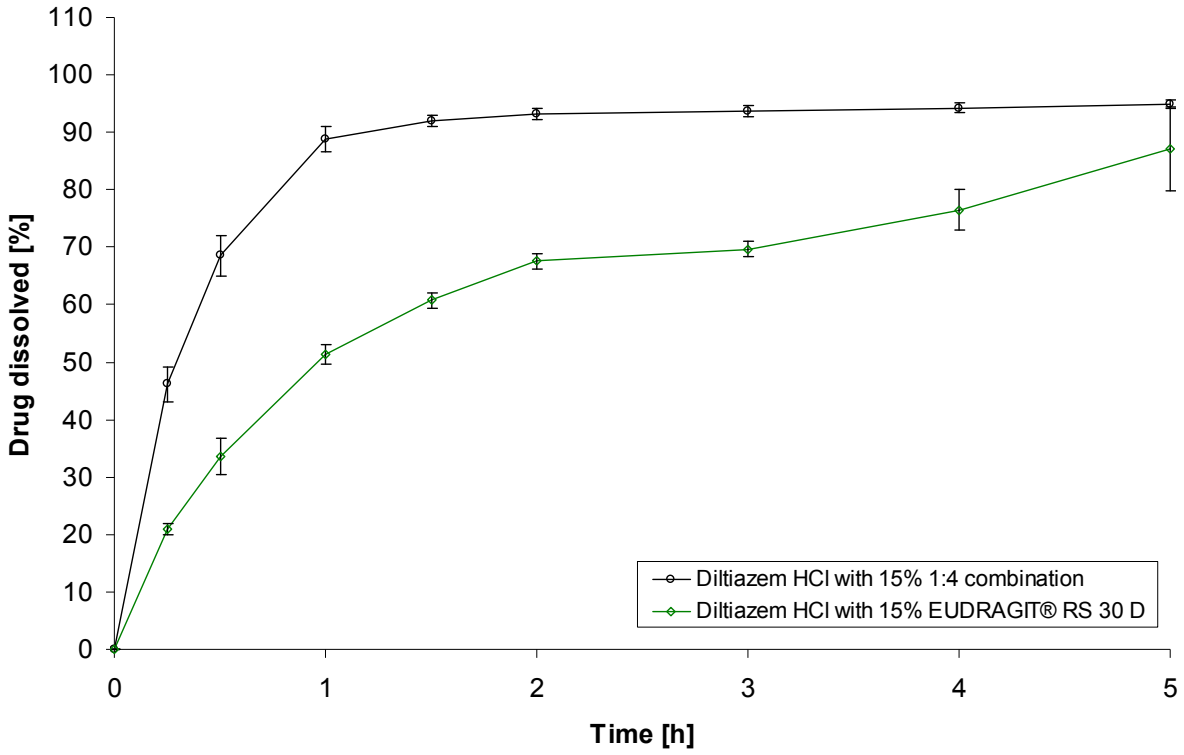


Figure 50 Release profile of diltiazem HCl matrix tablets in 914 ml of 0.1 N HCl+214 ml of $Na_3PO_4 \cdot 12H_2O$. Comparison of the effect of different polymers on the sustained release effect. Test Apparatus II, 50 rpm. Nominal weight 500 mg. Diameter 12 mm. Curvature radius 25 mm. Compression force 10 kN. (n=3)

3.4.4 Summary

The statistical trial performed to determine the significance of the factors on the sustained release property of the tablets, showed that the most significant factors were the polymer content and in a lower percentage the EUDRAGIT® E PO. The more total polymer amount and less amount of EUDRAGIT® E PO applied, the stronger the sustained release became. But even this significant factor did not produce a drastically change on the sustained release of diprophylline in the first two hours of release in 0.1 N HCl which varied within 10%. This low variability could be an effect of the high percentage of EMCOMPRESS® included in the formulation.

The variation on the volume of polymer mixtures applied showed slight differences on the physical characteristics of granules and tablets. These differences were easier to observe in the LOD values, breaking resistance and density of the tablets. The last parameter was also affected by the percentage of EMCOMPRESS® included in the formulation. The large

quantities of water applied, made the process long and complicated with a drying process in between.

Diprophylline granulations without EMCOMPRESS® and without stearic acid were performed obtaining similar release profiles to the trial plan. With 15% polymer content it seemed possible to provide sustained release properties. With 20% polymer the sustained release properties were similar to the 15% polymer content profile. A polymer content below 15% was not enough to build a matrix structure. EUDRAGIT® RS 30D showed better results at low polymer percentage, but the release profile in pH=6.8 was faster than the release from the polymer combination.

Use of cationic or anionic drug did not show any interaction with the IPEC that could provide a stronger sustained release. Only for captopril mixed with EUDRAGIT® E PO a strong interaction was observed. This interaction formed a soft and flexible mass impossible to granulate or compress.

3.5 Melt extrusion

3.5.1 Trial description

The trials were conducted in the extruder to obtain sustained release matrix tablets without using water. The great volume of water used in the high shear mixer was a problem for the process, making it long and complicated. With melt extrusion the polymers were mixed without water producing extrudates. The high density of the extrudates can improve the sustained release properties. Diprophylline was selected as model drug for the trials.

The trials were performed with a corotating twin screw extruder MICRO 18 GL 40 D Pharma (Leistritz Extrusionstechnik GmbH, Nürnberg, Germany). The formulation for these trials was changed compared to the formulation with the high shear mixer. EMCOMPRESS® was not included in the formulations and the percentage of drug and polymer was different compared to the percentages in the trial plan for the high shear mixer. The trials had 25% diprophylline and 75% polymer or 50% diprophylline and 50% polymer.

EUDRAGIT® L 100-55 needed 30% plasticizer (TEC) to perform the melt extrusion due to its high brittleness (Sauer et al. 2007). With this amount of plasticizer the extrusion of the polymer was possible and transparent extrudates were produced. The TEC was added through a hole into the extruder with the help of a peristaltic pump. The pump rate was synchronized with the feeder speed.

EUDRAGIT® E PO was combined with 15% stearic acid to have similar conditions as in the trials performed with the high shear mixer. Stearic acid was also used for its ability as plasticizer and lubricant to reduce the viscosity of the IPEC formed.

Two sets of trials were conducted. The first set of trials used diprophylline as model drug to evaluate the release profile and observe differences compared to the values obtained by wet granulation. For these trials, the polymers were combined in a 1:1 (w:w) ratio.

The other set of trials was performed without drug, to evaluate the changes in viscosity. The polymers were combined based on the molar ratio from 4:1 to 1:4 as described in point 6.2.1.1.1. Two additional formulations were performed without stearic acid to observe its influence on the viscosity.

The total weight of a batch was always 500 g. The description of all formulations is listed in the experimental section (point 6.2.3.2).

The temperature of the different barrels of the extruder was selected based on experience from former trials along with the rotation speed and feeding rate of the feeder (Figure 51).

The temperatures were necessary as the interaction between the two polymers caused an increase in the viscosity when forming the IPEC, otherwise the high viscosity of the IPEC blocked the die. The widest die available had a diameter of 3 mm.

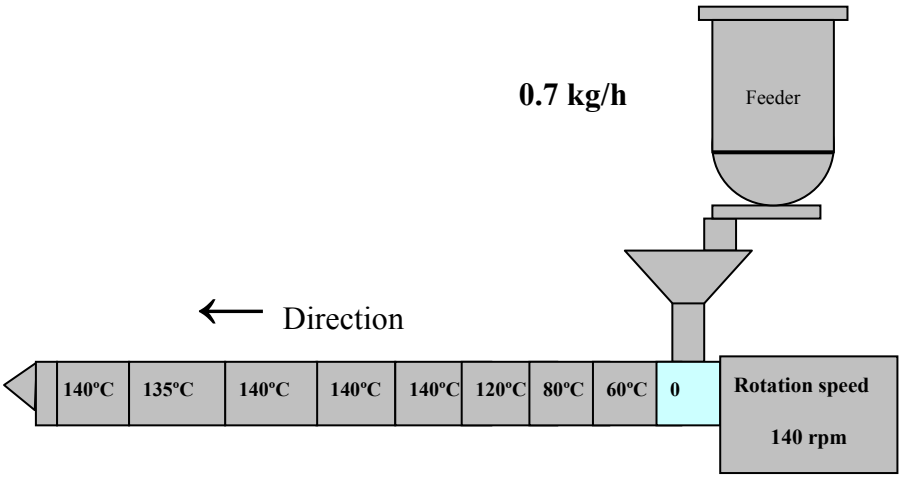


Figure 51 Description of the parameters selected for melt extrusion

The 3 mm die was too narrow to produce extrudates and increased the pressure up to 30 bars. Therefore a new die was designed. The die had a length of 5 cm and a diameter of 10 mm. The diameter was increased for two purposes. The first purpose was to reduce the pressure produced at the die and the second purpose was to obtain a wider extrudate that could be cut later directly into a matrix tablet (Bruce et al. 2007).

In some cases inhomogeneous extrudates occurred when the viscosity of the IPEC increased and the extruder speed had to be reduced compared to the feeding rate and the pump dosing the TEC. Therefore EUDRAGIT® L 100-55 was preplastizied by extruding it with 30% TEC. The obtained extrudates were milled. The powder was then mixed with EUDRAGIT® E PO and stearic acid.

3.5.2 Formulations with and without stearic acid

Stearic acid is widely used as lubricant (Iranloye et al. 1978). It can also react with the dimethylaminoethyl group of EUDRAGIT® E PO, inhibiting therefore the reaction of the carboxylic group of EUDRAGIT® L100-55. The lubricant effect and the inhibition of the reaction can reduce the viscosity of the material. These effects might have an influence on the release profile. If the release profiles of samples with stearic acid are different to the samples without stearic acid, an inhibition of the interaction between the polymers took place. If the profiles are similar, stearic acid acted as lubricant.

The maximum torque value of the different combinations without drug was collected. The torque increased as the EUDRAGIT® L 100-55+30% TEC fraction increased. The increase was more notable in the formulations without stearic acid (Table 16).

Table 16 Maximum values of torque for the polymer combinations with and without stearic acid. EL= EUDRAGIT® E PO:(EUDRAGIT® L 100-55+30% TEC); the number in brackets represent the molar ratio of the combination

Polymer combination	Maximum torque value [%]
EL (4:1) with stearic acid	32
EL (3:1) with stearic acid	36
EL (2:1) with stearic acid	37
EL (1:1) with stearic acid	37
EL (1:2) with stearic acid	39
EL (1:3) with stearic acid	46
EL (1:4) with stearic acid	88
EL (1:2) without stearic acid	98
EL (1:4) without stearic acid	98

Of all the combinations with stearic acid, only the 1:4 molar ratio was transparent. The extrudates without stearic acid had the same appearance. SEM pictures of the surface of the extrudate EUDRAGIT® E PO:(EUDRAGIT® L 100-55+30% TEC) 1:4 molar ratio with and without stearic acid were taken (Figure 52).

Even though both combinations were transparent, the combination without stearic acid showed a smooth surface, while the combination with stearic acid showed a rough surface with crystal formation on the surface.

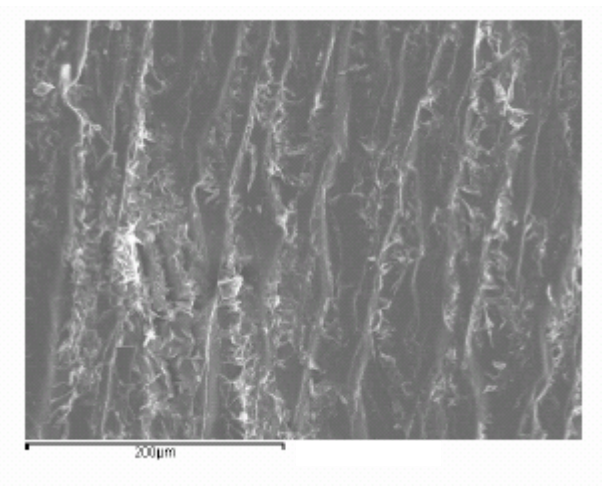
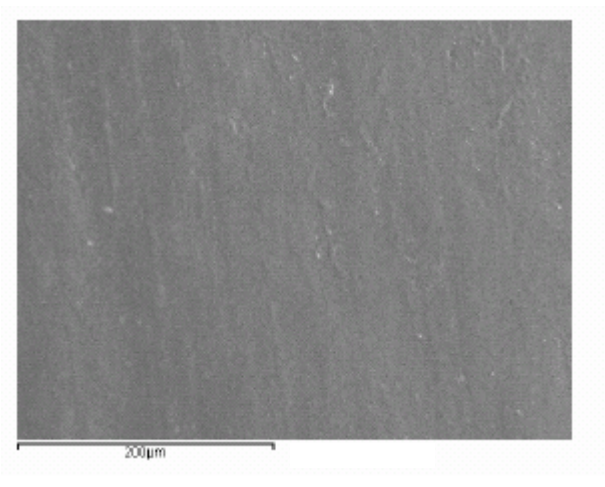
Surface of extrudate EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:4) with stearic acid	Surface of extrudate EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:4) without stearic acid
	

Figure 52 SEM pictures of the surface of extrudates with 1:4 molar ratio with stearic acid (left) and without stearic acid (right)

Stearic acid can act as a lubricant in the formulation reducing the torque of the extruder. The crystal formation on the surface can indicate that stearic acid did not interact with the active groups from EUDRAGIT® E PO. Stearic acid melted during the process and recrystallized when cooling the melt to room temperature after the process. The recrystallization causes the opaqueness of the extrudates (Figure 53).

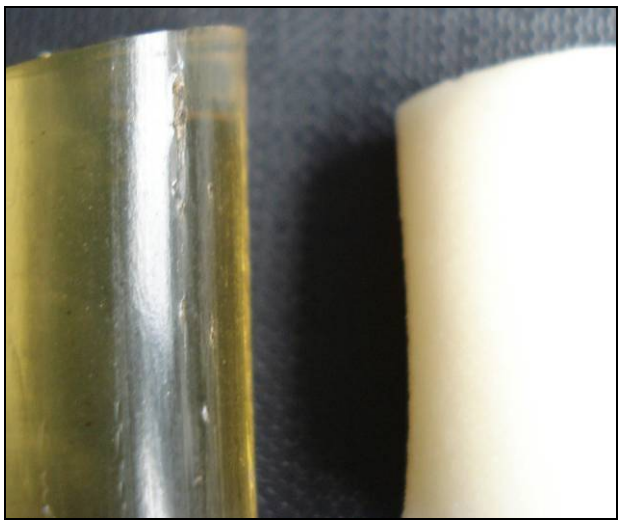


Figure 53 Appearance of extrudates of EUDRAGIT® E PO:(EUDRAGIT® L 100-55+30% TEC) 1:2 molar ratio. Without stearic acid (left) with stearic acid (right).

The IPEC was formed but the stearic acid did not react with the polymers. To confirm that stearic acid only acted as lubricant, the extrudates have to be tested with different analytical methods.

3.5.3 Analysis of extrudates

3.5.3.1 Viscosity measurements

The increase in viscosity can be an indication that the IPEC formation is taking place (Moustafine et al. 2005; Moustafine et al. 2006).

The viscosity of extrudates was measured with two different equipments: high pressure capillary viscosimeter and a rotational rheometer. The first one was used for all the combinations. The high viscosity values could not be measured properly due to the limitations of the sensor. Therefore the second equipment was used to confirm the values obtained with the first equipment.

A representation was made with the values obtained from the high pressure capillary viscosimeter. The concentration of EUDRAGIT® L 100-55 was represented versus the viscosity with a constant shear rate of 37600 Pa. There was a slow almost constant value of the viscosity for those combinations with a higher percentage of EUDRAGIT® E PO and then an exponential increase of the viscosity reaching a maximum value for the combination with 1:4 molar ratio (Figure 54).

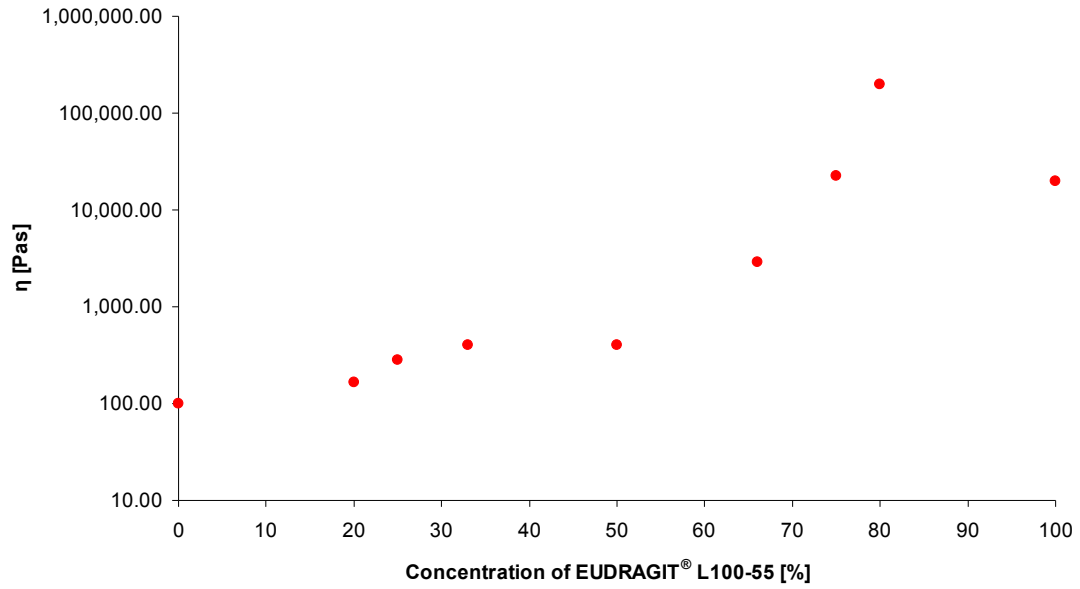


Figure 54 Viscosity values of all the polymer combinations with stearic acid versus the content of EUDRAGIT® L 100-55 of each combination. Also the viscosity of the pure polymers was measured: EUDRAGIT® E PO+15% stearic acid and EUDRAGIT® L 100-55+30% TEC

All the combinations with and without stearic acid were measured with the rotational rheometer. The values are represented in Figure 55.

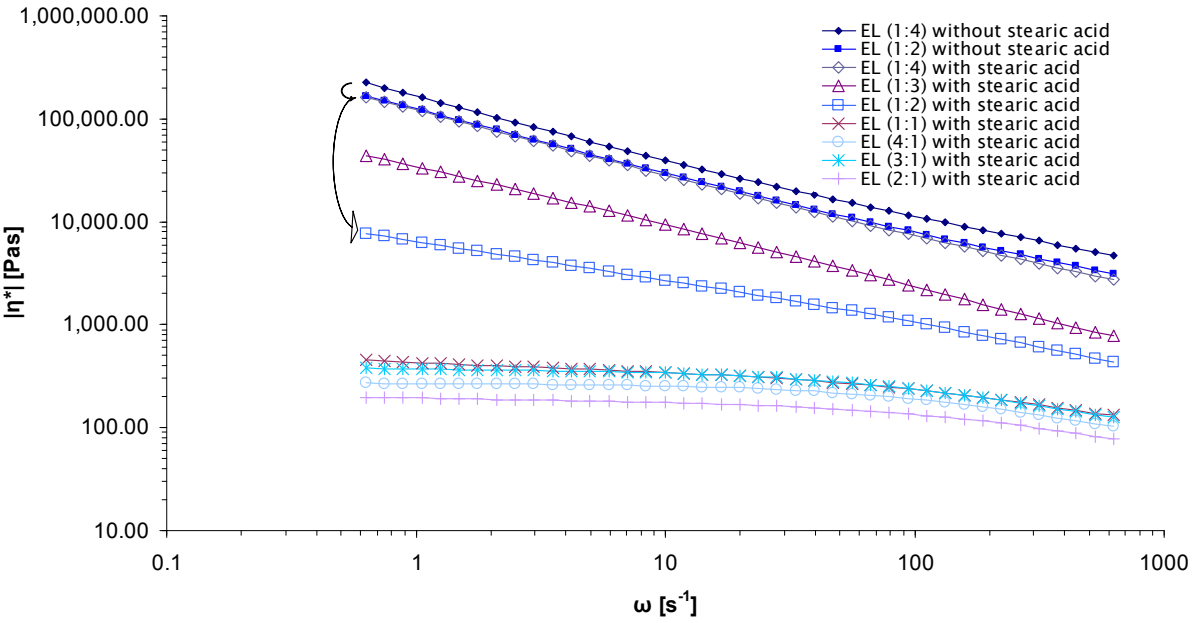


Figure 55 Viscosity values from the different combinations of EUDRAGIT® E PO with EUDRAGIT® L 100-55 versus the frequency of oscillation. The arrows showed the differences in viscosity between the combinations with and without stearic acid. EL= EUDRAGIT® E PO: (EUDRAGIT® L 100-55+30% TEC); the number in brackets represent the molar ratio in which the polymers were combined

Combinations with a higher percentage of EUDRAGIT® E PO showed the lowest viscosity values because of the higher flexibility of EUDRAGIT® E PO and the increase of the amount of stearic acid, acting as lubricant and/or plasticizer. When the percentage of EUDRAGIT® L 100-55 increased over the 1:1 molar ratio the viscosity increased dramatically.

Stearic acid showed a decrease in the viscosity due the lubricant effect. The arrows in the figure represent the difference in viscosity for the formulations 1:2 and 1:4 molar ratios. In the 1:2 molar ratio combination, the difference of the viscosity was higher. This greater difference was caused by the increasing amount of stearic acid increased when the EUDRAGIT® E PO fraction increased.

3.5.3.2 Differential scanning calorimetry (DSC)

DSC measurements were performed to identify the IPEC formation (unique T_g value) and to determine the effect of stearic acid.

The measurements were performed on the combinations with and without stearic acid. If stearic acid acted inhibiting partially the IPEC formation, the T_g of the extrudate with stearic acid would be lower than the T_g of the extrudate without stearic acid. The results showed a unique T_g value meaning that the IPEC was formed (Table 17).

The new T_g value in all cases was higher than the T_g values of the polymers used (EUDRAGIT® E PO and EUDRAGIT® L 100-55+30% TEC), meaning that the flexibility of the polymer chains was reduced by the reaction between the polymers.

Table 17 T_g values of extrudates with and without stearic acid

	1. Measure [ºC]	**2. Measure [ºC]**	**3. Measure [ºC]**
EUDRAGIT® E PO: (EUDRAGIT® L 100-55+30% TEC) (1:4) without stearic acid	77	78	73
EUDRAGIT® E PO: (EUDRAGIT® L 100-55+30% TEC) (1:4) with stearic acid	86	87	79
EUDRAGIT® E PO: (EUDRAGIT® L 100-55+30% TEC) (1:2) without stearic acid	80	81	81
EUDRAGIT® E PO: (EUDRAGIT® L 100-55+30% TEC) (1:2) with stearic acid	82	81	80
EUDRAGIT® L 100-55+30% TEC	43	53	59
EUDRAGIT® E PO+15% stearic acid	20		

No significant differences were observed in the T_g values when stearic acid was or was not present in the formulation (Figure 56 and Figure 57).

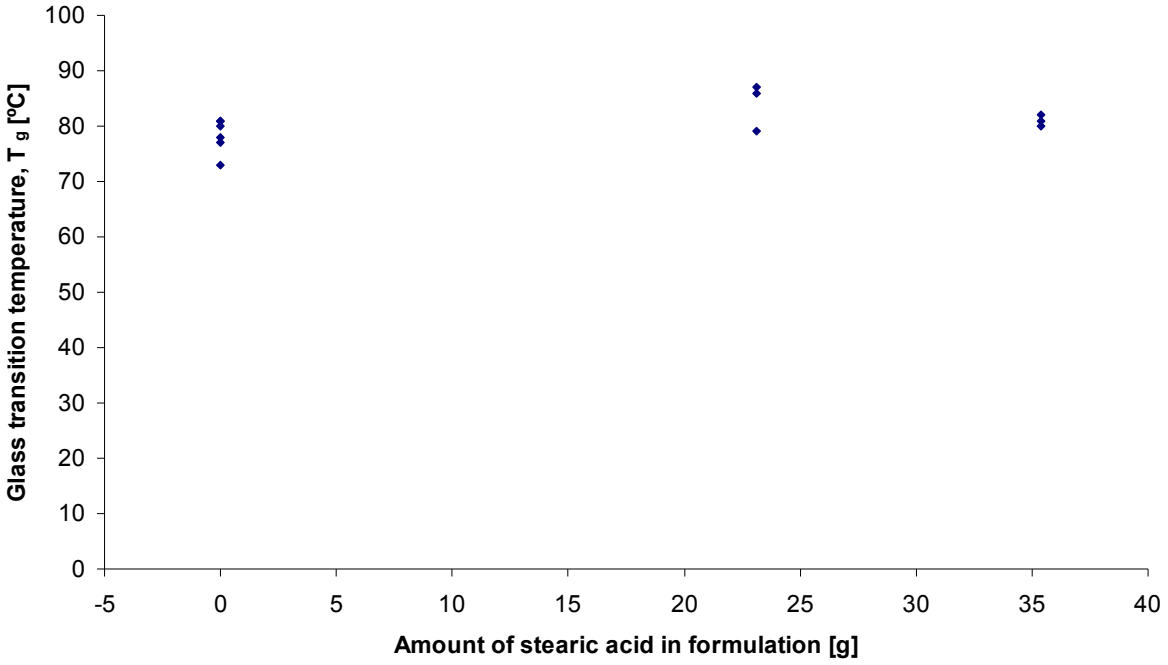


Figure 56 T_g values of extrudates with and without stearic acid.

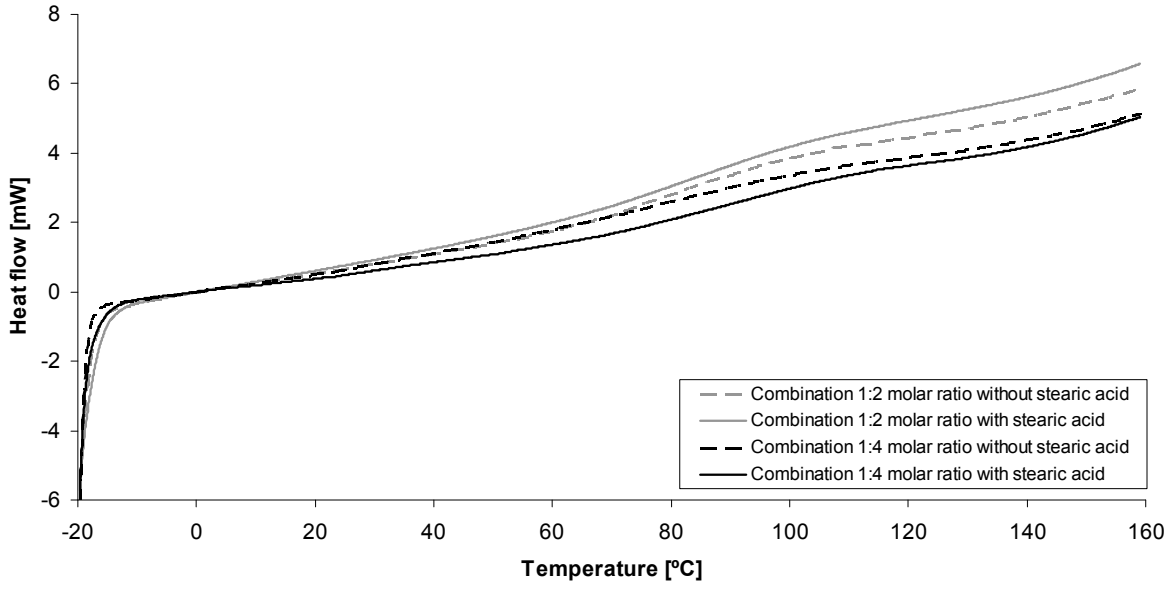


Figure 57 Comparison of the DSC diagram from extrudates with or without stearic acid in the formulation

The low variation on the Tg observed in the DSC measurements indicated that stearic acid did not act as plasticizer and did not block partially the active groups of EUDRAGIT® E PO inhibiting the IPEC formation.

3.5.3.3 Fourier-transform spectroscopy (FT-IR)

These trials were performed to identify the interaction between the polymers by observing the appearance of a carboxylate group's signal and the disappearance of dimethylaminoethyl signal and carboxylic signal. The extrudates were tested in demineralized water for a day, to observe the influence of water on the carboxylate group formation (Chavasit et al. 1988; Moustafine et al. 2008). The influence of stearic acid on the IPEC formation was also evaluated.

EUDRAGIT® E PO with EUDRAGIT® L 100-55+30%TEC 1:2 molar ratio combinations with and without stearic acid were tested.The extrudates were tested before and after dissolution test in demineralized water at 37±0.5ºC with 50 rpm rotation speed for one day. A swelling effect (picture of a transversal cut of extrudate) after the dissolution of the extrudate without stearic acid was observed (Figure 58).

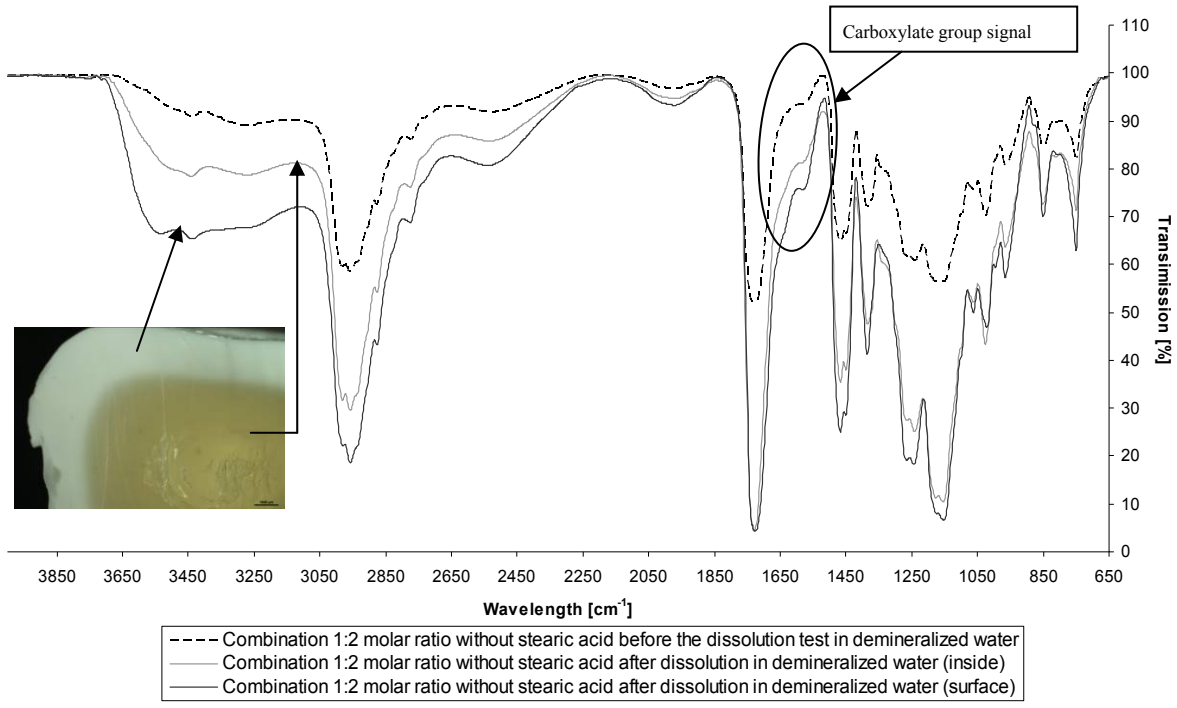


Figure 58 Picture of an extrudate from a 1:2 molar ratio combination without stearic acid after one day dissolution in demineralized water and its corresponding IR spectra for the dried extrudate (light grey), after dissolution inside part of the extrudate (middle grey) and after dissolution surface of the extrudate (dark grey)

The IR spectrum from this extrudate, before and after the dissolution, showed a stronger signal, especially on the surface. The water molecules react with the polymers accelerating the interpolymeric interactions through hydrogen bonds (Gallardo 2007).

The same test was performed for the extrudate with stearic acid. A similar swelling process was observed (picture of a transversal cut of extrudate). The IR spectra detected the same influence of water on the IPEC reaction, but the carboxylate signal was not as clear as it was in the previous example (Figure 59). The dimethylaminoethyl signal did not change much in the three spectra.

These results can indicate that stearic acid reacted with EUDRAGIT® E PO and blocks partially the interaction with EUDRAGIT® L 100-55.

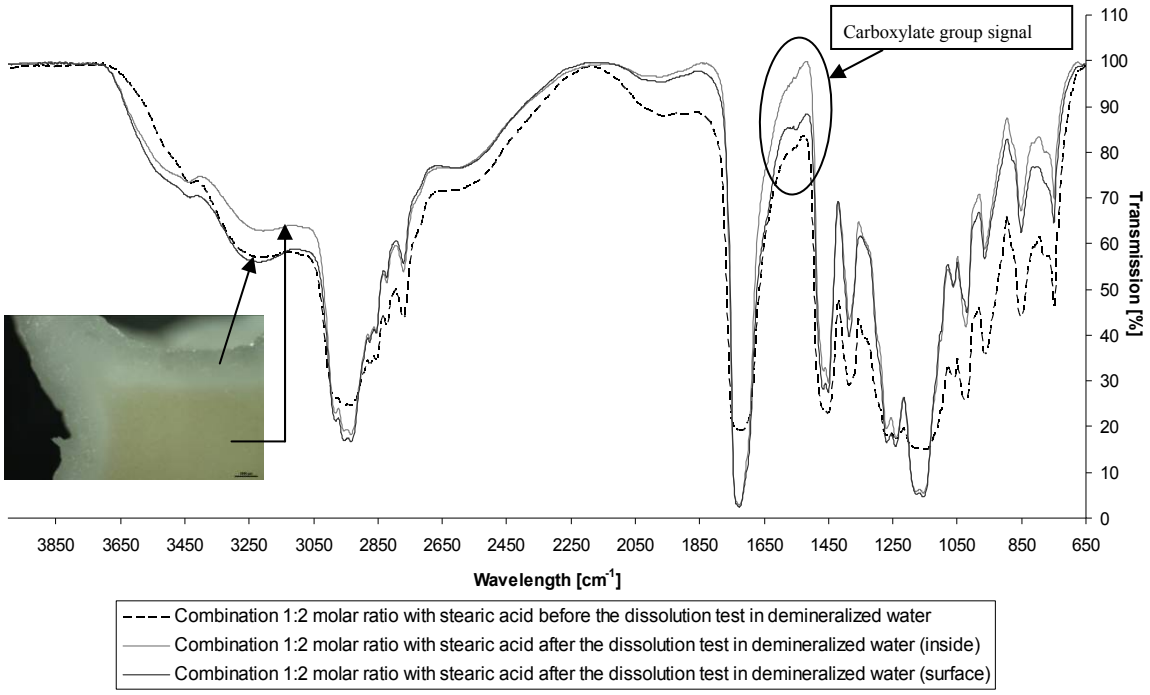


Figure 59 Picture of an extrudate from a 1:2 molar ratio combination with stearic acid after one day dissolution in demineralized water and its corresponding IR spectra for the dried extrudate (light grey), after dissolution inside part of the extrudate (middle grey) and after dissolution surface of the extrudate (dark grey)

3.5.3.4 Appearance and swelling behavior in acidic and alkali media

The appearance of the extrudates during the dissolution test was tested to determine the swelling behavior of the IPEC in different media (acidic and alkali) and the influence on the swelling effect when stearic acid was included in the formulation.

For the trials, extrudates from the combination EUDRAGIT® E PO: EUDRAGIT® L 100-55+30% TEC (1:2) with and without stearic acid were tested. They were tested in 700 ml 0.1 N HCl during 2 hours and then the pH was increased up to 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. The pictures were taken under the macroscope before the dissolution test, after the 2 hours in 0.1 N HCl and after 24 hours with 50 rpm paddle rotation speed (Figure 60).

The extrudate with stearic acid floated during the dissolution test. The presence of stearic acid was responsible for this behavior, due to the low density (0.980 g/cm^3).

During the first two hours (acidic medium) the extrudate with stearic acid eroded. The hydrophilic character of the IPEC, due to the dimethylaminoethyl groups previously detected (Figure 59), combined with the erodible character from stearic acid (Rodriguez et al. 1999) accelerated the erosion of the extrudate in acidic medium. The extrudate without stearic acid did not show erosion in acidic medium. It showed a slightly swelling effect due to hydration.

Once the dissolution medium was changed from acidic to alkali, both extrudates experiment a swelling process. The swelling process leads to a gel formation that sealed the surface of the extrudate.

The thickness of the gel layer is affected by the swelling/dissolution of the polymer. (Colombo 1993; Lowman 2000). When the swelling property of the polymer is greater than the dissolution, the gel layer is thicker and vice versa. The swelling property of an IPEC is related to the degree of interaction between the polymers. If the degree of interaction is high, the gel formed by the swelling effect is more stable and therefore less sensitive to erosion and vice versa.

The differences in the gel layer thickness can be clearly observed in Figure 60. The extrudate without stearic acid seemed to be more sensitive to erosion showing a thinner gel layer. These pictures confirm the results from the IR spectrum. The degree of polymer interaction in the extrudate without stearic acid was lower than in the extrudate with stearic acid.

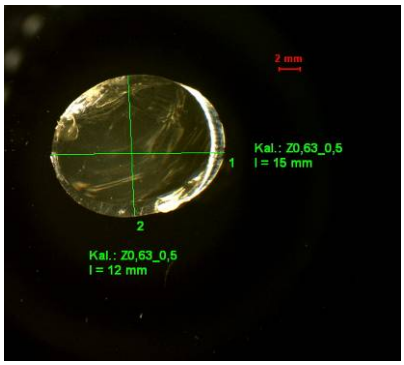
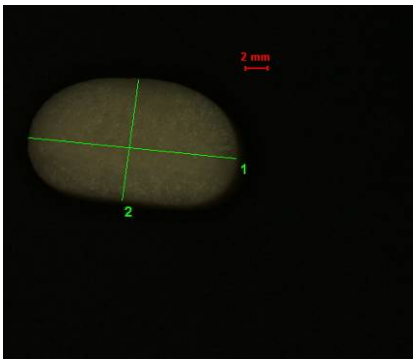
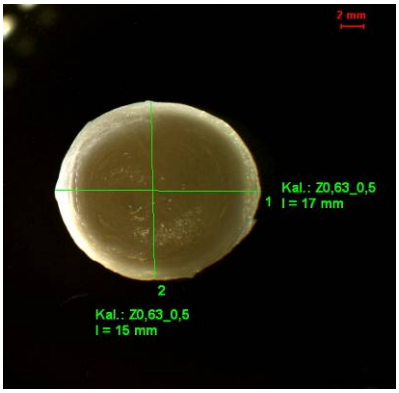
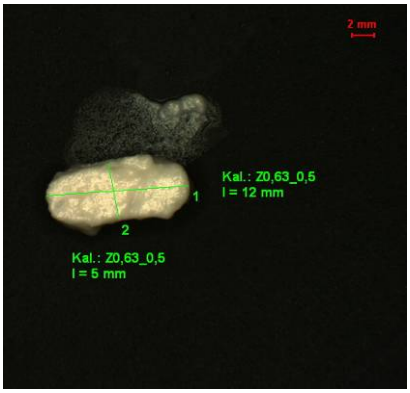
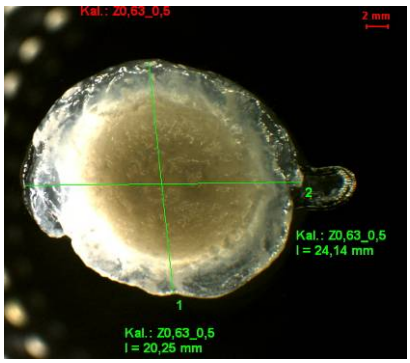
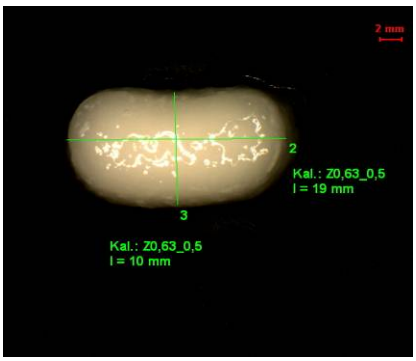
	Combination 1:2 molar ratio without stearic acid	Combination 1:2 molar ratio with stearic acid
Before dissolution test		
After 2 hours in 0.1 N HCl		
After 1 day in pH=6.8		

Figure 60 Pictures showing the swelling behavior of extrudates before, during and after dissolution test

3.5.3.5 Dissolution test

These trials were performed to observe the sustained release properties from the IPEC formed and to evaluate the influence of drug content and stearic acid.

Extrudates with diprophylline were produced with a combination of the polymers in 1:1 weight ratio. The drug content varied between 25% and 50%. Also polymer combinations with and without stearic acid were tested to evaluate its effect on the release profile (Figure 61).

The sizes of the extrudates tested are described in point 6.2.3.2.

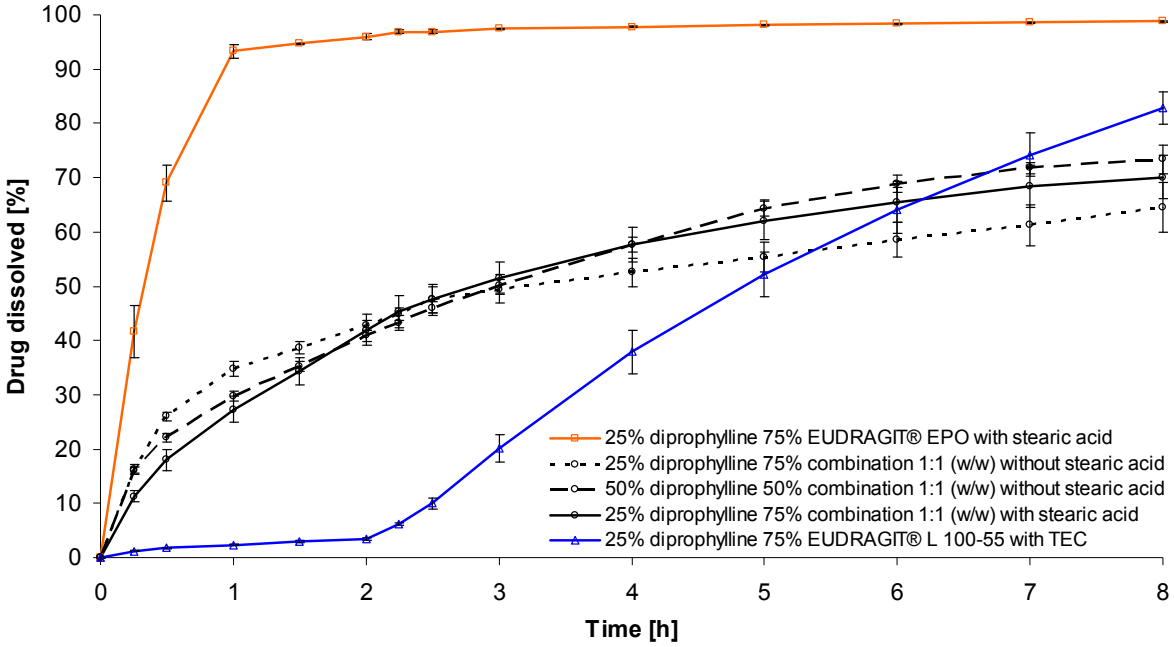


Figure 61 Dissolution test of extrudates with pure polymer or with combination in different percentages. Dissolution test performed in 700 ml of 0.1 N HCl the first two hours and then in phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Test Apparatus II, 50 rpm. (n=3)

The release profile from the IPEC showed a pH independent character along the different pH values.

The differences on the release profile after 2 hours in acidic medium changing 2 variables (presence of stearic acid and drug content) were within 2%. The differences on the release after 8 hours were within 9%. The low variability indicated that stearic acid did not have an influence on the sustained release properties of the extrudates.

The release profile of the formulation with 50% drug content was similar to the release profile of the same formulation with 25% drug content. These results and the results of the wet granulation with high shear mixer showed that the IPEC can provide similar sustained release properties even at lower percentages of polymer content.

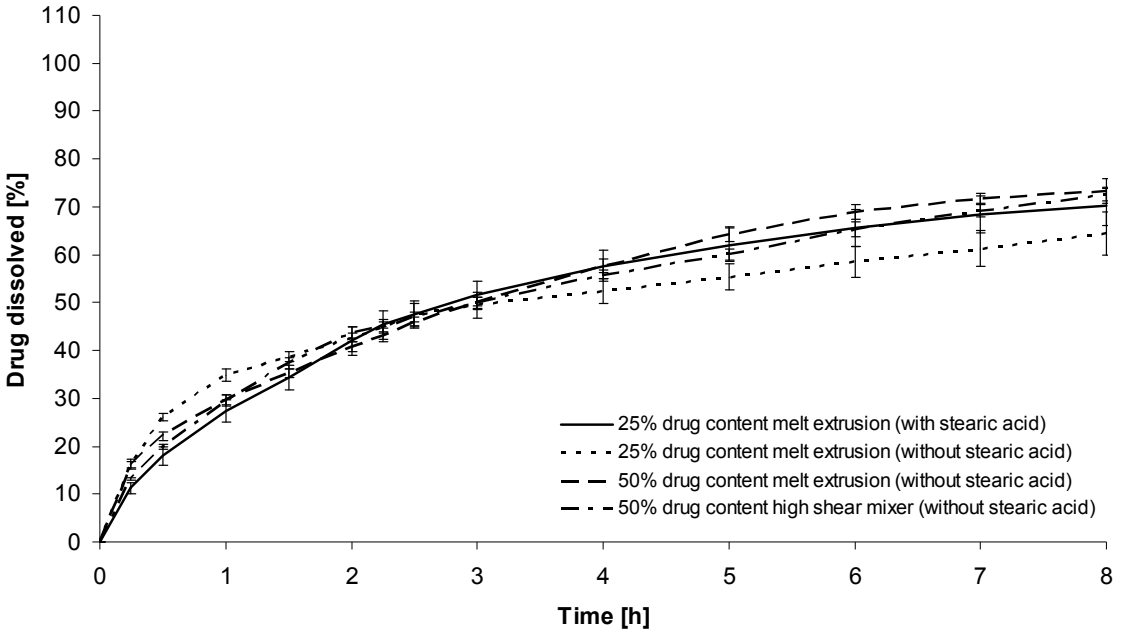


Figure 62 Comparison of the release profile between extrudates and tablets manufactured via wet granulation. Dissolution test performed in 700 ml of 0.1 N HCl the first two hours and then in phosphate buffer 6.8 by adding 214 ml of $Na_3PO_4 \cdot 12H_2O$. Test Apparatus II, 50 rpm. (n=3).Release profile from extrudate obtained from graphic represented in Figure 61. Release profile from tablet produced via wet granulation obtained from graphic represented in Figure 40 (formulation with 50 % polymer content).

No differences were observed on the release profiles from the matrix tablets produced via melt extrusion and wet granulation with high shear mixer (Figure 62). Even though the density values in extrudates are higher than in granules.

No improvement on the sustained release properties of the matrix tablets were observed by using melt-extrusion process.

3.5.4 Summary

Melt extrusion showed an improvement compared to the high shear mixer in the process time, although the combination of polymers forming the IPEC lead to a drastically increase in the viscosity making the extrusion difficult.

The influence of stearic acid in the formulation reduces the viscosity of the extrudates but has an influence on the formation of the IPEC, as shown in the IR spectra and in the swelling behavior of the extrudates. These changes were not detected in the determination of the T_g of the IPEC in the DSC trials. Stearic acid did not have an influence on the release profile of diprophylline. The IPEC provided similar sustained release properties to the extrudate with double amount of drug showing the robust character of the system.

4 Conclusion

Combination of countercharged poly(meth)acrylate polymers forming an IPEC was investigated to observe its application as matrix former for highly soluble drugs. The combination was first characterized to determine the influence of different factors on the IPEC formation.

The combination of countercharged poly(meth)acrylate in organic solvents or aqueous systems formed IPECs. The IPEC was the result of the interaction between carboxylic groups of anionic polymers and the dimethylaminoethyl groups of EUDRAGIT® E PO.

The IPECs produced via organic solution were analyzed with analytical techniques to characterize them. Titration, nitrogen content analysis or proton-NMR were used to determine the composition of the IPEC and to compare it with the weighed amount of polymers combined. Each technique confirmed that the amount of EUDRAGIT® E PO included in the IPEC was lower than the weighed amount at the beginning. The results confirmed the higher reactivity EUDRAGIT® E PO compared to the reactivity of the anionic polymers.

With the help of infrared spectroscopy, differential scanning calorimetry or C^{13}-NMR the interaction between the combined polymers could be qualitative detected. These techniques were also used to analyze the tablets produced via wet granulation or via melt extrusion. They were used to observe the influence on the IPEC built from stearic acid or from the different dissolution media where the tablets were tested.

The combination of the polymers was used for the manufacture of matrix tablets via wet granulation and melt-extrusion. The combination of countercharged poly(meth)acrylate showed not appropriate in both techniques. The great polymer volumes added via wet granulation made the process long. The IPEC formation during the melt extrusion process increased the viscosity producing high pressure and torque values.

The IPEC showed sustained release properties and pH independent release profile produced from the combination of two pH-dependent polymers. No interactions between drug with different ionic character and IPEC were found. The release profiles were characterized with a fast release in acidic medium and slow release in alkali medium. The sustained release properties were not as efficient as EUDRAGIT® RS 30 D (inert poly(meth)acrylate, used as matrix former). EUDRAGIT® RS 30 D provided stronger sustained release than the IPEC

with lower polymer content or when granulating drugs with extremely high solubility like diltiazem HCl.

Although the IPECs showed sustained release properties, the complications originated during the process and the faster release of the drug in acidic medium make them not the first option to choose to manufacture matrix tablets. Other polymers, for example cellulose-based polymers, are easier to handle and required less process time and polymer content to provide a stronger sustained release.

5 Zusammenfassung der Arbeit

Kombinationen von gegengeladenen Poly(meth)acrylaten, die Interpolyelektrolytkomplexe (IPEC) bilden, wurden hinsichtlich Ihrer Anwendung als Matrixbildner für hochlösliche Arzneistoffe untersucht. Im ersten Schritt wurden die Kombinationen charakterisiert um die verschiedenen Faktoren, die einen Einlfuss auf die Komplexbildung nehmen, zu bestimmen.

Die Kombinationen von gegensinnig geladenen Poly(meth)acrylaten bildeten sowohl in organischen Lösungsmitteln als auch in wässrigen Systemen IPECs. Der IPEC resultierte aus der Interaktion zwischen der Carboxlgruppe der anionischen Polymeren und der Dimethylaminoethylgruppe des EUDRAGIT® E PO.

Die IPECS hergestellt in organischen Lösungen wurden mit verschiedenen analytischen Methoden charakterisiert. Um die Zusammensetzung zu bestimmen, wurden Titrationen, Bestimmung des Stickstoffgehalts und ^{13}C-NMR durchgeführt und diese mit den zu Beginn eingewogenen Mengen an Polymer verglichen. Jede Methode bestätigte, dass die Menge an EUDRAGIT® E PO im IPEC geringer war als die zu Beginn eingewogene Menge. Dies bestätigt die hohe Reaktivität des EUDRAGIT® E PO verglichen mit der Reaktivität der anionischen Polymere.

Mit IR-Spektroskopie, DSC und ^{13}C-NMR konnten die Interaktionen zwischen den kombinierten Polymeren qualitativ bestimmt werden. Diese Methoden wurden ebenfalls zur Charakterisierung der Tabletten, hergestellt durch Feuchtgranulation oder Schmelzextrusion verwendet. Außerdem konnte der Einfluss der Stearinsäure auf die Bildung des IPECs oder der Einfluss der verschiedenen Dissolutionmedien, in denen die Tabletten freigesetzt wurden, bestimmt werden.

Die Kombinationen der Polymere wurden zur Herstellung von Matrixtabletten mittels Feuchtextrusion und Schmelzextrusion verwendet. Die Kombination der gegengeladenen Poly(meth)acrylate erwies sich nicht als vorteilhaft. In der Feuchtextrusion führte die hohe Menge an benötigtem Polymer zu einer Verlängerung des Prozesses. In der Schmelzextrusion führte die Bildung des IPECs zu einem Anstieg der Viskosität und damit zu einem hohen Drehmoment und Druck.

Der IPEC zeigte sustained release Eigenschaften und ein pH unabhängiges Freisetzungsprofil, obwohl die eingesetzten Polymere selbst pH-abhängig löslich sind. Zwischen den Arzneistoffen und dem IPEC konnten keine Interaktionen gefunden werden. Die

Freisetzungsprofile waren durch eine rasche Freisetzung im sauren Medium und eine verzögerte Freisetzung im basischen Medium gekennzeichnet. Die sustained release Eigenschaften waren nicht so effektiv wie mit EUDRAGIT® RS 30 D (inertes Poly(meth)acrylat, verwendet als Matrixbildner). EUDRAGIT® RS 30 D lieferte ein stärkeres sustained release Verhalten als der IPEC mit geringerem Polymergehalt oder nach Granulation mit einem sehr hochlöslichen Arzneistoff wie Diltiazem HCl.

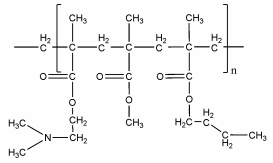
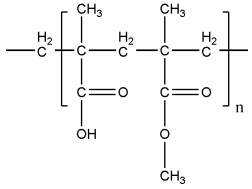
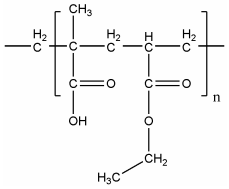
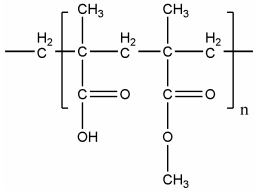
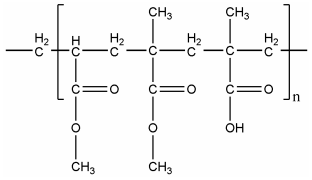
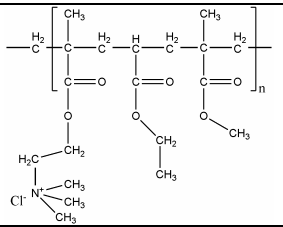
Obwohl der IPECs sustained release Eigenschaften zeigte, sind sie nicht als erste Wahl zur Herstellung von Matrixtabletten zu sehen, da während der Herstellung Komplikationen auftraten und der Wirkstoff im sauren Medium zu schnell freigesetzt wird. Andere Poylmere wie Cellulosederivate sind einfacher zu verarbeiten und zeigen ein starkes sustained release Verhalten.

6 Experimental section

6.1 Materials

6.1.1 Methacrylate copolymers

Table 18 General information of the polymers used

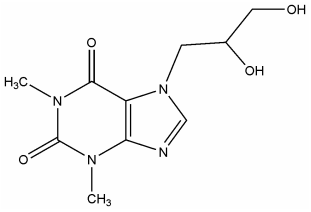
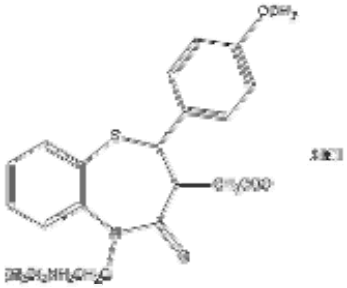
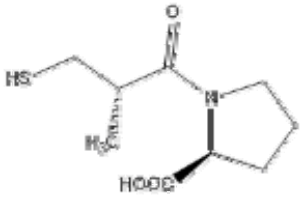
	EUDRAGIT® E PO	**EUDRAGIT® L 100**	**EUDRAGIT® L 100-55 / EUDRAGIT® L 30 D-55**	**EUDRAGIT® S 100**	**EUDRAGIT® FS**	**EUDRAGIT® RS 30 D**
Chemical name	Poly(butyl methacrylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1	Poly(methacrylic acid-co-methyl methacrylate) 1:1	Poly(methacrylic acid-co-ethyl acrylate) 1:1	Poly(methacrylic acid-co-methyl methacrylate) 1:2	Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1	Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1
Molecular weight	150,000	135,000	250,000	135,000	400,000	150,000
Structure						
Particle sizes (DV50-Value)	< 50µm	58-80µm	≈ 100nm	61-75µm	≈220µm	≈ 100nm
Basic value (mg KOH/g dry substance)	162-198					
Acid value (mg KOH/g dry substance)		300-330	300-330	180-200	60-80	17-22
Glass transition temperature	≈ 45ºC	>160ºC	≈ 115ºC	>160ºC	≈ 48ºC	≈50ºC

Continuation Table 18

	EUDRAGIT® E PO	**EUDRAGIT® L 100**	**EUDRAGIT® L 100-55 / EUDRAGIT® L 30 D-55**	**EUDRAGIT® S 100**	**EUDRAGIT® FS**	**EUDRAGIT® RS 30 D**
Decomposition temperature	>200ºC	>160ºC	>160ºC	>160ºC	>200ºC	>140ºC
Batch	G050631071 G060931183 G070331066 G070831117	B041203035	B030804067 B051004081 B050904057 B070214089 B070514252 B070514236	B041005026	G040645003	G060618095 G060318044
Supplier	Evonik Röhm GmbH, Darmstadt, Germany					
Character	Cationic	Anionic	Anionic	Anionic	Anionic	Cationic

6.1.2 Drugs

Table 19 Properties of the drugs used in this study

	Diprophylline	Diltiazem HCl	Captopril
Structure			
Molecular weight (g/mol)	254.2	451.0	217.3
Solubility in water (g/l)	333	590	160
Melting point (ºC)	160-165	212-215	104-108
Batch	C1194 D1068	DIL 1504 DIL 1107	5102-07-049
Supplier	NBS Biological Ltd. Cambridgeshire, United Kingdom	Lusochimica S.p.A., Lomagna, Italy	Zheijang Huahai Pharmaceutical Co., Ltd., Zhejiang, China
Character	Neutral	Cationic	Anionic

6.1.3 Other excipients

Table 20 List of excipients and chemicals used in the different processes and analytical methods

Material	Batch	Supplier
Isopropanol	Various, complies Eur. Ph.	Shell Chemicals
Acetone	Various, complies Eur. Ph.	Ineos Phenol GmbH & Co KG, Gladbeck, Germany
Dibasic calcium phosphate dihydrate, EMCOMPRESS® Premium	A74057A	JRS Pharma GmbH & CO. Kg, Rosenberg, Germany
Hydrochloric acid	Various	Merck KGaA, Darmstadt, Germany
$Na_3PO_4 \cdot 12H_2O$	A924378 811 p.a.	Merck KGaA, Darmstadt, Germany

Continuation Table 20

Sodium acetate trihydrate	72950 p.a.	Sigma-Aldrich Chemie GmbH, Steinheim, Germany
Potassium dihydrogen phosphate	A850773 748 p.a.	Merck KGaA, Darmstadt, Germany
di-Potassium hydrogen phosphate	A676204 720 p.a.	Merck KGaA, Darmstadt, Germany
Sodium Chloride	K37303004 719 p.a.	Merck KGaA, Darmstadt, Germany
Triethyl citrate	K 38212359 811 p.a. K 38212359 822 p.a.	Merck KGaA, Darmstadt, Germany
Stearic acid	B 16597	Mallinckrodt Chemicals J.T. Baker, New Jersey, USA
Talc	S 167 / 08 p.a.	Luzenac, Toulouse, France
Magnesium stearate	K 35442263 550 p.a.	Merck KGaA, Darmstadt, Germany
Sodium lauryl sulfate	434566/1 p.a.	Sigma-Aldrich Chemie GmbH, Steinheim, Germany
Acetic acid	K35566363 552 p.a.	Merck KGaA, Darmstadt, Germany
Perchloric acid	HX 754295	Merck KGaA, Darmstadt, Germany

6.2 Methods

6.2.1 Combination of methacrylate copolymers in organic solution

The polymers were separately dissolved in an organic mixture of isopropanol/acetone 60/40 (w/w) and stirred on a magnetic stirrer (IKA Ret control-visc, IKA® Werke, GmbH CO. KG, Staufen, Germany) until complete dissolution. The polymers were dissolved in organic solvents, to enhance the interaction between the polymers.

6.2.1.1 Gravimetric analysis

6.2.1.1.1 Mixing

The organic solutions were combined in a closed reactor (Schmizo AG, Zofingen, Switzerland). The final mixture volume was always 500ml and the total polymer content was always 1.6g. The reactor temperature was kept constant at 20ºC. The mixture was stirred with an overhead stirrer (EUROSTAR power control-visc P1, IKA® Werke GmbH & Co. KG,

Staufen, Germany) at a constant speed of 200rpm. For every polymer combination, three different incorporation orders were assayed:

- Cationic polymer over anionic polymer
- Anionic polymer over cationic polymer
- Both polymers at the same time

The polymers were added as the solutions previously described, to the reactor with a 100ml burette. The volume of the organic mixture of isopropanol/acetone 60/40 (w/w) in the reactor before the polymer was added was 400ml, when only one of the polymers was added, or 300ml, when both polymers were added at the same time with two burettes.

The polymers were combined in molar ratios. The molar ratios are calculated not on the molecular weight of the polymers, but in their amount of active groups. This can be calculated based on the acidic/alkali values of the polymer (Table 21).

Table 21 Acid or alkali mean values of poly(meth)acrylate used for the combinations

Polymer	**Acidic/alkali value**
EUDRAGIT® E PO	177.5 mg KOH/g DS
EUDRAGIT® L 100-55	317 mg KOH/g DS
EUDRAGIT® L 100	317 mg KOH/g DS
EUDRAGIT® S 100	190 mg KOH/g DS
EUDRAGIT® FS	65 mg KOH/g DS

The polymers were combined in different ratios varying from a 4:1 molar ratio to a 1:4 molar ratio (cationic polymer to anionic polymer). EUDRAGIT® E PO with EUDRAGIT® L 100-55 had an additional combination, 1:5 molar ratio, to observe the trend in the amount of sediment formation depending on the order of addition and concentration of the polymers in the burette and reactor. The amount and concentration values are listed below (Table 22 and Table 23).

Table 22 Weight of poly(meth)acrylate polymers combined in organic solution at different molar ratio

Molar ratios cationic to anionic	**EUDRAGIT® E PO: EUDRAGIT® L 100 / EUDRAGIT® L 100-55**		**EUDRAGIT® E PO: EUDRAGIT® S 100**		**EUDRAGIT® E PO: EUDRAGIT® FS**	
4 to 1	1.404 g	0.196 g	1.298 g	0.302 g	0.952 g	0.648 g
3 to 1	1.348 g	0.252 g	1.221 g	0.379 g	0.837 g	0.763 g
2 to 1	1.250 g	0.350 g	1.092 g	0.508 g	0.676 g	0.924 g
1 to 1	1.025 g	0.575 g	0.829 g	0.771 g	0.429 g	1.171 g
1 to 2	0.755 g	0.845 g	0.507 g	1.093 g	0.248 g	1.352 g
1 to 3	0.598 g	1.002 g	0.421 g	1.179 g	0.174 g	1.426 g
1 to 4	0.494 g	1.106 g	0.339 g	1.261 g	0.134 g	1.466 g
1 to 5	0.421 g	1.179 g				

Table 23 Concentration of poly(meth)acrylate polymers combined in organic solution. White columns (concentration in reactor) grey columns (concentration in burette)

	EUDRAGIT® E PO over EUDRAGIT® L 100 / EUDRAGIT® L 100-55		**EUDRAGIT® L 100 / EUDRAGIT® L 100-55 over EUDRAGIT® E PO**		**Simultaneous addition**	
4 to 1	14.04 mg/ml	0.49 mg/ml	1.96 mg/ml	3.51 mg/ml	14.04 mg/ml	1.96 mg/ml
3 to 1	13.48 mg/ml	0.63 mg/ml	2.52 mg/ml	3.37 mg/ml	13.48 mg/ml	2.52 mg/ml
2 to 1	12.50 mg/ml	0.88 mg/ml	3.50 mg/ml	3.13 mg/ml	12.50 mg/ml	3.50 mg/ml
1 to 1	10.25 mg/ml	1.44 mg/ml	5.75 mg/ml	2.56 mg/ml	10.25 mg/ml	5.75 mg/ml
1 to 2	7.55 mg/ml	2.11 mg/ml	8.45 mg/ml	1.89 mg/ml	7.55 mg/ml	8.45 mg/ml
1 to 3	5.98 mg/ml	2.51 mg/ml	10.02 mg/ml	1.50 mg/ml	5.98 mg/ml	10.02 mg/ml
1 to 4	4.94 mg/ml	2.77 mg/ml	11.06 mg/ml	1.24 mg/ml	4.94 mg/ml	11.06 mg/ml
1 to 5	4.21 mg/ml	2.95 mg/ml	11.79 mg/ml	1.05 mg/ml	4.21 mg/ml	1.05 mg/ml
	EUDRAGIT® E PO over EUDRAGIT® S 100		**EUDRAGIT® S 100 over EUDRAGIT® E PO**		**Simultaneous addition**	
4 to 1	12.98 mg/ml	0.76 mg/ml	3.02 mg/ml	3.25 mg/ml	12.98 mg/ml	3.02 mg/ml
3 to 1	12.21 mg/ml	0.95 mg/ml	3.79 mg/ml	3.05 mg/ml	12.21 mg/ml	3.79 mg/ml
2 to 1	10.92 mg/ml	1.27 mg/ml	5.08 mg/ml	2.73 mg/ml	10.92 mg/ml	5.08 mg/ml
1 to 1	8.29 mg/ml	1.93 mg/ml	7.71 mg/ml	2.07 mg/ml	8.29 mg/ml	7.71 mg/ml
1 to 2	5.07 mg/ml	2.73 mg/ml	10.93 mg/ml	1.27 mg/ml	5.07 mg/ml	10.93 mg/ml
1 to 3	4.21 mg/ml	2.95 mg/ml	11.79 mg/ml	1.05 mg/ml	4.21 mg/ml	11.79 mg/ml
1 to 4	3.39 mg/ml	3.15 mg/ml	12.61 mg/ml	0.85 mg/ml	3.39 mg/ml	12.61 mg/ml
	EUDRAGIT® E PO over EUDRAGIT® FS		**EUDRAGIT® FS over EUDRAGIT® E PO**		**Simultaneous addition**	
4 to 1	9.52 mg/ml	1.62 mg/ml	6.48 mg/ml	2.38 mg/ml	9.52 mg/ml	6.48 mg/ml
3 to 1	8.37 mg/ml	1.91 mg/ml	7.63 mg/ml	2.09 mg/ml	8.37 mg/ml	7.63 mg/ml
2 to 1	7.76 mg/ml	2.31 mg/ml	9.24 mg/ml	1.94 mg/ml	7.76 mg/ml	9.24 mg/ml
1 to 1	4.29 mg/ml	2.93 mg/ml	11.71 mg/ml	1.07 mg/ml	4.29 mg/ml	11.71 mg/ml
1 to 2	2.48 mg/ml	3.38 mg/ml	13.52 mg/ml	0.62 mg/ml	2.48 mg/ml	13.52 mg/ml
1 to 3	1.74 mg/ml	3.57 mg/ml	14.26 mg/ml	0.44 mg/ml	1.74 mg/ml	14.26 mg/ml
1 to 4	1.34 mg/ml	3.67 mg/ml	14.66 mg/ml	0.34 mg/ml	1.34 mg/ml	14.66 mg/ml

The feeding rate of the polymers from the burette was approximately 1.6 ml/min. Each combination was performed 3 times. When the polymers were mixed turbidity appeared within a minute. The turbidity was caused by precipitates formation between the anionic and cationic polymer, insoluble in the solvents used. The turbidity varied depending on the polymers and the ratios combined. After the polymers were combined the sediment could be centrifuged to separate it from the supernatant.

6.2.1.1.2 Centrifugation

The complete suspension was centrifuged with a speed of 5000rpm for 10 minutes in a centrifuge (Labofuge A, Heraeus Christ GmbH, Osterode, Germany). The clearness of the supernatant and the amount of sediment collected was different depending on the combination produced and the order of polymer addition.

6.2.1.1.3 Drying

Once the sediment was collected, it was placed in a drying oven (Memmert BE-40, Schwabach, Germany) at 60ºC until a constant mass value was achieved. The samples were cooled to room temperature in a desiccator and weighed again to obtain the final weight.

6.2.1.2 Statistical interpretation

A central composite design was used to evaluate the influence of the concentration, order of addition and the anionic polymers used for the combinations on the amount of sediment. The factors used were the percentage of carboxylic groups of the anionic polymers and the fraction of EUDRAGIT® E PO in the combination. The dependent value was the sediment final weight. This study was performed for the three different orders of addition.

6.2.2 Wet granulation with high shear mixer (DIOSNA)

6.2.2.1 Equipment description

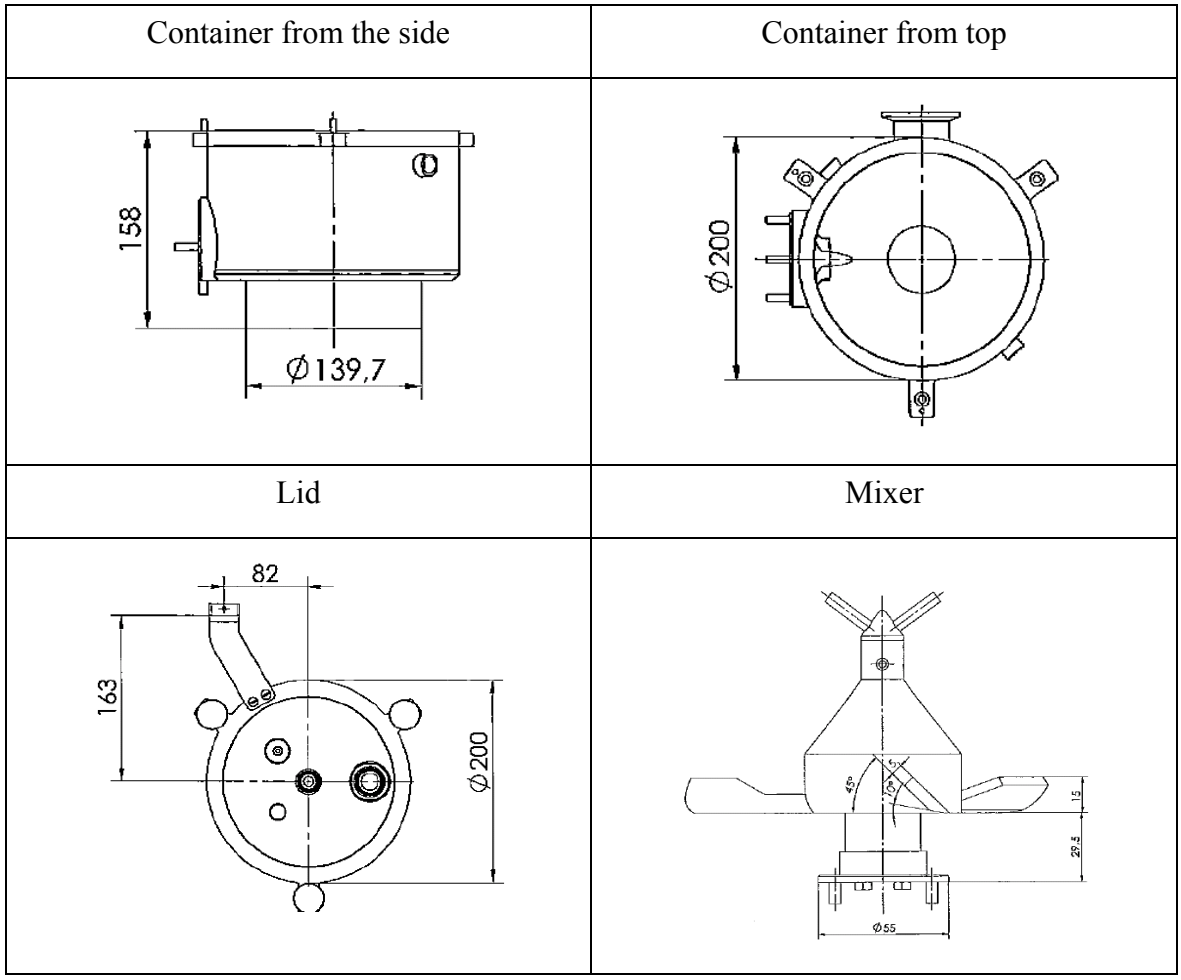


Figure 63 DIOSNA VAC-2 mixer granulator scheme

The wet granulation was performed in a mixer granulator (Laboratory processor P/VAC-10, Diosna Dierk & Söhne GmbH, Osnabrück, Germany) described in the figure above (Figure 63). The bowl used for the granulations was a 2 liters vacuum drying bowl. The temperature of the bowl can be regulated with a water circuit from 25ºC to 60ºC.

6.2.2.2 Preparation of the polymer suspension

The polymers used for these trials were EUDRAGIT® E PO and EUDRAGIT® L 30D-55. EUDRAGIT® E PO solution was prepared in two different ways. One was combined with sodium lauryl sulphate (SLS) and stearic acid. SLS (10%) is used as wetting and dispersing agent and stearic acid (15%) forms a soluble salt with the polymer. This formulation results in

a colloidal solution with a slight turbidity. The colloidal solutions were prepared with a total solid content not higher than 18% to maintain a low viscosity.

To prepare the colloidal solution it was necessary to add first the SLS in demineralised water and homogenize for 5 minutes with an Ultra Turrax (Ultra Turrax® T50, IKA Werke, GmbH CO. KG, Staufen, Germany). The stearic acid was added and stirred for 15 minutes. After that, EUDRAGIT® E PO was added slowly during 15 minutes. It is recommended to stir the entire formulation again in the end with a magnetic stirrer (IKA Ret control-visc, IKA Werke, GmbH CO. KG, Staufen, Germany) to eliminate the possible foam formed when the different elements were added.

The second EUDRAGIT® E PO formulation was prepared simply dispersing the polymer in water. In this case, the suspension had 30% polymer content. To prepare this suspension, the polymer was added slowly to the demineralised water and stirred with a magnetic stirrer (IKA Ret control-visc, IKA Werke, GmbH CO. KG, Staufen, Germany).

EUDRAGIT® L 30D-55 was mixed with 20% triethyl citrate (TEC), based on the polymer dry substance, in a magnetic stirrer (IKA Ret control-visc, IKA Werke, GmbH CO. KG, Staufen, Germany). TEC was used as plasticizer to increase the flexibility of the polymer to improve the formation of the matrix structure when pressing the granules into tablets.

6.2.2.3 Mixing

6.2.2.3.1 Wet granulation with EMCOMPRESS®

The powder mixture was prepared with Diprophylline and EMCOMPRESS®. The description of the different formulations is described later (point 6.2.2.7). The polymers were added to the mixer granulator through a dosing opening in the lid. Mixer speed was set at 100 rpm and the chopper was set at 1700 rpm. The chopper was connected during the addition of the polymer to improve the distribution of the polymers and to prevent excessive granule growth. The addition time of the polymer varied between 1 and 3 minutes each time. The total mixing time varied depending on the combination and percentage of polymer applied, ranging between 30 minutes and 90 minutes. After every polymer addition vacuum was applied (45 mbar) for approximately 10 minutes to accelerate the drying process. Since the volume of water in the polymer preparation was high, the process had to be stopped and intermediate drying with a source of heating air. This external drying process was performed at least once in every batch

and some cases up to 3 times. The drying time was between 5 and 10 minutes. After drying, the mass was sieved and placed again in the mixer granulator.

6.2.2.3.2 Wet granulation without EMCOMPRESS®

The powder mixture was prepared only with the drug (Diprophylline, Diltiazem HCl or Captopril). The process' characteristics were the same as in the trial described before (point 6.2.2.3.1). Only in the formulations where the polymer content was 50%, the mixing time increased up to 2 hours combined with more external drying steps, up to 6 in one of the batches. The polymers were combined only in one molar ratio EUDRAGIT® E PO:EUDRAGIT® L 30D-55 (1:4). The values are listed below (Table 24).

Table 24 Formulation of Diprophylline without EMCOMPRESS® with the combination EUDRAGIT® E PO: EUDRAGIT® L 30D-55(1:4). DS= dry substance

Diprophylline [g]	EUDRAGIT® E PO [g]	EUDRAGIT® L 30D-55 [g] DS	TEC [g]	Percentage polymer applied [%]
498.75	8.10	18.15	3.60	5
495.00	16.98	38.02	7.60	10
488.75	26.62	59.63	11.93	15
480.00	37.05	82.95	16.59	20
375.00	115.74	259.26	51.85	50

The same trial plan was performed with EUDRAGIT® RS 30 D to compare the sustained release effect. The values are listed in table below (Table 25).

Table 25 Formulation of Diprophylline without EMCOMPRESS® with EUDRAGIT® RS 30D. DS= dry substance

Diprophylline [g]	EUDRAGIT® RS 30D [g] DS	Percentage polymer applied [%]
498.75	26.25	5
495.00	55.00	10
488.75	86.25	15
480.00	120.00	20
375.00	375.00	50

From all the formulations without EMCOMPRESS®, the best was selected to use it with other drugs like Diltiazem HCl (cationic) and Captopril (anionic) to observe the influence on the release profile depending on the character of the drug. Granulations with EUDRAGIT® FS 30 D, EUDRAGIT® E PO, EUDRAGIT® RS 30D were performed to compare with the polymer combination. These different polymers were selected based on their ionic character, to observe a possible influence or interaction between the drug and the polymers leading to a different release profile. Details of the formulations are described in the tables below (Table 26-29).

Table 26 Formulation of Diltiazem HCl and Captopril without EMCOMPRESS® with the combination EUDRAGIT® E PO: EUDRAGIT® L 30D-55(1:4). DS= dry substance

Diltiazem HCl [g]	Captopril [g]	EUDRAGIT® E PO [g]	EUDRAGIT® L 30D-55 [g] DS	TEC	Percentage polymer applied [%]
488.75		26.62	59.63	11.93	15
	488.75	26.62	59.63	11.93	15

Table 27 Formulation of Diltiazem HCl and Captopril without EMCOMPRESS® with EUDRAGIT® RS 30D. DS= dry substance

Diltiazem HCl [g]	Captopril [g]	EUDRAGIT® RS 30D [g] DS	Percentage polymer applied [%]
488.75		86.25	15
	488.75	86.25	15

Table 28 Formulation of Diltiazem HCl and Captopril without EMCOMPRESS® with EUDRAGIT® FS 30D. DS= dry substance

Diltiazem HCl [g]	Captopril [g]	EUDRAGIT® FS 30D [g] DS	Percentage polymer applied [%]
488.75		86.25	15
	488.75	86.25	15

Table 29 Formulation of Diltiazem HCl and Captopril without EMCOMPRESS® with EUDRAGIT® E PO. DS= dry substance

Diltiazem HCl [g]	Captopril [g]	EUDRAGIT® E PO [g] DS	Percentage polymer applied [%]
488.75		86.25	15
	488.75	86.25	15

6.2.2.4 Sieving

Once the polymers were added, the wet mass was passed through an oscillator granulator (wet granulator, FGS, ERWEKA, Heusenstamm, Germany). The oscillation speed was 25rpm. The wet mass was sieved through sieves of different sizes 2.5mm, 1.6mm, 1.0mm and 0.8mm, to obtain in the end the particle size wanted. The size was 0.8 mm or lower.

6.2.2.5 Drying

The granules were dried until constant mass at 40ºC in a drying oven (Ehret TK/L 4250, EHRET GmbH & Co. KG, Emmendingen, Germany).

6.2.2.6 Compression

The granules were mixed with magnesium stearate as lubricant (0.5% based on the total weight of the granules). The mixing process was performed in a bicone mixer (Servolift ML 5-30, Servolift GmbH, Offenburg, Germany) at 25rpm for 10 minutes with a change on the rotation direction every 2 minutes. The mixture was then compressed with an eccentric compression machine (Korsch EK0, Korsch GmbH, Berlin, Germany). The compression force was 10kN. The punch dimensions were 12mm diameter and 25mm curvature radius. The nominal weight of the tablets was 500mg.

6.2.2.7 Statistical interpretation

A statistical study was performed for the Diprophylline and EMCOMPRESS® granulations. A 2^4 fractional factorial design with three central points was performed to understand the influence of the different factors on the release of the drug. The factors chosen for the study were the polymer molar ratio, the percentage of polymer applied, the drug:EMCOMPRESS® ratio and the granulation temperature. All these factors are described below (Table 30).

Table 30 Parameters chosen for the trial plan developed with the high shear mixer DIOSNA

Diprophylline: EMCOMPRESS® ratio	**EUDRAGIT® E PO: EUDRAGIT® L 30D-55 molar ratio**	**Temperature [ºC]**	**Polymer applied [%]**
175 g: 325 g	1:4	40	16.70
225 g: 275 g	1:1	50	18.35
275 g: 225 g	2:1	60	20.00

Table 31 Weight of the substances used in the wet granulation trial plan

Diprophylline	EMCOMPRESS®	EUDRAGIT® E PO	EUDRAGIT® L 30 D-55 (DS)	TEC	Molar ratio	Temperature [ºC]	Polymer applied [%]
175 g	325 g	37.00 g	83.00 g	16.60 g	1:4	40	20.00
275 g	225 g	37.00 g	83.00 g	16.60 g	1:4	40	20.00
225 g	275 g	70.50 g	39.50 g	7.90 g	1:1	50	18.35
275 g	225 g	93.75 g	26.25 g	5.25 g	2:1	60	20.00
275 g	225 g	78.10 g	21.90 g	4.38 g	2:1	60	16.70
175 g	325 g	78.10 g	21.90 g	4.38 g	2:1	40	16.70
175 g	325 g	37.00 g	83.00 g	16.60 g	1:4	60	20.00
175 g	325 g	93.75 g	26.25 g	5.25 g	2:1	60	20.00
175 g	325 g	30.90 g	69.10 g	13.82 g	1:4	40	16.70
225 g	275 g	70.50 g	39.50 g	7.90 g	1:1	50	18.35
175 g	325 g	78.10 g	21.90 g	4.38 g	2:1	60	16.70
275 g	225 g	93.75 g	26.25 g	5.25 g	2:1	40	20.00
175 g	325 g	93.75 g	26.25 g	5.25 g	2:1	40	20.00
275 g	225 g	30.90 g	69.10 g	13.82 g	1:4	40	16.70
275 g	225 g	30.90g	69.10 g	13.82 g	1:4	60	16.70
275 g	225 g	37.00 g	83.00 g	16.60 g	1:4	60	20.00
275 g	225 g	78.10 g	21.90 g	4.38 g	2:1	40	16.70
175 g	325 g	30.90 g	69.10 g	13.82 g	1:4	60	16.70
225 g	275 g	70.50 g	39.50 g	7.90 g	1:1	50	18.35

The amount used of each component of the formulation is described above (Table 31). The recipes highlighted corresponded to the three central points of the statistical design.

The percentage of drug released after 2 hours was chosen as the dependent variables.

6.2.3 Hot melt extrusion

6.2.3.1 Process description

Trials were performed on a corotating twin screw extruder MICRO 18 GL 40 D Pharma (Leistritz Extrusionstechnik GmbH, Nürnberg, Germany) (Figure 64). The diameter of the extruder screws was 18mm and the length 72cm. The extruder had 8 different barrels which could be independently heated. The extrusion was performed with 2 different dies (3mm and 10mm diameter). The powder mixture was added with a gravimetric feeder at a constant feeding rate of 0.7kg/h for the pure polymer combinations or added directly with a spoon by hand when the polymers were combined with Diprophylline.

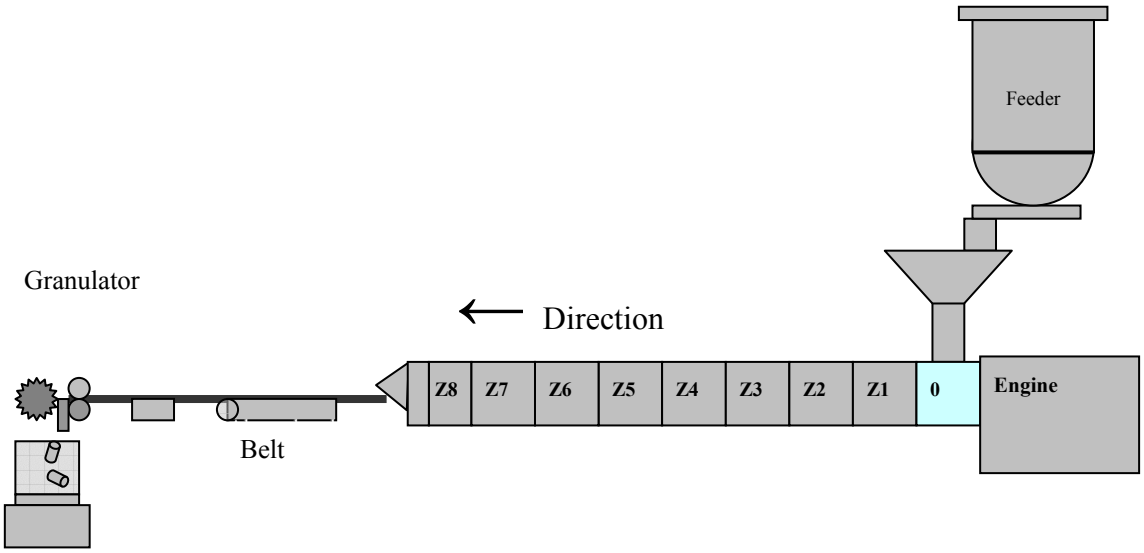


Figure 64 Scheme of the MICRO 18 GL 40 D pharma extruder

6.2.3.2 Mixture preparation

When the formulation included drug, the polymers were combined 1 to 1 (w/w).When the polymers were combined without drug, the combinations were based on the molar ratio like in the previous trial (point 6.2.1.1.1.).

EUDRAGIT® L 100-55 was first extruded with 30% TEC. The TEC was added with a pump through an opening into the extruder. The material was extruded through a 3 mm diameter die. After the extrusion, extrudates were milled with a rotor mill (Ultra centrifugal mill ZM 200, Retsch, Haan, Germany) with a 500 µm sieve at 6000rpm. The milled extrudate was mixed with EUDRAGIT® E PO and 15% stearic acid and the model drug (diprophylline) in the case that the formulation included drug in a bicone mixer (ERWEKA GmbH, Heusenstamm, Germany) at 25rpm for 10 minutes. The resulting mixture was extruded afterwards, obtaining in the final extrudates using a 5 cm long and 10 mm diameter die. The extrudates were manually cut to obtain the tablets. The resulting extrudates had a diameter between 12-15 mm and thickness between 4 and 6 mm. There were extrudates with oval shape with diameters of 12 mm and 7 mm

The formulations for the polymer combinations are described in Table 32.

Table 32 Formulation of the polymer combined in the extruder without drug

Combinations molar ratio EUDRAGIT® E PO to EUDRAGIT® L 100-55	**EUDRAGIT® E PO [g]**	**stearic acid [g]**	**EUDRAGIT® L 100-55 [g]**	**TEC [g]**
1 to 4	154.3	23.1	345.7	103.7
1 to 4	154.3		345.7	103.7
1 to 3	186.6	28.0	313.4	94.0
1 to 2	235.8	35.4	264.2	79.3
1 to 2	235.8		264.2	79.3
1 to 1	320.5	48.1	179.5	53.9
2 to 1	390.6	58.6	109.4	32.8
3 to 1	421.3	63.2	78.7	23.6
4 to 1	438.6	65.8	61.4	18.4

The formulation for the extrudates with polymer combination including drug are described in Table 33.

Table 33 Formulation from the polymer mixed and combined with the neutral model drug diprophylline

Diprophylline [g]	**EUDRAGIT® E PO [g]**	**Stearic acid [g]**	**EUDRAGIT® L 100-55 [g]**	**TEC [g]**
125	375.00	56.25		
125			375.00	112.50
125	187.50	28.13	187.50	56.25
125	187.50		187.50	56.25
250	125.00		125.00	37.50

6.3 Analytical methods

6.3.1 Common methods

6.3.1.1 Differential scanning calorimetry (DSC)

The sediments obtained from the organic combination of the polymers in the reactor and extrudates were dried in a drying oven at 70ºC in vacuum (Vacuthermm, Heraeus instruments, Hanau, Germany) for 2 hours before the measurement. A sample between 10 and 12mg was weighed into an aluminium pan covered with a pierced lid and heated with a heating rate of 20ºC/min in the DSC equipment (Pyris 1, Perkin Elmer, Massachusetts, USA). After cooling the sample a second heating run was performed from a temperature of -20ºC to 160ºC to determine the glass transition temperature (T_g) of the polymers.

6.3.1.2 Fourier-transform spectroscopy (FT-IR)

Samples of the sediments and extrudates obtained from the polymer combinations were tested (Nicolet 5700 FT-IR, Thermo Fisher Scientific Inc., Dreieich, Germany). No extra energy was applied to the samples to avoid possible changes to the structure of the sediment formed through the polymer combination. The samples were cut, shaped and placed on top of KBr disc and measured in transmission with the help of a microscope (Nicolet Continuum FT-IR Microscope, Thermo Fisher Scientific Inc., Dreieich, Germany).

6.3.1.3 *In Vitro* dissolution test

The dissolution of the matrix tablets obtained by wet granulation and hot melt extrusion were tested in 700 ml in 0.1 N HCl for 2 hours, followed by a change to 6.8 Phosphate buffer by adding 214 ml of 0.2 N $Na_3PO_4 \cdot 12H_2O$ for 6 hours. The paddle speed was 50rpm (USP Apparatus 2). The dissolution tester (DT-6, ERWEKA GmbH, Heusenstamm, Germany) was connected to a UV-VIS detector (Lambda 20, Perkin Elmer, Überlingen, Germany) with a 6 channels pump (Ismatec® IPC, Glattbrugg, Switzerland) that took automatically the samples through 10µm filters. At the end of every dissolution test, the samples were homogenized with an Ultra-Turrax (T-18 basic, IKA Werke, GmbH CO. KG, Staufen, Germany) and measured to ensure the complete release of the drug embedded in the matrix structure of the tablet.

6.3.1.3.1 Calibration of UV spectroscopy and HPLC

The model drugs used in this study were tested in the dissolution tester and the concentration was detected with a UV spectrometer or HPLC. Diprophylline and Diltiazem HCl were detected with the UV spectrometer and Captopril with HPLC. Calibrations of the drugs are described below (Figure 65-70):

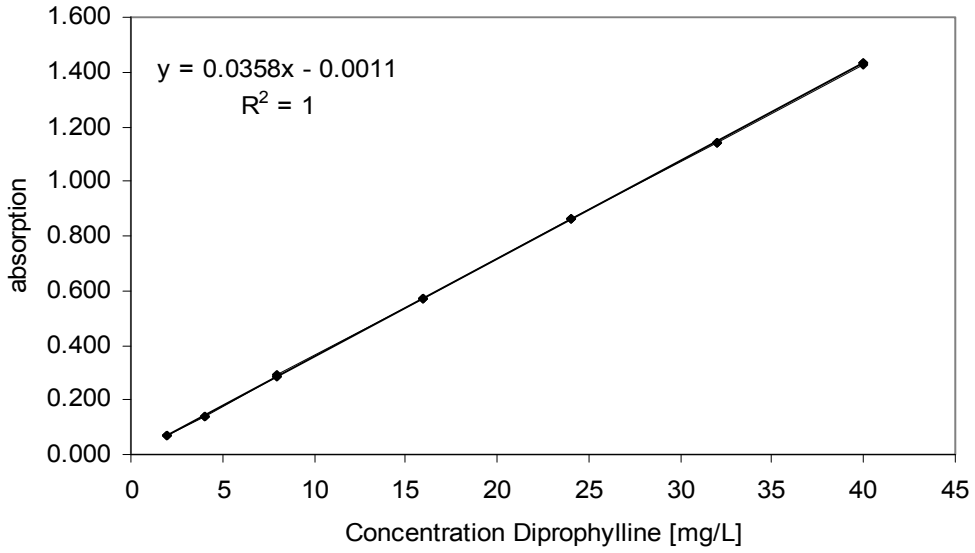


Figure 65 UV calibration of Diprophylline in 0.1 N HCl, 37ºC; wavelength 273 nm, cuvette 1 cm

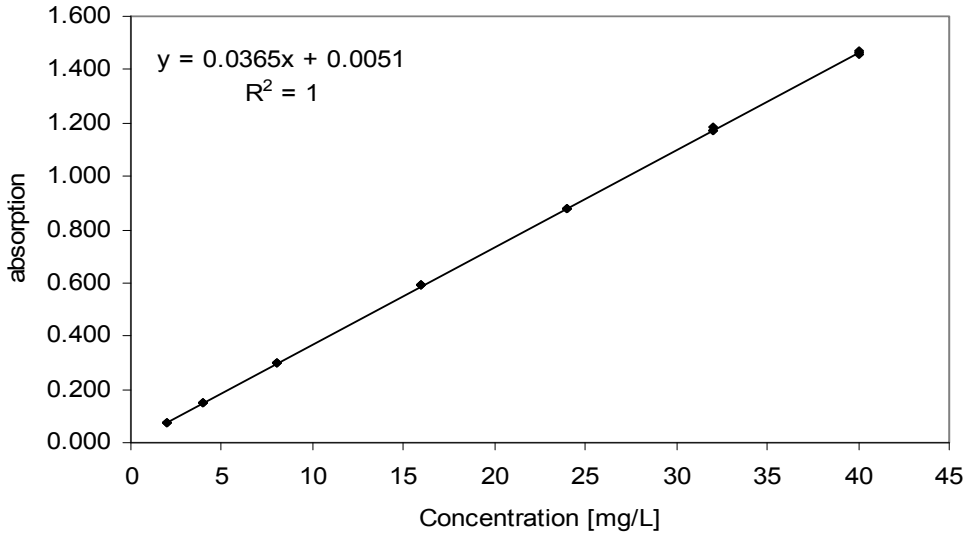


Figure 66 UV calibration of Diprophylline in 0.1 N HCl+$Na_3PO_4 \cdot 12H_2O$, 37ºC; wavelength 273 nm, cuvette 1 cm

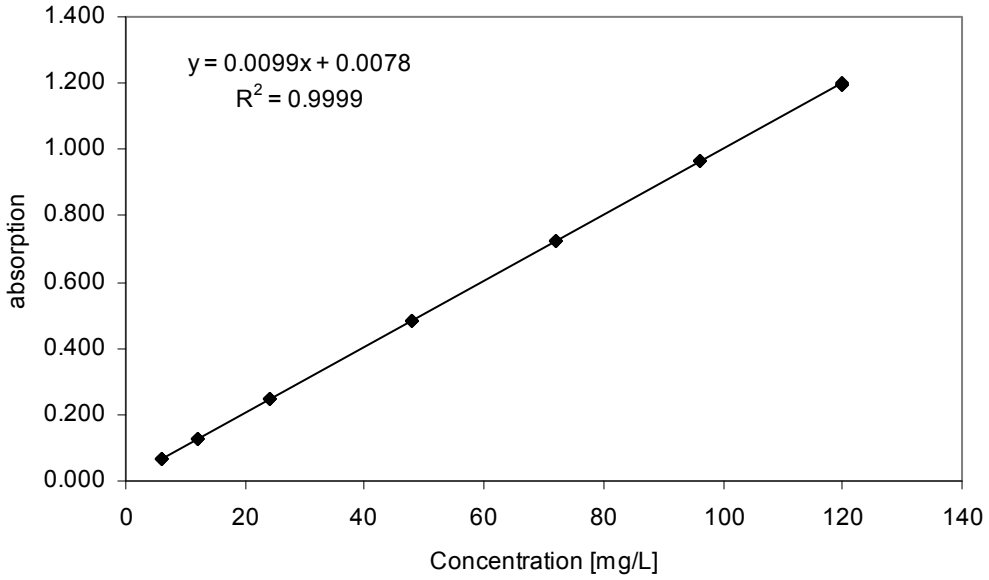


Figure 67 UV calibration of Diltiazem HCl in 0.1 N HCl, 37ºC; wavelength 269 nm, cuvette 1 cm

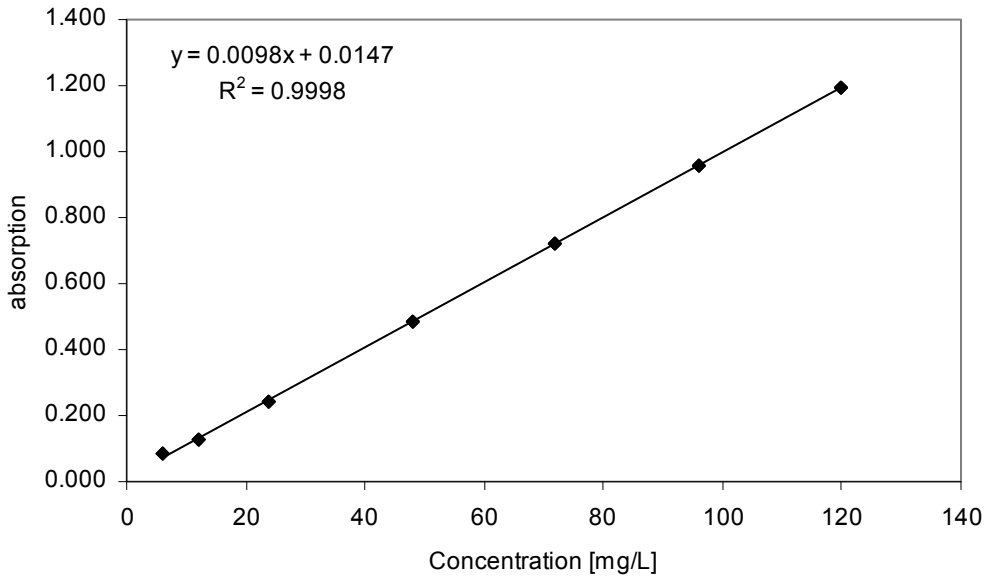


Figure 68 UV calibration of Diltiazem HCl in 0.1 N HCl+ $Na_3PO_4 \cdot 12H_2O$, 37ºC; wavelength 269 nm, cuvette 1 cm

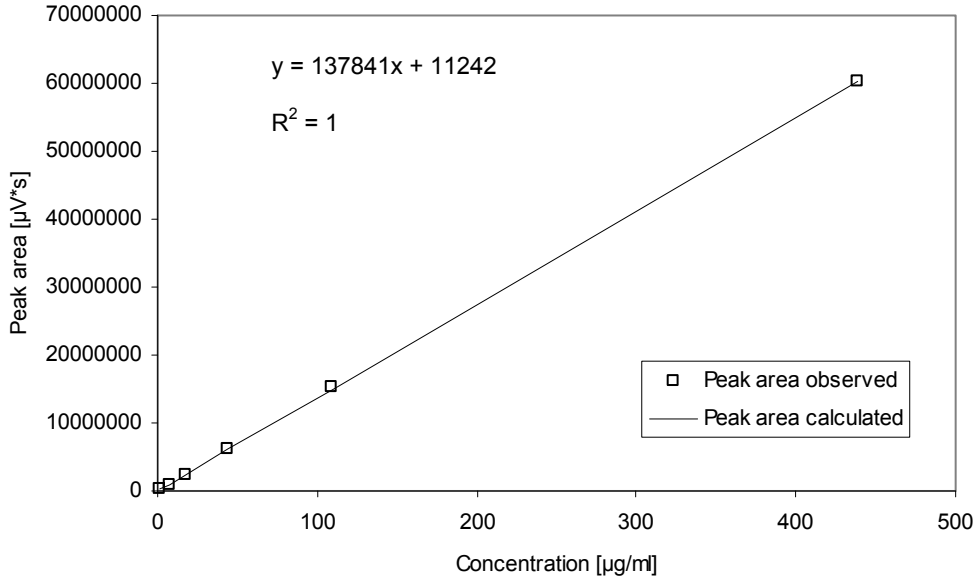


*Figure 69 UV calibration of Captopril in 0.1 N HCl, Column: Synergi 4µ Fusion-RP 80A 100*4.6mm, Fa.PhenomenexMobile phase: mixture of 0.1% phosphoric acid and methanol 70 : 30 (V/V). Flow: 2ml/min. Detection: UV, wavelength 210nm. Injection: 10µl. HPLC equipment: Agilent 1100 Series Standard Autosampler, Agilent 1100 Series Binary Pump, Agilent 1100 Series Variable Wavelength Detector*

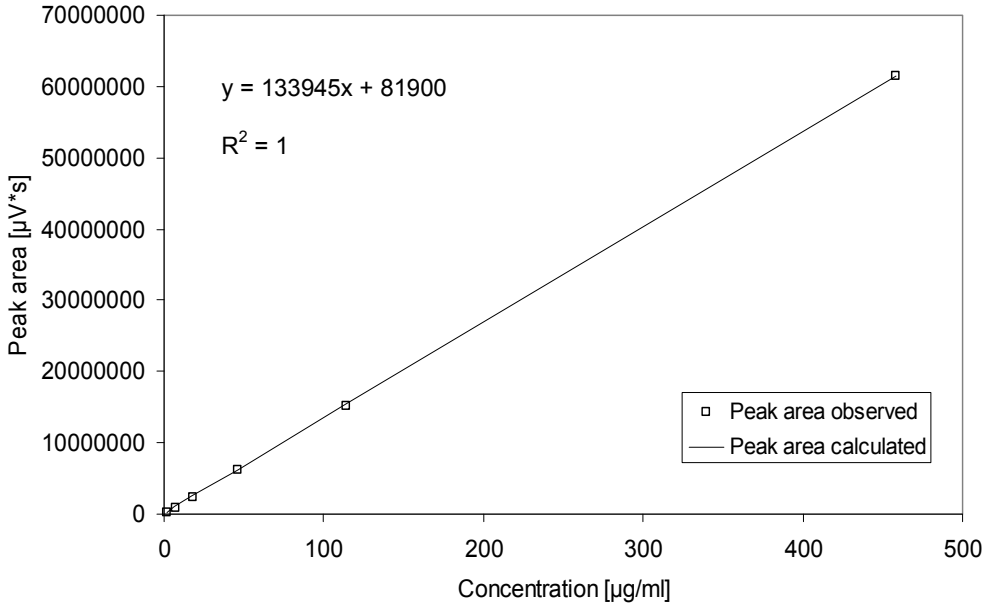


*Figure 70 UV calibration of Captopril in 0.1 N HCl+ $Na_3PO_4 \cdot 12H_2O$, Column: Synergi 4µ Fusion-RP 80A 100*4.6mm, Fa.PhenomenexMobile phase: mixture of 0.1% phosphoric acid and methanol 70 : 30 (V/V). Flow: 2ml/min. Detection: UV, wavelength 210nm. Injection: 10µl. HPLC equipment: Agilent 1100 Series Standard Autosampler, Agilent 1100 Series Binary Pump, Agilent 1100 Series Variable Wavelength Detector*

6.3.1.4 Scanning electron microscopy (SEM)

Tablets were tested before and after the dissolution test to evaluate the influence of the media on the structure. The tablets after the dissolution test were frozen with liquid nitrogen and dried with vacuum afterwards. Both samples were coated (Polaron, Sputter Coater, Quorum Technologies Ltd. Co. East Sussex, England) with a gold layer for 120 seconds in an Argon atmosphere with $6\text{-}8\cdot10^{-3}$ mbar vacuum. The samples were scanned with a JSM-840A SEM (Jeol GmbH, Eching, Germany). The scanning was performed under a vacuum of $1\cdot10^{-5}$ to $1\cdot10^{-7}$ mbar, and the magnifications used went from x100 to x2500.

6.3.2 Methods for the characterization of the methacrylate copolymers combination

6.3.2.1 Mass spectroscopy

This technique was performed to determine the degradation temperature of the components (Thermodesorption-GC/MS-System, Thermo Finigan Gerstel-TDS-Trace DSQ, Mühlheim an der Ruhr, Germany). Sediments from the combinations in organic solutions (point 6.2.1.1.1) EUDRAGIT® E PO:EUDRAGIT® L 100-55 (1:1) and (1:2) molar ratio were heated in two different temperature ranges: from 20ºC-190ºC, and from 20ºC-290ºC.

6.3.2.2 Nitrogen content analysis (Kjedahl method)

The same sediments used in the previous analysis were analyzed to determine the nitrogen content and therefore the amount of EUDRAGIT® E PO of the samples. The sediments were oxidated with H_2SO_4 and heated slowly up to 370ºC for 13 hours. The samples were then distilled with NaOH and H_3BO_3 (C.Gerhardt, Fabrik und Lager chemischer Apparate GmbH & Co. KG, Königswinter, Germany). After the distillation the sample were titrated with 0.1 N HCl.

Considering that

1 ml 0.1 mol/l HCl = 1.4007 mg N

the percentage of nitrogen can be calculated by using the equation (6.1):

$$\%N = \frac{(V - BV)\times 1.4007 \times t}{W}\times 100 \qquad (6.1)$$

where:

V= volume of 0.1 titration solution mol/l HCl used for the sample [ml]

BV= volume of 0.1 titration solution mol/l HCl used for the blind value [ml]

t= titer factor from the titration solution 0.1 mol/l HCl

W= weight of the sample [mg]

6.3.2.3 Particle size determination from complex in supernatant

The supernatants of the different polymer combinations in organic solution had different degrees of turbidity. The turbidity was inversely proportional to the amount of sediment collected. A laser diffraction particle size analyzer (Coulter LS 230VM, Beckman Coulter GmbH, Krefeld, Germany) was used to determine the minimum sizes of the precipitated particle that remained suspended in the supernatant. All supernatants were diluted to a 2% solid content with the solvent (isopropanol: acetone) to conduct the measurements. The samples were measured in a detection range of particle diameter between 0.382µm and 2000µm.

6.3.2.4 Solid state nuclear magnetic resonance analysis (^{13}C-NMR)

Sediments from the organic combination (point 6.2.1.1.1) and physical mixtures of EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:2), EUDRAGIT® S 100 (1:1) and EUDRAGIT® FS (2:1) were tested (Oxford instruments, NMR AS 400, Oxfordshire, England). These ratios were selected due to the greater amount of sediment formed.

In all cases 70mg of sediment or physical mixture of the polymers in the same ratio were placed in a ZrO_2 rotor. The samples were measured with the "magic angle spin" technique with a rotor frequency of 10 kHz. Besides, proton spectra were taken at 14 kHz.

6.3.2.5 Proton nuclear magnetic resonance analysis (^{1}H-NMR)

Sediments from the organic combination (point 6.2.1.1.1) of EUDRAGIT® E PO: EUDRAGIT® L 100-55 (1:2), EUDRAGIT® L 100 (1:2), EUDRAGIT® S 100 (1:1) and EUDRAGIT® FS (2:1) were tested (Oxford instruments, NMR AS 400, Oxfordshire, England). The ratios were selected due to the greater amount of sediment formed.

Approximately 10 mg of sample were dissolved in a mixture of deuterated chloroform/dimethylsulfoxyde and mixed with 10 µl of trifluoroacetic acid. The measurements were performed with a 400 MHz frequency.

6.3.2.6 Thermal gravimetric analysis (TGA)

The same sediment types (point 6.2.1.1.1) used for the DSC analysis, were analysed to determine their thermostability. The sample sizes varied between 7 and 20 mg. The loss on weight of the sample along the heating process was conducted using a Themogravimetric analyzer (TGA 2950, TA instrument, Eschborn, Germany). The measurements were performed with a heating rate of 5K/min with a temperature interval from 0ºC to 505ºC.

6.3.2.7 Titration

A new set of polymer combinations was performed using the same reactor. The samples were prepared in a greater volume (2 liters) and concentration (7.5mg/ml). This change was due to the need of a greater amount of sample required to conduct the trial. A titration based on the basic value of the sediment was conducted to determine the percentage of EUDRAGIT® E PO in sediment. The sediments were dried at 70ºC and 50 mbar over 2 hours in a drying oven (Heraeus vacuum drying cabinet VT 5042, Heraeus Christ GmbH, Osterode, Germany). Afterwards, approximately 0.5 g of sediment for each sample were dissolved in 96 ml acetic acid plus 4 ml demineralised water using a magnetic stirrer at 50ºC. This solution was posterior titrated with 0.1N perchloric acid (716 DMS Titrino, Metrohm AG, Filderstadt, Germany) with a combined electrode (Solvotrade, tetraethylammonium bromide in ethylene glycol).

Considering that

1 ml 0.1 mol/l $HClO_4$ = 5.6106 mg KOH

the alkali value of the sample can be calculated by using the equation (6.2):

$$AV = \frac{V \times t \times 5.6106 \times 100}{W \times DC} \qquad (6.2)$$

where:

AV= alkali value [mg KOH / g dry substance]

V= volume of 0.1 titration solution mol/l $HClO_4$ used for the sample [ml]

t= titer factor from the titration solution 0.1 mol/l $HClO_4$

W= weight of the sample [g]

DC= percentage of dry content of the sample [%]

6.3.3 Analysis of matrix tablets from wet granulation

6.3.3.1 Loss on drying (LOD)

The water content of the granules was determined directly after the wet granulation and after the drying process (Halogen Moisture Analyzer HG63, Mettler Toledo GmbH, Greifensee, Switzerland) at 110ºC. The determination was performed between one and ten minutes, depending on the humidity of the sample. The LOD was performed until the sample weight was constant.

6.3.3.2 Particle size distribution

The particle size distribution was determined following the method described in the United States Pharmacopeia, <786> "Particle Size Distribution Estimation by Analytical Sieving" (USP 31 NF 26 2008) by using 100 grams of granules for all the batches. A sieve shaker (Sieve Shaker AS 200 control "g", Retsch, Haan, Germany) was used to perform the analysis. The mass of the tested sample was 100g. The sizes of the sieves used were 800µm, 600µm, 400µm, 315µm, 250µm, 200µm, 150µm, 100µm. The analysis time was 5 minutes and the amplitude was 1.5 mm.

6.3.3.3 Determination of d'

Determination of d' was performed with a RRBS grid (Rosin, Rammler, Sperling, Bennet) DIN 66 145 with the data from the particle size distribution. The RRBS grid represents the percentage of the powder that passed through the sieve against the sizes of the sieve used for the analysis in logarithmic scale. The d' value corresponds to the value where 63.2% of the granules passed through the sieves.

6.3.3.4 Flow properties and compressibility of the granules

The calculation of the compressibility of the granules was performed with a tapped density tester (Ph Eur 2.9.15) following the method described in the United States Pharmacopeia "<616> Bulked and Tapped Density" (USP 31 NF 26 2008). The Hausner factor is a measure for the flowability/compressibility of powders and should be a value close to 1.

The Hausner factor is calculated following the equation (6.3)

$$Hausner\ factor = \frac{\rho_{tapped}}{\rho_{bulk}} \qquad (6.3)$$

The compressibility of the granules was tested with a tapped density tester (Pharma test PT-TD1, Hainburg, Germany).The tapped density is achieved by mechanical tapping of the samples. One hundred grams were used to perform this trial. The initial volume was the bulk volume. This value was noted and then the sample was tapped 500 times (tapped volume). The sample was again tapped 750 times. If the difference between the resulting volume and the previous volume was lower than 2% of the bulk volume, this last volume could be defined as tapped volume. If not, the sample had to be tapped again 1250 times. This tapping would be repeated until the difference in volume is less than 2%.

6.3.3.5 Angle of repose

To determine the angle of repose, the granules were placed in a funnel of a volume of 100ml DIN ISO 4324. The granules fell on a surface and formed a pile of granules with a certain height and diameter. The angle of repose is calculated with these values (equation 6.4)

$$\tan\alpha = \frac{h}{r} \qquad (6.4)$$

where:

α corresponds to the angle

h height of the pile of powder

r the radius of the pile of powder

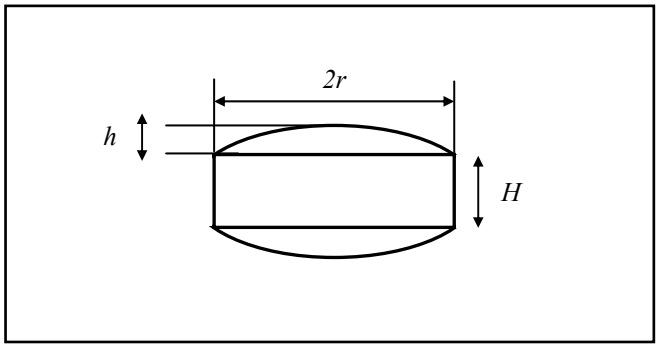
6.3.4 Methods for matrix tablets from wet granulation

6.3.4.1 Tablet density

The density was mathematically calculated (equation 6.5) based on the weight and volume of the tablets (Figure 71). The equation for to determine the volume was:

$$V = (r^2 H + r^2 h + \frac{h^3}{3})\cdot\pi \qquad (6.5)$$

Figure 71 Scheme of a biconvex tablet



Where :

r corresponds to the radius of the tablet

H corresponds to the height of the tablet band

h corresponds to the height of the curvature

6.3.4.2 Tablet breaking resistance

The breaking resistance along with the weight, height, and diameter of the tablets was tested in a tablet combination tester (Multicheck, ERWEKA GmbH, Heusenstamm, Germany) (n=10).

6.3.5 Analysis of extrudates from hot melt extrusion

6.3.5.1 Macroscope

The swelling properties of two samples of EUDRAGIT® E PO: (EUDRAGIT® L 100-55+30%TEC)(1:2) were tested under the macroscope. One of the samples had 15% stearic acid. Both were dissolved over 2 hours in 0.1 N HCl and then changed to 6.8 phosphate buffer by adding 214 ml 0.2 N $Na_3PO_4 \cdot 12\ H_2O$ with a paddle stirrer (USP, Apparatus 2) at a rotational speed of 50 rpm during one day. The media was constantly heated at 37±0.5ºC. Pictures of the tablets were taken every hour (Leica, WILD MZ8, Bensheim, Germany) up to 5 hours and then after 24 hours. The sizes of the tablets and the thickness of the gel layer were measured.

6.3.5.2 Rheological measurements

The viscosity of the different extrudates was performed by two different techniques. For these measurements the formulations listed below were extruded (Table 34).

Table 34 Formulation of extrudates from the polymer combination without drug

Extrudates of EUDRAGIT® E PO and EUDRAGIT® L 100-55 (molar ratio)
EUDRAGIT® L 100-55+30%TEC
(EUDRAGIT® EPO+15% Stearic acid): (EUDRAGIT® L 100-55+30%TEC) (1:4)
EUDRAGIT® EPO: (EUDRAGIT® L 100-55+30%TEC) (1:4)
(EUDRAGIT® EPO+15% Stearic acid): (EUDRAGIT® L 100-55+30%TEC) (1:3)
(EUDRAGIT® EPO+15% Stearic acid): (EUDRAGIT® L 100-55+30%TEC) (1:2)
EUDRAGIT® EPO: (EUDRAGIT® L 100-55+30%TEC) (1:2)
(EUDRAGIT® EPO+15% Stearic acid): (EUDRAGIT® L 100-55+30%TEC) (1:1)
(EUDRAGIT® EPO+15% Stearic acid): (EUDRAGIT® L 100-55+30%TEC) (2:1)
(EUDRAGIT® EPO+15% Stearic acid): (EUDRAGIT® L 100-55+30%TEC) (3:1)
(EUDRAGIT® EPO+15% Stearic acid): (EUDRAGIT® L 100-55+30%TEC) (4:1)
EUDRAGIT® E PO+15% Stearic acid

6.3.5.2.1 High pressure capillary viscosimeter

The extrudates were placed inside of a high pressure capillary viscosimeter (RHEOGRAPH 6000, Göttfert, Buchen, Germany) at 130ºC, ISO 11443. The samples were pushed through a 30 mm length and 1 mm diameter die with different shear rates ranging from the lowest value 10 s^{-1} to the highest value of 3981 s^{-1}. The maximum value for the pressure sensor was 2500 bar.

The viscosity is calculated based on the Hagen-Poiseuille principle (equation 6.6):

$$\Phi_v = \frac{\pi r^4 \Delta P}{8\eta L} \qquad (6.6)$$

where:

Φ_v corresponds to the laminar stationary flow [mm^3/s]

r corresponds to the internal radius of the die [mm]

Δp corresponds to the difference in pressure [Pa]

η corresponds to the dynamic viscosity [Pa·s]

L corresponds to the length of the die [mm]

6.3.5.2.2 Rotational rheometer

Some of the samples had high viscosity values that could not be measured with the previous method. Therefore the same samples (Table 34) were also tested in a rotational rheometer ISO 6721-10 (Modular compact rheometer MCR 300, Anton Paar, Graz, Austria). The samples were also heated at 130ºC and placed between two plates of 25 mm diameter with a separation in between of approximately 1mm. The angular frequency used was 628.32 rad/s. The amplitude of the oscillator was between 1 and 10 % based on the separation distance between the plates. The calculation of the complex viscosity is described below (equation 6.7):

$$\left|G^*\right| = \omega \cdot \left|\eta^*\right| \qquad (6.7)$$

where:

G^* corresponds to the complex shear modulus [Pa]

ω corresponds to the angular frequency of oscillation [s^{-1}]

η^* complex shear viscosity [Pa·s]

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8 Appendix

Table 35 Results from titration and determination of the amount of EUDRAGIT® E PO contained in the sediment. Comparison between the theoretical percentage and the experimental percentage. Alkali value from the batch= 174.5 mg KOH/ g of dry substance

Combinations in molar ratio	Alkali value [mg KOH/g of dry substance]	Theoretical percentage [%]	Experimental percentage [%]
1:5	64.30	26.32	**36.85**
1:5	54.20	26.32	**31.06**
1:5	54.15	26.32	**31.03**
1:3	58.40	37.32	**33.47**
1:3	61.20	37.32	**35.07**
1:3	61.00	37.32	**34.96**
1:2	69.00	47.17	**39.54**
1:2	69.40	47.17	**39.77**
1:2	71.30	47.17	**40.86**
1:1	101.2	64.10	**51.75**
1:1	90.2	64.10	**51.63**
1:1	98.30	64.10	**55.99**
3:1	73.6	84.20	**42.18**
3:1	119.3	84.20	**68.37**
3:1	117.6	84.20	**67.39**

Table 36 Description of the nitrogen percentages in the sediments. Comparison between the theoretical percentage and the experimental percentage obtained by the Kjedahl method

Molar ratio	Amount of EUDRAGIT® E PO weighed [g]	Amount of nitrogen [g]	Theoretical percentage of nitrogen [%]	Experimental percentage of nitrogen [%]
1:5	0.421	0.022	**1.36**	**1.63**
1:4	0.494	0.026	**1.60**	**1.47**
1:3	0.598	0.031	**1.94**	**1.57**
1:2	0.755	0.039	**2.44**	**1.85**
1:1	1.025	0.053	**3.32**	**2.48**
2:1	1.25	0.065	**4.05**	**2.71**
3:1	1.348	0.070	**4.36**	**2.83**
4:1	1.404	0.073	**4.55**	**2.89**

Table 37 Resume of the analytical results performed on the granules from the trial plan

Trial number	LOD	Hausner factor	Particle mean value [mm]
1	0.80	1.09	0.50
2	0.86	1.12	0.53
3	***0.87***	***1.09***	***0.53***
4	0.78	1.12	0.60
5	0.88	1.11	0.52
6	0.75	1.10	0.60
7	3.21	1.13	0.59
8	2.60	1.15	0.58
9	3.52	1.15	0.55
10	***2.62***	***1.12***	***0.77***
11	3.14	1.12	0.68
12	1.66	1.11	0.62
13	3.22	1.14	0.60
14	2.49	1.13	0.59
15	1.99	1.09	0.52
16	2.39	1.12	0.61
17	2.13	1.17	0.52
18	3.27	1.13	0.56
19	***2.73***	***1.12***	***0.75***
Mean value / SD	**2.10 / 1.00**	**1.12 / 0.02**	**0.59 / 007**

Table 38 Mean value and standard deviation (SD) of the breaking resistance values from the tablets manufactured in the trial plan. n=10

Trial number	Breaking resistance [N]	SD [%]
Trial 1	133	2.64
Trial 2	135	6.28
Trial 3	198	5.06
Trial 4	241	3.01
Trial 5	222	2.07
Trial 6	175	5.07
Trial 7	123	3.6
Trial 8	189	3.76
Trial 9	128	12.2
Trial 10	170	9.64
Trial 11	198	4.36
Trial 12	229	2.91
Trial 13	225	4.2
Trial 14	192	3.18
Trial 15	198	4.44
Trial 16	145	3.66
Trial 17	245	2.91
Trial 18	135	4.45
Trial 19	182	5.44

Table 39 Mean value and standard deviation (SD) of the weight values from the tablets manufactured in the trial plan. n=10

Trial number	Weight [mg]	SD [%]
Trial 1	499.5	0.31
Trial 2	504.7	0.33
Trial 3	503.4	0.83
Trial 4	506.2	0.46
Trial 5	497.3	0.2
Trial 6	501.5	1.9
Trial 7	503.3	0.56
Trial 8	498	0.6
Trial 9	495.3	1.56
Trial 10	506.1	1.19
Trial 11	507.1	0.81
Trial 12	507.6	0.74
Trial 13	504.5	0.72
Trial 14	496.8	0.45
Trial 15	503.6	0.63
Trial 16	501	0.56
Trial 17	501.3	0.48
Trial 18	498.9	0.45
Trial 19	498.2	0.84

Table 40 Density values calculated for the tablets manufactured in the trial plan. Values calculated from the mean values of weight and height of the tablets. n=10

Trial number	Density [g/ml]
Trial 1	1.93
Trial 2	1.82
Trial 3	1.88
Trial 4	1.8
Trial 5	1.85
Trial 6	1.96
Trial 7	1.92
Trial 8	1.92
Trial 9	1.94
Trial 10	1.89
Trial 11	1.96
Trial 12	1.8
Trial 13	1.93
Trial 14	1.84
Trial 15	1.82
Trial 16	1.8
Trial 17	1.82
Trial 18	1.96
Trial 19	1.89

Table 41 Percentage of drug dissolved after 2 hours of dissolution of the tablets manufactured in the trial plan

Trial number	Percentage dissolved [%]
Trial 1	53.8
Trial 2	52.3
Trial 3	53.7
Trial 4	55.4
Trial 5	58.9
Trial 6	61.4
Trial 7	49.9
Trial 8	50.5
Trial 9	57.4
Trial 10	53.1
Trial 11	55.7
Trial 12	55.4
Trial 13	52.3
Trial 14	54.4
Trial 15	53.9
Trial 16	54.7
Trial 17	58.7
Trial 18	55.6
Trial 19	54.7

Table 42 Summary of the analytical results performed on the granules with different percentages. Dip=diprophylline, EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); RS= EUDRAGIT® RS 30 D; the number in the formulation name represents the percentage of polymer applied.

Trial number	LOD	Hausner factor	Particle mean value [mm]	Flowability [sec/100 ml]	Angle of repose [°]
DipEL 5	0.45	1.16	0.37	12.01	37.2
DipEL 10	0.23	1.12	0.33	12.56	35.0
DipEL 15	0.30	1.20	0.44	12.66	36.5
DipEL 20	0.49	1.14	0.52	13.70	32.6
DipEL 50	0.87	1.17	0.80	14.38	35.0
Mean value / SD	**0.47 / 0.25**	**1.16 / 0.03**	**0.49 / 0.19**	**13.06 / 0.96**	**35.3 / 1.77**
DipRS 5	0.28	1.21	0.31	12.29	35.8
DipRS 10	0.23	1.21	0.36	11.63	31.8
DipRS 15	0.30	1.17	0.60	13.13	35.8
DipRS 20	0.31	1.17	0.48	11.85	35.0
DipRS 50	0.59	1.18	0.40	12.52	36.5
Mean value / SD	**0.34 / 0.14**	**1.19 / 0.02**	**0.43 / 0.11**	**12.28 / 0.59**	**35.0 / 1.86**

Table 43 Mean value and standard deviation (SD) of the breaking resistance, weight and density values from the tablets manufactured with different percentages. n=10. Dip=diprophylline; EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); RS= EUDRAGIT® RS 30 D; the number in the formulation name represents the percentage of polymer applied

Trial number	Breaking resistance [N] / SD [%]	Weight [mg] / SD [%]	Density [g/ml]
DipEL 5	244 / 25.16	509.8 / 0.69	1.66
DipEL 10	321 / 3.98	517.2 / 0.37	1.67
DipEL 15	352 / 3.89	518.1 / 0.47	1.66
DipEL 20	159 / 4.14	501.8 / 0.30	1.64
DipEL 50	78 / 6.73	506.7 / 0.59	1.42
Mean value / SD	**231 / 113.5**	**510.7 / 6.95**	**1.61 / 0.11**
DipRS 5	316 / 5.37	500.7 / 0.55	1.68
DipRS 10	374 / 3.27	507.6 / 0.31	1.68
DipRS 15	228 / 8.09	507.4 / 0.61	1.7
DipRS 20	338 / 3.85	521.1 / 0.56	1.72
DipRS 50	185 / 4.77	502.4 / 0.70	1.39
Mean value / SD	**288 / 78.89**	**507.8 / 8.01**	**1.63 / 0.14**

Table 44 Summary of the analytical results performed on the granules with different drugs and polymers different polymers and different drugs. n=10. Dilt= diltiazem HCl; Cap=captopril; EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); FS= EUDRAGIT® FS 30 D; RS= EUDRAGIT® RS 30 D; E= EUDRAGIT® E PO; the number in the formulation name represents the percentage of polymer applied

Trial number	LOD	Hausner factor	Particle mean value [mm]	Flowability [sec/100 ml]	Angle of repose [°]
DiltEL 15	0.23	1.19	0.28	11.43	37.2
DiltFS 15	0.16	1.15	0.26	11.78	36.5
DiltRS 15	0.35	1.25	0.48	12.98	35.8
DiltE 15	0.83	1.23	0.44	13.47	37.2
Mean value / SD	**0.39 / 030**	**1.21 /0.04**	**0.37 / 0.11**	**12.42 / 0.97**	**36.7 / 0.7**
CapEL 15	0.32	1.14	0.34	12.13	31.8
CapRS 15	0.33	1.13	0.42	12.84	35.8
CapFS 15	0.34	1.10	0.42	12.81	35.0
Mean value / SD	**0.33 / 0.01**	**1.12 / 0.02**	**0.39 / 0.05**	**12.59 / 0.40**	**34.2 / 2.1**

Table 45 Mean value and standard deviation (SD) of the breaking resistance, weight and density values from the tablets manufactured different polymers and different drugs. n=10. Dilt= diltiazem HCl; Cap=captopril; EL=EUDRAGIT® E PO:(EUDRAGIT® L 30 D-55+20% TEC) (1:4); FS= EUDRAGIT® FS 30 D; RS= EUDRAGIT® RS 30 D; E= EUDRAGIT® E PO; the number in the formulation name represents the percentage of polymer applied

Trial number	Breaking resistance [N] / SD [%]	Weight [mg] / SD [%]	Density [g/ml]
DiltEL 15	143 / 13.88	495.2 / 0.62	1.37
DiltFS 15	303 / 4.79	504.2 / 0.36	1.43
DiltRS 15	132 / 15.24	498.5 / 0.29	1.4
DiltE 15	340 / 5.18	498.2 / 0.24	1.42
Mean value / SD	**230 / 107.40**	**499.0 / 3.76**	**1.41 / 0.03**
CapEL 15	236 / 3.47	503.4 / 0.81	1.45
CapRS 15	237 / 9.02	499.1 / 0.45	1.47
CapFS 15	276 / 4.28	505.9 / 1.23	1.49
Mean value / SD	**250 / 22.81**	**502.8 / 3.44**	**1.47 / 0.02**

Selbsttätigkeitserklärung

Die hier vorgelegte Dissertation habe ich eigenhändig ohne unerlaubte Hilfe angefertigt. Die Dissertation wurde in der vorgelegten Form bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den 08 Dezember 2008

(Diego Gallardo)

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