Université Lille 2
Faculté des Sciences Pharmaceutiques et Biologiques
Ecole Doctorale Biologie Santé

PEO HOT MELT EXTRUDATES FOR CONTROLLED DRUG DELIVERY

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EXTRUDATS A BASE D'OXYDE DE POLY ETHYLENE POUR LA LIBERATION CONTROLEE

Thesis submitted to obtain the degree of Doctor in Pharmaceutical Sciences

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by

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I. INTRODUCTION

INTRODUCTION

1. General

The development of a medicine is a major step that is time, effort, and cost consumming. The major goal of the pharmaceutical industry is therefore to increase the productivity, reduce the costs, and increase the production flexibility. Nowadays, new tools have been developed in order to fulfill these objectives, e.g. (i) transition from traditional batch production manufacturing approach to continuous manufacturing model, (ii) implementation of Process Analytical Technology, (iii) quality by design approach to define critical quality attributes of the final product, critical parameters and critical steps of the process.

According to the US Food and Drug Administration [1], continuous manufacturing consists in a process where the material is simultaneously charged and discharged. There are many advantages of such process: (i) fewer steps, (ii) shorter processing times, (iii) increased efficiency and safety, (iv) improvement of the process flexibility, (v) increase in product quality with the possibilities of on-line quality controls, and (vi) certainly the potential for lower costs. Finally, continuous manufacturing can be related to an intense process which will maximize the material processing in a smallest process room [2]. Five critical steps can be reported [3]:

- Material specific critical steps (e.g. free flowing, low adhesiveness to surfaces),
- Equipment specific critical steps (e.g. equipment robustness, process control),
- Development specific critical steps (e.g. dosage form),
- Regulation critical steps (e.g. batch definition, materials traceability),
- Economics and company specific critical steps.

Nevertheless, various processes are adapted for continuous manufacturing, (e.g. feeding, roller compaction, extrusion, compression, encapsulation, milling, spray drying, prilling) [4]. However, it is mandatory to understand well the manufacturing process, the parameters and

their impacts on the product quality. In this purpose, critical process parameters and critical quality attributes are defined in quality by design approach. Once these critical parameters are defined, it is possible to monitor them in order to control the quality during the process by Process Analytical Technology.

In 2004, the Food and Drug Administration published a guidance to promote Process Analytical Technology and facilitate its use in pharmaceutical industry. Indeed, the main objective in developing pharmaceutical product is the quality. According to the FDA [5], Process Analytical Technology is "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality". Various analytical tools can be used to ensure the product quality such as spectroscopy (e.g. Raman spectroscopy, infra-red spectroscopy, fluorescence, UV–vis spectroscopy and nuclear magnetic resonance) and microscopic techniques (e.g. polarized light microscopy, hot stage microscopy and scanning electron microscopy) to give information about the crystalline state, the drug-carrier interactions, the drug homogeneity and distribution, the surface morphology of a product [6]. Importantly these techniques can be at-line (samples removed and analyzed during the process), on-line (samples re-introduced after the analysis) or better, in-line (samples are analyzed during the process without being removed).

2. Hot melt extrusion technique

2.1. Definition

Commonly used in the plastic industry, the Hot Melt Extrusion (HME) process has been introduced for pharmaceutical applications in the 1980s [7]. Since then, it became a very interesting technique used by scientists worldwide with a high number of publications per year (Figure 1).

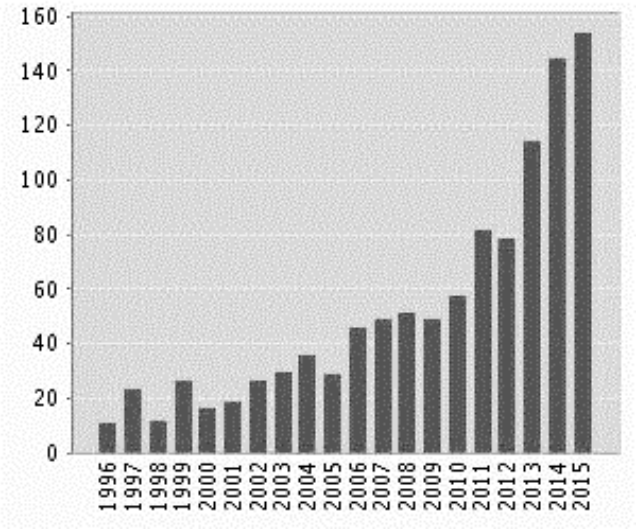


Figure 1: Number of published items with the "hot melt extrusion" key word per year indexed within Web of Science Core Collection. Source: from [8].

HME is a continuous process that enables the formation of new dosage forms, "extrudates", by forcing a mixture through a die under controlled conditions [9]. During the process, the material is subjected to heating and intense mixing allowing a homogeneous dispersion of drug particles in a molten carrier (generally polymeric or lipidic material). It is a free solvent process consisting in three parts: (i) a conveying system to transport and mix the mixture (drug and excipient), (ii) a die that give the final shape to the extrudate and (iii) some downstream additional equipment to cool down, cutting or collecting the final product. There are two types of extruders: single screw extruder (easier to use and cheaper) and twin screw extruders (where the screw can turn in opposite –"counter rotative" or same –"co-rotative" way with better mixing capacities).

The machine is composed of several elements (Figure 2): a feeder that bring the mix inside a heating barrel at a controlled rate ("feed rate"), the screw(s) with a defined speed ("screw speed") and at the end, the die. The screws are composed of different elements with various functions: carrying (conveying elements), mixing / densifying (kneading elements). These elements and their design are of utmost importance in the manufacturing process and will have a strong influence on the final formulation. At the end of the screws, the die can have various

shapes and diameters. Again, the temperature range chosen in the different heating zones during the process is of utmost importance.

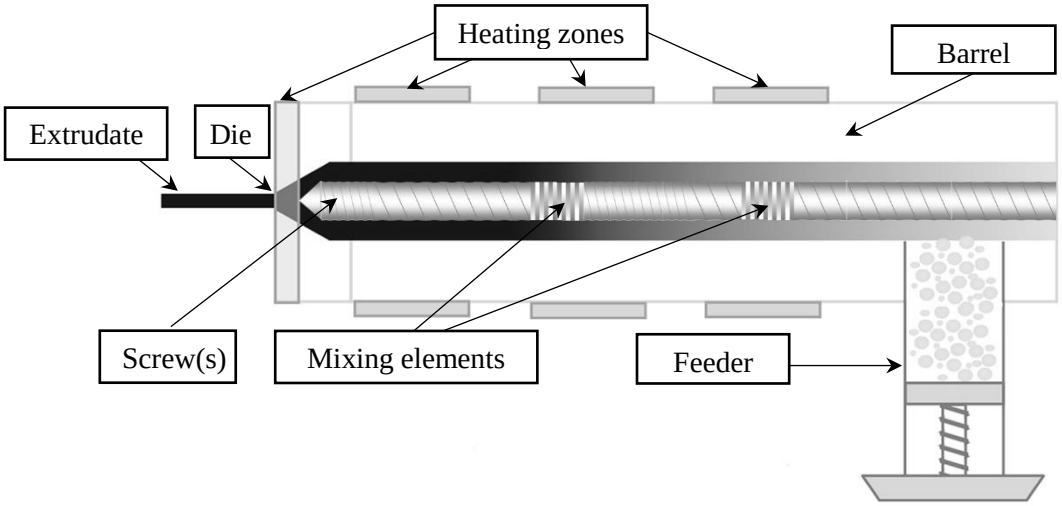


Figure 2: Schematic representation of the hot melt extrusion process. *Source: adapted from [7]*.

The critical process parameters of this technique are therefore: the screw design, the screw speed, the feed rate and the extrusion temperature. These parameters should be well controlled and it is mandatory to determine their impact on critical quality attributes of the final product such as drug homogeneity and drug release. In this purpose, extruders are equipped with sensors that are able to measure the barrel and die temperatures, the feed rate, the screw speed, the torque, the melt pressure and the melt temperature during the process. However, many other techniques "Process Analytical Technology" can help to ensure the final product quality, visualizing the material behavior and critical process parameters during the manufacturing process [10–16].

2.2. Pharmaceutical applications of hot melt extrusion

HME produces solid dispersion, namely a dispersion of a drug in a solid carrier obtained by melting [7]. Three types of solid dispersions can be produced: (i) a "glassy suspension" (or "solid suspension") where both the drug and the carrier are amorphous but the drug forms

clusters within the polymer, (ii) a "crystalline suspension" where the drug remains crystalline in an amorphous carrier, and (iii) a "glassy solution" (or "solid solution") where both the drug and the carrier are amorphous and completely miscible. In both glassy suspension and crystalline suspension, the drug is dispersed at the particular level, whereas in glassy solution, the drug is dispersed at the molecular level [9]. Extrudates with glassy solution have the advantage to increase drug availability. In a crystalline suspension, the drug crystals are dispersed in the amorphous matrix which releases drug in a sustained manner. Glassy suspension are the less stable with a high tendency to recrystallization due to the amorphous form of the drug clusters remaining in the formulation. The formation of one of these three solid dispersions depends on the drug solubility in the polymer, the drug - polymer interactions, and the stability of the formulation.

Hot melt extrusion pharmaceutical applications are:

- Immediate release: hot melt extrusion enables to entrap a drug in a molten material, so the bioavailability enhancement of poorly soluble drugs can be easily achieved [17–24],
- Modified release drug delivery systems such as time controlled, delayed, extended or site specific delivery can also be achieved by the preparation of hot melt extrudates [25–29],
- Taste masking of drug bitterness [30,31].

In addition to these current applications, some recent innovations have to be mentioned, such as abuse-deterrent/tamper-resistant formulations [14,32], co-extrusion [33–38], co-crystallization [39–42], and 3D printing [43–45].

Finally, thanks to the diverse downstream additional equipments (e.g. roller, pelletizer, grinder), the dosage forms can be varied [46]: granules, pellets and spheres [47–49], tablets and capsules [50], films [22,28], implants [51] for oral, transdermal, and transmucosal routes.

2.3. Material choice

2.3.1. Drugs

In order to be suitable for hot melt extrusion, some relevant characteristics of the drug should be considered, (e.g. solubility, physical state, particle shape and size, flowability, melting temperature, thermal stability, glass transition temperature). In addition, particular properties will guide the choice of HME, for instance (i) if the drug is poorly soluble and need to have an enhanced bioavailability, (ii) if the drug is instable in acidic media or can irritate the gastric mucosa, (iii) if the drug has a specific absorption window and need to be targeted at a specific area of the gastro intestinal tract for the systemic or localized treatment of diseases (e.g. Crohn's disease and ulcerative colitis).

2.3.2. Carriers

Many carriers are suitable for hot melt extrusion. They can be distinguished by their applications (immediate or sustained release) and also by their chemical nature (polymeric or lipidic).

For polymer, some relevant characteristics should be considered such as [7]: the chemical structure, the solubility, the glass transition temperature (suitable between 50-180 °C), the melting temperature, the melt viscosity that can be improved by the addition of plasticizer, the flowability, the lipophilicity, the dissolution properties, the thermal stability, the drug-carrier interactions, the solubilizing capacity increasing thermodynamic stability, and the compatibility.

Enclosed a list of pharmaceutical excipients suitable for hot melt extrusion and their references:

- Cellulose derivatives: Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC), Ethyl Cellulose (EC) [52–56],
- Poly(meth)acrylates polymers "Eudragit" for immediate release (E100, E12.5, EPO), delayed release (L100-55, S100, L100) or sustained release (NE, NM, RL, RS) [57–62],

- Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) [19,63,64],
- Poly Ethylene Glycols (PEG) and Poly Ethylene Oxides (PEO) [65–67],
- Ethylene Vinyl Acetate (EVA) [68],
- Poly Vinyl Pyrrolidone (PVP) [69–72].

Lipidic matrices can also be produced. The main advantage over polymeric matrices is the processability, which is facilitated by the low melting point of these compounds. Fortunately, in this case, plasticizer are not required [73].

Some examples of lipidic matrices application can be found in the literature. For instance, waxes, stearic acid, and triglyceride are widely used for hot melt extrusion [37,66,74,75].

2.3.3. Plasticizer and other additives

The extrusion can be difficult, due to the high viscosity [76–79] or thermal degradation [80–82] of the polymeric material, that can be in some cases overcame by the addition of plasticizers. Plasticizers are low molecular weight compounds that can increase the free volume between polymer chains, allowing the decrease of the polymer glass transition temperature and melt viscosity [83]. Being more flexible, the polymer can be manufactured at lower temperature, improving the processing conditions (lower torque), and the physical and mechanical properties of the final product. Furthermore, a plasticizer should have a good affinity and compatibility to the polymer, and be sufficiently stable at elevated temperature. Some plasticizers often used for hot melt extrusion are: triacetin, citrate esters, fatty acid esters, and low molecular weight polyethylene glycols. It is also interesting to note that some drugs (e.g. ibuprofen, metoprolol tartrate) can have a plasticizing effect [71,84–88].

Other additives can also be used, especially to enhance the stability of polymers susceptible to degradation during hot melt extrusion, e.g. antioxidants, acid receptors and light absorbers.

2.4. Advantages and disadvantages of hot melt extrusion

As discussed previously, HME has many advantages: it is a continuous, free-solvent process with fewer processing steps, easy to scale-up with the possibility of in-line controls, it is suitable for many applications, and it is able to manufacture difficult processing drugs, for instance with low compressibility or poor stability (e.g. thermodynamic instability or instability due to processing method such as hydrolysis).

However, some disadvantages have been reported in the literature [7,73]. The main one is related to thermal processing, that limits the utilization of thermo-degradable compounds (e.g. microbial species and proteins), despite the addition of plasticizer may decrease the extrusion temperature. Moreover, although HME is an economical process with reduced production time and fewer processing steps, the initial cost induced by the investment in equipment, may be a real hurdle for the implementation of HME in the pharmaceutical industry. Finally, specific excipient are required and cleaning of the process is, with some cases, not flawless.

2.5. Commercially marketed products

Despite the increase number of patents since the 1980's and many companies specialized in the use of HME (PharmaForm (TX, US) and SOLIQS (Abbott, Germany) [73]), only a few HME pharmaceutical products are currently marketed [89,90] (Table 1).

Table 1: Commercially products produced by hot melt extrusion technique. Source: adapted from [89,90].

Name	Formulation	Indication	Company
Norvir® (ritonavir)	oral tablet made of PEG and glyceride	HIV treatment	Abbott
Kaletra® (lopinavir and ritonavir)	oral tablet made of PVP and PolyVinyl Acetate	HIV treatment	Abbott
Ozurdex® (dexamethasone)	ocular implant made of Poly(lactic-co-glycolic acid) (PLGA)	macular edema and uveitis treatment	Allergan
Zoladex® (goserelin acetate)	subcutaneous implant made of PLGA	prostate cancer treatment	AstraZeneca
Fenoglide™ (fenofibrate)	oral tablet made of PEG	Hyperlipidemia treatment	Lifecycle pharma
Implanon® (etonogestrel)	subcutaneous implant made of EVA	contraceptive	Merck
Noxafil® (posaconazole)	oral tablet made of HPMCAS and Poly(Vinyl Alcohol)	antifungal	Merck
NuvaRing® (etonogestrel and ethylvinyl estradiol)	intravaginal ring made of EVA	contraceptive	Merck
Onmel® (itraconazole)	oral tablet made of HPMC	onychomycosis treatment	Merz
Eucreas® (vildagliptin and metformin HCl)	oral tablet made of HPC	diabete type 2 treatment	Novartis
Covera-HS® (verapamil HCl)	oral tablet made of HPC	hypertension and angina pectoris treatment	Pfizer
Zithromax® (azithromycin)	oral tablet made of pregelatinized starch	bacterial infection treatment	Pfizer
Gris-PEG® (griseofulvin)	oral tablet made of PEG	onychomycosis treatment	Pedinol
Nurofen Meltlets lemon® (ibuprofen)	oral tablet made of HPMC	analgesic	Reckitt Benckiser Healthcare
Isoptin SRE® (verapamil HCl)	oral tablet made of HPC and HPMC	hypertension and angina pectoris treatment	SOLIQS
Lacrisert® (no drug, the implant acts as a wetting agent)	ocular implant made of HPC	dry eye syndrome treatment	Valeant

3. Oral drug administration and controlled drug delivery

3.1. Administration via oral route

Oral route is the most common route of administration because of its simplicity of application, the good patient compliance and the cheap manufacturing cost (does not need to be sterilized for instance). However, some hurdles have to be overcame: the drug can be degraded before reaching the site of action, the absorption rate can be modified by multiple factors (e.g. food uptake, different pH in the gastro intestinal tract, gastric motility and emptying time) leading to the failure of the medical treatment. Moreover, the drug can be harmful for some healthy body part (e.g. gastric mucosa). As consequence, drug concentration as well as efficacy at the site of action can be very low. This requests the administration of several doses among the day with the risk of forgetting a dose by patients. In addition, the variation of the drug concentration in the plasma (increased drug concentration with serious side effects or decreased drug concentration with less efficacy of the treatment) during the day can be considerable [91]. This can be highly questionable, for instance with antibiotics or drug for long term treatment. Thus, controlled drug delivery systems are widely used in order to incorporate a high amount of drug to achieve a desired drug release profile during the whole day. On one hand, serious side effects can be avoided, on the other hand the efficacy of the treatment can be increased and the patient compliance improved.

3.2. Controlled drug delivery

There are several types of controlled drug delivery systems modifying the drug delivery: immediate, delayed, site specific and sustained drug delivery systems (Figure 3). In immediate or delayed drug delivery, the drug release profile is accelerated in the first case or retarded in the second case. The aim of immediate release is to release the initial doses of drug for an immediate effect. The goal of delayed release is to target the drug in a specific area, for example,

(i) to prevent the drug from gastric degradation, (ii) to protect the gastric mucosa from the drug, (iii) to bring the drug to its specific absorption window or even (iv) to target a specific area in the gastro intestinal tract (e.g. colon targeting).

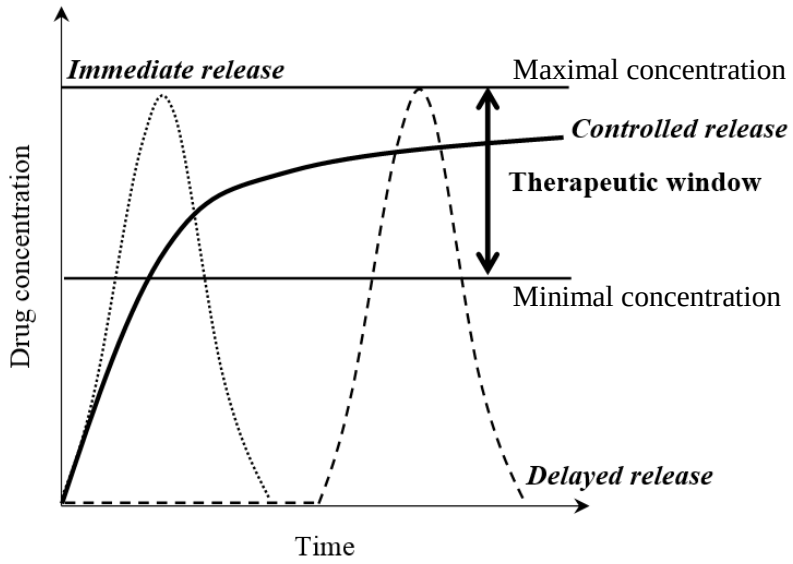


Figure 3: Schematic representation of various drug release profiles. Source: adapted from [92].

Contrary to conventional drug delivery systems, the controlled drug delivery systems provide progressively drug release from the dosage form during several hours. As mentioned before, this will reduce the number of medicine uptake with the aim to improve the drug efficacy, to minimize serious side effects, and to improve the patient compliance. Nevertheless, the development costs are high since it requires expensive equipments and specific carriers. Great caution should be taken when administering controlled dosage forms (e.g. tablets), which cannot be crushed or chewed [93].

These dosage forms can be manufactured with various technologies obtaining reservoir, matrix, and particularly osmotic pump, bio adhesive, or floating systems (Figure 4).

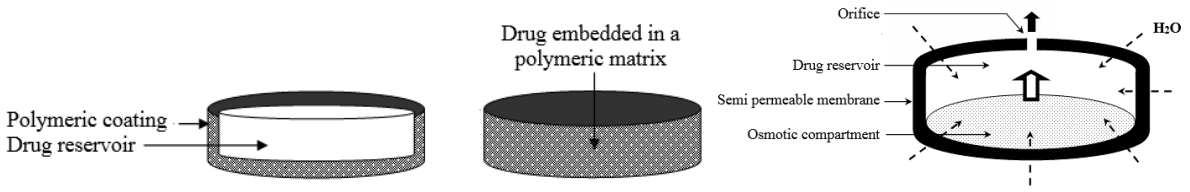


Figure 4: Schematic representation of reservoir system (on the left), matrix system (in the middle), and osmotic pump system (on the right). Source: adapted from [94].

In reservoir systems, drug content is surrounded by a permeable polymeric membrane that is insoluble or pH dependent soluble in the gastro intestinal tract. The osmotic pump systems are composed of a semi permeable membrane with a micro orifice, one compartment for the drug and one for the osmotic additives. Water penetrates into the compartment and leads to increased osmotic pressure inside. The release will depend on the nature and thickness of the membrane as well as the nature of the osmotic additives. The floating systems are made of hydrocolloids which are hydro soluble macromolecules with a very low density that float in the stomach, increasing the gastric residence time. It is also possible to increase the stomach residence time with bio-adhesive matrix that have the tendency to stick on the mucosa.

Finally, matrices are monolithic systems containing drug in a homogeneous form within excipients. The advantages comparing to other technologies are the easy manufacturing and the possibility to entrap drugs with high molar weight. They can be classified depending on the chemical nature of the carrier (polymeric, inert or lipidic), the physical state of the drug (dispersed at a molecular and/or particular level), and the mechanism of the release (e.g. diffusion, swelling, erosion).

3.3. Drug release mechanisms

Various mechanisms of drug release can be involved in sustained release systems: (i) the penetration of the water into the system, (ii) the drug dissolution, (iii) the drug diffusion outside the matrix, (iv) the swelling of the matrix (when composed by hydrophilic swellable polymers),

(v) the polymer dissolution or erosion, and eventually (vi) the osmotic effects [95]. One or several mechanisms can be occurred but if they happen in a sequential order or if one is slower, the latter is the rate-limiting step and thus can control the drug release. By considering this step, it is therefore possible to mathematically predict the drug release rate taking into account the critical impacting factors. For instance, diffusion step is impacted by several factors such as the structure of the dosage form (e.g. reservoir or matrix system), the ratio initial drug concentration *vs* drug solubility, and the device geometry (e.g. film, sphere, cylinder) whereas the dissolution step is impacted by the surface area, the drug solubility, the concentration gradient between the system and the bulk fluid, and the distance to run [96,97].

Depending on the matrix composition, various behaviors may occur (Figure 5).

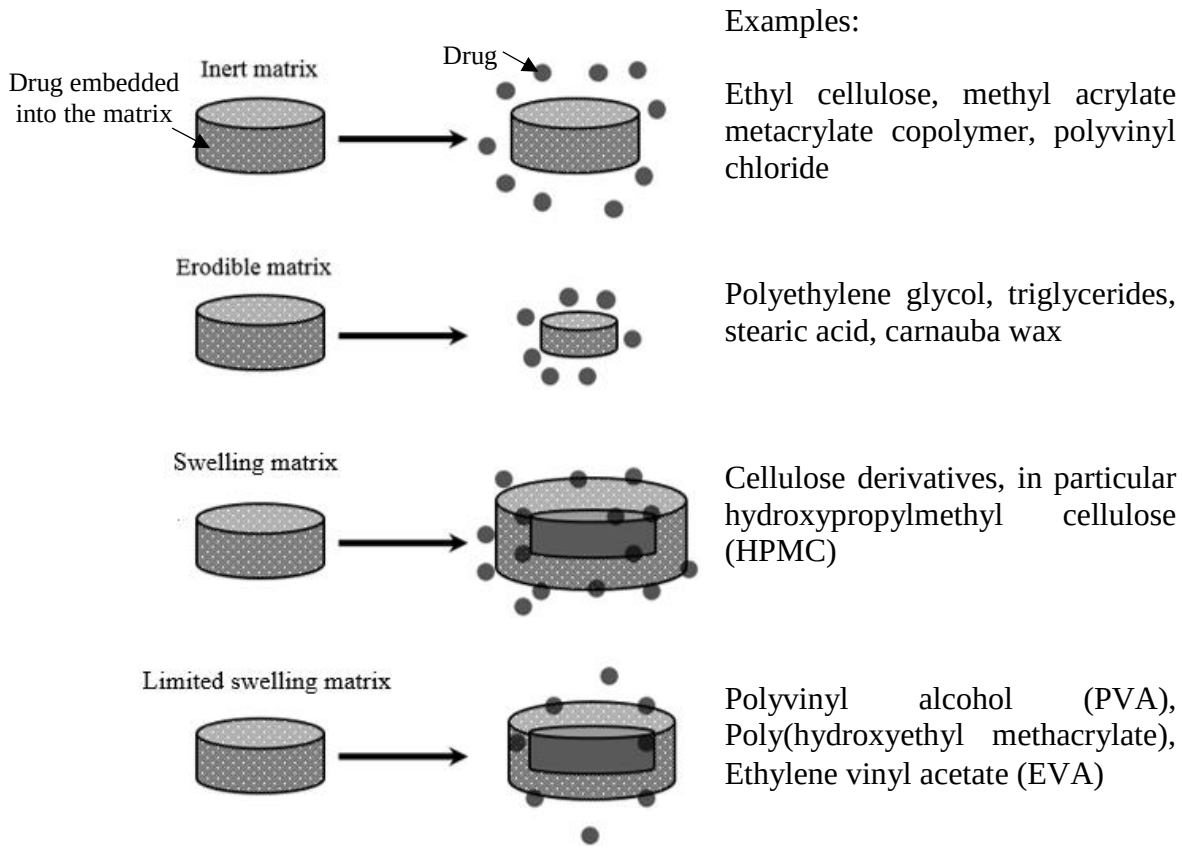


Figure 5: Schematic representation of the classification of matrix systems according to the mechanism of release. Source: adapted from [98].

For instance, the penetration of water inside the swellable system allows the mobility and swelling of the polymer chains (transition from glassy to rubbery phase) [99]. The entanglement of the chain will be more or less tight depending on the water amount, the drug state and the polymeric chain length. This will lead to the creation of three fronts [99,100]: (i) the swelling front that separates the swollen matrix from the non-swollen matrix, (ii) the diffusion front that separates the part containing the dissolved drug from the part containing dissolved and dispersed drug, and (iii) the erosion front that separates the entire system from the bulk fluid (Figure 6).

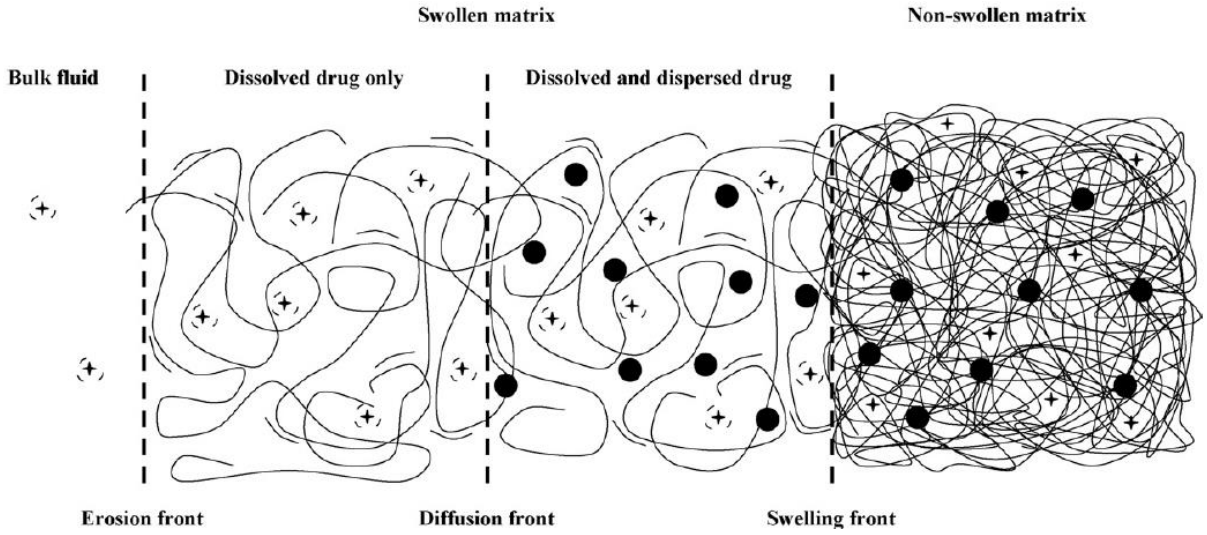


Figure 6: Schematic representation of a swelling matrix. Source: from [100].

Several examples in the literature relate the importance of swelling [101–105] and fronts displacement [106–108] to the drug release profile. More specifically, the distance between the swelling front and the erosion front was defined to be of utmost importance for the drug release (e.g. with Hydroxy Propyl Methyl Cellulose, Poly Vinyl Alcohol and Carboxymethylcellulose [109]).

In general, drug release depends on a huge number of factors [110,111] that can be divided in two categories:

Formulation parameters

Among the formulation factors, critical parameters are related to the drug (e.g. drug solubility, drug loading, and drug particle size [112–116]) or to the polymer (e.g. type, percentage, particle size, and degree of viscosity / chain length, degree of crystallinity [53,68,117–119]).

Process parameters

Process factors included process type [54], process parameters, and dimensions and shape of the dosage form [120].

4. Poly Ethylene Oxide

4.1. Synthesis and chemical information

Poly ethylene oxide (PEO) is a synthetic polymer obtained by the catalyst of an ethylene oxide monomer into an unbranched linear chain with the repeated unit -CH_2-CH_2-O- [121]. The synthesis and PEO chemical structure are briefly shown in Figure 7.

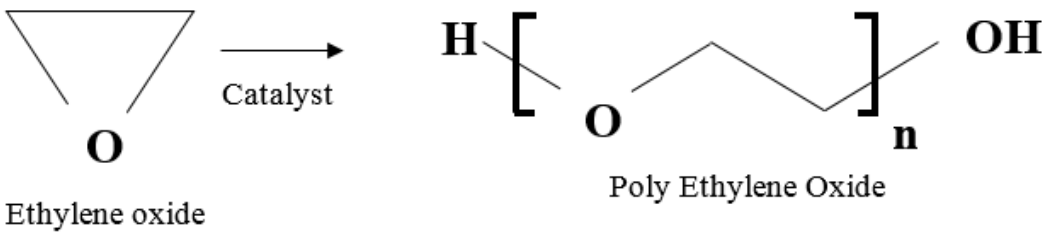


Figure 7: PEO synthesis. Source: adapted from [121].

PEO has the same chemical structure than poly ethylene glycol (PEG) but with molecular weight greater than 100 kDa. In fact, PEO can be synthetized in a wide range of molecular weights, from 100 to 7,000 kDa (Table 2).

Table 2: List of PEO commercial products and corresponding molecular weights.

Brand name	Molecular weight, kDa
Polyox WSR N-10	100
Polyox WSR N-80	200
Polyox WSR N-750	300
Polyox WSR 205	600
Polyox WSR 1105	900
Polyox WSR N12K	1,000
Polyox WSR N60K	2,000
Polyox WSR 301	4,000
Polyox WSR Coagulant	5,000
Polyox WSR 303	7,000

These linear, homo-polymers can be degraded as follows: oxidation and chain scission with cleavage of C-O bonds at low temperature (150 °C) or of C-C bonds at high temperature (550 °C) [122] although weight loss does not appear before 350 °C [123]. These degradations have been reported to become more pronounced during melting process (at 150 °C) [124]. During hot melt extrusion [81] mechanical (induced by shear forces due to the screws), thermal (due to the high extrusion temperatures) and oxidative (due to reaction between the oxygen and the polymer) degradations occur. It was reported that the lower molecular weight polymers are degraded more rapidly than the higher molecular weight polymers which results in smaller chain segments [81,125]. Interestingly, study reported also no degradation of PEO (100, 1,000 and 7,000 kDa) after extrusion at 200 °C [126].

PEO is a semi crystalline polymer with a melting point varying from 63 to 67 °C depending on the molecular weight, and a glass transition temperature ranging from -50 to -57 °C [127] which make it suitable for hot melt extrusion with a broad processing window (from the melting to the decomposition temperature). However, since PEO is a semi crystalline polymer, the thermodynamics of the drug-polymer mixture can be more complicated. The analysis of such

polymers can be more complicated than the fully amorphous polymer because of the appearance of various physical states [128].

According to the supplier, in animal studies, the polymer has a very low toxicity by all routes of exposure with neither deaths nor signs of toxicity reported at the maximum practical oral dose (about 2 g/kg of body weight) [129]. Neither skin irritation, nor eye irritation were reported. Finally, since it is a high molecular weight polymer, it is poorly absorbed and completely eliminated from the body.

4.2. PEO applications

According to the supplier [130], PEO can be used to formulate products for agriculture, building and construction, ceramics processing, personal-care and cosmetics, electronics and telecommunication, mining, paper, and pharmaceuticals.

In pharmaceutical applications, the below listed properties make PEO useful in various processes:

- Good flow properties, high binding efficiency and lubricity properties make it suitable as a binder for direct compression. Many examples in the literature reported the use of PEO in direct compression [116,118,119,131–137] and more specifically for the fabrication of osmotic pumps [138–140],
- Solubility in water and thickening of many organic solvents, strong hydrogen bonding affinity and crosslinking ability make it suitable to form gel [141] and especially mucosal bio-adhesive gel with strong interpenetrating network with mucus [142,143]. It can also form flexible films by thermoplastic processing and casting techniques [82,87,144,145],
- Fast hydration and rapid swelling upon exposure to water or physiological fluids control the drug delivery from PEO-matrix systems. PEO molecular weights from 400 to 7,000 kDa are recommended in tablets manufacturing with amount of 20 to 90 % to obtain robust and

reproducible release profile. Many examples can be found in the literature [116,119,132–135] and in particular, the fabrication of inserts for ocular drug delivery [146–148],

- Low glass transition temperature, low melting point, good flow properties and thermo-plasticity make it suitable for hot melt extrusion, injection molding and film-casting. PEO can be used (i) as a plasticizer [149], (ii) as drug release enhancer (pore former) [35,126,150,151], (iii) for sustained release [81,152–155] and (iv) immediate release [156],
- More recently, PEO is also used as a nano-carrier [157–159], for the formation of nanofibers [160], or to form complexes with other molecules.

4.3. Drug release mechanisms

As mentioned before, PEO is generally used for its hydration and swelling properties. Thus the drug release mechanism from PEO matrices corresponds to those of hydrophilic matrices presented previously. Nevertheless, it was recorded to be relatively complex [120,161–164]. Once administered, upon exposure to gastric fluids, the water penetrates inside the dosage form allowing the hydration of PEO chains, the swelling and creation of a gel layer and the drug dissolution [97,165]. Once dissolved, the drug diffuses out of the system, through the polymeric matrix [95]. At the same time, PEO chains start to be dissolved in the medium which leads to the erosion of the system [100]. To summarize, all these mechanisms generally could occur simultaneously. Nevertheless, depending on PEO molecular weight, one or several mechanisms can have a stronger influence on drug release. Indeed, it has been reported that the drug release from PEO high molecular weight is governed by the swelling of the polymer and diffusion of the drug whereas from the PEO low molecular weight it is controlled only by the swelling and erosion of the polymer [104,117,135,136,146].

In this hydrophilic matrices, two parts are created inside the system with three boundaries [117,166–168] (from inside to outside): (i) a solid core separated by the swelling front from the

gel layer (ii) the gel layer (solid + solution drug) separated by the diffusion front, and (iii) the gel layer (solution drug) separated by the erosion front from the bulk-medium (Figure 8).

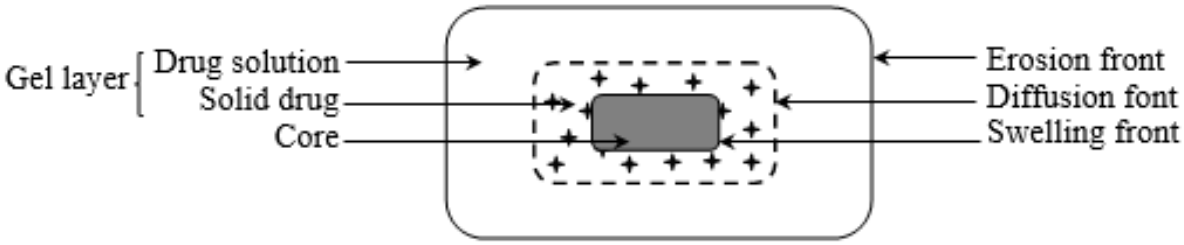


Figure 8: Schematic representation of PEO matrix after swelling. Source: adapted from [110].

4.4. Advantages and disadvantages

Despite the many advantages of PEO (e.g. wide range of molecular weight, various applications, low toxicity), some disadvantages should be reminded such as (i) the possible degradation during the process or the storage although it can be avoided by the use of stabilizer, e.g. vitamin E [79,81], and (ii) the possibility of structural changes due to the semi crystalline nature of the polymer which might result in storage instability during physical aging of the dosage form [169].

4.5. Commercially marketed products based on PEO

PEO is used in osmotic pumps and gastro-retentive dosage forms [127]. Nevertheless, the most important application is abuse deterrent dosage forms [170–172]. These systems are sustained release matrices which are made of high amount of drug and can provide therapeutic effects over a long period of time. Due to the high amount of drug, risk of opioid overdosing may occur by a misuse of drug abuser (e.g. crushing or chewing) [173,174]. To overcome this problem, entrapment of opioids by PEO matrix can be a very useful tool [175]. The PEO matrix is highly mechanically stable. Crushing or pulverizing the PEO dosage form is extremely difficult and the formation of gel layer during dissolution make the injection impossible.

Some examples of PEO-based dosage forms are listed below (Table 3).

Table 3: Commercially products manufactured with PEO.

Name	Formulation	Indication	Company
DynaCirc CR® (isradipine)	Osmotic pump	hypertension treatment	GlaxoSmithKline
Cardura® XL (doxazosin mesylate)	Osmotic pump	benign prostatic hyperplasia treatment	Pfizer
Glucotrol®XL (glipizide)	Osmotic pump	type 2 diabetes treatment	Pfizer
Procardia®XL (nifedipine)	Osmotic pump	Angina and hypertension treatment	Pfizer
Covera-HS® (verapamil hydrochloride)	Osmotic pump	hypertension and angina treatment	Pfizer
Gralise® (gabapentin)	modified-release dosage form	neuropathic pain	Depomed
Glumetza® (metformin hydrochloride)	modified-release dosage form	type 2 diabetes treatment	Santarus
Janumet®XR (sitagliptine, metformine)	modified-release dosage form	type 2 diabetes treatment	Merck
OxyContin® (oxycodone)	abuse deterrent dosage form	management of pain	Purdue Pharma
Nucynta®ER (tapentadol)	abuse deterrent dosage form	management of pain	Janssen
Oxecta® (oxycodone)	abuse deterrent dosage form	management of pain	Janssen
Opana® (oxymorphone)	abuse deterrent dosage form	management of pain	Endo Pharmaceuticals

5. Purposes of this work

The aim of this thesis was to develop PEO hot melt extrudates for controlled drug delivery. The impact of various parameters (formulation and process parameters) on drug release has been studied. Particular aims included:

(i) The impact of critical process parameters, temperature and extrusion speed on *in vitro* drug release with respect to the PEO molecular weight,

(ii) The impact of PEO molecular weight on *in vitro* drug release,

(iii) The impact of drug -nature and -loading, on *in vitro* drug release,

(iv) The comparison of hot melt extrusion *vs* direct compression.

II. MATERIALS AND METHODS

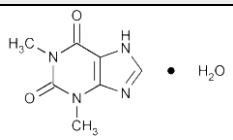
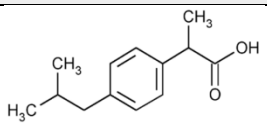
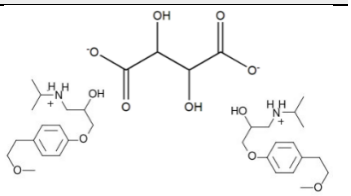
MATERIALS AND METHODS

1. Materials

Poly(ethylene oxide) (PEO, Sentry Polyox® WSR LEO NF, Dow chemicals, Midland, U.S.A.) was kindly supplied by Colorcon (Dartford, U.K.). All PEO available on the market with molecular weights ranging from 100 to 7,000 kDa were studied in this thesis: Polyox WSR N-10 (100 kDa), Polyox WSR N-80 (200 kDa), Polyox WSR N-750 (300 kDa), Polyox WSR-205 (600 kDa), Polyox WSR-1105 (900 kDa), Polyox WSR N-12K (1,000 kDa), Polyox WSR N-60K (2,000 kDa), Polyox WSR-301 (4,000 kDa), Polyox WSR Coagulant (5,000 kDa) and Polyox WSR-303 (7,000 kDa).

Model drugs used in this thesis are: theophylline monohydrate (theophylline; BASF, Ludwigshafen, Germany), ibuprofen 50 (ibuprofen; Salutas Pharma, Barleben, Germany) and metoprolol tartrate (metoprolol; Ipca, Mumbai, India) (Table 4).

Table 4: Chemical properties of model drugs.

Drug	Theophylline	Ibuprofen	Metoprolol
Chemical structure[1]			
Chemical formula[1]	$C_7H_8N_4O_2 \cdot H_2O$	$C_{13}H_{18}O2$	$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$
Molecular weight[1]	198.18 g/mol	206.28 g/mol	684.81 g/mol
BCS class	I [176]	II [177]	I [176]
Solubility (H_2O, 25 °C)[2]	7360 mg/L	21 mg/L	$1.69x10^4$ mg/L
Melting point[2]	273 °C	75-77.5 °C	120 °C
Decomposition	375 °C [178]	280 °C [179]	N/A
Tg	94 °C [180]	-45.15 °C [181]	1.9 °C [182]

[1]http://www.pharmacopeia.cn/
[2]http://www.drugbank.ca/

2. Experimental methods

2.1. Preparation of PEO-hot melt extrudates

Various PEO molecular weights were used for the preparation of hot melt extrudates containing various drug loadings (10, 20, 40 and 60 %).The drug and PEO powders were sieved (1 mm sieve; Saulas, Paris, France) and blended for 10 min at 98 rpm (Turbula T2A; Willy A. Bachofen AG Maschinenfabrik, Muttenz, Switzerland). The blends were extruded using a twin screw extruder Nano 16 (Leistritz, Nuremberg, Germany), equipped with a 4 mm diameter die (screw diameter = 16 mm, length/diameter ratio = 26.25). The process temperatures were kept constant at 100 – 97 – 95 – 90 °C (die – zone 3 – zone 2 – zone 1) or 135 – 133 – 100 – 125 °C (die – zone 3 – zone 2 – zone 1). The screw speed and feed rate were set at 30, 60 or 90 rpm and 3 cc/min, respectively. After cooling down, hot melt extrudates were manually cut into cylindrical matrices of 0.25, 0.5 or 1 cm length.

2.2. Preparation of PEO-tablets by direct compression

PEO-tablets were prepared by direct compression. Pure polymer and drug were mixed for 10 min at 98 rpm (Turbula T2A; Willy A. Bachofen AG Maschinenfabrik, Muttenz, Switzerland). Direct compressed tablets were produced manually with a single punch press tableting machine (Korsch EK0; Korsch, Berlin, Germany) equipped with flat 5 mm punches.

2.3. In vitro drug release from PEO-solid dosage forms

Drug release was measured in triplicate at 37.0 ± 0.5 °C using (i) the basket apparatus USP I upon exposure to 900 mL of 0.1 N HCl to mimic the stomac pH or phosphate buffer pH 7.4 to mimic the intestinal pH, 50, 100 or 150 rpm; Sotax AT7; Aesch, Switzerland), (ii) the paddle apparatus USP II (50 rpm; Sotax AT7; Aesch, Switzerland), (iii) the reciprocating cylinder USP III (5, 10 or 20 dpm; Vankel, Cary, U.S.A.) and (iv) the flow-through cell USP IV at a flow rate of 30 mL/min (Sotax CE7; Aesch, Switzerland). At pre-determined time points, samples were

automatically withdrawn by a peristaltic pump and analyzed on-line / off-line for their drug content by UV-spectrophotometry at λ = 272, 221 or 220 nm for theophylline, ibuprofen or metoprolol, respectively (UV-1800/1650; Shimadzu, Kyoto, Japan). Please note that the placebo extrudates does not absorb UV at 272, 221 or 220 nm.

2.4. In vitro swelling studies of hot melt extrudates

Swelling studies were conducted under the same experimental conditions (phosphate buffer pH 7.4, USP I, 50 rpm, 37.0 ± 0.5 °C). Three parts could be distinguished (Figure 9): a gel layer where the drug is either solubilized (external part, "transparent gel") or non-solubilized (internal part, "non-transparent gel"), and a core where the drug is non-solubilized ("solid core").

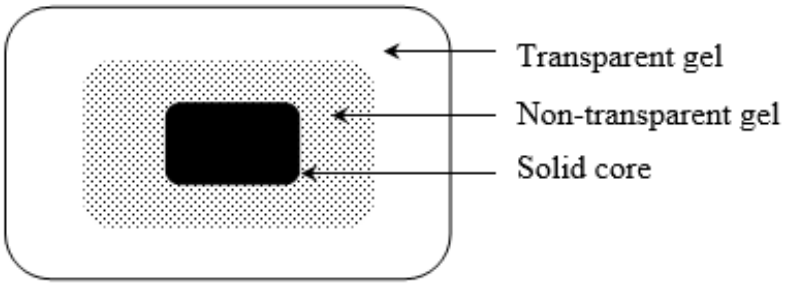


Figure 9: Schematic representation of the hot met extrudate swelling during dissolution.

The extrudates were first weighted before the study (dry mass t=0). At predetermined time points (0.5, 1, 2, 4, 6, 8 hours), extrudates and the excess of water were removed, weighted (wet mass), and dried in an oven at 60 °C to constant weight (dry mass t). The dry mass, water content, and PEO remaining were calculated as the following:

$$dry\ mass\ (\%)(t) = \frac{dry\ mass(t)}{dry\ mass(t=0)}\ x\ 100 \quad (1)$$

$$water\ content\ (\%)(t) = \frac{wet\ mass(t) - dry\ mass(t)}{wet\ mass(t)}\ x\ 100 \quad (2)$$

$$PEO\ remaining\ (\%)(t) = \frac{dry\ mass(t)-(0.1\ x\ dry\ mass(t=0)-Dt)}{0.9\ x\ dry\ mass(t=0)}\ x\ 100 \quad (3)$$

where Dt = the drug released at time t in g.

In addition, macroscopic pictures were taken using a binocular loupe (Nikon SMZ-U; Nikon,

Tokyo, Japan) and Axiocam ICc1 camera (Axiovision software; Carl Zeiss MicroImaging GmbH, Jena, Germany). These three parts were separated with a scalpel and the changes in dimensions (core length, core diameter, core volume, and gel thickness) and mass (dry mass, water content) were monitored for each part. Drug distribution was also determined by separating each part of the extrudate ("transparent and non-transparent" gels and "core") with a scalpel. Drug content was measured UV-spectrometrically (UV 1650; Shimadzu, Kyoto, Japan) in each part at predetermined dissolution times (0.5, 1, 2, 4, 6 and 8 hours and at wavelengths: λ = 272, 221 or 220 nm for theophylline, ibuprofen or metoprolol, respectively).

2.5. Solubility measurements

The solubility of each drug was assessed by saturating a solution of phosphate buffer pH 7.4 kept under horizontal shaking at 80 rpm and 37 °C (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Germany). Samples of the saturated solution were withdrawn every week with a syringe equipped by a filter (5 µm filter; BD, Franklin Lakes, U.S.A.). Drug content was measured by UV spectrophotometer (UV 1650; Shimadzu, Kyoto, Japan).

2.6. Density measurements by gaz picnometry

The porosity of each dosage form was evaluated with a pycnometer (AccuPyc 1330; Micromeritics, Norcross, U.S.A.). Porosity (P) was calculated with the following equation:

$$P\ (\%) = \frac{Vs-Vt}{Vt} \quad (4)$$

where Vs = the volume without pore in mm^3 given by the pycnometer and Vt = the total volume in mm^3 calculated with the following equation:

$$Vt = \pi\ x\ (\frac{d}{2})^2\ x\ h \quad (5)$$

where d = the diameter in mm and h the high in mm (tablet and extrudate were considered as cylinder).

2.7. Optical microscopy

Optical microscopy of physical mixture, pure drugs and polymers were obtained by a microscope (Zeiss Scope A1, Carl Zeiss MicroImaging GmbH, Jena, Germany) with a heating platform and Axiocam ICc1 camera coupled with Axiovision software (Carl Zeiss MicroImaging GmbH, Jena, Germany). Samples were heated from ambient temperature to 100 °C at heating speed10 °C/min.

2.8. Physical analysis

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) thermograms (DSC 1, STARe system; Mettler Toledo, Greifensee, Switzerland) were conducted with the extrudate, physical mixture (drug + polymer), pure polymer and drug. Samples of 3-5 mg were prepared in covered aluminium pans. Two heating cycles were performed with a heating speed of 10 °C/min under nitrogen gas atmosphere. Depending on the drug, the heating cycles were performed from 0 °C to 320 °C, 0 °C to 140 °C or 0 °C to 160 °C for theophylline, ibuprofen and metoprolol, respectively.
DSC thermograms (DSC Q1000, TA Instruments, New Castle, U.S.A.) were also conducted with placebo extrudates and pure polymers. Samples of 3 mg were prepared in aluminium pans. One heating cycle was performed from 0 °C to 100 °C with a heating speed of 5 °C/min under nitrogen gas atmosphere. On pure polymer only, two heating cycles were also performed from 0 °C to 100 °C or from 0 °C to 135 °C with a heating speed of 5 °C/min to simulate extrusion conditions.

X-rays powder diffraction

X-Rays (X'pert pro; Panalytical, Almelo, Netherlands) analyses were performed following a reflexion mode using a spinning flat sample holder. An X'celerator detector was used with a copper tube (λ= 1.54 Å). The angular range (2θ) varied from 5 to 60 ° at a speed of 100 sec by step (1 step = 0.0167 °).

Scanning electron microscopy

The external morphology of the tablets and hot melt extrudates were studied using a Hitachi S-4000 scanning electron microscope (Hitachi High-Technologies Europe; Krefeld, Germany). Samples were fixed with a ribbon carbon double-sided adhesive and covered with a fine carbon layer.

Raman microscopy

Raman spectra were measured with an InVia Raman spectrometer (Renishaw; Wotton-under-Edge, U.K.), comprising a single-grating spectrograph coupled to an optical microscope (Leica, Wetzlar, Germany). The 785 nm line of a Renishaw diode laser was used for the analysis of dosage forms sections. The spectra of each pure component of dosage forms were separately recorded in back scattering geometry, with a resolution of 2 cm^{-1} in the 600 – 3800 cm^{-1} frequency range and an acquisition time of 30s. It was found that the theophylline and PEO give preponderant and separate contribution in the 300 – 700 cm^{-1} region. Consequently this spectral region was selected for Raman mapping of both tablet and extrudate samples.

2.9. Stability studies of hot melt extrudates

The dosage forms were stored in closed glass vials for 1 year in an oven at 25 °C and 60 % of relative humidity (Binder, Tuttlingen, Germany). Dissolution studies were performed after 1, 3 and 12 months of storage.

III. RESULTS AND DISCUSSION

CHAPTER 1: ADJUSTMENT OF EXTRUSION PROCESS PARAMETERS

ADJUSTEMENT OF EXTRUSION PROCESS PARAMETERS

Keys process parameters of HME are the screw design, the screw speed and the extrusion temperature [7]. Their impact on drug release will depends mainly on the carrier chosen and the type of application. For instance, for sustained release drug delivery application, studies reported a decrease in drug release when increasing the temperature during the extrusion [71,151,183,184] whereas the opposite trend has been noticed for immediate release [62,68]. In addition, the impact of extrusion temperature may be more complex when changing polymer molecular weight and the extrusion speed [185]. The aim of this study was therefore to understand the impact of process parameters on *in vitro* drug release from sustained drug delivery matrices based on various PEO molecular weights. Two different barrel extrusion temperatures: 100–97–95–90 °C and 135–133–100–125 °C (die–zone 3–zone 2–zone 1) and three different screw speeds: 30, 60 and 90 rpm were applied. The size of the final dosage form was cut in different lengths (0.25, 0.5 and 1 cm). All these formulations were prepared with different PEO molecular weights (from 100 to 7,000 kDa) containing 10 % theophylline.

1. The impact of extrusion temperature

It is important to understand the impact of the critical process parameters on the drug release profile in order to develop products with the desired drug delivery and quality. Results showed that a higher temperature (135 °C) leads generally to a slight decrease of pressure during the extrusion (less than 10 bars) compared to a lower temperature (100 °C) but except for PEO 300 and 7,000 kDa where the decrease is more pronounced (reduction of 19 or 28 bars respectively, data not shown). For PEO 300 kDa, the increase of temperature leads to an improvement of the extrudate appearance, as it can be seen in Figure 10 and Figure 11 (at 100 °C: shark skinning; at 135 °C: smooth extrudate). Shark skinning is a surface defect due to a perturbation in the flow of the molten polymer when the flow exceeds the critical velocity, and

the point where the melt strength of the polymer is surpassed by internal stresses [186]. This was also reported during the extrusion of ethylcellulose [55] and was easy to be understood. Shark skinning can be improved by a decrease in the polymer viscosity as the extrusion temperature increases [153]. But unexpectedly, for the majority of PEO polymers, an increase in the extrusion temperature led to a deterioration of the surface appearance with remarkable defects called melt fracture (Figure 11). In addition, low PEO molecular weights hot melt extrudates are mellow at the die output making the collection of the extrudates very difficult.

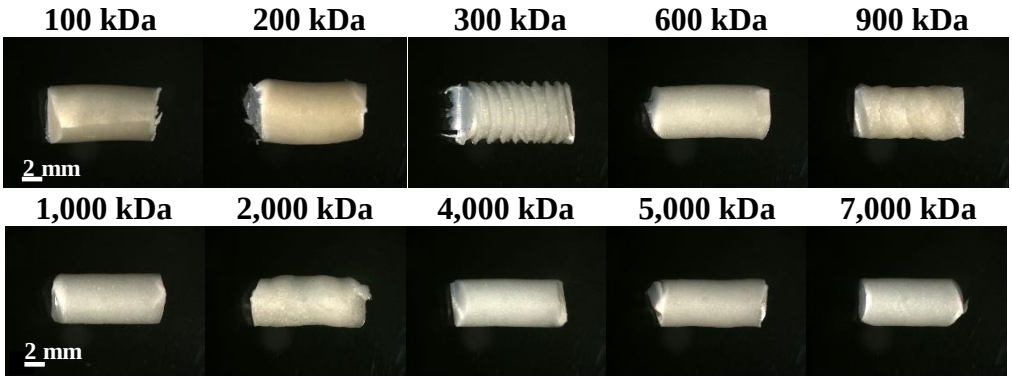


Figure 10: Impact of the PEO molecular weight on the appearance of hot melt extrudates processed at 100 °C.

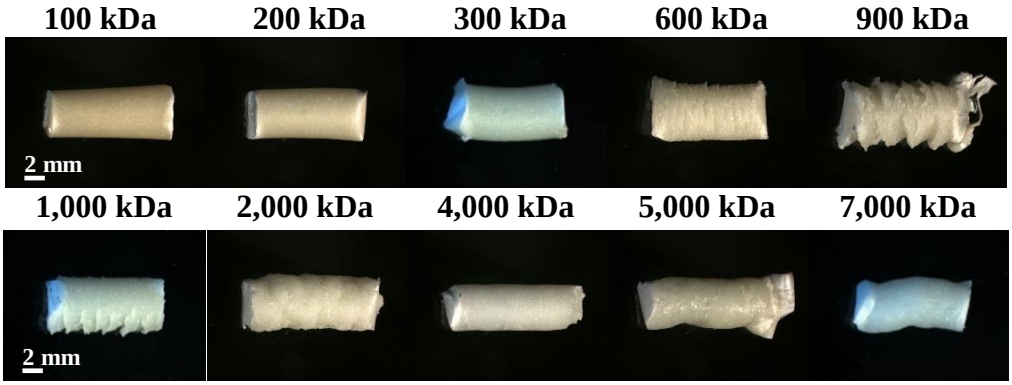


Figure 11: Impact of the PEO molecular weight on the appearance of hot melt extrudates processed at 135 °C.

The impact of extrusion temperature on drug release was also investigated (Figure 12).

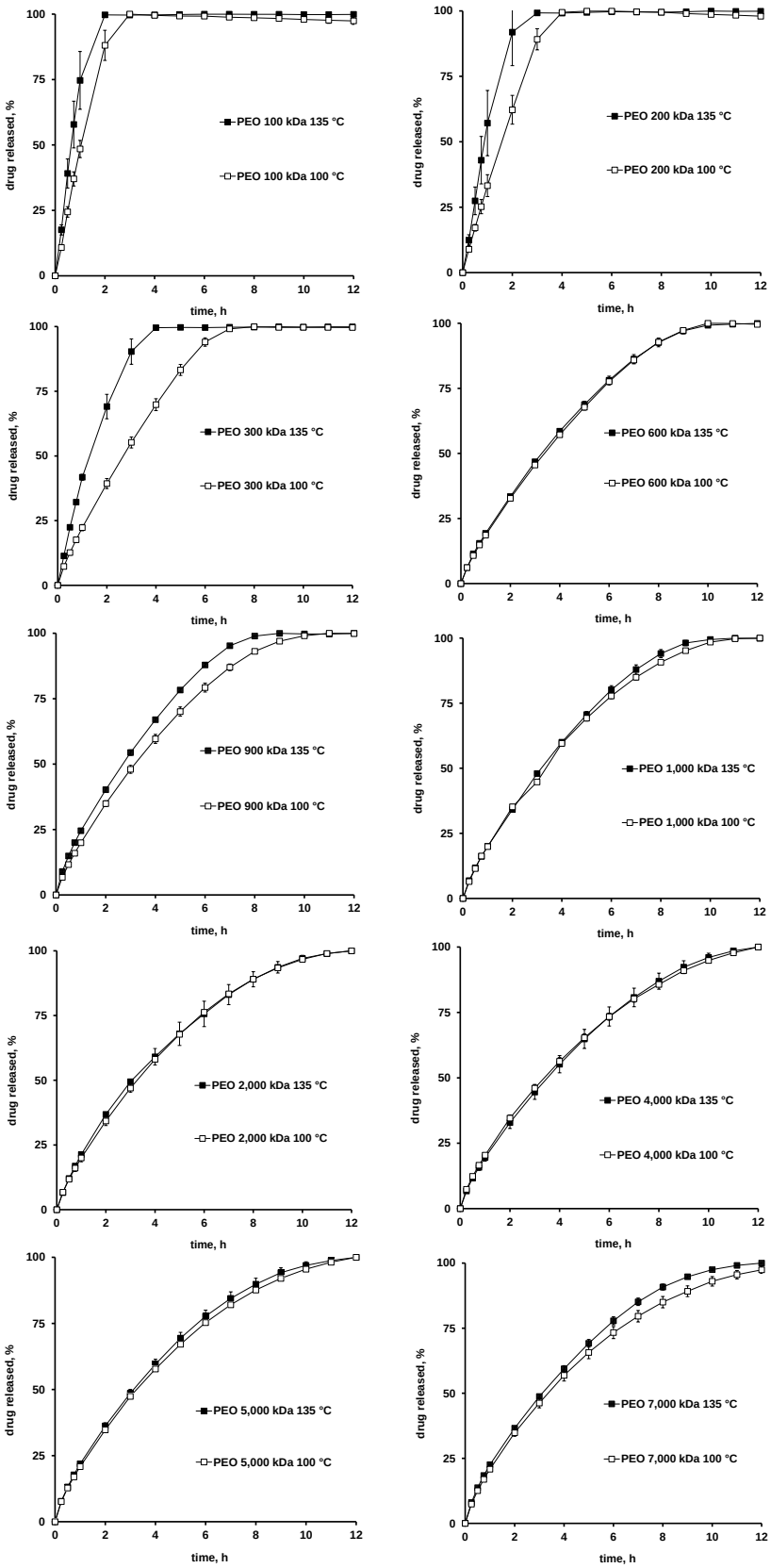


Figure 12: Impact of the extrusion temperature (indicated in the diagrams) on theophylline release from PEO hot melt extrudates in phosphate buffer pH 7.4.

For intermediate and high molecular weight (greater than 300 kDa), the increase in the extrusion temperature did not impact the drug release. Interestingly, for low molecular weight (less than 600 kDa) a slight increase of drug release was observed when increasing the processing temperature. This was unexpected as many authors reported the opposite trend in the literature but for other polymers [151,183,184]. It could probably be explained by (i) a highest sensibility of short polymeric chains to thermal degradation or (ii) a change in polymer crystallinity degree. Crowley and coworkers studied and confirmed the impact of the extrusion temperature on PEO extrudates [81]. The main conclusion of this work is the high thermal sensitivity of low PEO molecular weights compared to high PEO molecular weights. If low PEO molecular weight are more sensible to thermal degradation during hot melt extrusion, an increase in the temperature during the extrusion process will lead to chain scission and therefore to a faster drug release.
Previously studies demonstrated a loss of PEO crystallinity after extrusion [187]. The polymer crystals slow down the drug diffusion and subsequently the drug release [188]. This can be confirmed by calculating the enthalpy of PEO melting peak with DSC. Pure PEO powders (300, 1,000 and 7,000 kDa) were analysed at 100 °C or 135 °C along two heating cycles. The difference in the enthalpy between the first and second cycle was measured in order to determine the crystallinity loss after heating. A loss was observed for all PEO molecular weights with a small difference between 100 and 135 °C. Importantly, there were no difference observed between each molecular weight (data not shown).

In addition, after one month storage stability (25 °C, 60 % RH humidity) of the formulation processed at 135 °C with PEO 300 kDa (sensitive to the extrusion temperature) *in vitro* drug release was slightly slower than the initial drug release directly after the extrusion (data not shown). Interestingly, the flexibility as well as the crystallinity could be impacted by high extrusion temperature. However, at the storage stage, this transformation could be returned to the initial physical state. But it is mandatory that these eventually changes during storage can

be avoided or limited in order to keep a stable and reproducible drug release in long term. Referred to the improvement of the hot melt extrudate appearance, *in vitro* drug release, as well as the probably transformed physical state, the extrusion temperature was set at 100 °C for the following studies.

2. The impact of extrusion screw speed

The impact of extrusion screw speed on hot melt extrudate appearance was studied with three different PEO molecular weights: low (300 kDa), intermediate (1,000 kDa) and high (7,000 kDa) molecular weight (Figure 13). No change in pressure was observed when the screw speed was increased (data not shown) but fortunately, the increase of the screw speed from 30 to 90 rpm improved the surface appearance of PEO (no shark skinning occurred at 30 and 60 rpm with PEO 300 kDa). For other PEO molecular weights, no particular changes were detected. Moreover, no changes in drug release when varying the screw speed were observed (Figure 14).

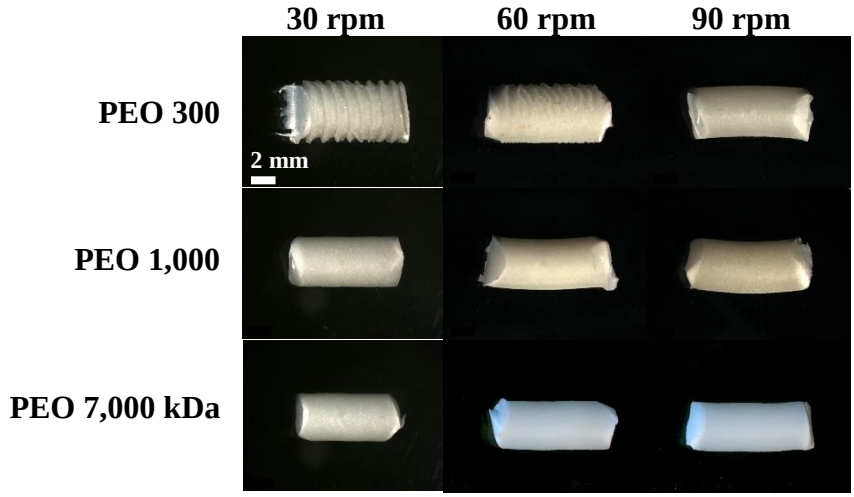


Figure 13: Impact of the extrusion screw speeds (indicated on the top) on PEO hot melt extrudates appearance (molecular weights are indicated on the left).

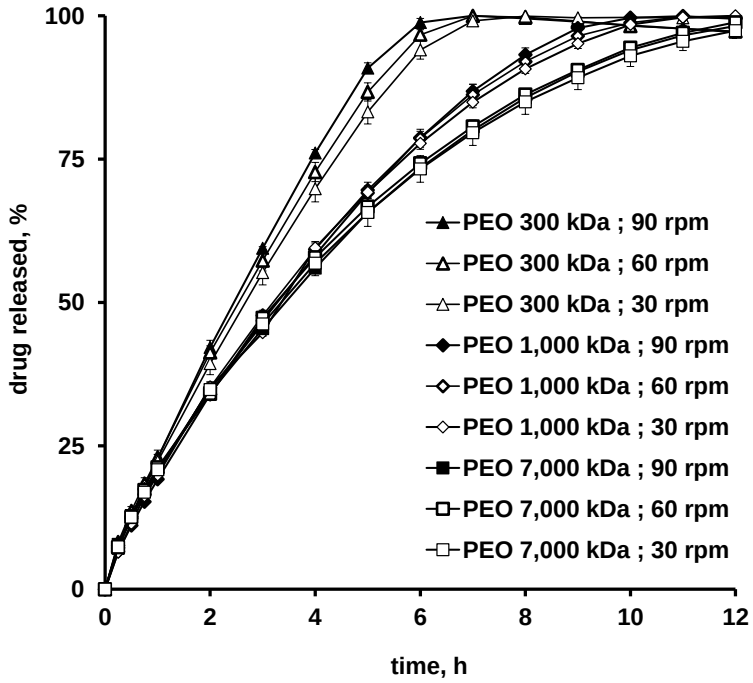


Figure 14: Impact of the extrusion screw speeds (indicated in the diagram) on theophylline release from PEO hot melt extrudates in phosphate buffer pH 7.4.

3. The impact of the dosage form size

Finally, hot melt extrudates were manually cut to 0.25, 0.5 or 1 cm length pieces in order to study the impact of the dosage form size. For reasons of comparison, same weight of hot melt extrudate was placed in the vessel for drug release measurement (four pieces of 0.25 cm, two pieces of 0.5 cm and one piece of 1 cm). Relative surface area was then higher for 0.25 cm pieces than for 0.5 or 1 cm pieces. As expected, drug release increased with the increase of the relative surface area (Figure 15). For the following work, extrudates were cut to 1 cm length in order to control better the drug release during a long period.

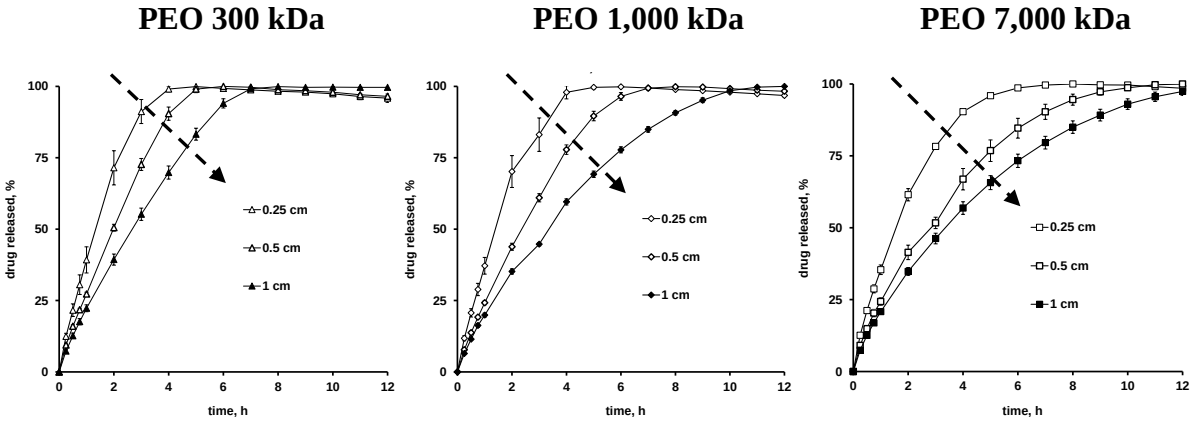


Figure 15: Impact of the dosage form size (indicated in the diagrams) on theophylline release from PEO hot melt extrudates (molecular weights are indicated on the top) in phosphate buffer pH 7.4.

4. Stability studies

Stability of all formulations (extrusion temperature at 100 °C, screw speed at 30 rpm) was monitored one year in an oven at 25 °C and 60 % of relative humidity. Some formulation examples are shown in Figure 16. As it can be seen, the drug release remained stable for all PEO grades.

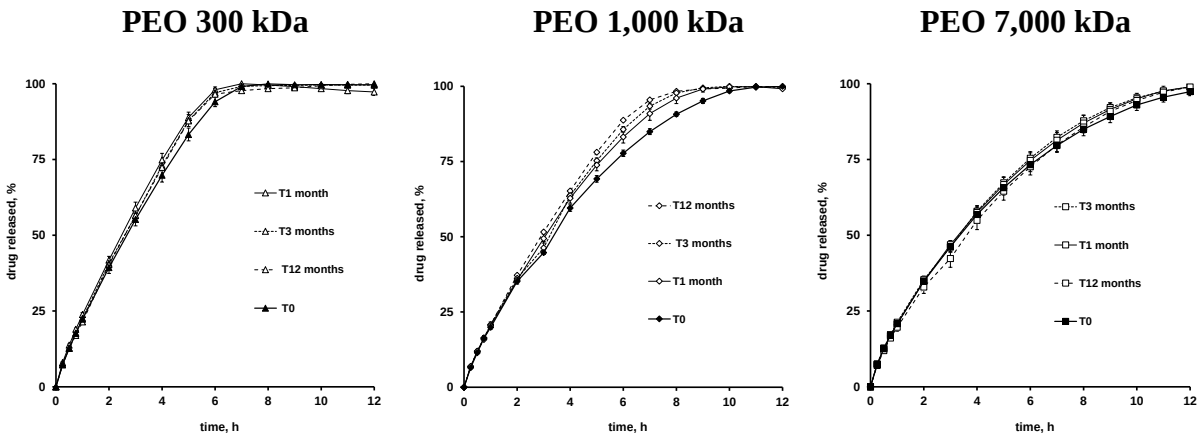


Figure 16: Storage stability (indicated in the diagrams) on theophylline release from PEO hot melt extrudates (molecular weights are indicated on the top) in phosphate buffer pH 7.4.

This chapter enables the selection of appropriate parameters for the extrusion process (temperature 100 °C; screw speed 30 rpm; dosage form size 1 cm). The impact of these process parameters was important to be studied since unexpected tendencies were observed and different behaviors were found relating to PEO molecular weights.

CHAPITER 2: IMPORTANCE OF PEO MOLECULAR WEIGHT

Cantin, O., et al., Journal of Drug Delivery Science and Technology, 36 (2016) 130-140

IMPORTANCE OF PEO MOLECULAR WEIGHT

Hydrophilic matrices are commonly used for the preparation of sustained dosage forms because they are easier to produce compared to reservoir type system and they can deliver high molecular weight compounds [189]. However, drug release from hydrophilic matrices are impacted by various critical factors such as the nature of drug (molecular weight, solubility, particle size, load), the polymer (type, molecular weight, percentage) and formulation factors [110]. Depending on the polymer used, the mechanism of drug release follows the underneath steps: water penetration into the matrix, polymer swelling, drug solubilization, and finally drug diffusion through the gel layer [101]. Several studies highlight the importance of the gel layer in the drug release, in particular the dissolved drug gel layer thickness [99,104,107,109] and the matrix surface area [101].

Poly ethylene oxide (PEO) is a hydrophilic and semi crystalline polymer suitable for the preparation of sustained dosage forms [119,120,132]. Ten grades are available on the market with molecular weights ranging from 100 to 7,000 kDa. The release from these systems is correlated to the polymer molecular weight: with increasing molecular weights, the release decreased. The standard explanation is the difference in swelling capacity between low and high PEO molecular weights. Indeed, drug is released from low PEO molecular weight matrices due to the polymer erosion whereas the drug release from high PEO molecular weight matrices is due to the swelling of the polymer and subsequently drug diffusion [117,127,135].

The aim of this study was therefore to determine the impact of PEO molecular weights prepared by hot melt extrusion and containing 10 % theophylline monohydrate on the release kinetics of the sustained dosage forms. All available PEO grades were tested and drug release was correlated with swelling capacities of each matrices.

1. *In vitro* drug release from hot melt extrudates

All formulations were extruded at the same conditions for reasons of comparison. To enable appropriate extrudate processability and desired drug release, extrusion temperature and screw speed were fixed at 100 °C and 30 rpm, respectively, as selected previously (in chapter 1). Some extrudate presented surface defects such as shark skinning (PEO 300 kDa) or melt fracture (PEO 900 and 2,000 kDa) but the majority presented a smooth surface (chapter 1: Figure 10). The surface aspect was not really correlated to the melt pressure observed during the extrusion since the melt pressure increased with PEO molecular weight until reaching a plateau (PEO 600 – 7,000 kDa) (Figure 17). In addition, the torque was not clearly impacted by the PEO molecular weight (Figure 17). But interestingly, it was possible to process all formulations within the extruder limits in term of pressure and torque.

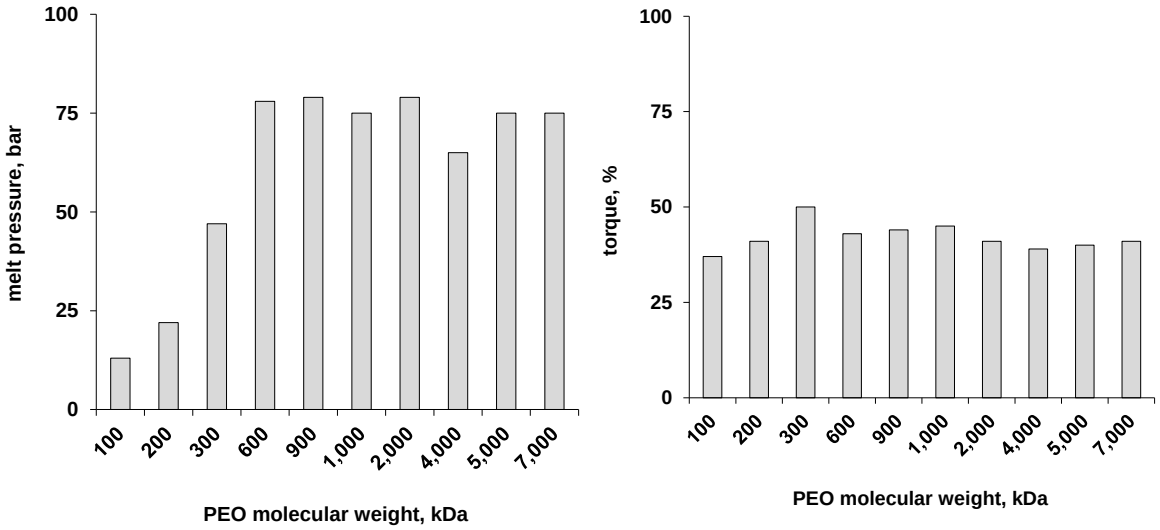


Figure 17: Impact of the PEO molecular weight on the melt pressure (left) or torque (right) during the extrusion.

Figure 18 shows the *in vitro* theophylline release from these hot melt extrudates upon exposure to phosphate buffer pH 7.4 (10 % drug loading). As expected, the impact of PEO molecular weight can be clearly seen with a decrease of the drug release when the molecular weight increased. Nevertheless, it was surprisingly noticed that from a certain molecular weight (600

kDa), the drug releases were almost the same. The aim of this work was then to understand how this behavior can be reached. In this matter, some PEO molecular weights will be particularly studied: PEO 100, 200, 300, 1,000 and 7,000 kDa.

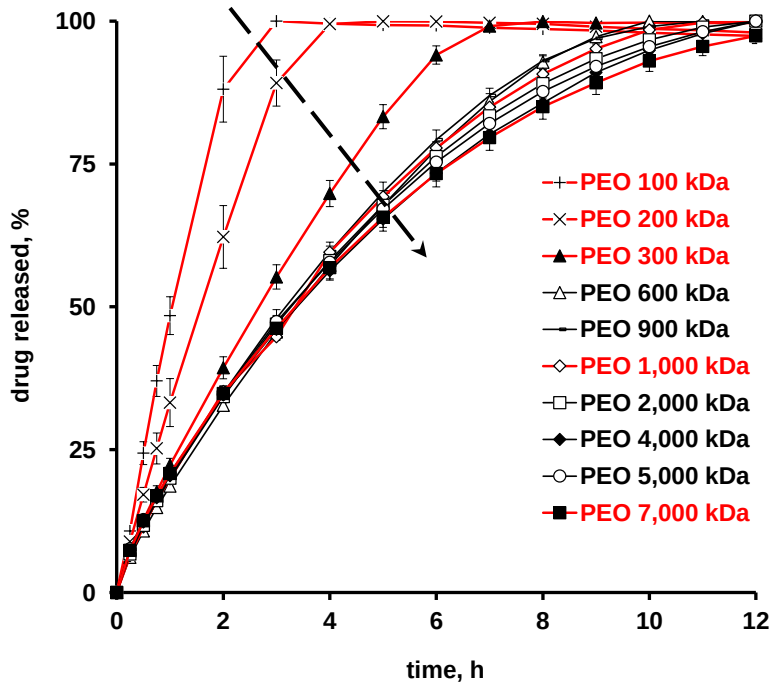


Figure 18: Impact of the PEO molecular weight (indicated in the diagram) on theophylline release from PEO hot melt extrudates in phosphate buffer pH 7.4.

2. Physical characterization of hot melt extrudates

DSC study was conducted in order to determine the drug physical state within the PEO hot melt extrudates. Unfortunately, no peak of the drug could be detected either in the physical mixture or in the hot melt extrudates (Figure 19). This could be explained by the solubilization of the drug within the molten polymer during the heating cycle, which confirms the data published in the literature [190]. It has also been verified with the microscope by heating a physical mixture of the drug and the polymer that the drug has progressively been dissolved into the molten polymer along the heating and without reaching the drug melting point (data not shown).

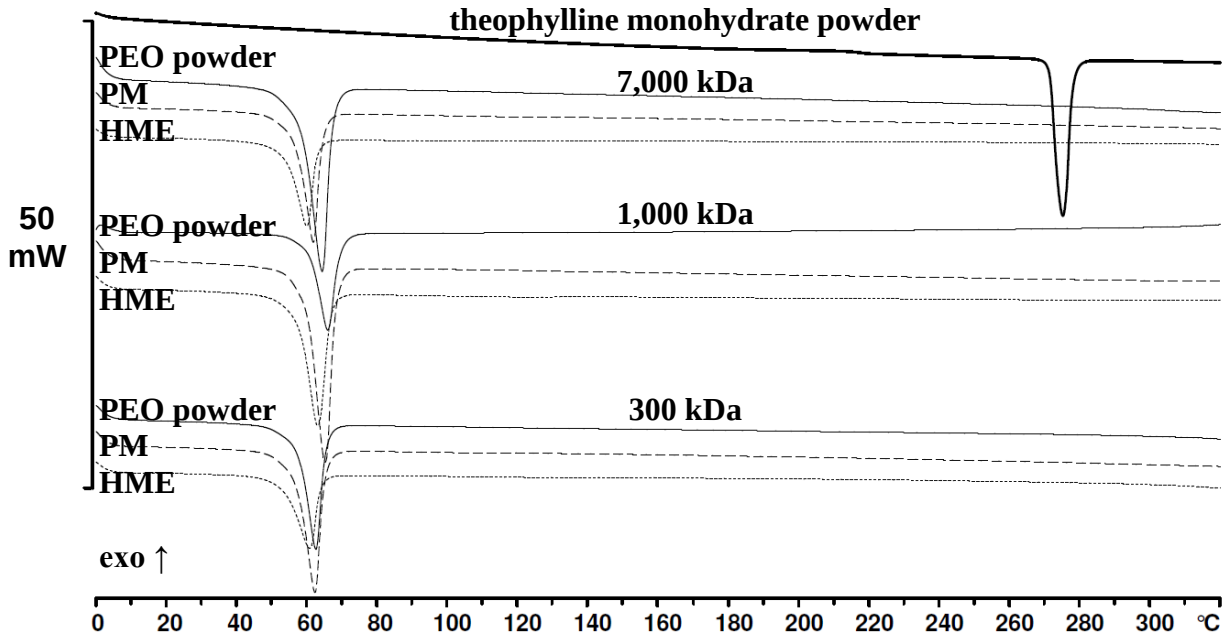


Figure 19: DSC thermograms of PEO hot melt extrudates ("HME", dotted line) and physical mixtures ("PM", dashed line). The data obtained with the pure PEO 300, 1,000 or 7,000 kDa (full line) and theophylline monohydrate (bold line) are also presented.

Since DSC could not give clear information about drug physical state into the hot melt extrudates, X-rays studies were performed (Figure 20). Extrudates were analyzed and compared with pure drug, pure PEO and physical mixtures. Drug physical state were determined by observing the region without PEO signals, between 5 and 12 °. In this particular region, three peaks can be attributed to theophylline in physical mixture and pure drug at 7.2, 8.8 and 11.6 °. However, only the peak at 7.2° could be detected in hot melt extrudates. By comparison with data from the literature [191,192] this peak could be attributed to the anhydrous form of theophylline. This means that a drug conversion occurred during hot melt extrusion from the monohydrate to the anhydrous form of the drug due to the extrusion temperature (100 °C). Importantly, this peak indicates the presence of crystalline form of theophylline within the extrudate, regardless of the PEO molecular weight.

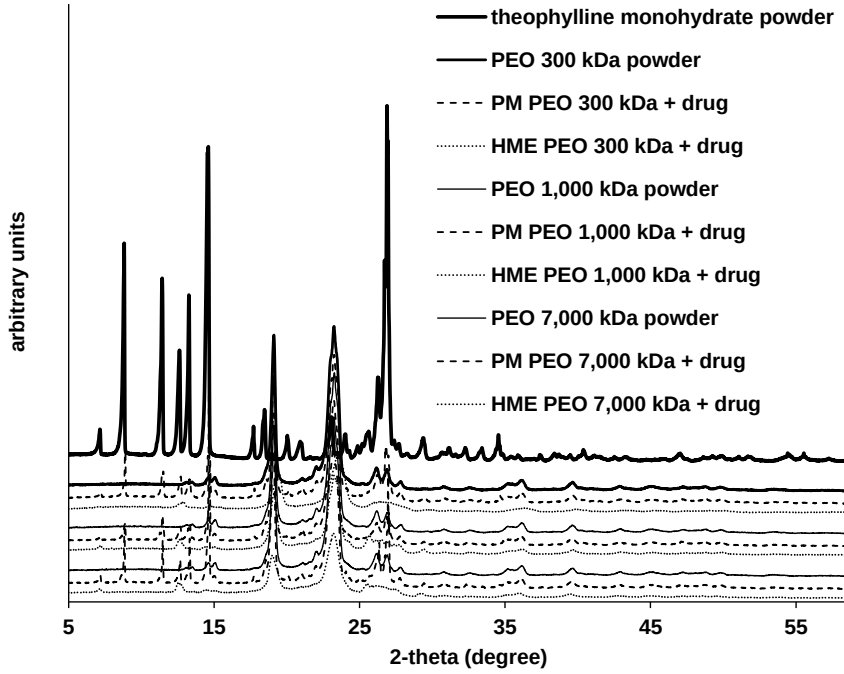


Figure 20: X-rays diffraction patterns of PEO hot melt extrudates ("HME", dotted line) and physical mixtures ("PM", dashed line). The data obtained with the pure PEO 300, 1,000 or 7,000 kDa (full line) and theophylline monohydrate (bold line) are also presented.

3. *In vitro* swelling behavior of hot melt extrudates during dissolution test

To understand the drug release profiles obtained, swelling studies were investigated with five PEO hot melt extrudates: PEO 100, 200, 300, 1,000 and 7,000 kDa. The aim was to explain the remarkable difference in drug release between PEO 100 - 300 kDa and the nearly similar release between PEO 1,000 and 7,000 kDa.

It is to note that the initial water content of hot melt extrudates was less than 0.4 % for all PEO formulations used in this work (data not shown). Pictures in Figure 21 show that extrudates prepared with PEO 100, 200 or 300 kDa completely disappeared after 1, 2 or 4 hours dissolution, respectively. On the contrary, PEO 1,000 or 7,000 kDa hot melt extrudates remained after 8 hours of dissolution.

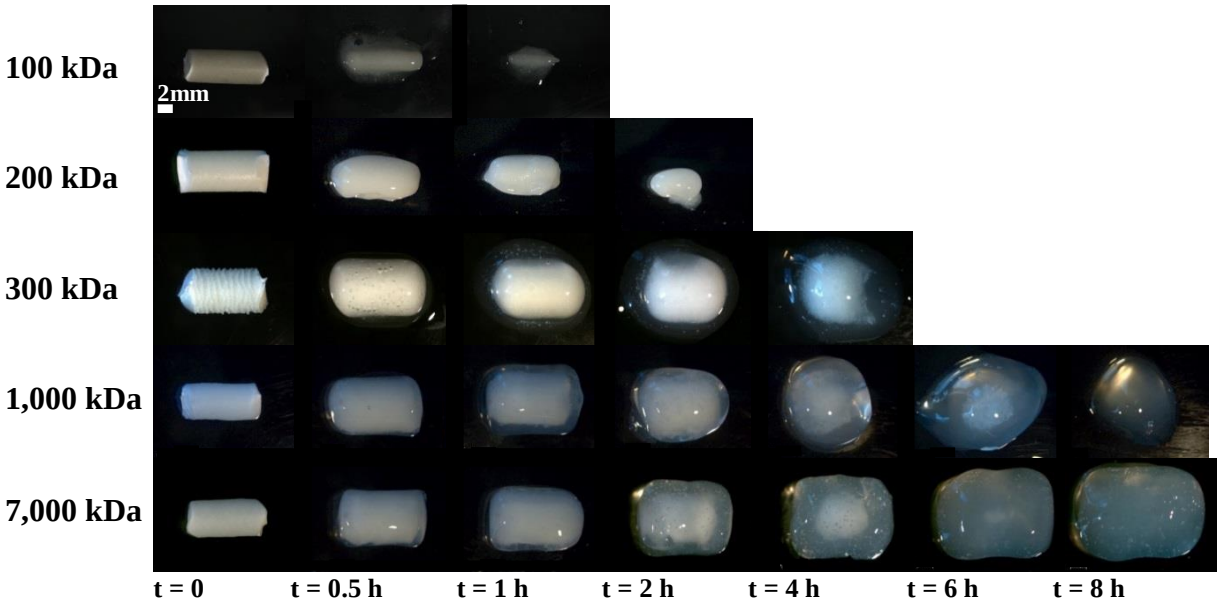


Figure 21: Macroscopic pictures of hot melt extrudates at various dissolution times: impact of PEO molecular weight on the swelling of hot melt extrudates in phosphate buffer pH 7.4:.

This could be explained by differences in the swelling and/or erosion behavior of the low and high PEO molecular weights upon exposure to release medium. The water content increased as the PEO molecular weight increased, with respect to the entire extrudates, however, the dry mass loss was slower and PEO remaining became more pronounced (Figure 22). This was also reported in the literature with direct compressed tablets based on PEO [120,135], which indicates that the drug release mechanism from low PEO molecular weights (low water content and high dry mass loss) is due to the erosion whereas high PEO molecular weights (high water content, little dry mass loss) show swelling behavior. In other words, the contribution of the erosion and the swelling in the drug release will depend on the PEO molecular weight: (i) strong contribution of the erosion and weak contribution of the swelling for low molecular weights, (ii) equivalent contribution of both swelling and erosion in intermediate molecular weights and (iii) weak contribution of the erosion and strong contribution of the swelling in high molecular weights.

This could also be explained by the dimensions changes (length, diameter or volume) of the hot melt extrudates (Figure 22). Please note that after 6 hours of dissolution, the extrudates tended to spread on the glass slide due to a softening in gel structure. This behavior was not indicated in the diagram (for example PEO 1,000 and 7,000 kDa after 8 hours). For PEO 100 and 200 kDa, the dimensions decreased rapidly due to the gel erosion whereas for higher PEO molecular weights, the dimensions increased due to the swelling of the matrix system. This increase was proportional to the PEO chains length with the highest increase for PEO 7,000kDa. Unfortunately, this cannot explain by the narrow release between PEO 1,000 and 7,000 kDa. Tajiri and coworkers concluded that the liquid uptake of the matrix was not correlated to the drug release. However, the hydrogel layer thickness was the primary factor of controlling drug release by diffusion from the PEO/PEG matrices [104]. Thus, a separation between the different parts of the extrudate was considered.

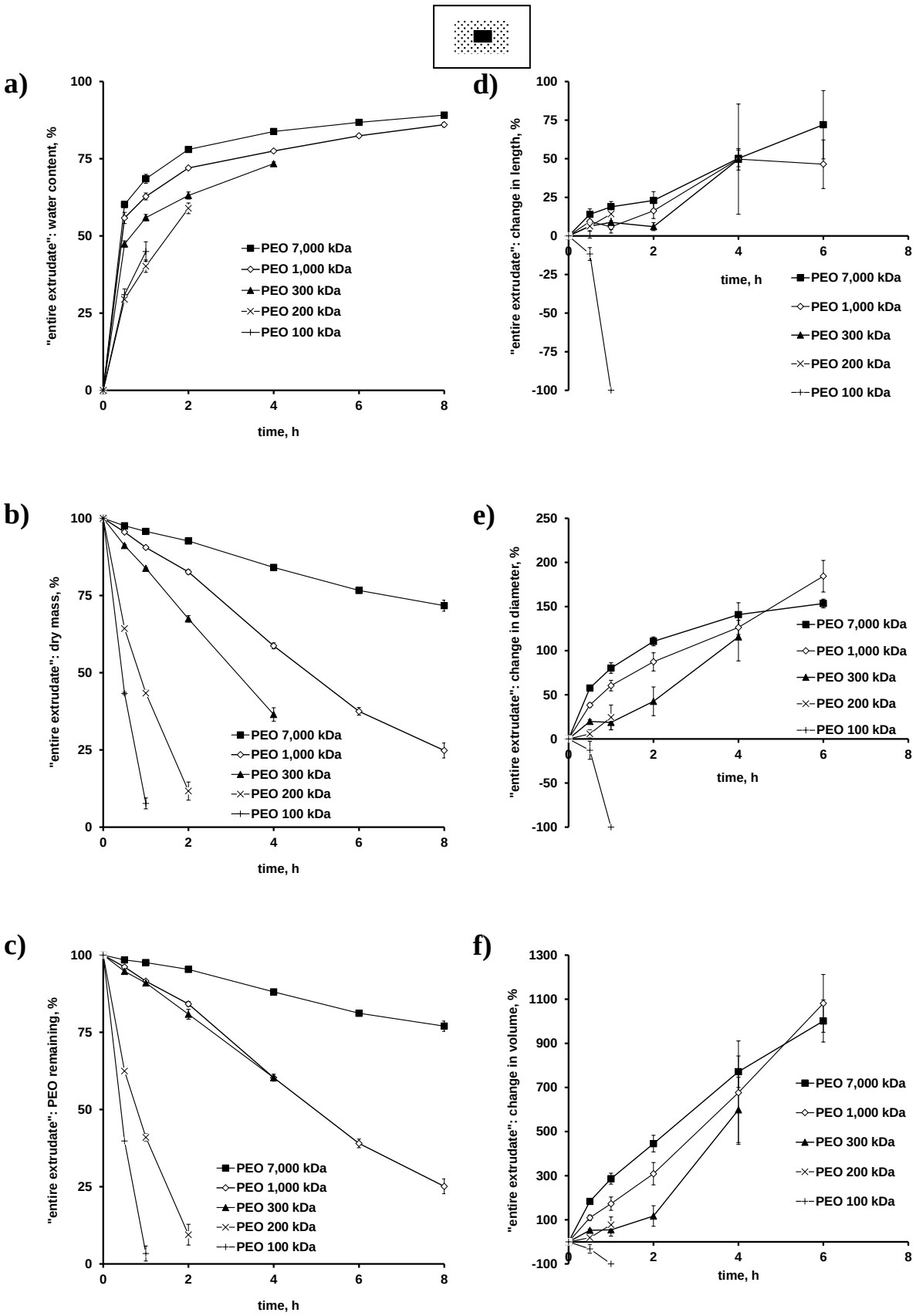


Figure 22: Changes in (a) water content, (b) dry mass, (c) PEO remaining, (d) length, (e) diameter and (f) volume of "entire hot melt extrudates" in phosphate buffer pH 7.4. The PEO molecular weights are indicated in the diagrams.

Two types of separation were possible (Figure 23): (i) a separation between the gel (transparent and non-transparent, which correspond to the soft part of the extrudate) and the solid core (corresponding to the remaining solid part of the extrudate) and (ii) a separation between the drug-solubilized (transparent) and drug-non-solubilized (non-transparent) part of the extrudate.

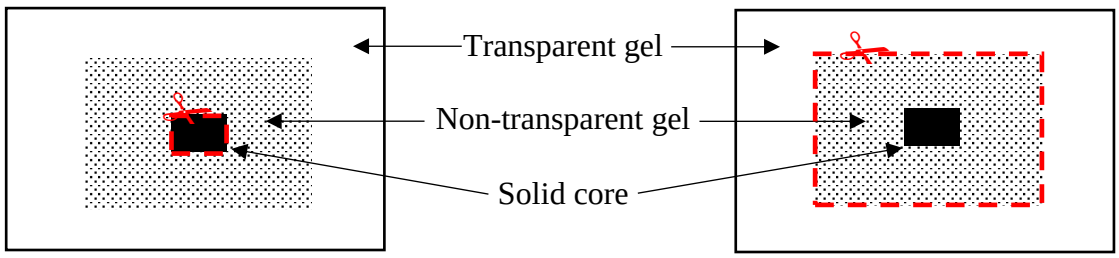


Figure 23: Schematic representation of the two methods of separation.

The gel (transparent and non-transparent) thicknesses were studied (Figure 24). However, the transparent gel layer could not be isolated in the case of low PEO molecular weights (100 and 200 kDa) due to high erosion effect. Nevertheless, in both separation methods, the gel thickness was similar during the first 4 hours for PEO 300, 1,000 and 7,000 kDa which did not correlate well with the drug release.

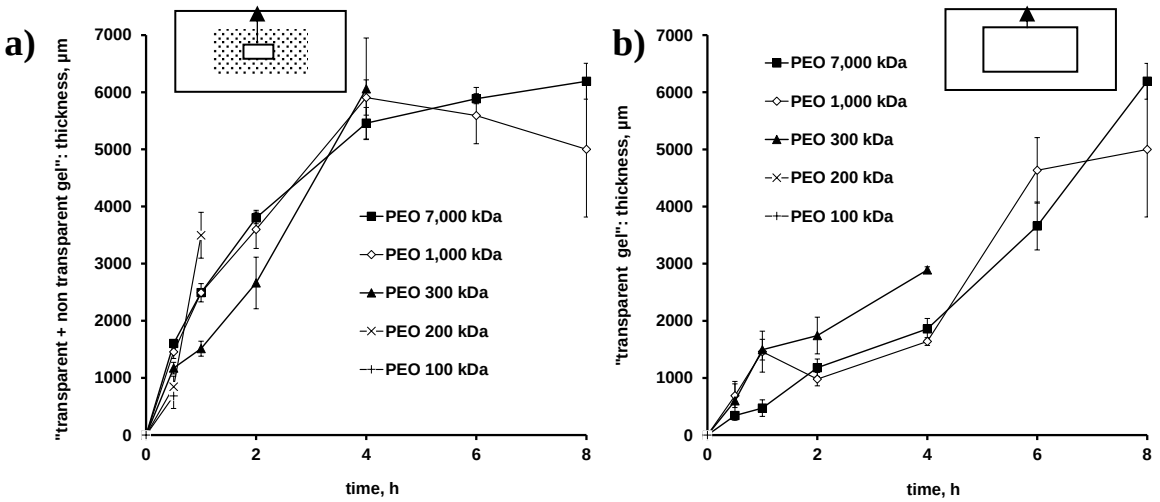


Figure 24: Thickness of the (a) "transparent and non-transparent gel" or (b) "transparent gel" only of hot melt extrudates in phosphate buffer pH 7.4. The PEO molecular weights are indicated in the diagrams.

First separation method ("transparent + non transparent gels" *vs* "solid core"):

The drug repartition was analysed in the gels ("transparent and non-transparent") as well as in the "solid core" (Figure 25). The "solid core" disappeared after 2 hours. Consequently, the drug remaining decreased very fast. It can be concluded from these results that the majority of the drug was localized in the gels. The gels drug content between all PEO was well distinguished. In fact, drug content decreased faster with decreasing PEO molecular weights.

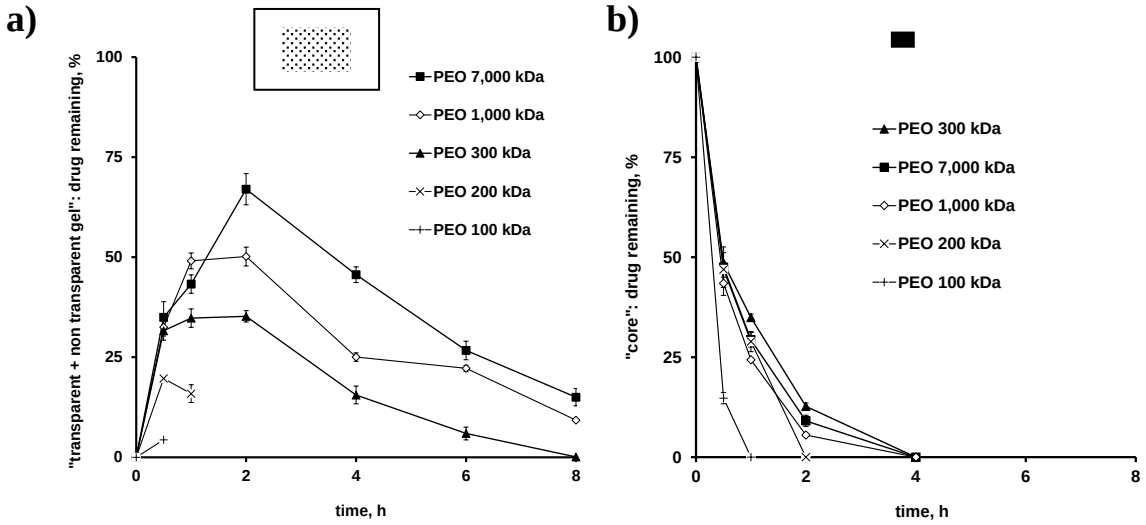


Figure 25: Drug content in (a) the "transparent and non-transparent gel" and (b) the "solid core" of hot melt extrudates in phosphate buffer pH 7.4.

The water content of the "solid core" was quite different in all formulations (Figure 26), whereas the dry mass and PEO remaining were nearly similar, at least for PEO 300, 1,000 and 7,000 kDa. The dimensions of the "solid core" were also almost similar between PEO 300, 1,000 and 7,000 kDa but only PEO 100 and 200 kDa were different. For the water content of "transparent and non-transparent gel" (data not shown), all PEO showed different results (40 % water content to more than 75 % for PEO 100 to 7,000 kDa). These results suggest that the drug release probably does not strongly depend on the "solid core" with respect to the drug content.

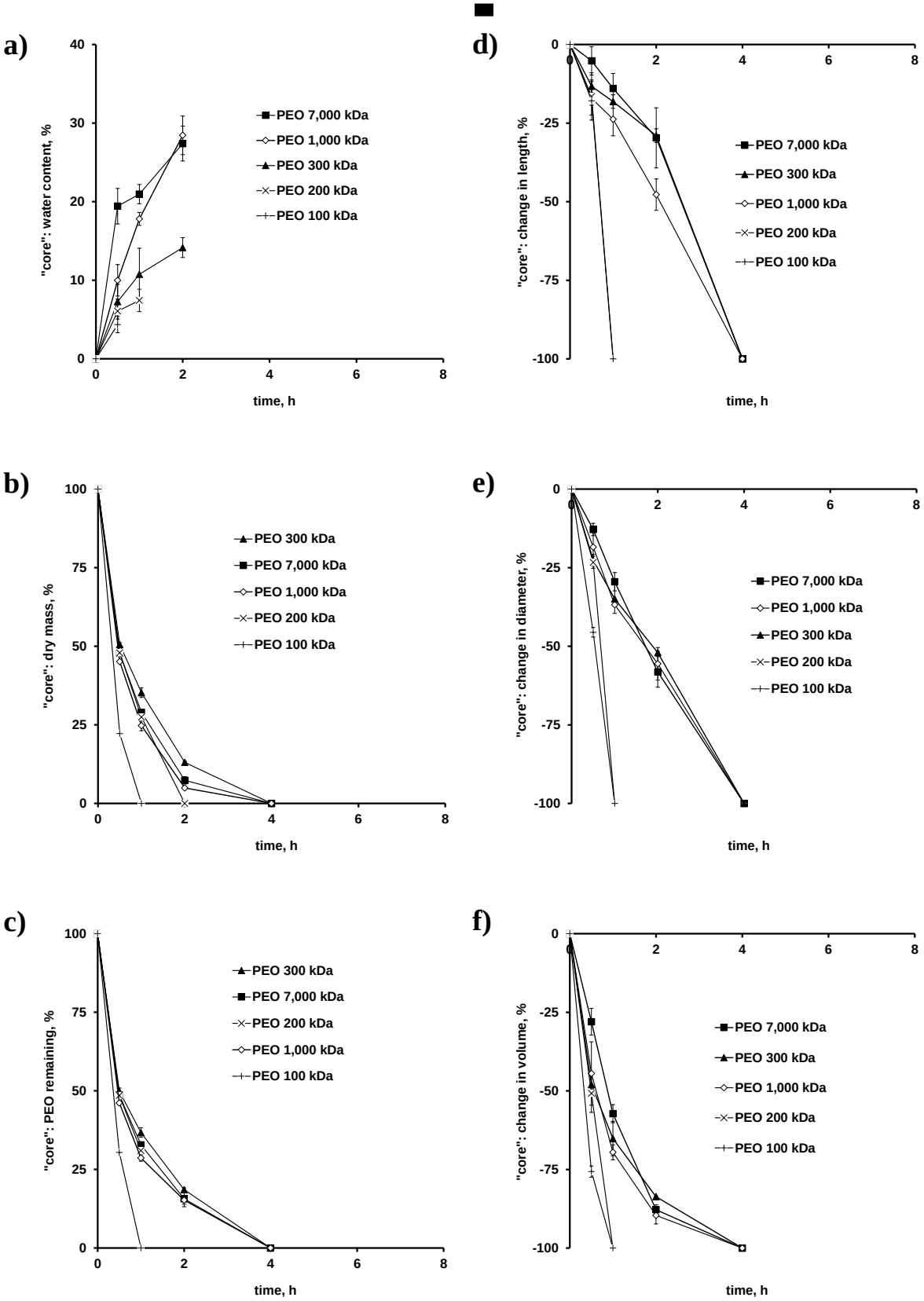


Figure 26: Changes in (a) water content, (b) dry mass, (c) PEO remaining, (d) length, (e) diameter and (f) volume of "solid core" of hot melt extrudates in phosphate buffer pH 7.4. The PEO molecular weights are indicated in the diagrams.

Second separation method ("transparent gel" *vs* "solid core + non-transparent gel"):

Drug concentration in the solubilized ("transparent gel") and non-solubilized ("solid core + non-transparent gel") part is presented in Figure 27. Data indicated that drug content in the "transparent gel" was never higher than 15 % for all formulations. Adding to the previous results that showed that the drug content in the "solid core" was very low, it can be concluded that the majority of the drug is localized in the "non-transparent gel".

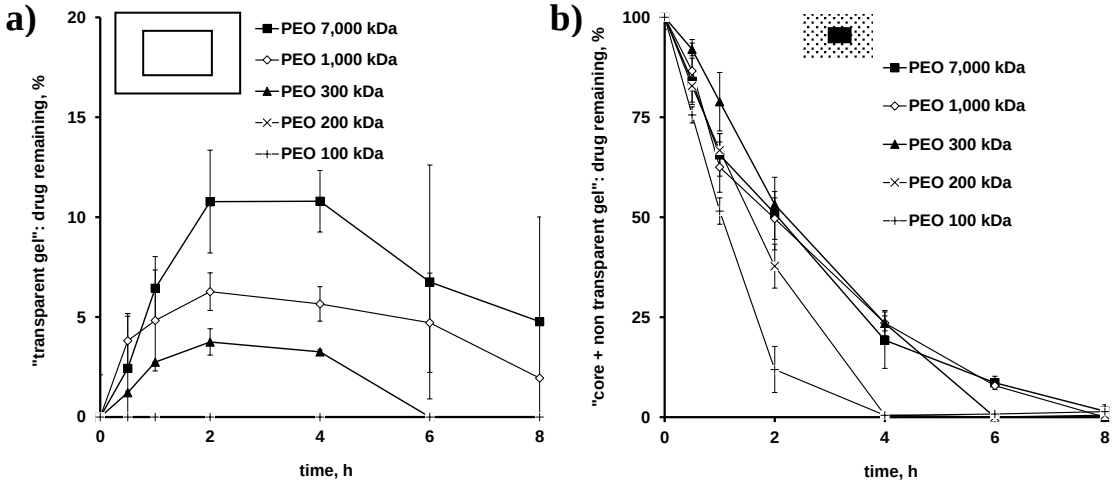


Figure 27: Drug content in (a) the "transparent gel" and (b) the "solid core and non-transparent gel" of hot melt extrudates in phosphate buffer pH 7.4.

Thus, the swelling of the "solid core + non–transparent gel" was studied (Figure 28), but no remarkable difference between PEO 300, 1,000 and 7,000 kDa could be observed. Nevertheless, we noticed that PEO 100 and 200 were well distinguished from other PEO molecular weights, especially in the dry mass and PEO remaining. The water content of "transparent gel" (not applicable for PEO 100 and 200 kDa) was similar and above 75 % for PEO 300, 1,000 and 7,000 kDa (data not shown). Finally, changes in dimensions of the non-solubilized part were also calculated. The changes in diameter and volume especially presented interesting results since a big difference between low molecular weights and others could be observed but a similar trend could be observed between intermediate and high molecular weights. It could be then hypothesized that the drug release is mainly governed by the diffusion pathway from non-solubilized part to the bulk medium through the transparent gel layer.

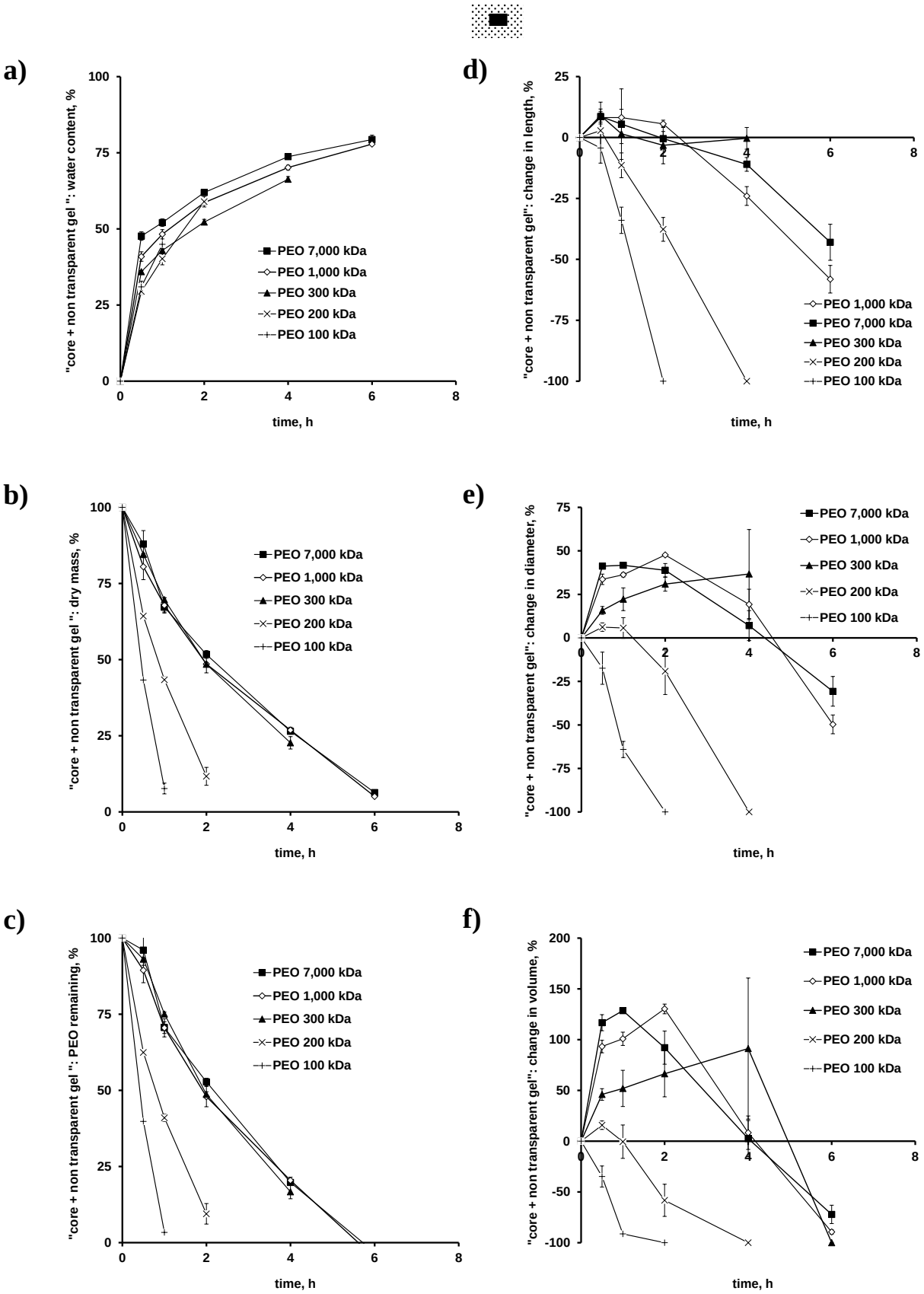


Figure 28: Changes in (a) water content, (b) dry mass, (c) PEO remaining, (d) length, (e) diameter and (f) volume of "solid core and non-transparent gel" of hot melt extrudates in phosphate buffer pH 7.4. The PEO molecular weights are indicated in the diagrams.

Polyethylene oxide polymers are suitable polymers for hot melt extrusion allowing good processability with reasonable pressure under appropriate conditions. Importantly, sustained drug release was achievable from polymers with molecular weights of 600 kDa or more. Interestingly, with a drug loading of 10 %, no particular difference in sustained release was found with high molecular weights (600 kDa – 7,000 kDa). Surprisingly, swelling could not be the explanation of the drug release in case of the entire dosage form. More detailed investigations should have been done. Indeed, three different parts could be distinguished: the "transparent gel" where the drug is solubilized, a "non-transparent gel" where the drug is solubilized and non-solubilized and a "solid core" where the drug is non-solubilized. The drug content was different in all these parts, with the majority of the drug remaining in the "non-transparent gel". It has been found that the volume changes of the non-solubilized part especially ("solid core + non-transparent gel") could be responsible of different drug release behaviors. Nevertheless, the drug solubility might very probably affect these changes in the drug release. Moreover, the drug nature and loading, could also have an impact on the swelling behaviors and hence on the drug release. Thus, further studies should be conducted in order to determine more specifically the impact of the drug (loading and solubility) on the drug release kinetics.

CHAPTER 3: THE IMPACT OF DRUG NATURE AND LOADING ON DRUG RELEASE FROM PEO HOT MELT EXTRUDATES

THE IMPACT OF DRUG NATURE AND LOADING ON DRUG RELEASE FROM PEO HOT MELT EXTRUDATES

Sustained drug delivery systems enhance drug efficacy and patient compliance by decreasing serious side effects [91]. Their development requires the best knowledge of drug properties such as desirable half-life and high therapeutic index, desirable absorption and solubility characteristics and more importantly, a reduced dose [119]. Indeed, dose comprised between 0.5 and 1 g is generally recommended for oral delivery to facilitate the administration of the medicine [193]. Thus, the more the drug content is, the smaller the final dosage form size can be.

Unfortunately, high drug loading dosage forms are often difficult to be formulated. Depending on the process used, the quantity of carrier can be more or less important. For instance, formulations prepared by hot melt extrusion can be quite simple, containing the drug and a polymer (sometimes the addition of plasticizer or other processing aids might be helpful but only a small concentration is required) [83].

However, it is known that problems can appear during the process of hot melt extrusion when drug loading increases, such as the increase in torque [194,195] or extrudates surface defects [68,196]. The worst case conditions for processing is often when drug load is higher than 50 % [197] or even 20 % in some cases [153]. Nevertheless, some drugs act as plasticizer and facilitate the manufacturing process [52,53,87,128].

More importantly, the drug loading can also have an influence on drug release but its impact may be complex. Indeed, some studies reported an increase in the drug release when drug loading increases [19,20,25,53,71,194,198,199] with various drugs (theophylline, diltiazem, ibuprofen, indomethacin, nimodipine, acetaminophen) and polymers (PVA, Eudragit, HPMC, Kollidon) but other studies reported a decrease [197] (indomethacin and various polymers), or no effect [134] (caffeine varied from 8.3 to 80 %) on the drug release.

This highlights the role of other phenomena in the drug release:

- the drug solubility [112,200]: water soluble drugs were reported to be released preferentially by diffusion through the gel layer whereas poorly water soluble drugs were released due to the gel erosion [127],
- the matrix composition: for instance, poly ethylene oxide is a semi crystalline polymer with various drug release mechanisms depending on the molecular weight (e.g. erosion, swelling, and drug diffusion).

The aim of this study was therefore to determine the impact of drug solubility and drug loading on (i) the processability and (ii) the *in vitro* drug release. Three drugs with different solubility were used: theophylline monohydrate, ibuprofen and metoprolol tartrate (12 mg/mL, 50 mg/mL, 250 mg/mL, respectively, in phosphate buffer pH 7.4, at 37 °C). Four drug loadings were chosen (10, 20, 40 and 60 %) and three PEO molecular weights were selected (300, 1,000 and 7,000 kDa) for this study.

1. The impact on processability and *in vitro* drug release

The appearance of all formulations is shown in Figure 29. All extrudates presented a smooth surface except those formulated with PEO 300 kDa. With this particular molecular weight, shark skinning appeared during the process (Chapter 1: PEO 300 kDa, 10 % theophylline) for all drugs used. But surprisingly, shark skinning progressively disappeared as the drug loading increased up to 60 %, with respect to all drugs. Moreover, all extrudates were white opaque except with low drug loading of ibuprofen where the extrudate were more translucent. It is possible that the drug physical state changed when varying the drug loading. This point will be verified in the following analysis.

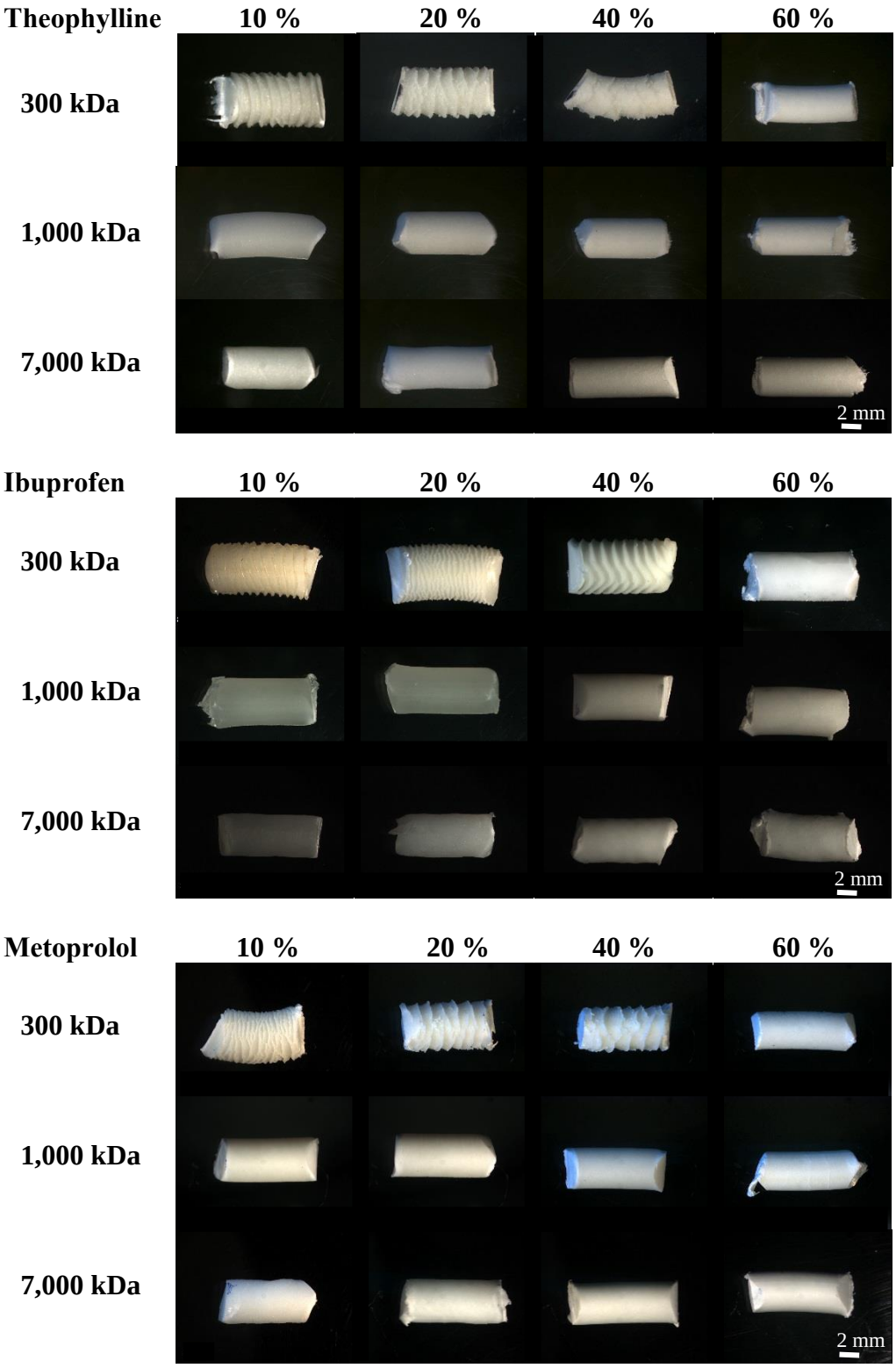


Figure 29: Macroscopic pictures of the investigated hot melt extrudates consisting of 10 to 60 % theophylline, ibuprofen or metoprolol and 90 to 40 % PEO of various polymer molecular weights (as indicated on the left) before exposure to the release medium.

In addition, all formulations were easily produced at reasonable melt pressure and extruder torque (Figure 30). For formulations containing theophylline, no particular increase of pressure was noticed when the drug loading was increased despite the non-plasticizing effect of this drug. However the hydrate form of theophylline was used for this study and water is known to act as a plasticizer [88]. That could be the explanation for a stable pressure despite the increase in drug loading. On the contrary, ibuprofen is known to have a plasticizing effect which decreases the melt pressure at high loading level [71,85,86]. In addition, metoprolol has also been reported to have a plasticizing effect with another polymer (Eudragit RS [86]). The plasticizing effect of metoprolol was evident at least for PEO 300 kDa. Finally, the increase in drug content within all formulations reduced the viscosity of the mixture since the torque is decreased.

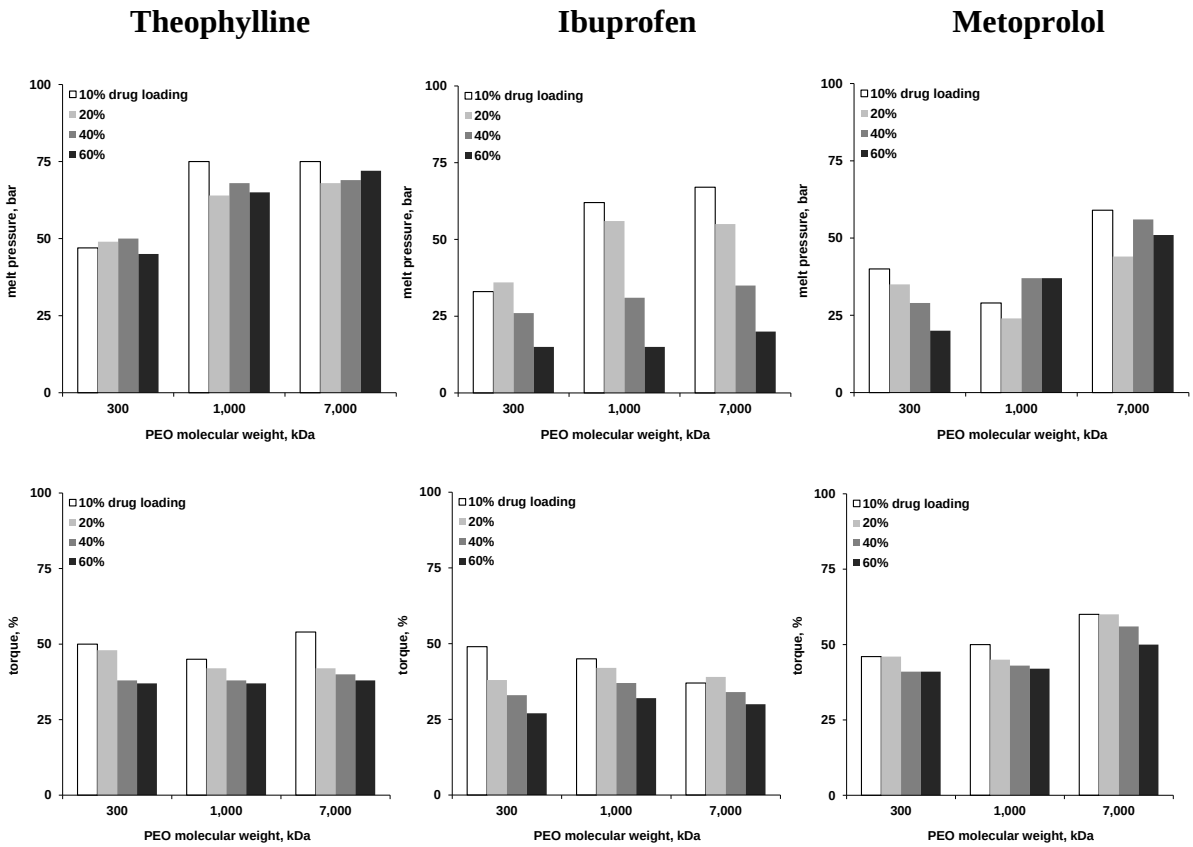


Figure 30: Impact of the drug type (indicated on the top) and loading (indicated in the diagrams) on the melt pressure (top) or torque(bottom) during the extrusion.

In vitro drug released was conducted upon exposure to phosphate buffer pH 7.4 from hot melt extrudates (Figure 31). In this medium, experimental solubility data were 12 mg/mL for theophylline monohydrate, 50 mg/mL for ibuprofen and 250 mg/mL for metoprolol tartrate. In particular, sink conditions during dissolution testing were respected for all drug loadings. The drug releases followed the tendency presented in chapter 2, which indicates that the drug release decreased with increasing PEO molecular weight. Nevertheless, an unexpected tendency was observed when the impact of drug loading was studied.

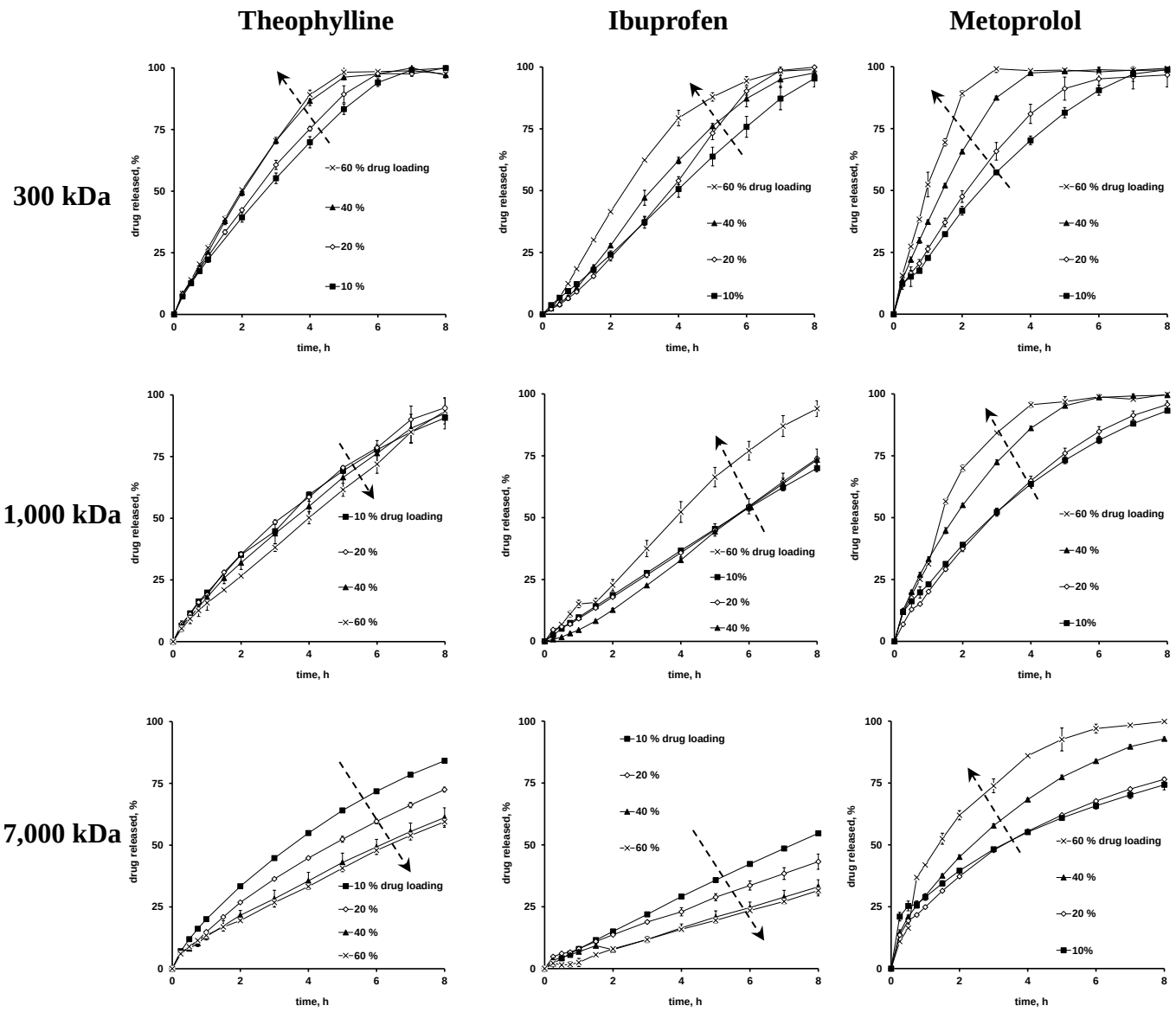


Figure 31: Theophylline, ibuprofen and metoprolol release from the hot melt extrudates in phosphate buffer pH 7.4: impact of the PEO molecular weight (indicated on the left) and drug loading (indicated in the diagrams).

For theophylline and ibuprofen formulations containing low PEO molecular weight, the drug release increased with increasing drug loading. On the contrary, formulations with high PEO molecular weight showed a decreased drug release when the drug loading increased. This observed opposite trend occurred in the case of theophylline at 1,000 kDa but in case of ibuprofen, this phenomenon occurred later.

This could be explained by (i) the percolation threshold theory and (ii) the difference in PEO release mechanisms. The percolation threshold is a point defined by a critical drug loading: above this point, a continuous network of pores is created during the dissolution and enhances the release. Below this point, the majority of drug remains as clusters within the matrix whereas only drug particles located at the surface can be released [201]. In addition, the predominant release mechanism from low molecular weight is the erosion whereas the predominant release mechanism from high molecular weight is the swelling [117,127,135].

By associating these two theories, we could therefore assume that with high molecular weight, a gel with higher density polymeric network is formed and retards the access of water inside the matrix. In these conditions, with 60 % of drug, more drug stayed insoluble and entrapped inside the matrix whereas with low molecular weights, the erosion mechanism facilitates the water ingress (less denser polymeric network). All the drug particles are in contact with water even if the percentage of drug is high and can be solubilized creating pores. The more the drug is into the system, the more pores are formed leading to an increased release (increased porosity). Finally, in both cases, the release depends on whether or not the drug is dissolved. This is in agreement with another study that stated the importance of drug dissolution from hydrophilic matrices, in addition to drug diffusion or matrix erosion [107]. Another study using PEO by direct compression containing various drug loading and different drug solubility also showed that the mechanisms of the release was changed when varying the drug solubility and drug loading [112]. For instance, drug dissolution was the main mechanism of the release with high drug loading whereas drug diffusion was predominant for low drug loading. However,

metoprolol formulations containing various drug loadings and PEO molecular weights present the same trend as drug release increased with increasing drug loading. This is probably due to the very high solubility of metoprolol tartrate. This is confirmed with another study from the literature using PEO by direct compression [135]. This work showed that depending on the PEO molecular weight, the impact of drug loading changes except with the high soluble metoprolol tartrate.

2. Physical characterization

It has been shown in the literature [202] that the drug loading influences the crystallinity of PEG polymer in matrices with an increased polymer amorphisation as drug loading increased (with 52 % of indomethacin, the polymer was completely amorphous). DSC studies were then performed on each formulation in order to understand the PEO and drug physical states. As mentioned before, for theophylline formulations (Figure 32) the drug peak could not be detected due to the solubilization during the heating cycle. When the drug concentration increased, the peak became detectable (from 40 %). The melting temperature of the drug peak in 40 and 60 % hot melt extrudates was below the one in pure drug, which shows the drug dissolution within the PEO. This was the case for all PEO. The same thing happened for metoprolol tartrate (Figure 34). For ibuprofen formulation however (Figure 33), the drug peak was very close to PEO peak. Thus the two peaks are probably mingled in formulation thermograms. Nevertheless, with 60 % of drug, we can see from the shape of the peak that probably dissolution occurred, for all the drugs.

In addition, the study of PEO melting peak indicated a decrease of the melting temperature (T_{onset}) and an increase of enthalpy when drug loading increased (all PEO formulations containing ibuprofen). For theophylline and metoprolol formulations, the changes were less pronounced (Figure 35).

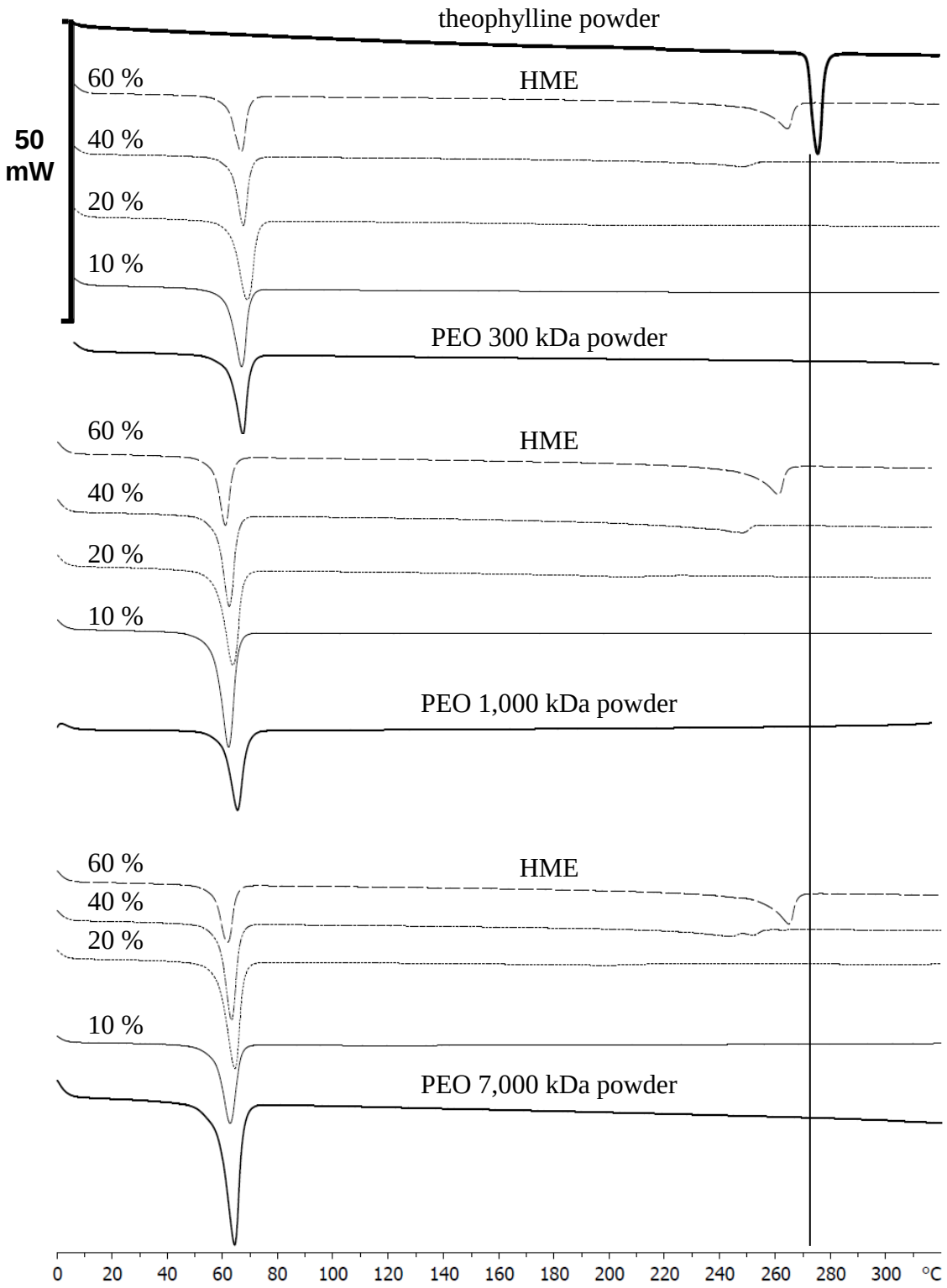


Figure 32: DSC thermograms of PEO hot melt extrudates ("HME"). The data obtained with the pure PEO 300, 1,000 or 7,000 kDa (full line) and theophylline (bold line) are also presented.

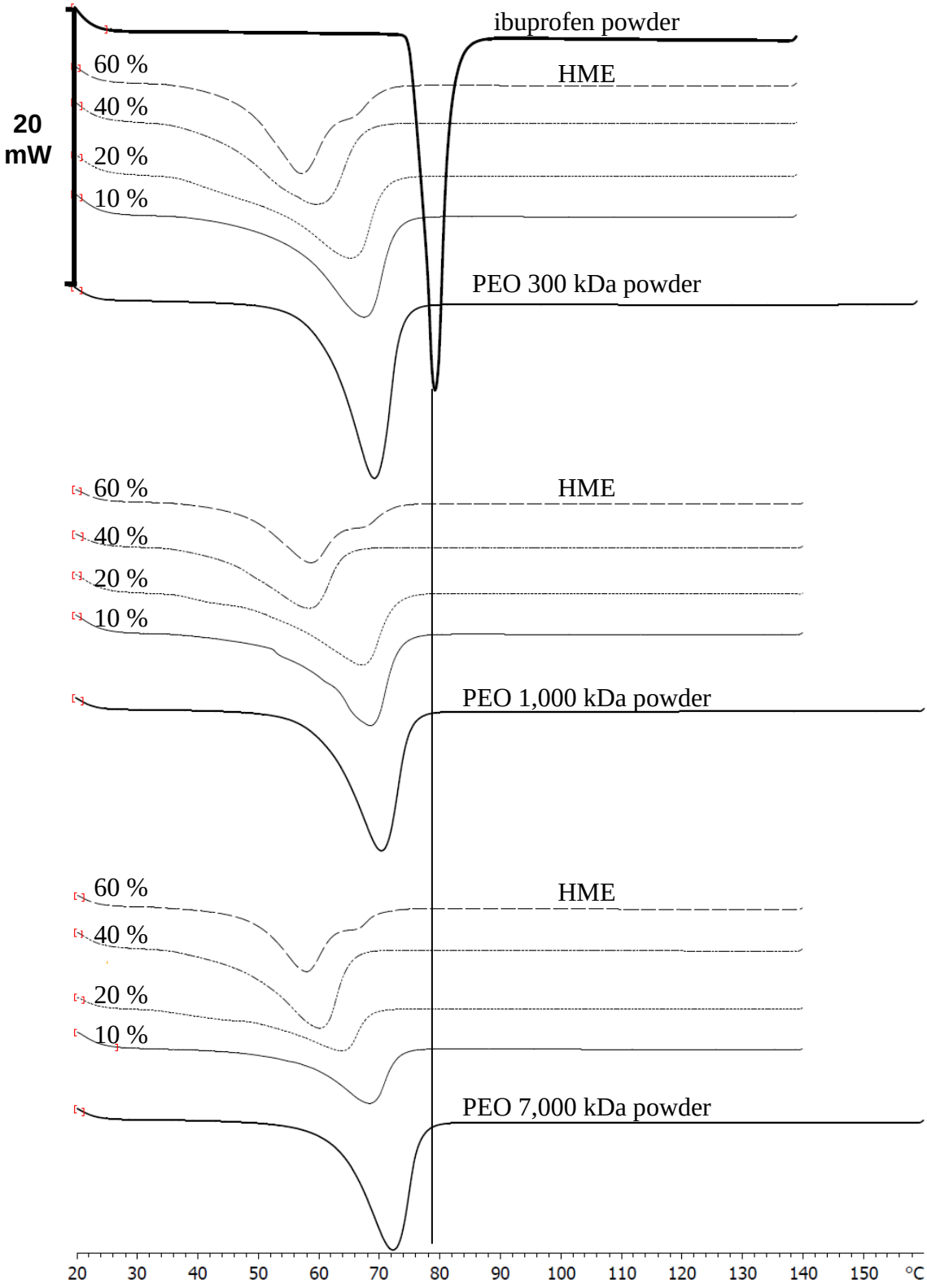


Figure 33: DSC thermograms of PEO hot melt extrudates ("HME"). The data obtained with the pure PEO 300, 1,000 or 7,000 kDa (full line) and ibuprofen (bold line) are also presented.

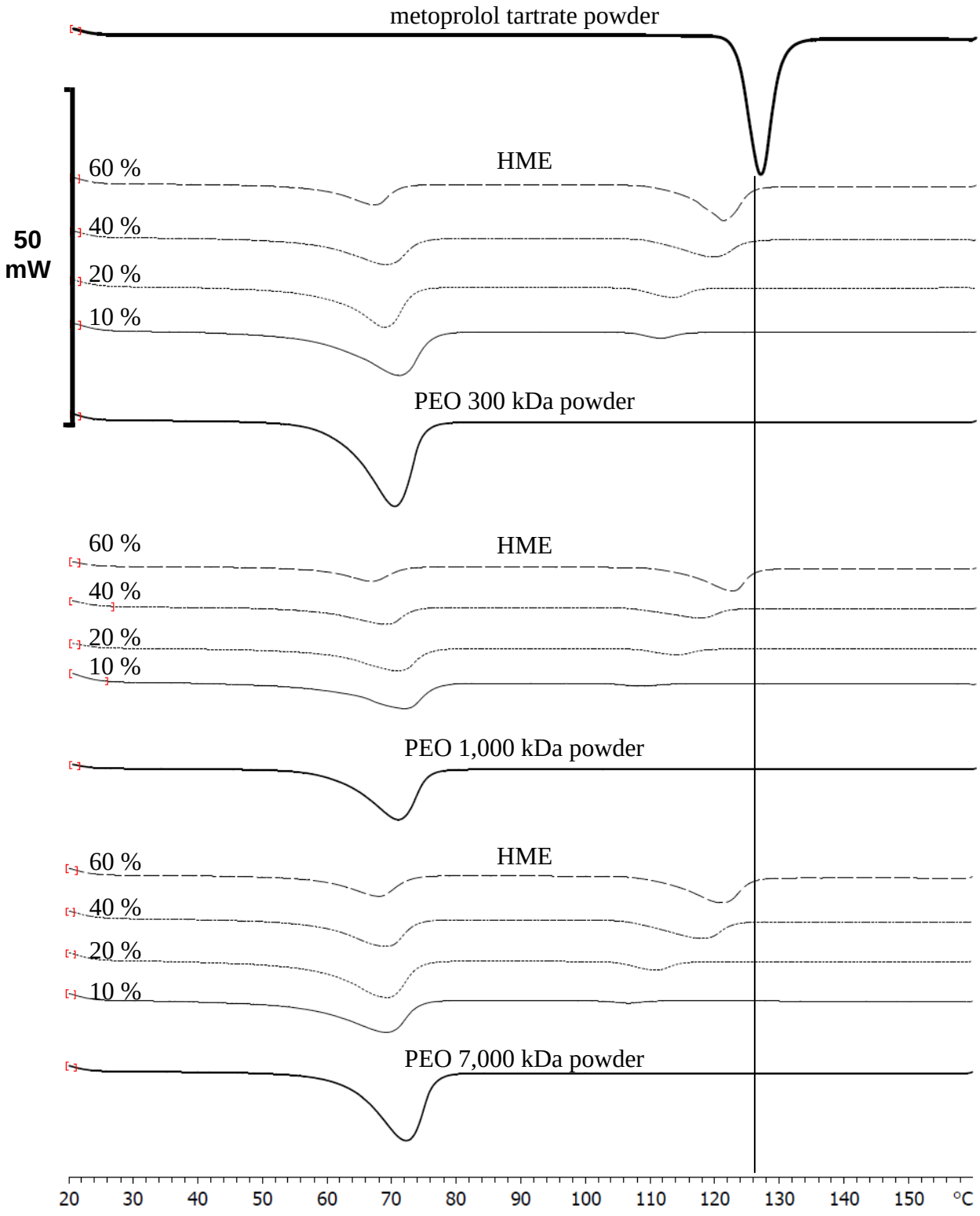


Figure 34: DSC thermograms of PEO hot melt extrudates ("HME"). The data obtained with the pure PEO 300, 1,000 or 7,000 kDa (full line) and metoprolol (bold line) are also presented.

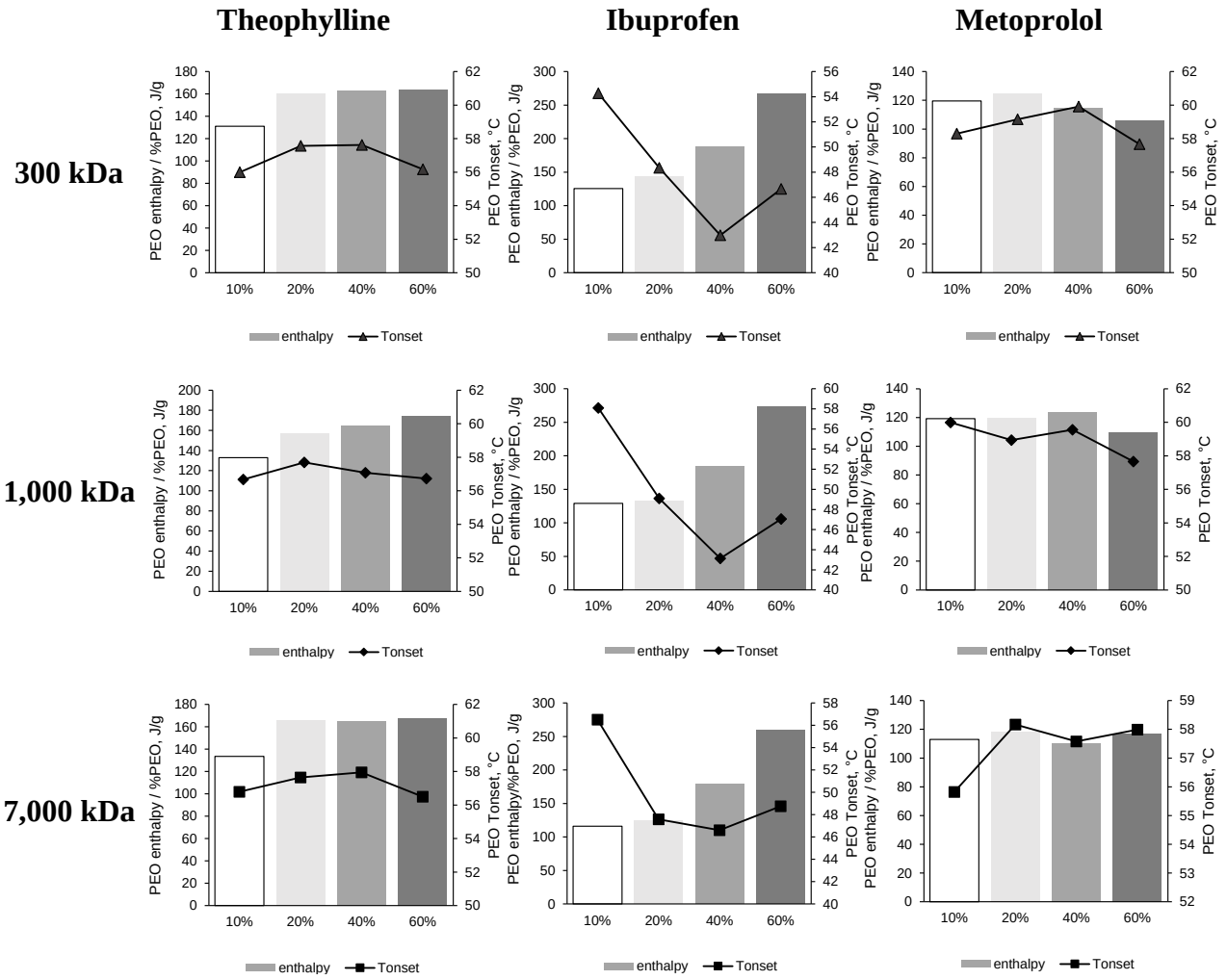


Figure 35: Enthalpy (represented by histograms) and T_{onset} (represented by the curve) of the PEO melting peak in hot melt extrudates prepared with various drugs (indicated on the top) of different loadings (indicated in diagrams) and various PEO molecular weight (on the left).

Pictures by the microscope of heated samples were taken in order to understand if dissolution occurred during the extrusion (Figure 36). Physical mixtures containing 10 % of drug and PEO 7,000 kDa were heated until 100 °C. Neither theophylline nor metoprolol showed a dissolution at this temperature but ibuprofen, however, was able to be dissolved in PEO particles under these conditions. This could be explained by the changes observed in PEO melting temperature and enthalpy during the DSC measurements.

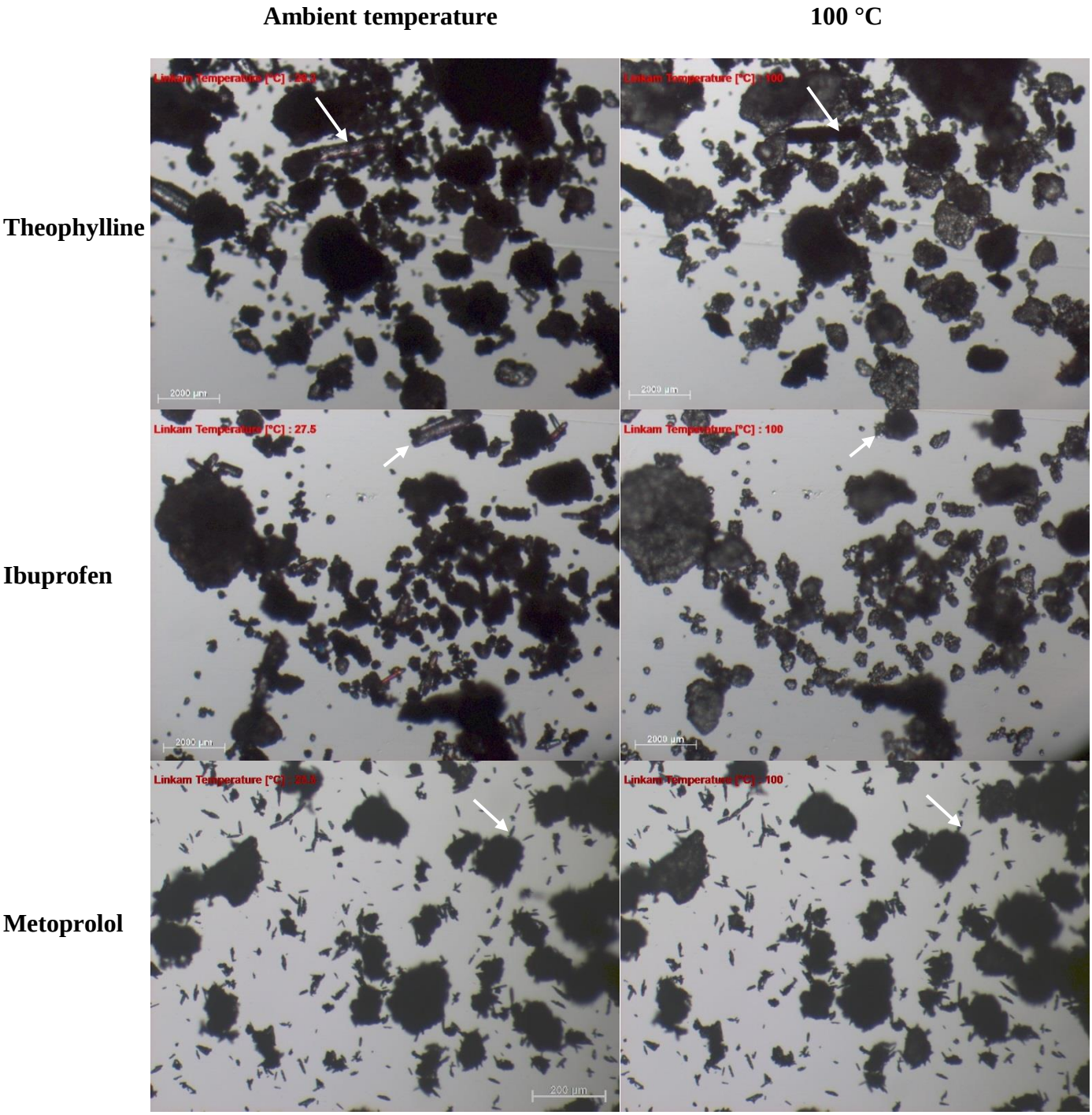


Figure 36: Microscopic pictures of physical mixtures containing 10 % of drug (indicated on the left) and PEO 7,000 kDa at room temperature (left) or heaten at 100 °C (right). The white arrow indicates a drug particle in each physical mixture as an example.

Due to the dissolution phenomenon in DSC, X-rays were also performed. As shown previously with 10 % of theophylline, the drug was already crystalline within the extrudate. We assume that theophylline will be in crystalline form even with high drug loading. However, 10 %

ibuprofen formulation does not show any characteristic peak of the drug at 6° or 12° which can be attributed probably to the amorphisation of the drug within the PEO matrix. However, extrudates with 60 % showed peaks at 6.2° and 12.3°, which indicates that drug was in crystalline form at high loading level. Metoprolol formulations showed surely peaks at 10.8° and 12.1° of the metoprolol crystals.

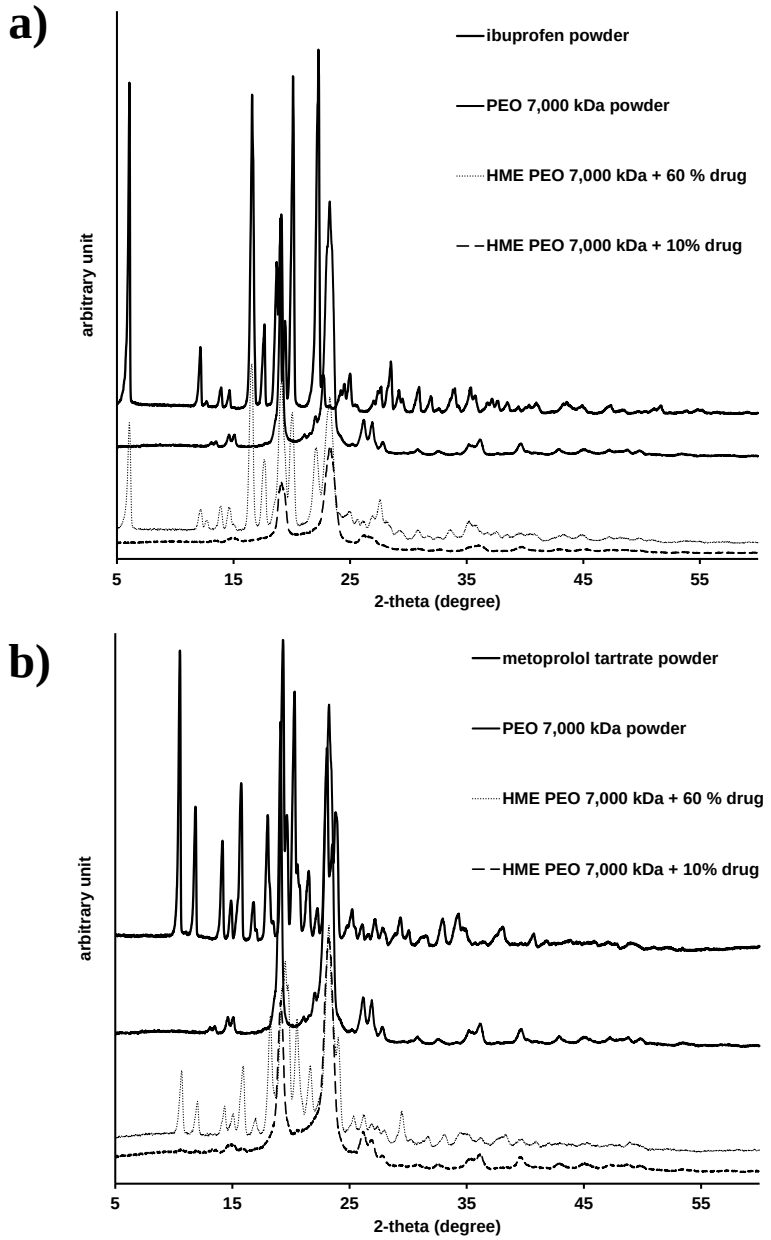


Figure 37: X-rays diffraction patterns of PEO hot melt extrudates ("HME", dotted line) with 10 % (dashed line) or 60 % (dotted line) of a) ibuprofen or b) metoprolol. The data obtained with the pure PEO 7,000 kDa (full line) and the drug (bold line) are also presented.

3. *In vitro* swelling studies

Swelling studies were performed in order to explain the drug release behaviors (opposite trend occurred in the case of theophylline at 1,000 kDa but in case of ibuprofen, this phenomenon occurred later, no inversion for metoprolol). As it has been seen previously, it was possible to correlate the non-solubilized part of the extrudate ("solid core + non-transparent gel") with the drug release of 10 % theophylline formulations. Therefore, the same method of separation was chosen for the drug loading studies.

Figure 38-40 show pictures of hot melt extrudates at predetermined dissolution times. As it can be seen on the figures, the swelling behaviors were different among drugs, drug loadings as well as PEO molecular weights. As mentioned before, spreading of the dosage forms may occur on glass slide but here, all the curves would be presented since the spreading depended on too many parameters (dissolution times, drug loading and drug type). Please note that stars in the diagrams indicate the spreading of the extrudates.

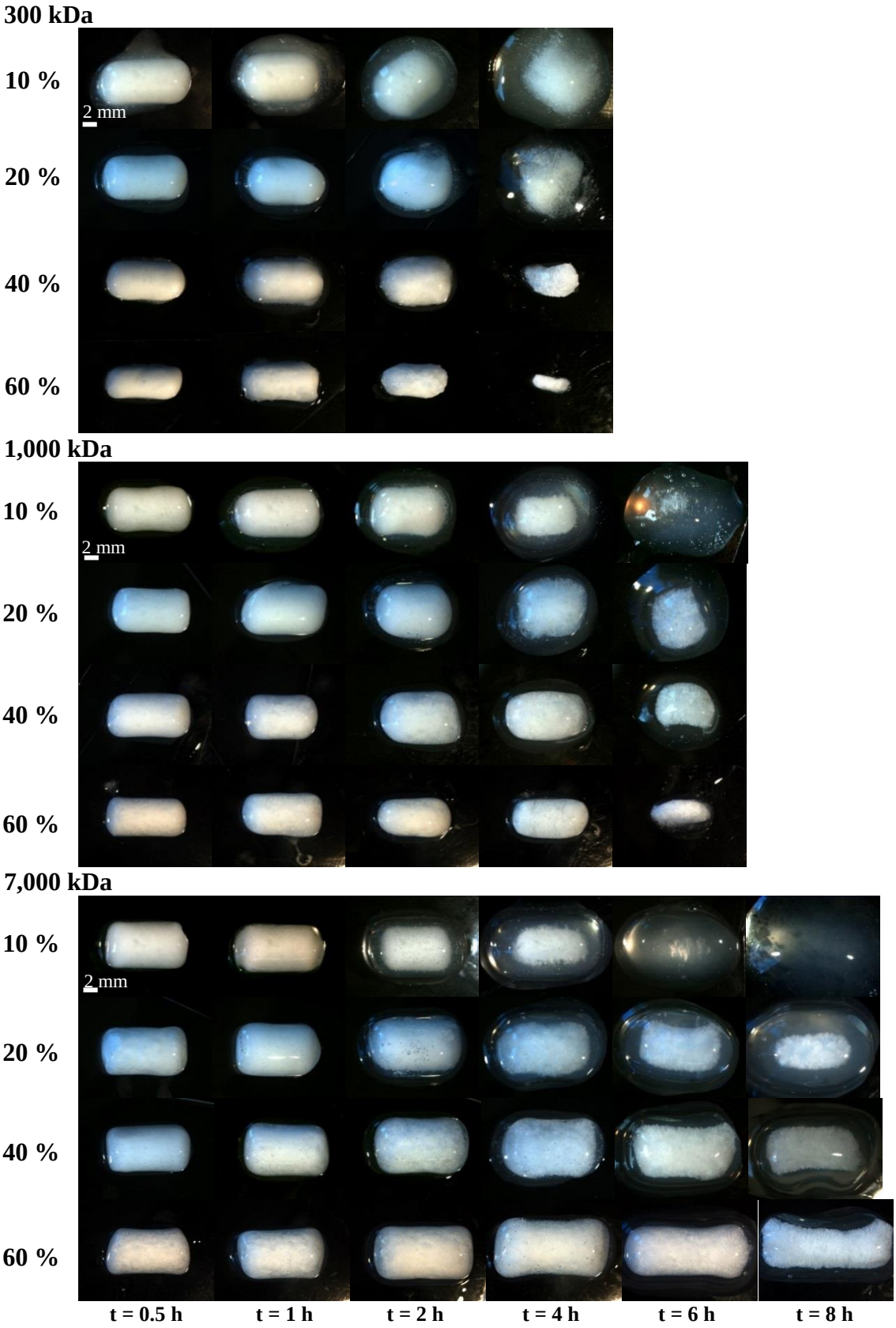


Figure 38: Impact of the drug loading (10 to 60 %) on the swelling behavior of theophylline hot melt extrudates with various PEO molecular weights: macroscopic pictures of samples after different time periods upon exposure to phosphate buffer pH 7.4 at 37 °C.

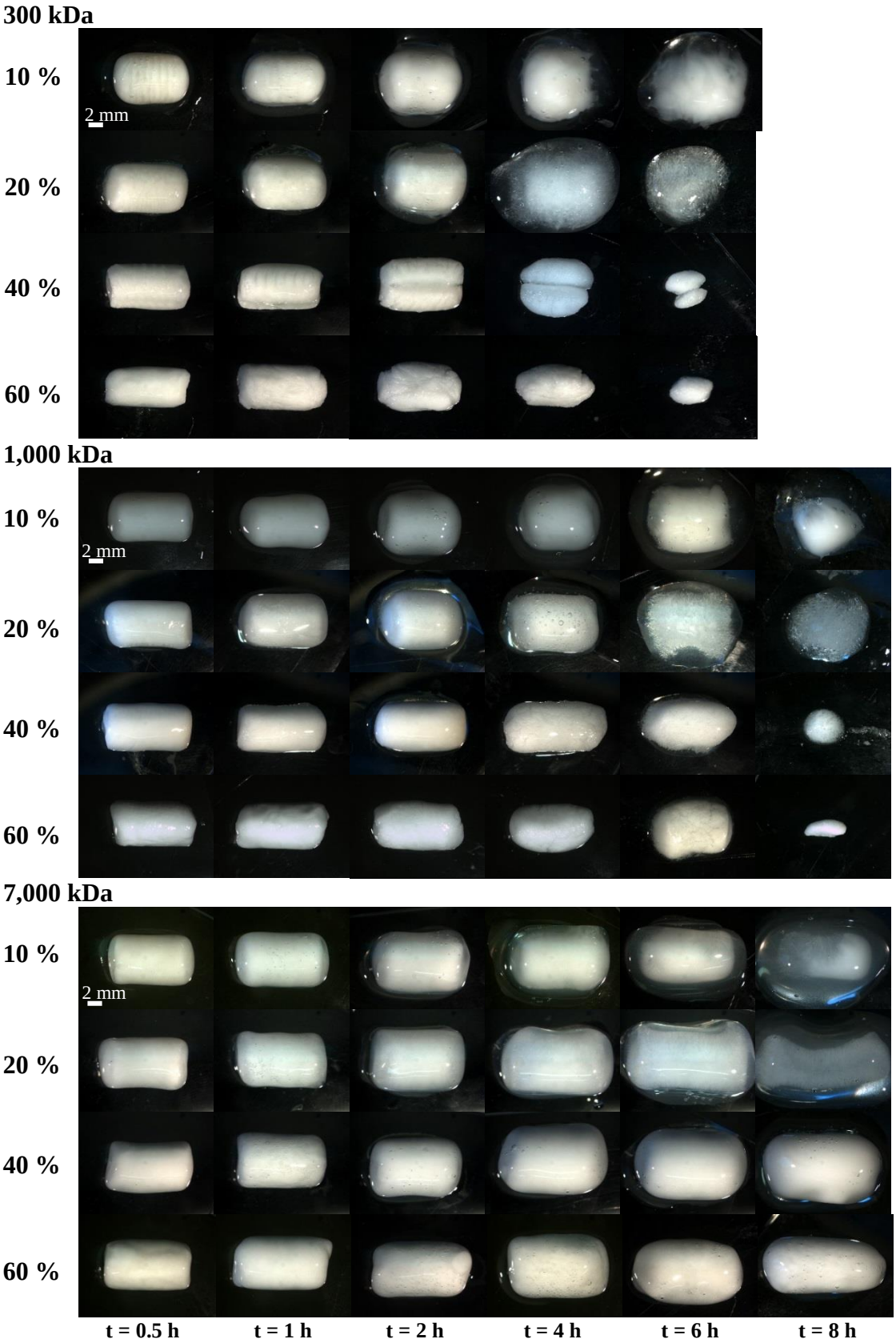


Figure 39: Impact of the drug loading (10 to 60 %) on the swelling behavior of ibuprofen hot melt extrudates with various PEO molecular weights: macroscopic pictures of samples after different time periods upon exposure to phosphate buffer pH 7.4 at 37 °C.

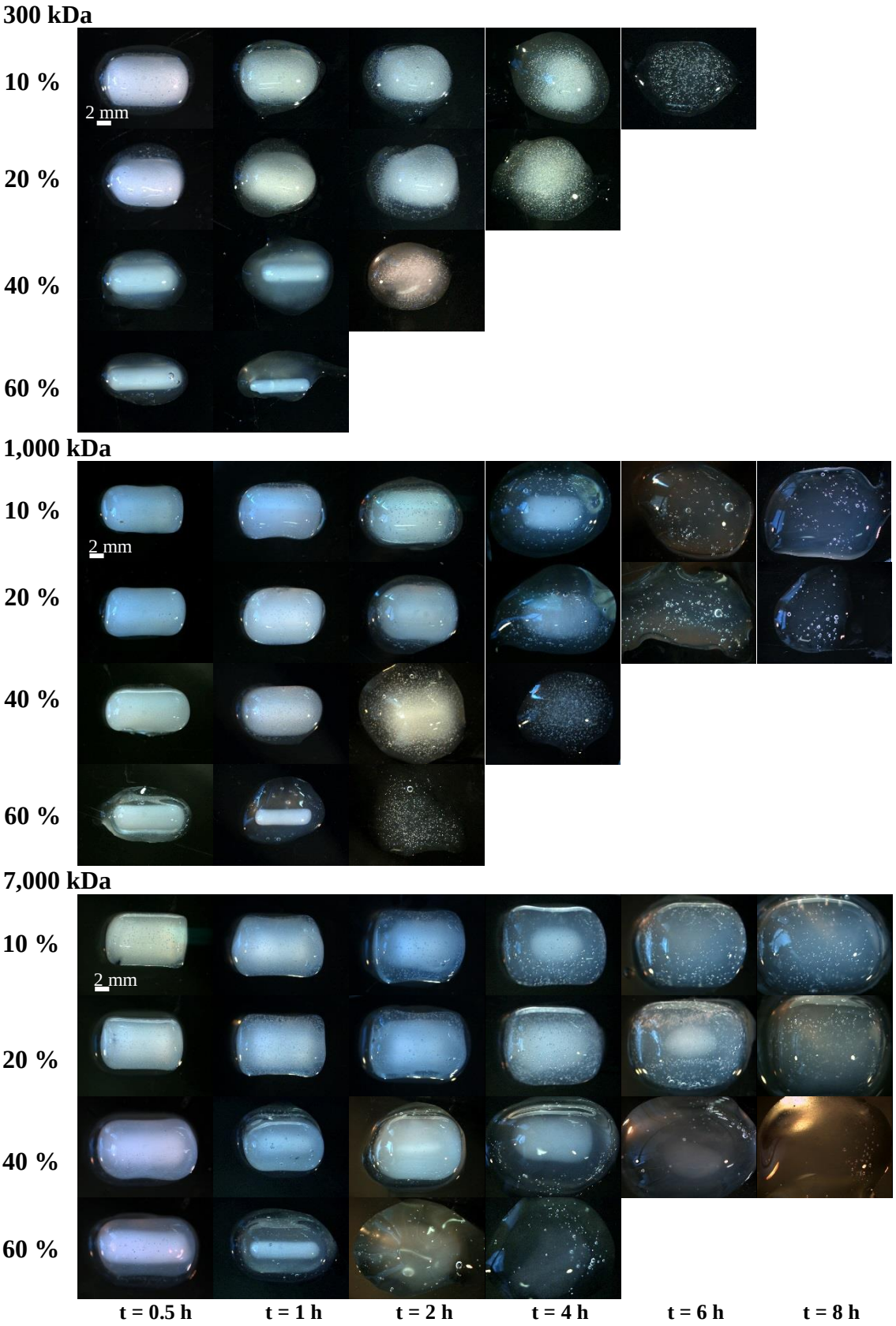


Figure 40: Impact of the drug loading (10 to 60 %) on the swelling behavior of metoprolol hot melt extrudates with various PEO molecular weights: macroscopic pictures of samples after different time periods upon exposure to phosphate buffer pH 7.4 at 37 °C.

Firstly, swelling of the entire hot melt extrudates were analysed. As it can be seen in Figure 41, the water content is almost similar irrespectively of the drug loading as well as the molecular weights.

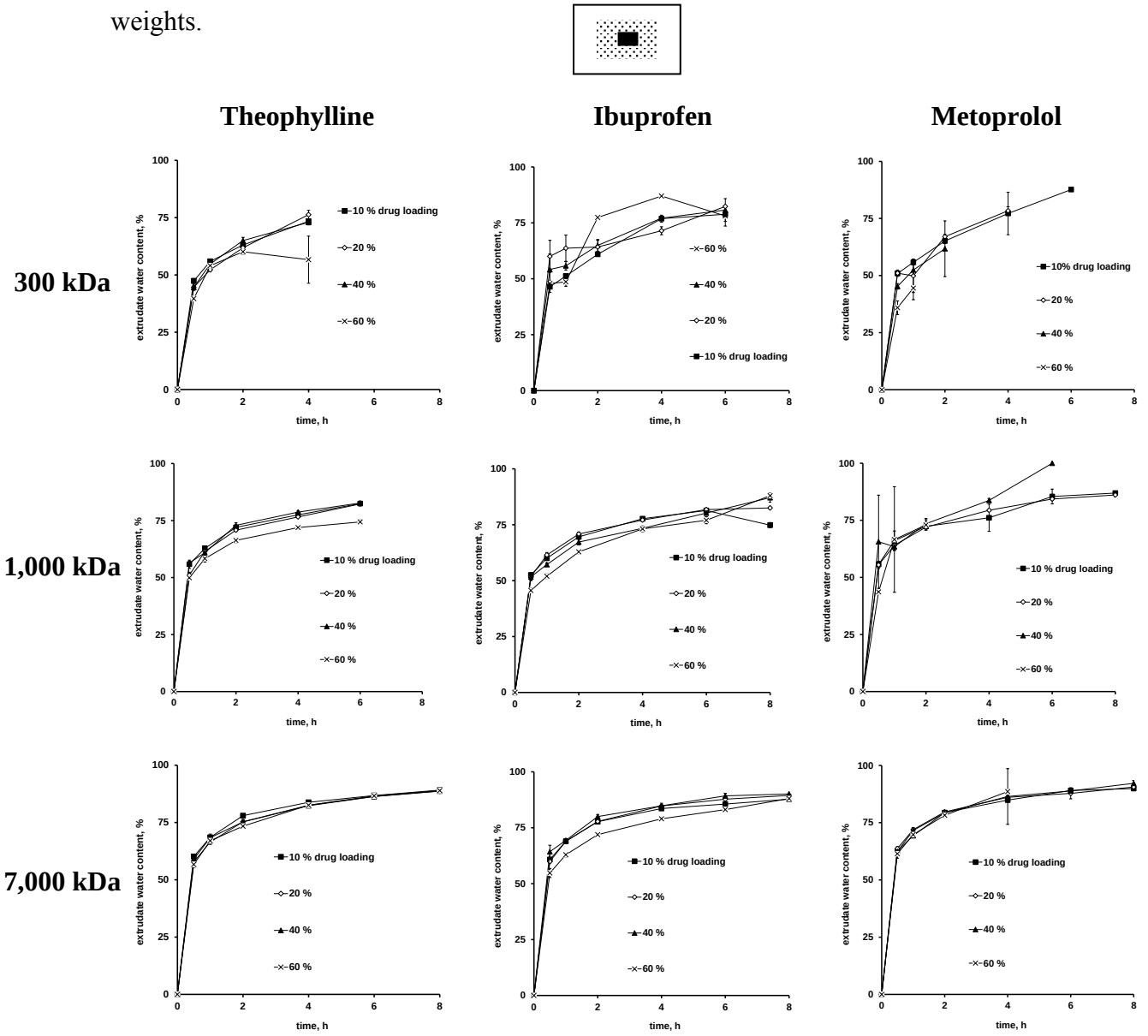


Figure 41: Changes in the water content (%) of the entire extrudates with various PEO molecular weights (indicated on the left) and various drug types (indicated on the top) upon exposure to phosphate buffer pH 7.4. The drug loadings are indicated in the diagrams.

The dry mass (Figure 42) was different depending on the drug loading but the trend was similar for all PEO: the dry mass decreased rapidly with the increase of drug loading. This matches to the metoprolol drug release profiles but not to the one of theophylline and ibuprofen.

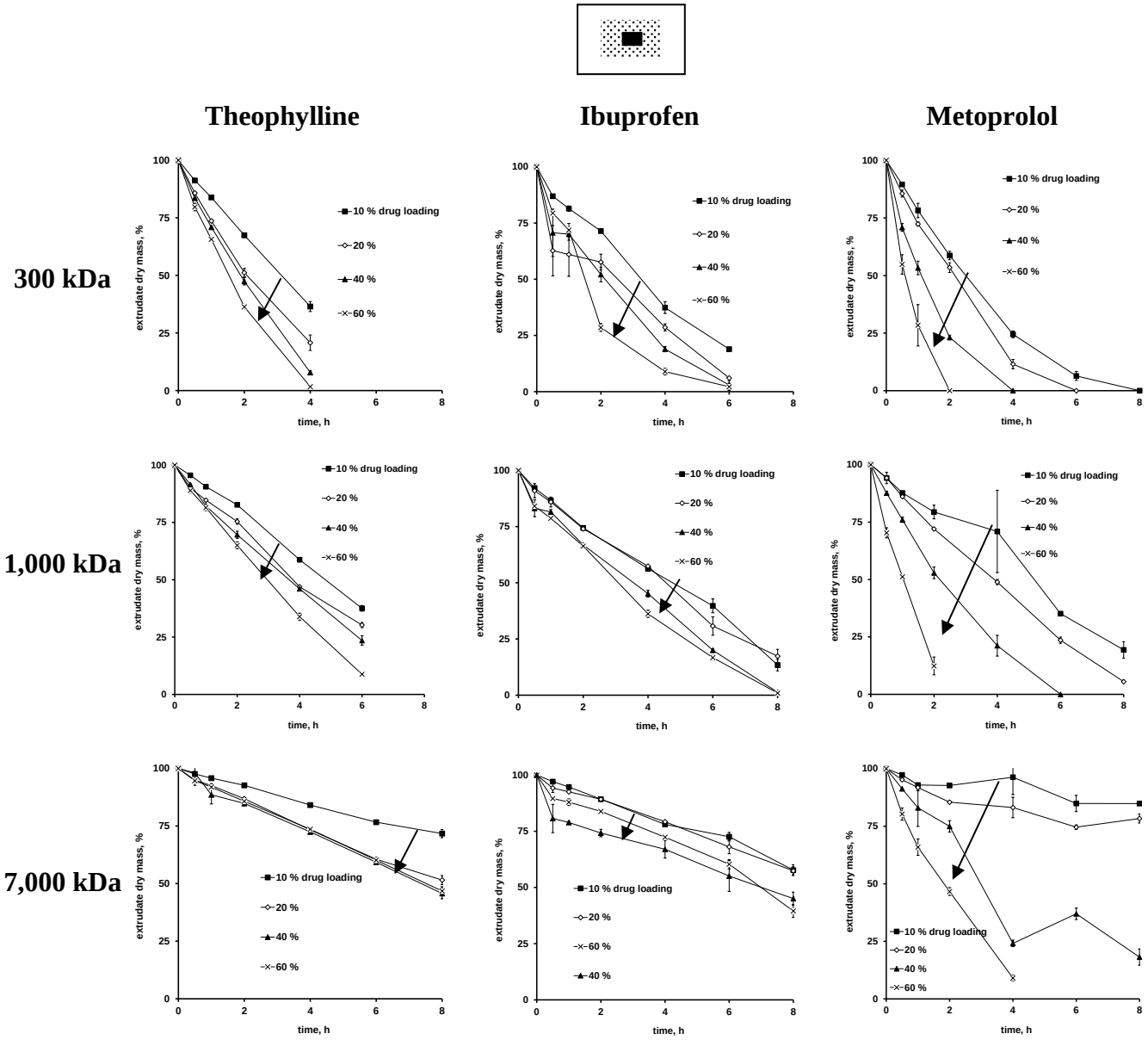


Figure 42: Dry mass (%) of the entire extrudates with various PEO molecular weights (indicated on the left) and various drug types (indicated on the top) upon exposure to phosphate buffer pH 7.4. The drug loadings are indicated in the diagrams.

Finally, the changes in dimensions (Figure 43: change in volume) did not correspond to the theophylline and ibuprofen release profiles but correspond to the metoprolol release profiles. When measuring the "transparent gel" thickness and the corresponding drug content (Figure 44 and Figure 45), it indicates that the "transparent gel" layer in theophylline and ibuprofen

formulations was very thin and did not contain much drug. On the contrary, the gel layer of metoprolol extrudates was more pronounced in term of thickness and drug content. Thus, it was important, at least for the two less soluble drugs theophylline and ibuprofen, to study in depth the non-solubilized part of the extrudate ("solid core + non-transparent gel").

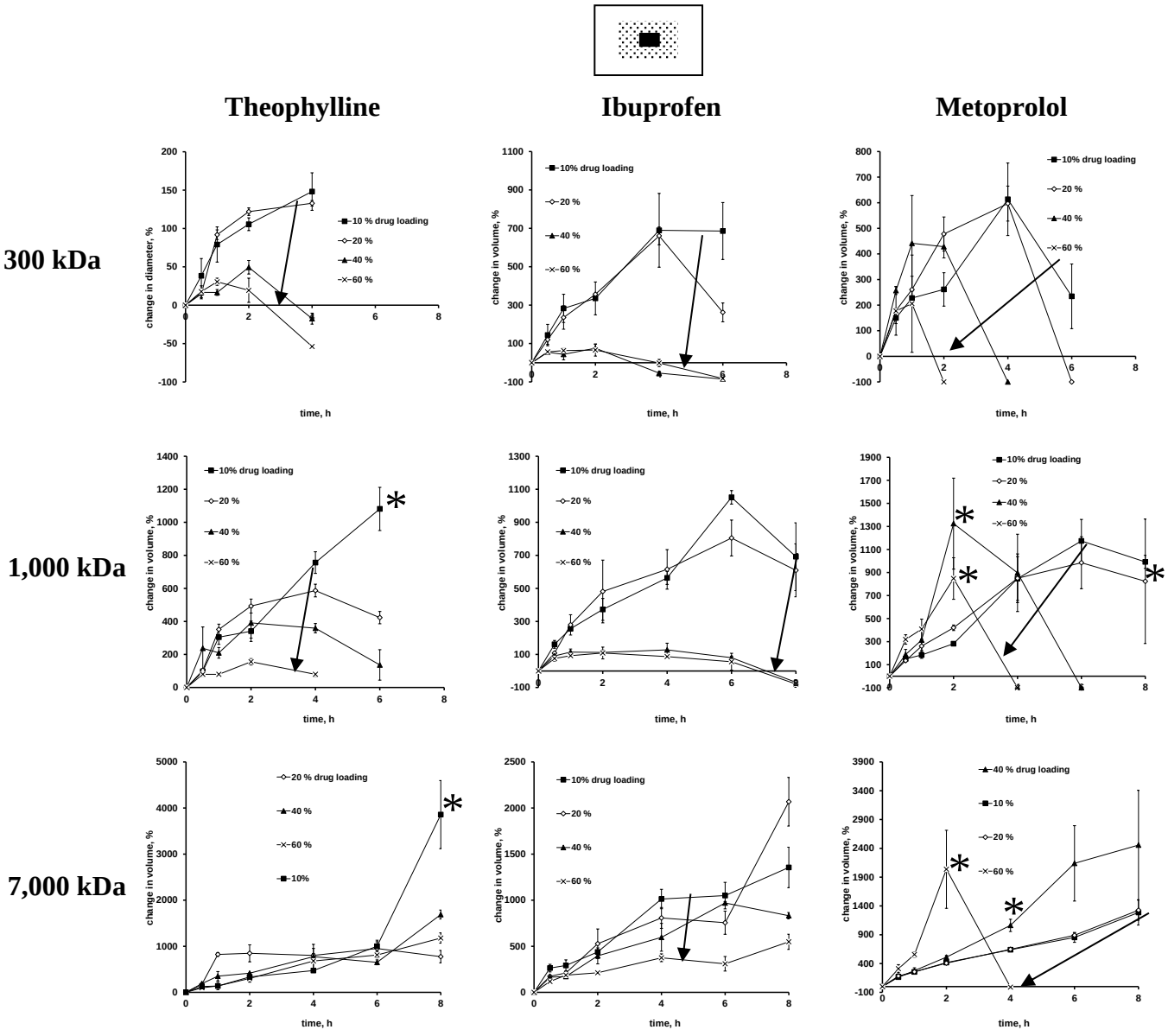


Figure 43: Changes in the volume (%) of the entire extrudates with various PEO molecular weights (indicated on the left) and various drug types (indicated on the top) upon exposure to phosphate buffer pH 7.4. The drug loadings are indicated in the diagrams.

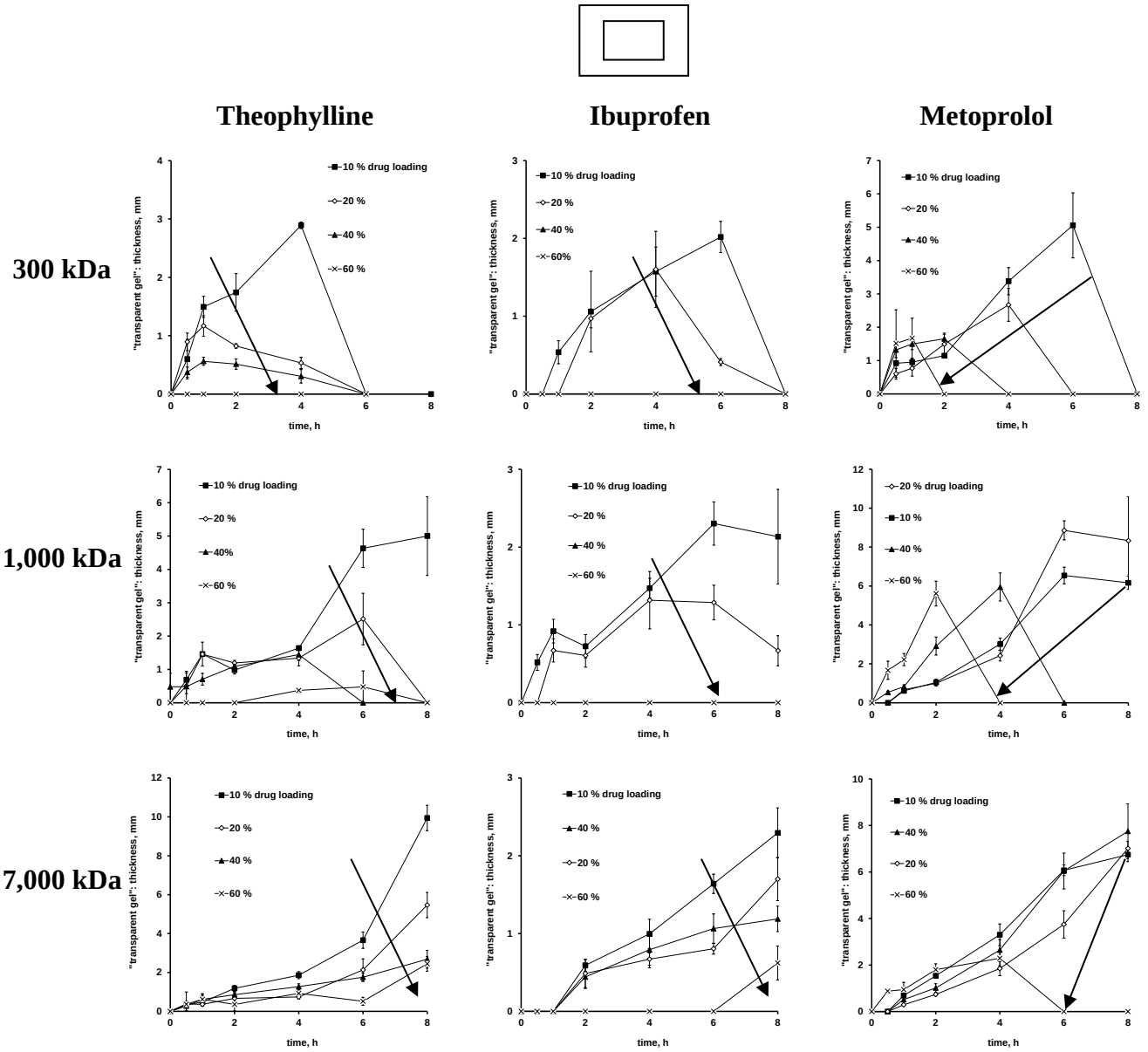


Figure 44: Dynamic changes in the thickness of the "transparent gel" layer of hot melt extrudates upon exposure to phosphate buffer pH 7.4. The PEO polymer molecular weights are indicated on the left, drug types on the top and drug loadings in the diagrams.

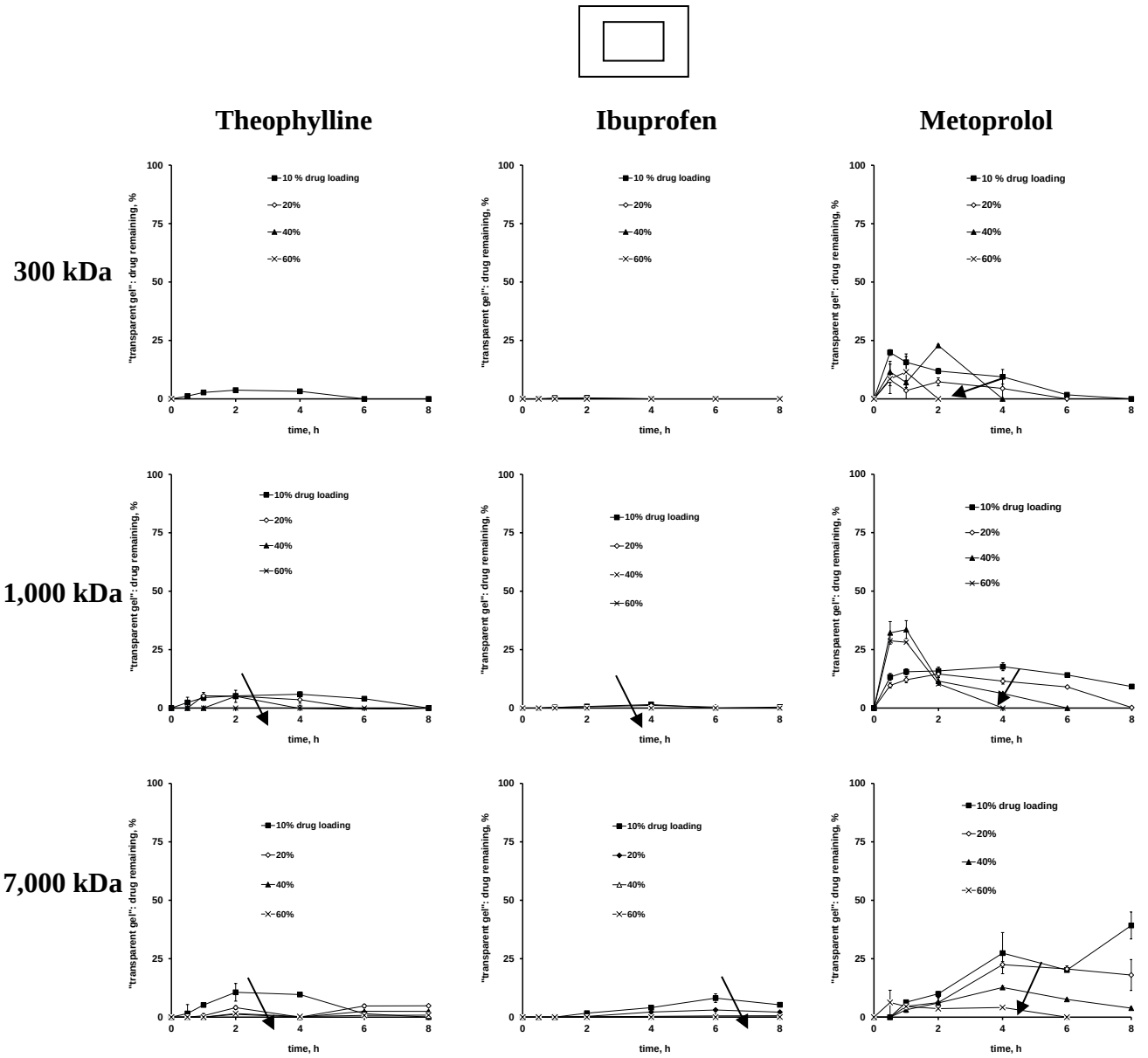


Figure 45: Drug content in the "transparent gel" of hot melt extrudates upon exposure to phosphate buffer pH 7.4. The PEO polymer molecular weights are indicated on the left, drug types on the top and drug loadings in the diagrams.

The water content of the "solid core + non-transparent gel" was the same for all drug loadings of theophylline and ibuprofen formulations (Figure 46). However, the dry mass evolution presented an inversion which corresponds well to the drug release profiles (Figure 47). Interestingly, as shown in the chapter 2, the changes in volume of "solid core + non-transparent gel" also correlate well with the drug release profile (Figure 48).

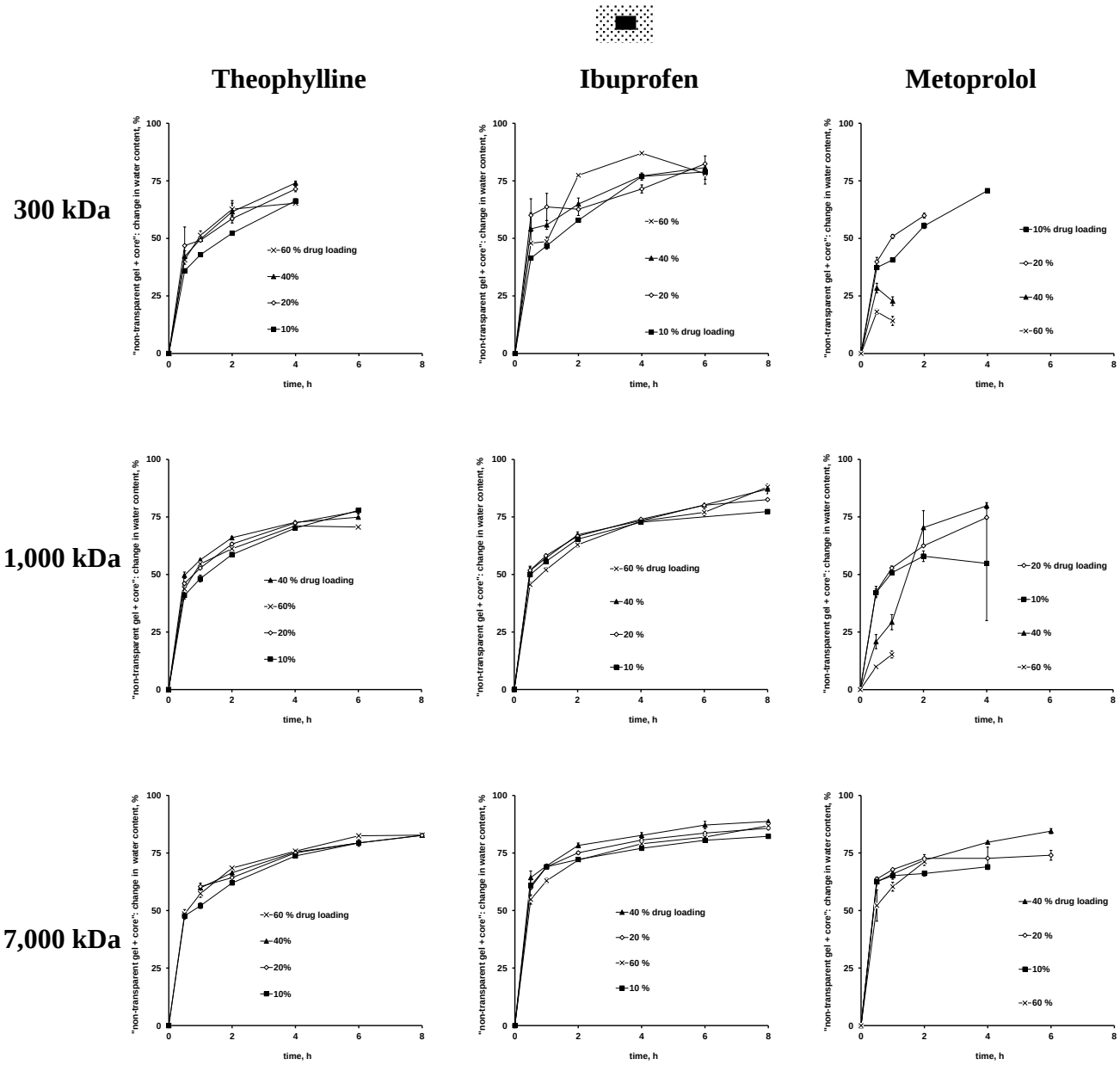


Figure 46: Changes in the water content (%) of "solid core + non-transparent gel" of the extrudates with various PEO molecular weights (indicated on the left) and various drug types (indicated on the top) upon exposure to phosphate buffer pH 7.4. The drug loadings are indicated in the diagrams.

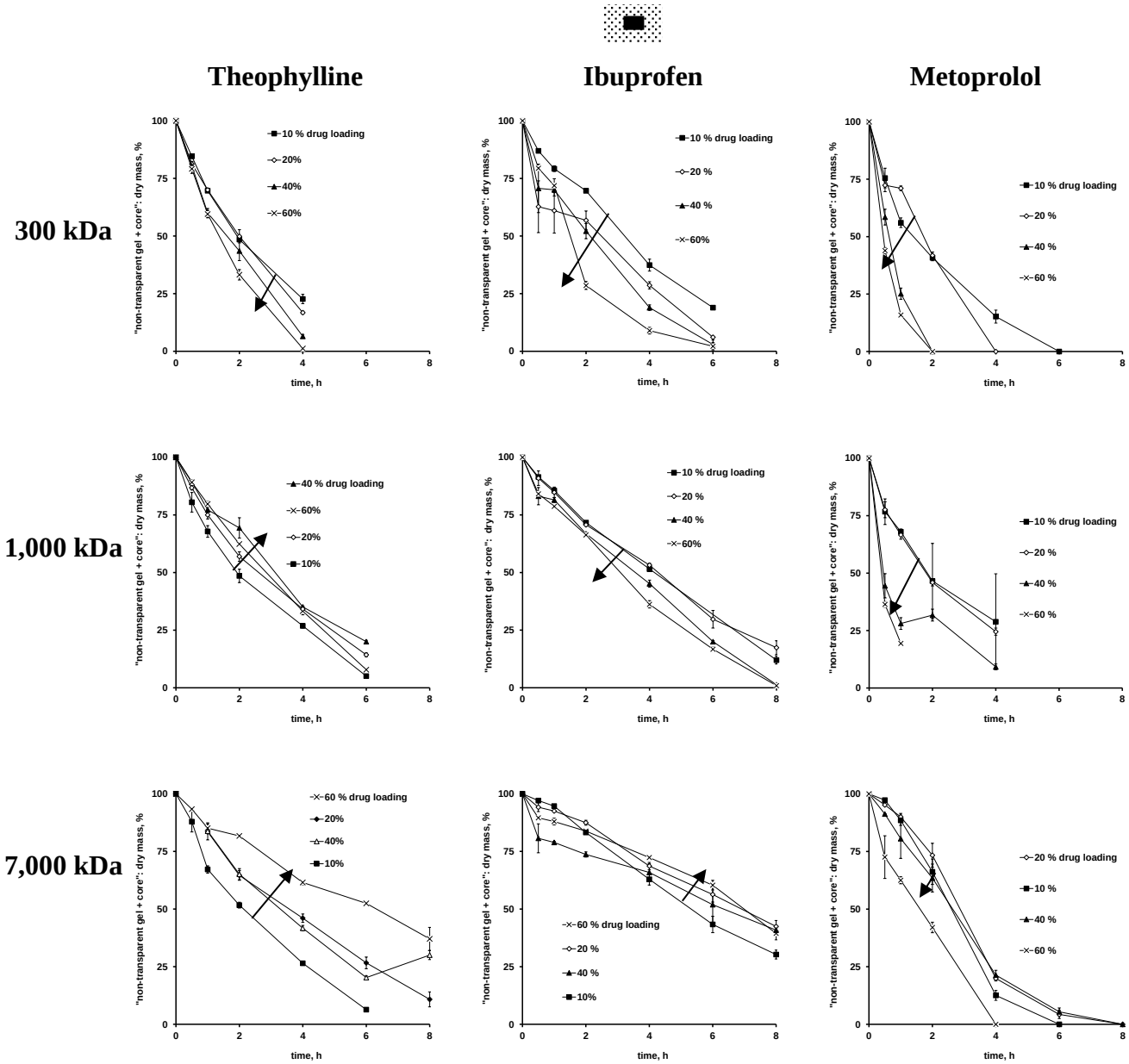


Figure 47: Dry mass (%) of the "solid core + non-transparent gel" of the extrudates with various PEO molecular weights (indicated on the left) and various drug types (indicated on the top) upon exposure to phosphate buffer pH 7.4. The drug loadings are indicated in the diagrams.

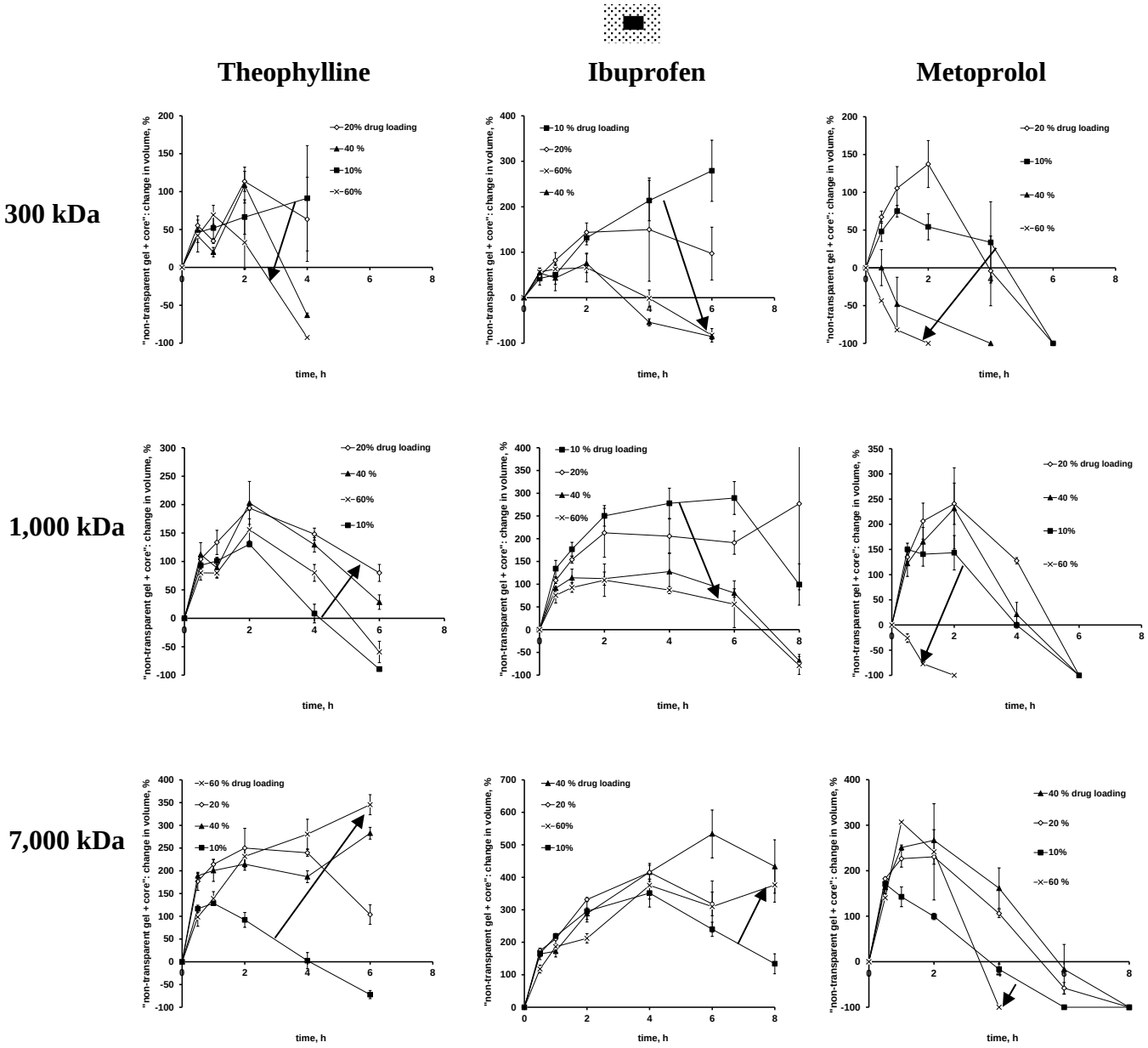


Figure 48: Changes in the volume (%) of the "solid core + non-transparent gel" of the extrudates with various PEO molecular weights (indicated on the left) and various drug types (indicated on the top) upon exposure to phosphate buffer pH 7.4. The drug loadings are indicated in the diagrams.

In this study the impacts of drug loading and drug type showed unexpected results. Fortunately, all formulations were feasible even with high drug loading. On the other hand, the drug release depended on three parameters: the drug nature, the drug loading, and the PEO

molecular weight. Interestingly, a change in the impact of drug loading occurred when varying the PEO molecular weight but especially with theophylline and ibuprofen. Importantly, this change could be correlated to the same parameter than in chapter 2 (change in volume of the "solid core + non-transparent gel"). In addition, the change in dry mass of this particular part correlated well with the drug release profiles. Finally, it is to emphasize that the swelling of the highly soluble drug metoprolol tartrate could be correlated with several parameters: change in volume of entire extrudate and non-solubilized part, "transparent gel" thickness and dry mass of the entire extrudate and non-solubilized part. This can be attributed to the highest impact of the gel layer on the release of highly soluble drugs. Probably, the release of poorly soluble drugs is more driven by the non-solubilized part of the matrix.

CHAPTER 4: HOT MELT EXTRUSION *VERSUS* DIRECT COMPRESSION

HOT MELT EXTRUSION *VERSUS* DIRECT COMPRESSION

For oral dosage forms, direct compression is preferentially the most attempted fabrication method since it is well accepted by the patients and it is a continuous process which requires few preparation steps, i.e. mixing and tableting. Nevertheless, the formulation needs good properties to be suitable for direct compression such as good flowability and good compressibility. Therefore, additives such as lubricant, diluant or glidant are generally required to afford the compression process.

Hot melt extrusion is also a continuous method consisting in mixing and extruding a mixture of drug and carrier. Additives such as plasticizer or stabilizer can also be added but the formulation remains generally simple compared to direct compression. Poly ethylene oxide is a hydrophilic polymer which can be used for controlled drug delivery depending on the molecular weight chosen. This polymer is suitable for both direct compression and hot melt extrusion. Thus, the aim of this study was to compare PEO-direct compressed tablets to PEO-hot melt extrudates with respect to the physicochemical characterization.

1. *In vitro* drug release from hot melt extrudates *vs* direct compressed tablets

Hot melt extrudates and direct compressed tablets were prepared with the same composition: 10 % theophylline monohydrate and 90 % PEO 200 or 7,000 kDa. Since no other additives were added to the formulation, the tablets were prepared manually (bad flowability and weak compressibility). In addition, both dosage forms are obtained with similar surface and drug loading (Table 5) to provide nearly the same *in vitro* drug release conditions. As it can been see in Figure 49, after 1.5 hours, drug release from hot melt extrudates is faster than from direct compressed tablets irrespective of PEO molecular weights. This was not expected as hot melt extrusion is a process well known to form denser matrices due to well mixed and molten

drug-carrier mixture [47,183,196,203]. Therefore, we tried to understand this unexpected tendency by physical characterization.

Table 5: Surface (mm²) and drug loading (mg) of dosage forms made by hot melt extrusion "HME" or direct compression "DC".

	PEO 200 kDa		PEO 7,000 kDa	
	DC	**HME**	**DC**	**HME**
Surface, mm²	99.8 ± 0.3	102.7 ± 4.2	97.6 ± 1.0	97.9 ± 4.6
Drug loading, mg	8.44 ± 0.62	9.05 ± 0.58	6.77 ± 1.68	8.97 ± 0.89

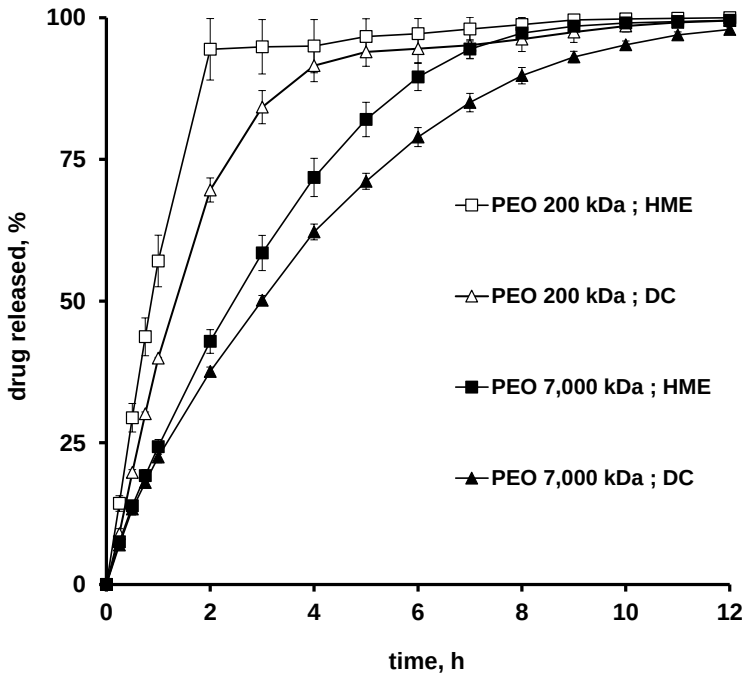


Figure 49: Impact of the process (hot melt extrusion "HME" versus direct compression "DC") on theophylline release from dosage forms with two PEO molecular weights (indicated in the diagram) in phosphate buffer pH 7.4.

2. Physical characterization

Firstly, the porosity was calculated with a gas-pycnometer. Results indicated that the

porosity of the tablets was higher than the porosity of the hot melt extrudates (Table 6). Therefore, the drug release cannot be attributed to the effect of the porosity. Several studies from the literature showed that dry porosity of hydrophilic matrices cannot be responsible for change in drug release kinetics [204–206]. However, the wet porosity created during dissolution by the water penetration is the main trigger of the drug release. To confirm this theory, tablets with different compression forces (different dry porosities) were prepared. As it can be seen in Figure 50, it is evident that the porosity does not influence the drug release which confirms data in the literature [135].

Table 6: Porosity (%) of dosage forms made by hot melt extrusion "HME" or direct compression "DC".

	PEO 200 kDa		**PEO 7,000 kDa**	
	DC	**HME**	**DC**	**HME**
Porosity, %	19.5 ± 1.5	6.4 ± 0.8	14.9 ± 2.6	5.4 ± 0.6

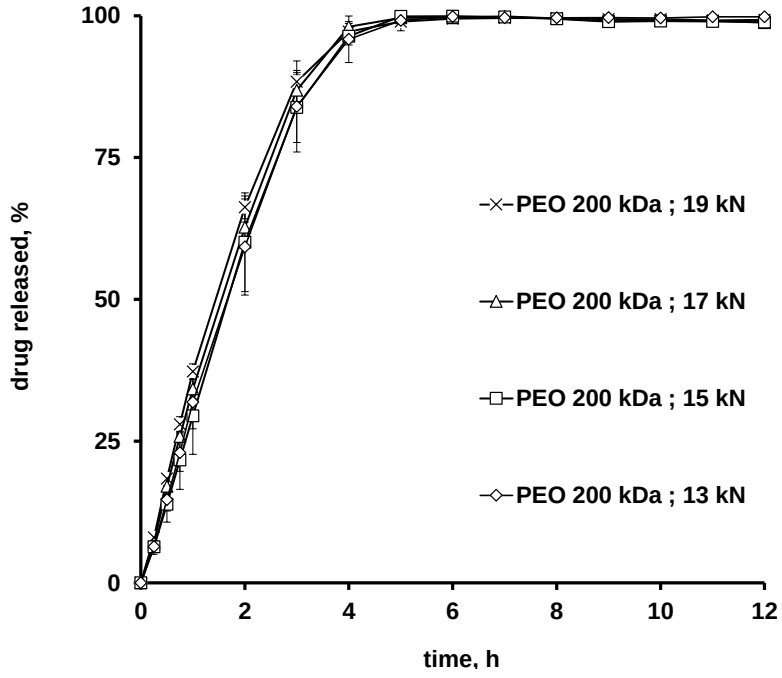


Figure 50: Impact of compression force (indicated in the diagram) on theophylline release from direct compressed tablets made with PEO 200 kDa in phosphate buffer pH 7.4.

Since the dry porosity could not be the right explanation for the drug release, deeper physical characterizations such as Raman spectroscopy and DSC were performed. However, for better drug detection (chapter 3: no drug detection by DSC with less than 40 % loading), dosage forms containing 60 % of drug were prepared by hot melt extrusion and direct compression. No particular problem occurred during hot melt extrusion (see chapter 3), however, the direct compressed tablets were difficult to be produced even with the manually filling of the single punch press machine.

The direct classical least-squares (DCLS) method found the linear combination of spectra from the pure components (Figure 51). It can be concluded that theophylline monohydrate was transformed into the anhydrous form during the extrusion due to the heating process of the hot melt extrusion. In direct compressed tablets, the drug keeps its polymorphic form which was a mix of monohydrate and anhydrous form (due probably to a partial conversion of the drug in bulk during storage). Thus, drug release from hot melt extrudate could probably be faster due to the difference in solubility between anhydrous and monohydrate forms. Indeed, the solubility of anhydrous theophylline is greater than the solubility of monohydrate theophylline. Consequently, the drug dissolution release of anhydrous form can be faster than monohydrate form. Nevertheless, it has been reported that a conversion of anhydrous crystals into hydrate occurred during the first steps of the dissolution test upon contact with water [207]. After few minutes, the dissolution rate between anhydrous and monohydrate became equal [208]. Then, the difference in solubility between anhydrous and monohydrate theophylline form cannot be really responsible for the differences in the drug release from PEO hot melt extrudates and tablets.

Nevertheless, the change in drug physical state could induce differences in mixing, affinity or interactions with the PEO polymers. For instance a better affinity of PEO to the drug monohydrate form would lead to a better interaction and drug release controlling than the

anhydrous form. Probably, the anhydrous forms are isolated from the polymer and does not interact with PEO polymeric network, which enables the faster drug release.

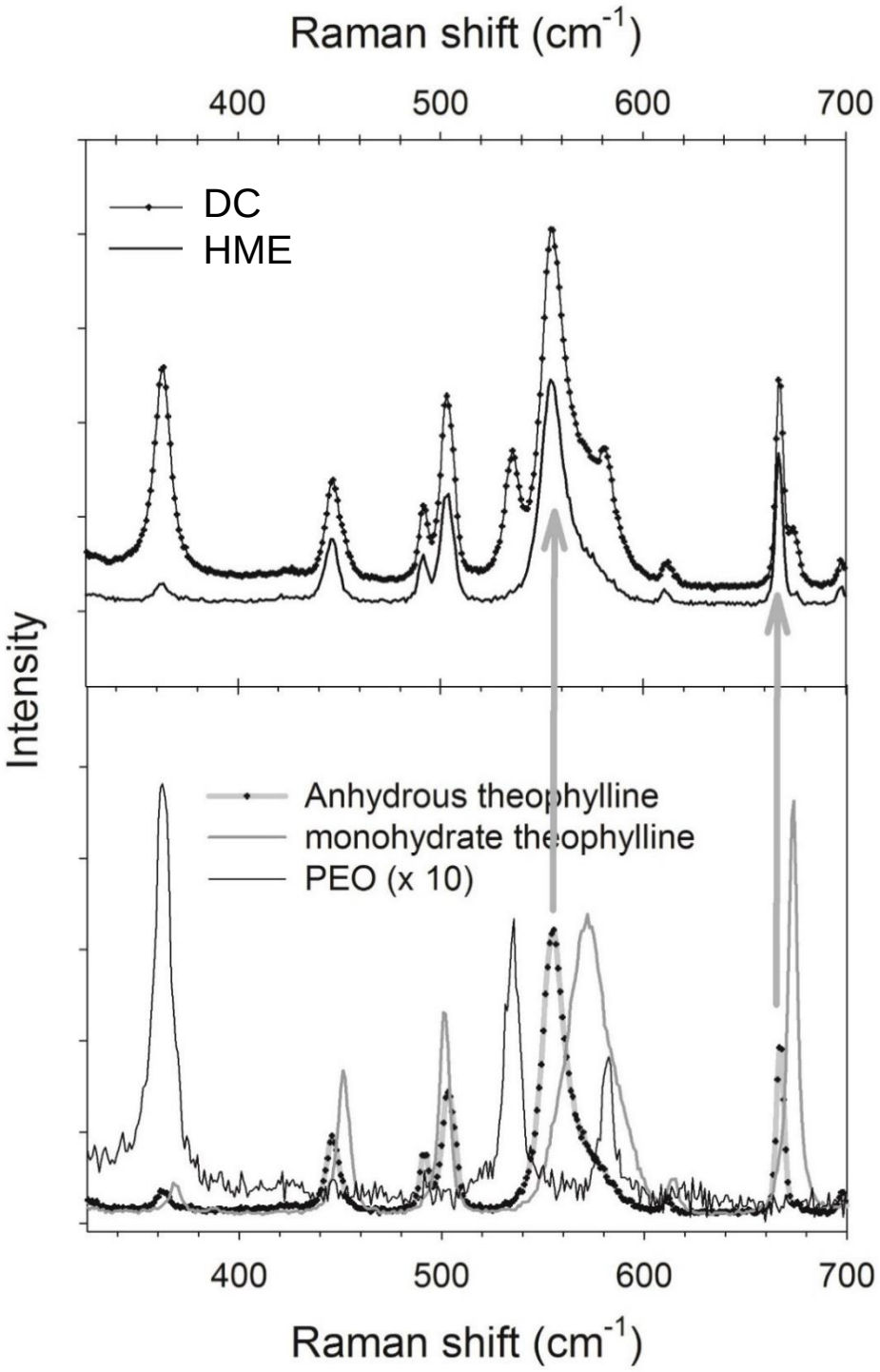


Figure 51: Raman spectra of both PEO direct compressed tablets ("DC", dotted curve) and PEO hot melt extrudates ("HME", solid curve). For comparison, also spectra of pure components (PEO 7,000 kDa, black solid line; anhydrous theophylline, grey dotted line; and monohydrate theophylline, grey solid line) were represented (at the bottom).

Images of the dosage forms surface obtained with Scanning Electron Microscopy (SEM) in Figure 52 confirmed the higher porosity of direct compressed tablets than the extrudate. More importantly, the images revealed the localization of big drug crystals at the surface of hot melt extrudates. Contrary to hot melt extrudates, direct compressed tablets surface remained generally clear.

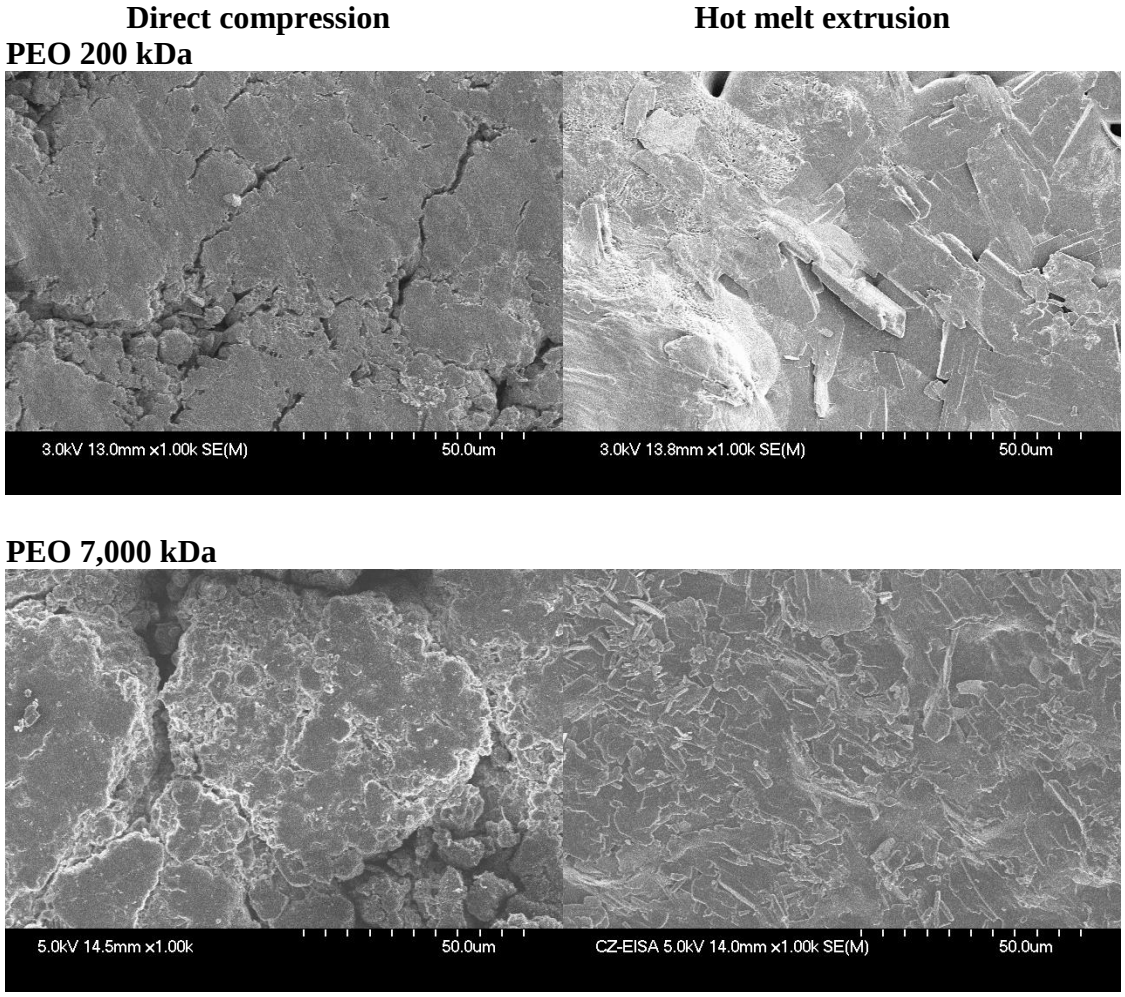


Figure 52: Impact of the process (hot melt extrusion versus direct compression) on surface appearance of dosage forms composed of 10 % drug and PEO with different molecular weights (indicated on the top of each image).

The difference in drug distribution between tablets and hot melt extrudates could in this case explain the different drug release behaviors. Finally, DSC analysis were also performed. Hot melt extrusion, especially for improvement of drug efficacy and bioavailability, can show this

behavior compared to direct compression because (i) the drug becomes amorphous during the hot melt extrusion process and (ii) hot melt extrusion facilitates drug and polymer interactions, thus increasing drug dissolution [17,19,20]. In the case of theophylline, despite the fact that the extrusion temperature was set well below the drug melting point (273 °C), the enthalpy measurement of both PEO and drug melting peaks reveals a loss in crystallinity compared to tablets (Figure 53). In fact, similar results have been found with HPC-based hot melt extrudates and were also attributed to a partial loss of drug crystallinity [54].

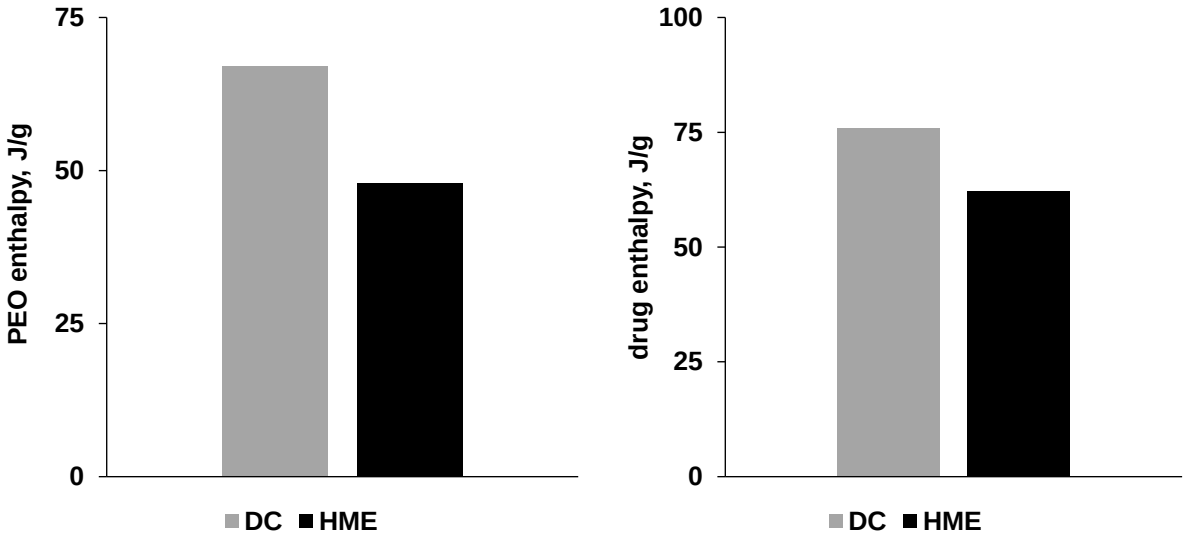


Figure 53: Enthalpy of the melting point of PEO (left) or the drug (right) in direct compressed tablets "DC" in grey or hot melt extrudates "HME" in black (PEO 7,000 kDa, 60 % theophylline).

3. The impact of *in vitro* release conditions

Several studies have demonstrated the impact of *in vitro* dissolution conditions on the drug release from PEO direct compressed tablets. The main conclusions were that the agitation speed, position of the matrix and USP method (paddle or basket) have an impact on drug release from PEO tablets [209,210]. The impact of the release medium of PEO-based tablets or PEO-based hot melt extrudates with various drugs has also been studied and no impact on drug release was found in all cases [133,153]. Therefore, deeper studies were carried out about the

effect of *in vitro* conditions on drug release kinetics of PEO direct compressed tablets and PEO hot melt extrudates.

As it can be seen in Figure 54, the drug release is impacted by the USP method apparatus for both PEO hot melt extrudates and direct compressed tablets. Nevertheless, hot melt extrudates containing, especially, high PEO molecular weight show more robustness than direct compressed tablets to the different dissolution methods.

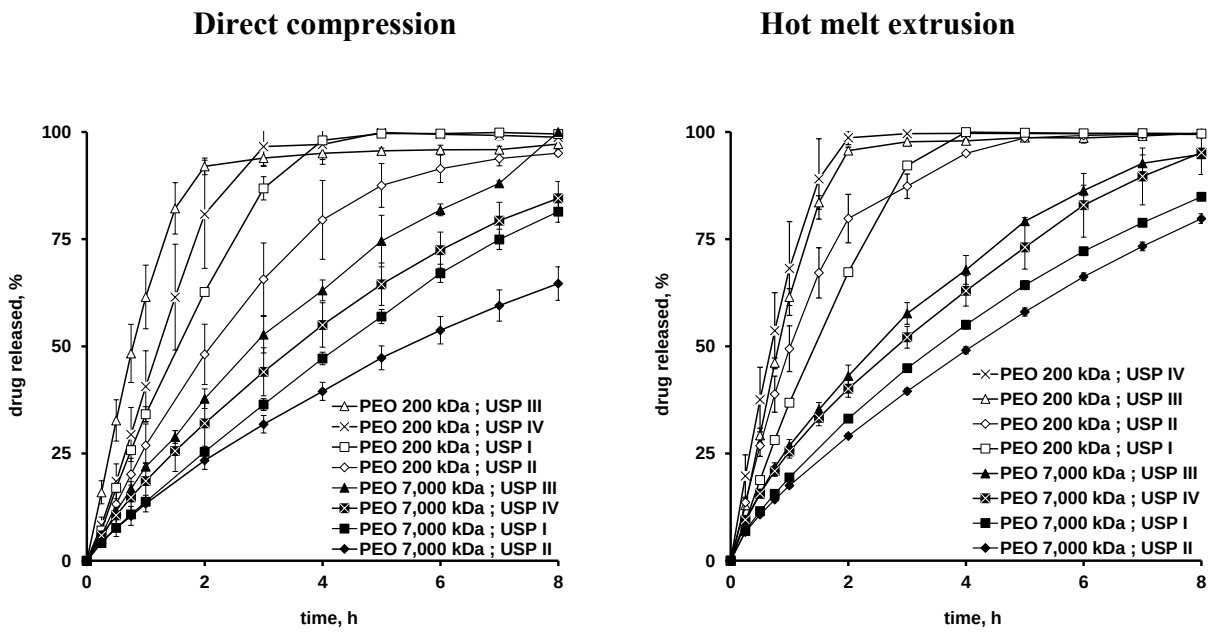


Figure 54: Impact of release conditions (indicated in the diagrams) on theophylline release from direct compressed tablets (left) or hot melt extrudates (right) made with PEO 200 kDa or 7,000 kDa in phosphate buffer pH 7.4.

Considering the dipping or agitation speed (Figure 55), direct compressed tablets and hot melt extrudates seem to be not impacted in case of high PEO molecular weight. Nevertheless, the effect of the *in vitro* conditions is more pronounced with low PEO molecular weights.

Finally, no change was observed between theophylline release from PEO hot melt extrudates by the change of the release medium from 0.1 N HCl to phosphate buffer pH 7.4 (Figure 56). This could be due to the pH-independent solubility of theophylline. However, the pH-dependent

ibuprofen (very low solubility in 0.1 N HCl and high solubility in phosphate buffer pH 7.4) showed a clear difference when changing the release medium (data not shown).

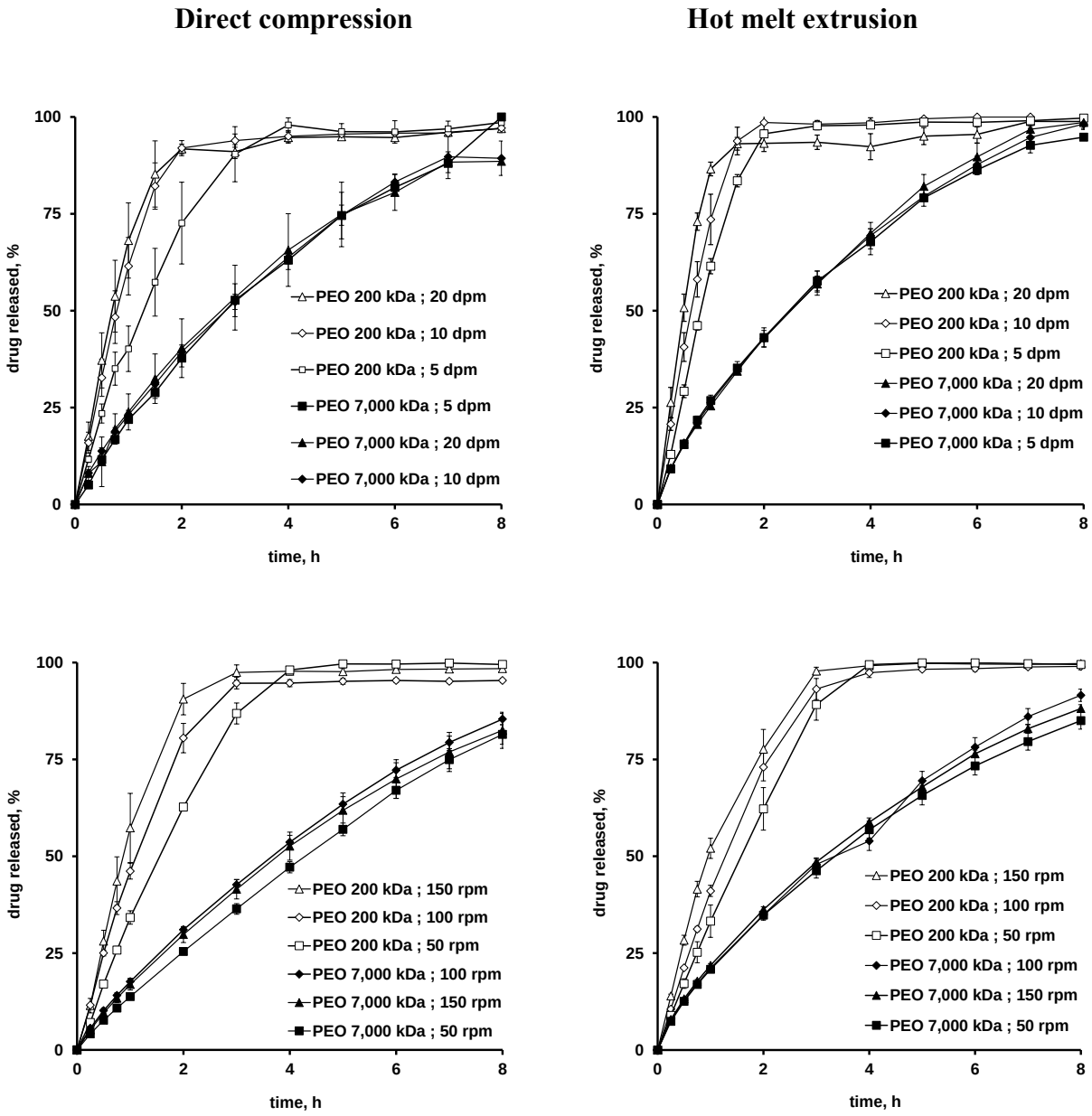


Figure 55: Impact of dipping or rotation speeds (indicated in the diagrams) on theophylline release from direct compressed tablets (left) or hot melt extrudates (right) made with PEO 200 kDa or 7,000 kDa in phosphate buffer pH 7.4 (USP III / I).

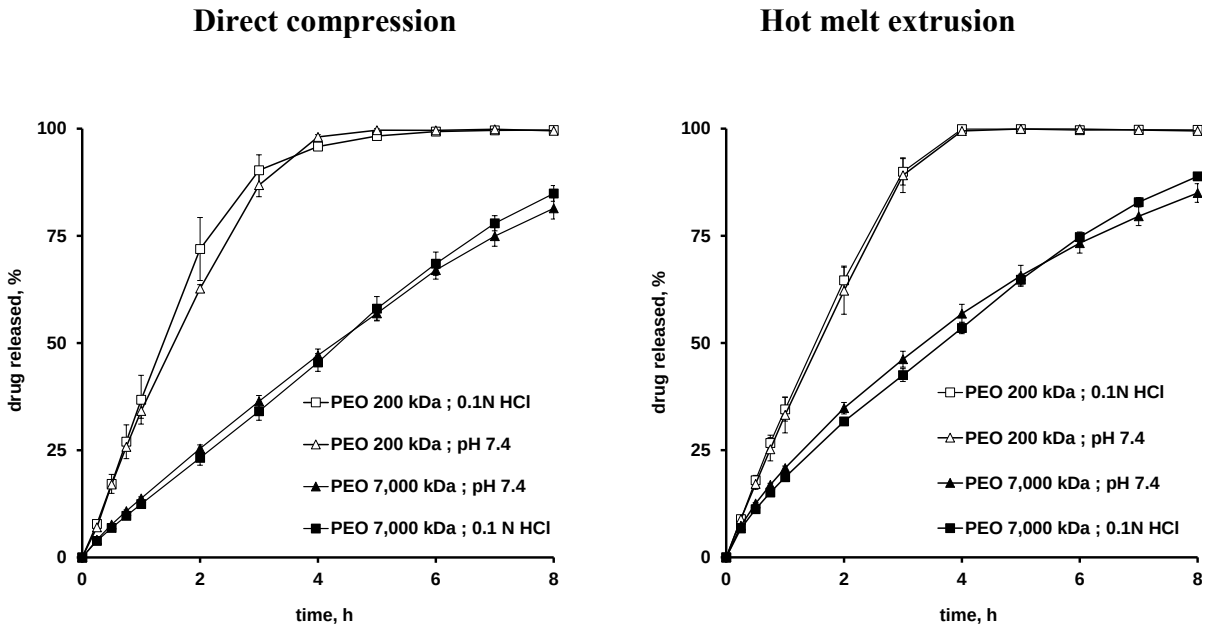


Figure 56: Impact of medium type (indicated in the diagrams) on theophylline release from direct compressed tablets (left) or hot melt extrudates (right) made with PEO 200 kDa or 7,000 kDa (USP I, 50 rpm).

It has to be pointed out that the choice of the dissolution method can be of utmost importance when varying the dissolution-setups. Nevertheless, this study has shown that drug release from hot melt extrudates with high molecular weights PEO is generally robust upon different dissolution conditions, even with harsh conditions. However, drug properties should be also taken into account since the drug behavior and especially the drug solubility is likely to play a major role in the release profile of the pharmaceutical dosage forms.

Surprisingly, direct compressed tablets have shown slower drug release compared to hot melt extrudates, which can be dependent on the drug. Moreover, tablets with similar formulation than hot melt extrudates could not be manufactured automatically since the mixture possessed bad flowability and compressibility.

IV. CONCLUSIONS AND PERSPECTIVES

CONCLUSIONS AND PERSPECTIVES

A large spectre of hot melt extrudates based on PEO molecular weights containing various drugs at different drug loadings have been identified in this thesis. It has to be pointed out that formulation and process parameters directly impact the drug release *in vitro*. Therefore, investigations are required to better understand the impact of each element on the drug release kinetics.

In particular, the impact of extrusion temperature and screw speed were studied on the processability and *in vitro* drug release. Interestingly, hot melt extrudates presented more surface defects (shark skinning/melt fracture) when processed at high temperature (135 °C) which did not lead to a drastic decrease in pressure during the extrusion. In addition, the release of low molecular weights was affected by the extrusion temperature 135 °C compared to 100 °C, leading to a faster drug release. This is probably due to changes in the matrix composition (changing in the polymer physical state) which are probably reversible since the drug release profile changed after storage. Nevertheless, the hot melt extrudates processed at lower temperature (100 °C) were stable after 1 year at 25 °C and 60 % relative humidity. Finally, the change in screw speed (30, 60, 90 rpm) did not impact the drug release.

However, the drug release kinetics are affected by the change in PEO molecular weights: drug release decreased with increasing molecular weights but only to a certain level. In fact, if PEO molecular weights were from 600 kDa to 7,000 kDa, slightly alteration of the drug release could be observed. The monitoring of the swelling behaviors was complicated since various physicochemical reactions (polymer swelling and erosion, drug dissolution and diffusion) occurred also depending on PEO molecular weights. Thus, three parts of the dosage form could be distinguished during the dissolution test: a “solid core” and a “non-transparent gel” where the drug is mainly non-solubilized, surrounded by a “transparent gel” where the drug is solubilized. No correlation could be found between the change in dimensions, water content or

dry mass of the entire extrudates or even of the "solid core". Importantly, the change in volume of the "solid core + non-transparent gel" correlates well with the drug release. The difference was more pronounced between PEO 100 and 1,000 kDa, whereas a slightly difference between PEO 1,000 and 7,000 kDa was observed.

Furthermore, a great care should be taken when changing the drug– nature and –loading. For instance, the drug release from metoprolol tartrate hot melt extrudates increased with increasing drug loading due to its high solubility. However, for theophylline and ibuprofen, an inversion of trend was observed. For low molecular weight PEO, the drug release increased with the increase of the drug loading but for high molecular weight, the opposite trend was observed. The swelling of the entire extrudates and the "solid core + non-transparent gel" part have been investigated. For metoprolol tartrate, practically all swelling parameters correspond well to the drug release: the change in volume and dry mass of the entire extrudates, "solid core + non-transparent gel" and also the gel thickness. For theophylline and ibuprofen, only the changes in volume and dry mass of the "solid core + non-transparent gel" could be correlated to the drug release profiles. This can confirm that the "solid core + non-transparent gel" is the main part that controls the theophylline and ibuprofen releases from PEO hot-melt extrudates.

Finally, direct compressed tablets were manufactured with the same formulation and surface as hot melt extrudates. The compression was not processed flawless compared to the extrusion and tablets were coercively produced manually. Surprisingly, the release showed slower kinetics from the tablets compared to the extrudates. It has to be pointed out that Raman spectroscopical analysis of the extrudates importantly revealed completely physical transformation of theophylline monohydrate into the theophylline anhydrous form, whereas in compressed tablets the drug remains as a mixture of monohydrate and anhydrous forms. Based on these results, the PEO affinity to the drug as well as the drug repartition within the matrix might probably change. Importantly, drug crystals were observed by SEM at the surface of hot melt extrudates but not of the tablets. In addition, DSC analysis showed a decrease in drug

crystallinity into hot melt extrudates. The above mentioned phenomena could probably explain the fastest drug release from hot-melt-extrudates. In addition, tablets and extrudates were also evaluated in term of their robustness against *in vitro* conditions (method, speed and medium). Both dosage forms were robust except when changing the dissolution method where the highest impact could be seen. In all cases, the formulation with high PEO molecular weight showed better robustness compared to the one with low PEO molecular weight.

To conclude, this thesis has shown a potential of Poly ethylene oxide as a carrier for sustained drug delivery using hot melt extrusion technique. Moreover, it could be also interesting to mix several PEO molecular weights in order to adjust the desirable drug release kinetics. In addition, mathematical modelling for the drug release predictions could be attempted. Deeper studies using bio relevant media as well as the proof of concept *in vivo* should be done in order to avoid the potential *in vitro in vivo* discapancy.

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TABLE OF FIGURES

RESUME IN DETAIL (FRENCH)

1. INTRODUCTION

1.1. Généralités

Le développement d'un médicament est une étape importante qui nécessite temps, efforts et coût. Aussi, le principal objectif de l'industrie pharmaceutique est d'augmenter la productivité, réduire les coûts et améliorer la production. A l'heure actuelle, de nouveaux outils ont été élaborés afin de remplir ces objectifs, par exemple le passage de la production traditionnelle en lot à la production en continu, l'implémentation de technique d'analyses au sein du procédé appelée « technologie analytique des procédés » (PAT « Process Analytical Technology ») et de méthode de travail permettant de définir les critères importants pour la qualité finale du produit, les paramètres critiques et les étapes clés de la fabrication. D'après la Food and Drug Administration [1], la fabrication en continu est un procédé où le produit est simultanément introduit et récupéré. Les avantages de ce type de fabrication sont le peu d'étapes requises, les temps de fabrication raccourcis, la meilleure efficacité et sécurité, la meilleure flexibilité, l'amélioration de la qualité du produit avec la possibilité de contrôles en ligne et la potentielle diminution des coûts. Ainsi, il s'agit d'un procédé intense qui maximise la production du produit dans de plus petits espaces [2]. De nombreux procédés sont adaptés à la fabrication en continu, par exemple la compression, l'encapsulation, l'extrusion, la granulation sèche, le broyage [4]. Cependant, il est important de mieux comprendre le procédé en question afin d'identifier les étapes critiques et les paramètres qui vont impacter la qualité du produit. Une fois ces paramètres identifiés, il est possible de les contrôler avec les techniques d'analyses « PAT » comme la spectroscopie (Raman, infra rouge, fluorescence, UV visible ou la résonnance magnétique nucléaire) et la microscopie (à lumière polarisée, à plaque chauffante, microscopie électronique à balayage) qui vont donner des informations sur l'état cristallin, les

interactions entre la substance active et les excipients, l'homogénéité et la distribution de la substance active, la morphologie de surface du produit [6].

1.2. Technique d'extrusion par fusion à chaud

Communément utilisé dans l'industrie plastique, le procédé d'extrusion à chaud a été introduit dans l'industrie pharmaceutique à partir des années 1980 [7]. L'extrusion est un procédé continu qui permet la création d'une forme galénique appelée « extrudat » par passage de la formulation à travers un orifice [9]. Pendant le procédé, la formulation est chauffée et intensivement mélangée, ce qui permet une dispersion homogène des particules de substance active au sein de l'excipient fondu (généralement de nature polymérique ou lipidique). C'est un procédé qui ne requiert pas l'utilisation de solvant et qui est composé de trois parties : une partie qui transporte et mélange la formulation, une partie composée d'un orifice à travers lequel la formulation passe afin d'obtenir sa forme finale et des outils supplémentaires pour refroidir, couper et récupérer la forme galénique. Plusieurs éléments composent la machine : un réceptacle pour alimenter la machine en poudre suivant un débit bien défini, un tunnel cylindrique dans lequel la formulation est chauffée à des températures précises et transportée par des vis à une vitesse spécifiée et à la fin, un orifice de forme et taille variable. Les vis sont composées de différents éléments qui permettent de transporter, mélanger et compacter la formulation. Ces éléments ont un grand impact sur le produit fini et leur ordre est très important. De nombreuses zones de chauffe permettent de chauffer la formulation de façon graduelle et précise. Les températures choisies ont également une grande importance et un grand impact sur le produit fini. Ainsi, les paramètres à contrôler sont le débit d'alimentation, la vitesse et la composition des vis et l'intervalle de température utilisé.

L'extrusion produit une dispersion solide, c'est-à-dire la dispersion d'une substance active au sein d'un excipient solide par fusion [7]. Trois types de dispersion solide peuvent être formés : une suspension vitreuse (la substance active est amorphe mais sous forme de particules au sein

de l'excipient amorphe), une suspension cristalline (substance active restée cristalline dans l'excipient amorphe) ou une solution vitreuse (substance active amorphe et complètement miscible dans l'excipient amorphe) [9]. Les solutions vitreuses sont idéales pour augmenter la vitesse de dissolution de la substance active, les suspensions cristallines sont souvent préférées pour la libération modifiée alors que les suspensions vitreuses sont les moins stables (probabilité de recristallisation de la substance active). La formation d'un de ces trois types de dispersions solides va dépendre de la solubilité de la substance active dans l'excipient, de leurs possibles interactions et de la stabilité de la formulation. Ainsi, parmi toutes les applications permises par l'extrusion, les trois plus importantes sont : la libération immédiate [17–24], la libération modifiée [25–29] et le masquage du goût de certaines substances actives amères[30,31]. Des applications plus modernes comme les formulations anti-abus [14,32], les co-extrusions [33–38], la co-cristallisation [39–42] et l'impression 3D [43–45] sont également à mentionner. Enfin, les formes galéniques ainsi que les voies d'administration sont également variées : sphéroïdes, comprimés, capsules, films, implants pour l'administration par voie orale, transdermale et transmucosale [22,28,46–51].

Afin de pouvoir être utilisée par extrusion, la substance active doit avoir des propriétés particulières compatibles comme la solubilité, l'état physique, la forme et la taille des particules, l'écoulement, le point de fusion, la stabilité thermique. De plus, d'autres caractéristiques vont orienter le choix de l'extrusion par exemple si la substance active est peu soluble, si elle est instable dans certains milieux physiologiques ou si elle est irritante pour certaines parties biologiques ou encore si elle doit cibler un site d'action spécifique.

De nombreux excipients peuvent être utilisés par extrusion, en général des polymères ou des lipides. L'utilisation d'un polymère va dépendre de sa structure chimique, sa solubilité, sa température de transition vitreuse (qui devrait être au mieux entre 50 et 180 °C), son point de fusion, sa viscosité une fois fondu, son écoulement, sa stabilité thermique, son affinité pour la substance active, sa capacité de solubilisation et son absence de toxicité. Ainsi les polymères

les plus utilisés sont par exemple : les dérivées cellulosiques, les polymères poly méthacrylates, le soluplus, le poly éthylène glycol et l'oxyde de poly éthylène, l'éthylène vinyl acétate ou encore la poly vinyl pyrrolidone [19,52–72]. Les lipides également sont souvent utilisés (les cires, l'acide stéarique ou les triglycérides [37,66,74,75]) car ils sont facilement utilisables grâce à leur bas point de fusion [73]. Lorsque que l'extrusion est difficile (viscosité élevée ou dégradation thermique), d'autres additifs peuvent être utilisés comme des plastifiants et des stabilisants. Il est à noter par ailleurs que certaines substances actives peuvent avoir elles même un effet plastifiant [71,84–88].

Les nombreux avantages de l'extrusion ont été mentionnés précédemment, néanmoins il existe également des inconvénients qui doivent être cités. Le principal inconvénient est relatif à la température utilisée pendant la fabrication. En effet, certaines substances actives thermo labiles comme les agents microbiens ou les protéines seront plus difficilement utilisables par extrusion. Néanmoins, l'ajout de plastifiant peut permettre de diminuer les températures utilisées pendant le procédé.

Malgré le nombre grandissant de brevets déposés et les industries spécialisées comme PharmaForm (TX, Etats Unis) et SOLIQS (Abbott, Allemagne) [73], seulement 16 spécialités sont commercialisées à l'heure actuelle [89,90].

1.3. Systèmes à libération contrôlée pour une administration orale

La voie orale est la voie d'administration la plus fréquemment utilisée du fait de sa facilité d'administration, de la bonne acceptation des patients et des bas coûts de production. Cependant, certains désavantages sont à considérer par exemple si la substance active est dégradée avant d'atteindre son site d'action ou si elle est toxique pour les tissus biologiques (muqueuse gastrique par exemple), son taux d'administration peut être modifié par de nombreux facteurs (prise alimentaire, pH des milieux biologiques, mobilité de l'estomac et vidange gastrique) et les concentrations dans le plasma peuvent fluctuer ou diminuer

rapidement ce qui nécessite l'administration de plusieurs doses par jour et augmente ainsi les contraintes du traitement [91]. Aussi, des systèmes à libération contrôlée se développent depuis les années 1960. Ils permettent d'incorporer une dose importante de substance active avec des excipients spécifiques permettant de contrôler la libération. Cela permet de diminuer les effets indésirables et d'augmenter l'efficacité de la substance active, dans le but d'améliorer l'observance des patients.

Différents systèmes permettent de modifier la libération : système à libération immédiate, retardée ou contrôlée. La libération immédiate permet d'administrer rapidement la substance active à son site d'action alors que la libération retardée permet au contraire de libérer la substance active à un moment précis ce qui permet de protéger la substance active d'une dégradation gastrique ou de protéger la muqueuse gastrique de la substance active ou encore de cibler le site d'absorption de la substance active. Les systèmes à libération contrôlée quant à eux permettent de libérer progressivement la substance active sur une durée de plusieurs heures. Ces systèmes peuvent être fabriqués grâce à diverses technologies permettant d'obtenir des systèmes réservoir, matriciel, bio adhésif, flottant ou des pompes osmotiques. Les systèmes matriciels sont une dispersion homogène de la substance active au sein d'un excipient. Leur classification peut être faite en fonction de plusieurs facteurs : la nature chimique de l'excipient (polymérique, lipidique ou inerte), l'état physique de la substance active (dispersé au niveau moléculaire / particulaire), et le mécanisme de libération (diffusion, gonflement, érosion).

De nombreux mécanismes de libération peuvent être impliqués dans les systèmes à libération contrôlée : (i) entrée de l'eau dans le système, (ii) dissolution de la substance active, (iii) diffusion de la substance active hors de la matrice, (iv) gonflement de la matrice, (v) dissolution ou érosion du polymère, (vi) effets osmotiques [95]. Il est intéressant d'étudier précisément ces mécanismes de libération pour savoir quel est le plus limitant et donc quel est celui qui contrôle la libération de la substance active. Dans le cas des matrices gonflantes par exemple, l'entrée de l'eau dans la matrice va permettre la mobilité et le gonflement des chaînes de polymère. En

fonction de la quantité d'eau, de l'état de la substance active et de la taille des chaînes polymériques, l'enchevêtrement des chaînes sera plus ou moins serré, ce qui permet la création de différents fronts [99,100] : (i) le front de gonflement qui sépare la partie gonflée de la matrice de la partie non gonflée, (ii) le front de diffusion qui sépare la partie contenant la substance active à l'état dispersé et dissous de la partie contenant la substance active à l'état dissous uniquement et (iii) le front d'érosion qui sépare le système du milieu environnant. Le gonflement et le déplacement de ces fronts sont très importants car ils vont conditionner la libération de la substance active, comme le montrent de nombreux exemples dans la littérature [101–108]. Enfin, la libération de la substance active dépend aussi de nombreux autres facteurs, généralement des facteurs de formulation (charge, taille des particules et solubilité de la substance active, type, quantité, taille des particules et longueur des chaines de polymère) et de procédé (type, paramètres, dimensions et forme de la forme galénique).

1.4. Oxyde de poly éthylène

L'oxyde de poly éthylène (PEO) est un polymère synthétique obtenu par catalyse d'un monomère d'éthylène oxide en une chaîne linéaire simple formée d'unités répétées $–CH_2-CH_2-O-$ [121]. Le PEO existe sous de nombreux poids moléculaires allant de 100 à 7 000 kDa. C'est un polymère semi cristallin de point de fusion variant entre 63 et 67 °C en fonction du poids moléculaire et une température de transition vitreuse varient entre -50 et -57 °C, ce qui le rend utilisable par extrusion.

Les applications du PEO dans l'industrie pharmaceutique sont nombreuses. En effet, ce polymère a de nombreuses propriétés qui le rendent utile pour de nombreuses techniques :

- Bon écoulement, agent liant et lubrifiant qui permet son utilisation par compression directe,
- Solubilité dans l'eau et capacité de liaison le rendent utile pour former des gels ou des films,

- Hydratation et gonflement rapide qui permettent de préparer des systèmes matriciels à libération contrôlée,
- Température de transition vitreuse et point de fusion bas, propriétés thermoplastiques qui permettent l'utilisation par extrusion à chaud.

Grace à ses propriétés d'hydratation et de gonflement, le mécanisme de libération de la substance active à partir de matrice de PEO correspond à celui des matrices hydrophiles gonflantes décrit précédemment, à savoir : (i) diffusion de l'eau et de la substance active, (ii) dissolution du polymère et de la substance active, (iii) gonflement du polymère. Cependant, en fonction du poids moléculaire utilisé, certains mécanismes seront plus importants que d'autres. En effet, la libération à partir de PEO de haut poids moléculaire est contrôlée par le gonflement du polymère et la diffusion de la substance active alors qu'à partir de PEO de bas poids moléculaire, le gonflement et l'érosion du polymère seront plus déterminants [104,117,135,136,146]. En plus du poids moléculaire du PEO, d'autres paramètres ont un impact sur la libération (solubilité et charge de la substance active, addition d'autres excipients, paramètres de procédé), cependant leur impact est parfois complexe et pas toujours bien compris.

Les avantages du PEO sont nombreux (grand choix de poids moléculaires, nombreuses applications, faible toxicité), néanmoins certains désavantages peuvent exister comme (i) la possibilité de dégradation durant le procédé ou le stockage, et (ii) la possibilité de modification structurale due à la nature semi cristalline du polymère qui peut se traduire par des instabilités avec le temps [169].

Le PEO est commercialisé sous forme de pompes osmotiques (DynaCirc CR®, Cardura®XL, Glucotrol®XL, Procardia®XL et Covera-HS®) et de formes galéniques gastro résistantes (Gralise®, Glumetza® et Janumet®XR) [127]. Cependant, la plus grande application du PEO est la fabrication de formes galéniques anti-abus notamment pour la formulation d'opioïdes

comme par exemple, OxyContin® (oxycodone), Nucynta®ER (tapentadol), Oxecta® (oxycodone) et Opana® (oxymorphone) [170–172].

1.5. Objectifs de travail

L'objectif de cette thèse est de développer des extrudats à base de PEO pour une libération contrôlée et en particulier, d'étudier :

(i) L'impact des paramètres critiques de procédé sur la libération *in vitro,*

(ii) L'impact du poids moléculaire du PEO sur la libération *in vitro,*

(iii) L'impact de la nature et la charge de la substance active sur la libération *in vitro,*

(iv) La comparaison entre extrusion à chaud et compression directe.

2. MATERIELS ET METHODES

2.1. Matériels

Le polymère utilisé pour obtenir une libération prolongée est le Poly Ethylène Oxide (« PEO », Sentry Polyox® WSR LEO NF, Dow chemicals, Midland, Etats Unis). Les grades utilisés sont : Polyox WSR N-10 (100 kDa), Polyox WSR N-80 (200 kDa), Polyox WSR N-750 (300 kDa), Polyox WSR-205 (600 kDa), Polyox WSR-1105 (900 kDa), Polyox WSR N-12K (1,000 kDa), Polyox WSR N-60K (2,000 kDa), Polyox WSR-301 (4,000 kDa), Polyox WSR Coagulant (5,000 kDa) et Polyox WSR-303 (7,000 kDa).

Les substances actives modèles utilisées sont la théophylline monohydrate (« theophylline »; BASF, Ludwigshafen, Allemagne), l'ibuprofène 50 (« ibuprofen »; Salutas Pharma, Barleben, Allemagne) et le métoprolol tartrate (« metoprolol »; Ipca, Mumbai, Inde) à des concentrations variant de 10 à 60 %.

2.2. Méthodes

Préparation des extrudats

La substance active et le polymère sont mélangés 10 minutes à 98 rpm en Turbula T2A (Willy A. Bachofen AG Maschinenfabrik, Muttenz, Suisse). Une extrudeuse à double vis co-rotative de type Nano 16 (Leistritz, Nuremberg, Allemagne) est utilisée pour préparer des extrudats (diamètre 4 mm). Les paramètres d'extrusion sont les suivants : quatre zones de chauffe réglées à 100 – 97 – 95 – 90 °C (orifice – zone 3 – zone 2 – zone 1) ou 135 – 133 – 130 – 125 °C (orifice – zone 3 – zone 2 – zone 1), un débit d'alimentation fixé à 3 cc/min, et une vitesse de rotation des vis paramétrée à 30, 60 ou 90 rpm. Après extrusion, les extrudats sont refroidis à température ambiante puis manuellement coupés en matrices de 0,25, 0,5 ou 1 cm de long.

Préparation des comprimés par compression directe

Des comprimés ont été fabriqués avec une presse alternative (Korsch EK0; Korsch, Berlin, Allemagne) manuellement, c'est-à-dire en remplissant manuellement la matrice entre chaque comprimé (pas d'utilisation de la trémie de remplissage). La composition des comprimés est la même que celle des extrudats. La force de compression est réglée afin d'obtenir une dureté des comprimés suffisante et un poinçon plat de 5 mm est utilisé.

Dissolution et étude du gonflement

Des tests de dissolution sont réalisés en triplicata pour étudier la libération de la substance active en fonction du temps (USP 35, 37,0 ± 0,5 °C). On utilise les méthodes suivantes : USP I (panier, Sotax AT7; Aesch, Suisse), USP II (pale, Sotax AT7; Aesch, Suisse), USP III (cylindre réciproque, Vankel, Cary, Etats Unis) et USP IV (cellule à flux continu, Sotax CE7; Aesch, Suisse), avec 900 mL de milieu pH 7,4 ou HCl 0,1 N, et une vitesse de rotation de 50, 100 ou 150 rpm (USP I), une vitesse de trempage de 5, 10 or 20 tpm (USP III) ou un débit de 30 mL/min (USP IV). Un échantillon de milieu est prélevé toutes les 15 minutes la première heure

puis toutes les heures et la concentration en substance active est déterminée par UV (λ = 272, 221 or 220 nm pour theophylline, ibuprofen ou metoprolol respectivement; UV-1800/1650; Shimadzu, Kyoto, Japon).

Pour le test de gonflement, les mêmes conditions sont utilisées (pH 7,4, USP I, 50 rpm, 37,0 ± 0,5 °C). Les extrudats (n=3) sont pesés et mesurés (diamètre et longueur) avant immersion dans le milieu. A 0,5, 1, 2, 4, 6 et 8 heures, les extrudats sont retirés des bols, pesées et mesurés. Trois parties peuvent être distinguées: une couche de gel où la substance active est soit solubilisée (partie extérieure, « gel transparent ») ou non solubilisée (partie interne, « gel non transparent ») et un cœur où la substance active est non solubilisée (« cœur solide »). Les dimensions ainsi que la teneur en eau, la perte en masse et la teneur en substance active sont calculées pour comprendre les capacités de gonflement des matrices et les corréler au profil de libération (loupe binoculaire Nikon SMZ-U; Nikon, Tokyo, Japon et caméra Axiocam ICc1 camera Axiovision software; Carl Zeiss MicroImaging GmbH, Jena, Allemagne). Ces calculs sont effectués sur la matrice entière ou uniquement sur le(s) gel(s) ou le cœur en retirant la/les couche(s) de gel grâce à un scalpel.

Caractérisation

La solubilité des substances actives est déterminée après saturation d'une solution pH 7.4 laissée à 37 °C et sous agitation horizontale à 80 rpm (GFL 3033; Gesellschaft fuer Labortechnik, Burgwedel, Allemagne). La mesure de la concentration est réalisée par spectrométrie UV après échantillonnage à l'aide de seringue à filtre (5 µm; BD, Franklin Lakes, Etats Unis ; UV 1650; Shimadzu, Kyoto, Japon).

La porosité des formes galéniques est mesurée par pycnométrie (AccuPyc 1330; Micromeritics, Norcross, Etats Unis).

Enfin, des images des mélanges physiques et des produits purs chauffés jusqu'à 100 °C à 10 °C/min ont été réalisées avec un microscope équipé d'une plateforme chauffante (Zeiss Scope A1, Carl Zeiss MicroImaging GmbH, Jena, Allemagne).

Analyses physiques

Le comportement thermique des produits (PEO, substance active, mélange physique et extrudat) a été étudié par calorimétrie différentielle à balayage (DSC 1, STARe system; Mettler Toledo, Greifensee, Suisse). Environ 3-5 mg d'échantillon est pesé dans des coupelles en aluminium. Les échantillons sont chauffés de 0 à 320, 140 ou 160 °C (pour théophylline, ibuprofène et métoprolol respectivement) à 10 °C/min puis refroidis à 0 °C et chauffés à nouveau.

Une étude par rayons X a été réalisée en mode réflexion avec un X'pert pro (Panalytical, Almelo, Pays Bas) avec un porte échantillon Spinner plaquette. On a utilisé pour l'analyse un détecteur X'celerator avec un tube de cuivre de longueur d'onde 1,54 Å. L'angle de détection varie entre 5 et 60 ° en 2θ à une vitesse de 100 secondes par pas (1 pas = 0,0167 °). L'analyse dure 45 minutes par échantillon.

Des analyses par microscopie Raman ont également été faites pour approfondir la caractérisation des extrudats et comprimés via un spectromètre InVia Raman (Renishaw; Wotton-under-Edge, Royaume Unis), comprenant un spectrographe couplé à un microscope optique (Leica, Wetzlar, Allemagne). Le spectre de chaque composé a été enregistré séparément dans la région de fréquence 600 – 3800 cm^{-1}. Il a été observé que le PEO et la théophylline étaient prépondérants dans la région 300 –700 cm^{-1}. Aussi, cette région a été choisie pour analyser les formes galéniques.

Enfin, des photos en microscopie électronique à balayage (Hitachi High-Technologies Europe; Krefeld, Allemagne) ont été réalisées pour observer la porosité de surface des extrudats et

comprimés. Les échantillons sont fixés avec un ruban adhésif de carbone et recouverts d'une fine couche de carbone avant observation sous un microscope.

Tests de stabilité

Toutes les formulations sont mises en étuve à 25 °C et 60 % d'humidité relative (flacon en verre fermé) pour étudier la stabilité (Binder, Tuttlingen, Allemagne).

3. RESULTATS ET DISCUSSION

L'impact des paramètres du procédé d'extrusion à chaud : température et vitesse de vis

Pour cette étude, tous les poids moléculaires de PEO ont été testés en formulation avec 10 % de théophylline monohydrate. Deux températures d'extrusion ont été testées : 100 ou 135 °C. Pour les formulations contenant les poids moléculaires 100, 200 et 300 kDa, la libération de la substance active est accélérée quand la température d'extrusion augmente. Pour les autres grades, la température n'a pas d'effet sur le profil de libération. En revanche, la température impacte le comportement de l'extrudat en sortie d'extrusion. A 135 °C, tous les grades supérieurs à 300 kDa présentent des défauts de surface (cassure ou rugosité). Pour les grades inférieurs, l'extrudat était très fondu en sortie, rendant difficile sa manipulation. Pour la majorité de ces grades, la diminution de la température d'extrusion à 100 °C permet d'éliminer ces défauts et la surface des extrudats devient lisse. La vitesse des vis également a un impact sur l'apparence des extrudats (notamment une disparition de la rugosité à vitesse élevée), mais pas sur la libération de la substance active.

L'impact de la géométrie de la forme galénique

Les extrudats sont coupés en morceaux de 1, 0,5 ou 0,25 cm pour observer l'impact de la surface des extrudats sur la libération de la substance active. Les bols sont remplis avec une

masse égale d'extrudat, soit un morceau d'1 cm, deux morceaux de 0.5 cm ou quatre morceaux de 0.25 cm. Plus la taille d'extrudat est petite et plus le profil de libération est accéléré car la surface spécifique est plus grande.

L'impact du poids moléculaire du PEO

Tous les grades de polymères commercialisés ont été testés en formulation avec 10 % de théophylline monohydrate et fabriqués avec les paramètres d'extrusion retenus lors de la première étude : température 100 °C, vitesse des vis 30 rpm et une taille d'échantillon de 1 cm. On observe que la pression pendant le procédé augmente avec le poids moléculaire du polymère. Cela est dû à l'augmentation de la longueur des chaînes de polymère et à l'augmentation consécutive de leur viscosité. Une modification de la couleur des extrudats est également remarquée : les grades de poids moléculaires inférieurs à 600 kDa présentent une coloration jaune, les autres grades sont blancs. De plus, plus le poids moléculaire augmente et plus la libération est ralentie. Cependant, à partir de 600 kDa, on ne remarque pas de ralentissement très conséquent de la libération. Une étude de gonflement est réalisée pour corréler les cinétiques de libération. Il a été trouvé que le changement de volume de la partie « gel non transparent + cœur solide » de l'extrudat (c'est-à-dire les parties contenant la substance active sous forme saturée) correspondait aux cinétiques de libération.

L'impact du type de substance active et de sa charge

Des formulations avec 10, 20, 40 et 60 % de substance active sont réalisées par extrusion. Les substances actives suivantes sont utilisées : théophylline, ibuprofène et métoprolol tartrate. Avec la théophylline, le procédé d'extrusion se déroule sans difficulté avec seulement une très légère augmentation de pression lors de l'augmentation en substance active mais qui reste en deçà des limites autorisées. Aucune apparition de défaut de surface n'a lieu et on note même une amélioration pour la formulation à 60 % de substance active avec disparition de la rugosité

pour le PEO qui en présentait initialement. Pour les autres substances actives, la pression diminue lorsque la charge en substance active augmente (probablement dû à un effet plastifiant).

Concernant le profil de libération de la théophylline et de l'ibuprofène, les tendances dépendent du poids moléculaire du PEO. Avec un PEO de bas poids moléculaire, la libération augmente avec la charge en substance active mais avec un PEO de haut poids moléculaire, l'inverse se produit : la libération ralentit quand la quantité de substance active augmente. Pour un PEO de poids moléculaire intermédiaire, le résultat dépend de la solubilité en substance active. Avec le métoprolol, toutes les cinétiques sont accélérées lorsque la charge augmente, pour tous les PEO. Cela est probablement dû à la haute solubilité de cette substance active.

Pour comprendre les tendances de libération observées, des tests de gonflements ont été réalisés sur les matrices. Comme dans l'étude précédente, une corrélation a pu être trouvée avec notamment le changement de volume de la partie « gel non transparent + cœur solide » de l'extrudat.

Comparaison de procédé : extrusion à chaud *vs* compression directe

Le procédé d'extrusion à chaud a été comparé à la compression directe. Pour cela, deux poids moléculaires de PEO sont choisis : 200 et 7,000 kDa. Ils sont formulés avec 10 % de théophylline monohydrate. Des formes galéniques de même surface et même teneur en substance active sont comparées et les extrudats donnent des cinétiques de libération plus rapides que les comprimés. Pourtant, la porosité des comprimés est supérieure, comme vérifié par pycnométrie et microscopie à balayage. Néanmoins, les images réalisées par microscopie à balayage montrent la présence de cristaux de substance active en surface des extrudats, ce qui pourrait expliquer la libération plus rapide. Des comprimés et extrudats ont également été fabriqués avec 60 % de substance active pour réaliser des tests de microscopie Raman. Ces tests indiquent que la substance active est transformée pendant l'extrusion en forme anhydre, ce qui

pourrait modifier son affinité pour le PEO, et donc la différence de libération observée. Enfin, il est à noter que les comprimés ont été réalisés manuellement et ne pourraient pas être fabriqués automatiquement avec cette formulation, au contraire de l'extrusion.

L'impact des conditions *in vitro*

Le milieu de dissolution (pH 7,4 ou HCl 0,1 N), la vitesse de rotation des tiges (50,100 ou 150 rpm) ou la vitesse de trempage (5, 10, 20 tpm) ainsi que la méthode de dissolution (USP I à IV) sont testés avec deux grades de polymère différents (200 et 7,000 kDa) formulés par extrusion ou compression directe. Il n'y a pas d'impact du milieu de dissolution, ni des vitesses utilisées sur la libération de la substance active pour les deux types de formes galéniques. En revanche, le changement de méthode de dissolution modifie les cinétiques aussi bien pour les comprimés que pour les extrudats bien que cela soit plus prononcé pour les comprimés.

4. CONCLUSIONS ET PERSPECTIVES

Les objectifs de cette thèse étaient d'une part, de réaliser des extrudats à base de PEO pour la libération prolongée et d'autre part, d'étudier l'impact des facteurs de formulation et de procédés sur les cinétiques de libération.

Il a été montré que l'extrusion n'avait pas d'avantage par rapport à la compression directe (à formulation identique) quant à la prolongation de la libération. Néanmoins, le procédé de compression directe requiert une formulation plus complexe pour être transposable à l'échelle industrielle, ce qui n'est pas le cas pour l'extrusion. De plus, les extrudats sont légèrement plus robustes face aux conditions de la libération par rapport aux comprimés. Enfin, l'extrusion ne comporte aucune difficulté technique et cela, même avec 60 % de substance active. Ainsi, le procédé d'extrusion à chaud semble avoir des avantages certains.

La charge en substance active a un impact sur le profil de libération mais cet impact dépend beaucoup du poids moléculaire du polymère. Cet impact dépend également de la solubilité de la substance active.

Enfin, une corrélation a pu être trouvée entre les profils de libération et le changement de volume de la partie « gel non transparent + cœur solide » notamment.

La caractérisation des extrudats reste à approfondir, notamment une analyse plus fine de la cristallinité de chaque système (substance active et polymère). De plus, un travail de modélisation des cinétiques pourrait être fait et des mélanges entre différents PEO pourront être envisagés afin de moduler d'avantage les profils de libération. Enfin, des libérations en milieu simulés pourraient être envisagées ainsi qu'une étude *in vivo* afin d'évaluer les corrélations *in vitro/ in vivo*.

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<u>Titre de la thèse :</u> Extrudats à base d'Oxyde de Poly Ethylène pour la libération contrôlée

Parmi les procédés de fabrication continue, l'extrusion par fusion à chaud est une technique dont l'intérêt dans le domaine pharmaceutique est grandissant. Ce procédé permet la formation des dispersions solides des substances actives au sein des matrices polymériques ou lipidiques. En fonction de l'excipient et de la substance active, cela peut être largement utilisé pour la conception des systèmes: (i) pour une libération immédiate, (ii) pour une libération modifiée et (iii) pour le masquage de goût. Les systèmes à libération modifiée sont des dispositifs intéressants qui permettent d'améliorer la biodisponibilité de la substance active, son efficacité ainsi que l'observance des patients. En fonction de la nature de l'excipient, différents systèmes avec des mécanismes de libération variés peuvent être produit, notamment des matrices inerte, érodable ou gonflante. L'oxyde de poly éthylène est un polymère semi- cristallin et hydrophile qui peut être utilisé pour la libération contrôlée. Son point de fusion compris entre 63 et 67 °C le rend adapté pour l'extrusion. Surtout, ses capacités de gonflement permettent d'administrer la substance active de façon contrôlée en fonction du poids moléculaire de l'oxide de poly éthylène. Les objectifs de ce travail sont (i) d'étudier l'impact des paramètres critiques du procédé (température d'extrusion et vitesse des vis d'extrudeuse) sur le profil de libération de la substance active, (ii) de déterminer l'impact des paramètres de formulation (poids moléculaire de l'oxyde de poly éthylène, charge et type de substance active) sur le profil de libération de la substance active et (iii) d'évaluer des formes galéniques solides conçues par le procédé d'extrusion ou par compression directe. Il a été montré que la variation de la température d'extrusion et de la vitesse des vis altérait l'apparence de l'extrudat. Il s'est avéré dans notre étude que la libération de la substance active n'était pas particulièrement affectée par ces changements de température et vitesse de vis de l'extrudeuse. De plus, cette étude a permis de fixer les paramètres pour les projets suivants: température 100 °C ; vitesse des vis 30 rpm ; longueur de la forme galénique 1 cm. Des extrudats d'oxyde de poly éthylène contenant 10 % de théophylline et d'oxyde du poly éthylène de 100 à 7000 kDa ont été utilisés dans ce travail. Il a été observé que lorsque le poids moléculaire de l'oxyde du poly éthylène augmente de 100 à 600 kDa, la libération en substance active diminue de façon importante alors qu'une augmentation jusqu'à 7000 kDa ne diminue que légèrement la libération. Des études du gonflement ont montré que ce phénomène corrélait aux variations de volume de la partie opaque de l'extrudat (gel non transparent et cœur solide).

Mots clés : oxyde de poly éthylène, extrusion par fusion à chaud, libération contrôlée

Thesis title: **PEO hot melt extrudates for controlled drug delivery**

Among continuous manufacturing processes, hot melt extrusion is a technique with growing interest in the pharmaceutical field. This process enables the formation of solid dispersions of many drugs within a polymeric or lipidic carrier. Hot melt extrusion can be widely used for different issues using the appropriate carrier and drug. Here are the mostly used concepts in pharmaceutical solid dosage forms: (i) immediate release, (ii) modified release and (iii) taste masking. Modified release systems have been taken into account to be very interesting devices for the improvement of drug- bioavailability, drug- efficacy as well as the patient compliance. Various systems with different release mechanisms can be manufactured, depending on the nature of the carrier (inert, erodible, and swelling matrices). Poly ethylene oxide is a semi crystalline and hydrophilic polymer which can be used to control drug delivery. The poly ethylene oxide melting point ranging from 63 to 67 °C makes it suitable for hot melt extrusion. Importantly, the swelling capacities of the hydrophilic poly ethylene oxide matrices are able to deliver drug in a time controlled manner, in respect of the poly ethylene oxide molecular weights. The purposes of this work were (i) to study the impact of critical process parameters (extrusion temperature and screw speed) on the drug release behavior, (ii) to determine the drug loading) on drug release kinetics, and (iii) to evaluate solid dosage forms prepared by hot melt extrusion versus direct compression. Interestingly, the variation of the extrusion temperature and the screw speed leads to the altering of the extrudate appearance. However, this changing has not influenced the drug release remarkably. Thus, this study was useful to set the parameters for the following projects (temperature 100 °C; screw speed 30 rpm; dosage form size 1 cm). Poly ethylene oxide hot melt extrudates containing 10 % theophylline and based on 100 - 7,000 kDa poly ethylene oxide are used for this thesis. Importantly, the drug release decreased substantially with the increase of the poly ethylene oxide molecular weight from 100 to 600 kDa. However, further increasing of the molecular weights leads to only a slight decrease in the release rate. Swelling studies have shown that this phenomenon correlated with the change in volume of the opaque part of the extrudates (non-transparent gel and solid core).

Key words: poly ethylene oxide, hot melt extrusion, sustained release