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INJECTION MOLDING/MICROMOLDING APPLICATIONS TO DRUG DELIVERY

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Preface

Nowadays, the application of new manufacturing techniques, generally derived from other industrial fields, is one of the most promising innovation tools in the pharmaceutical technology area. This may indeed lead to a reduction of costs development and manufacturing, simplification of industrial scalability and, not least, to the patentability of drug products. In this respect, injection molding (IM) and micromolding (μIM), commonly employed within the plastic industry for a fast production of objects with different size, shape and, potentially, many details, were identified as especially interesting techniques to be exploited in the pharmaceutical field. In particular, μIM applies to the manufacturing of parts of few milligrams weight or with features where dimensions or dimension tolerances should be in the micrometer range, *i.e.* the potential scope of drug products. The topic appeared from the beginning as particularly innovative and challenging, and thus the availability of an in-depth scientific background was judged essential. IM technology and its use within the plastic industry (*e.g.* process, equipment and formulation aspects) as well as the applications already proposed in the pharmaceutical field were initially investigated (Part I). Afterwards, based on the knowledge acquired and on some experience already gained by the research group within which I carried out my PhD project, a few original products prepared by IM/μIM were developed, either drug delivery systems (DDSs) or conventional dosage forms (Part II and III).

The μIM technique had already been applied to the manufacturing of a functional container in the form of a capsule shell, *i.e.* consisting of two parts to be assembled, based on hydrophilic polymers (different grades of hydroxypropyl cellulose) [1-4]. The obtained capsular system (Chronocap™) demonstrated the ability of delaying the release of the conveyed drug and was recently protected by a patent. Since the polymeric shell works like a barrier, functional containers, filled with various active principles/formulations (*e.g.* solid, semisolid and liquid), may represent an alternative configuration to reservoir systems and a step forward in controlled release. In fact, the nature of the container enables an independent development of the inner formulation, while the performance of the device is

determined by the composition and design features (*i.e.* morphology and thickness) of the shell. This would offer major benefits in terms of time and costs required for the development and avoid the need for setting up specific coating processes for different drug products. Based on the encouraging results obtained with the Chronocap™, the possibility of exploiting other polymers, characterized by a different behavior in aqueous fluids (*e.g.* insoluble but permeable or with a pH-dependent solubility), for the manufacturing of new capsular delivery systems was investigated. In particular, since a large number of enteric coated systems are present in the pharmaceutical market, the production of an enteric soluble device turned out to be of special interest. Being filled and sealed after manufacturing, it would represent a ready-to-use alternative to traditional gastro-resistant coated dosage forms, also for extemporaneous applications. The obtained shells, based on hydroxypropyl methylcellulose acetate succinate, showed promising *in vitro* and *in vivo* results (Part II and relevant Appendix).

Improving the efficiency of manufacturing methods and exploiting more cost-effective as well as eco-friendly processes are among the main current objectives of the pharmaceutical industry. Besides the use of IM/μIM for the production of DDSs that would not be feasible by means of already available techniques, the interest in the application of these techniques can also be justified by a possible cost reduction, an easier scale-up and the patentability of the resulting products. Indeed, this trend is confirmed by the growing interest towards the introduction in the pharmaceutical field of continuous manufacturing (CM) [5]. Hot melt extrusion (HME) and IM/μIM techniques already demonstrated to fulfill the needs of this manufacturing approach. However, in order to employ such techniques for the production of dosage forms within a CM plant, knowledge in this respect needs to be broaden. A final part of my PhD work was therefore dedicated to investigate the feasibility of well-known DDSs, such as prolonged-release hydrophilic matrices, and conventional dosage forms, *i.e.* immediate release (IR) tablets, by HME and IM (Part III, Chapter I and II).

All the results reported in the thesis have been already disclosed, *i.e.* published, submitted for publication or presented in the form of oral and poster communications to national/international meetings.

Articles

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Part I

The content of Part I has already been published in:

Zema L., Loreti G., Melocchi A., Maroni A., Gazzaniga A., Injection molding and its application to drug delivery, J. Control. Release 159: 324-331, 2012.

INJECTION MOLDING AND ITS APPLICATION TO DRUG DELIVERY

Abstract

Injection molding (IM) consists in the injection, under high pressure conditions, of heat-induced softened materials into a mold cavity where they are shaped. The advantages the technique may offer in the development of drug products concern both production costs (no need for water or other solvents, continuous manufacturing, scalability, patentability) and technological/biopharmaceutical characteristics of the molded items (versatility of the design and composition, possibility of obtaining solid molecular dispersions/solutions of the active ingredient). In this article, process steps and formulation aspects relevant to IM are discussed, with emphasis on the issues and advantages connected with the transfer of this technique from the plastics industry to the production of conventional and controlled-release dosage forms. Moreover, its pharmaceutical applications thus far proposed in the primary literature, intended as either alternative manufacturing strategies for existing products or innovative systems with improved design and performance characteristics, are critically reviewed.

Contents

Keywords: injection molding, thermoplastic polymer, dosage forms, controlled release, continuous manufacturing, microinjection molding.

1. Introduction

Injection molding (IM) is a rapid and versatile manufacturing technique used in the plastics industry to produce objects with different size, shape and, if needed, many details [1,2]. It consists in the injection, under high pressure and temperature conditions, of melted thermoplastic or thermoset materials into a closed mold. The finished product cools down and/or solidifies inside the mold and is ejected at the end of the manufacturing cycle.

A thermoplastic polymer is one that, when heated, undergoes a physical change, a transition to a viscous state, thanks to which it can be molded to give the desired shape. This process can be repeated many times when reworking is needed (*e.g.* polyethylene, PE; polyvinyl chloride, PVC). On the other hand, a thermoset polymer solidifies following heat-induced cross-linking. This chemical modification is thus responsible for the hardness of the resulting product. The latter cannot be molded again because reheating would cause degradation (*e.g.* phenol formaldehyde resins like bakelite) [3,4].

IM is a relatively young technique, born between the end of 1800 and the beginning of 1900, with a real explosion around 1940 associated with an increased demand for inexpensive products. The improvement brought about by IM in plastics processing as compared with previous manufacturing techniques relies on the concurrent use of pressure and heat in order to turn a polymer, or a polymeric formulation, into a solid object with defined characteristics in terms of shape, dimension and features.

IM has commonly been used for cosmetic/pharmaceutical packaging and, more recently, also for the production of biomedical devices such as scaffolds and microneedles [5-10]. Within the development of portable micropump delivery systems for chemotherapeutic drugs, insulin or immunization agents, promising results were also obtained in the manufacturing of microfluidic devices [11]. The idea of IM application to the preparation of drug dosage forms was first suggested by Speiser [12].

The chief determinants of the success of this technique in the pharmaceutical area are related to its scalability and patentability [13-15]. Indeed, IM is a potentially automated cyclic process (continuous production) that can easily be transferred to the industrial scale by the use of larger equipment and molds. A single IM cycle can last few seconds, and in many cases molds even enable the concurrent production of more than one unit, thus aiding the reduction of process time.

The versatility of IM technique can be exploited for the production of drug delivery systems with defined shape and/or dimension characteristics [16-18]. Moreover, the

process does not require the use of solvents, which is advantageous in terms of manufacturing times and costs as well as of preserved stability [19].

Furthermore, the process conditions typically involved, pressure and heat, both reduce microbial contamination (autosterilization) and promote drug-polymer interactions with the possible formation of solid solutions or dispersions [20,21]. As in hot melt extrusion (HME) technique, this would increase the dissolution rate and, possibly, improve the bioavailability of poorly soluble drugs [22,23].

The great potential of IM for producing drug delivery systems is demonstrated by the multiplicity of patents filed over the last ten years, although the number of products at an advanced development stage or already on the market is still limited (*e.g.* Capill®, Chronocap™, Egalet®, Septacin™); hence, there is still room for improvement and in-depth investigation.

On the basis of these premises, the aim of the present review is to critically describe the use of IM as an alternative technique to produce dosage forms, while highlighting those applications that might reach innovative formulation targets and/or advantageous therapeutic goals.

2. Process and equipment

IM process is performed in appropriate equipment, IM machines, that generally consist of two parts: the plasticating/injecting unit (PI_U) and the clamping unit (C_U). Depending on the configuration of such units, horizontal, vertical or hybrid IM machines are distinguished. The latter present horizontal PI_U and vertical C_U or *vice versa* [2].

PI_U is composed of a hopper that feeds a heated barrel, where heating, mixing, compression and melting steps take place. Thanks to various heater bands located along the barrel, it is possible to set and maintain different temperatures.

A pressure-generating element is present in the barrel. While this was a plunger in the past (Hyatt's IM machine, 1872), modern equipment are screw-type [1].

By moving forward, the screw acts like a plunger exerting the injection pressure needed, whereas its rotation results in the movement/compression of the solid material/melt and concurrent development of shear forces that help increase the temperature of the latter (mechanical heating). Although the screw design should adapt to the characteristics of the processing material, the metering screw is the most popular one. In such screw, the rear section (feed zone) has a smaller diameter than the front end (meter zone), where the

material is forced to flow into a progressively narrower space: this is associated with an increased speed that generates frictional heat (squeezing action). The intermediate area of the screw (melt zone) is a transition area between the meter and feed zones.

The screw ends in a tip that fits the nozzle cap. A backward flow of the melt is prevented by a non-return valve, located before the tip. The nozzle area, heated by its own heater band, is even smaller. Therefore, unwanted temperature increases might occur, possibly resulting in degradation phenomena, depending on the thermal stability and viscosity characteristics of the material.

The terminal element of the IM machine is the mold. It is generally composed of two halves that combine to form a cavity of defined 3D shape that forms the outer surfaces of the molded object (single unit production cycle). It is also possible to design molds with several cavities in order to produce, within the same cycle, more than one unit. One part of the mold is mounted on a stationary platen, while the other is mobile, thus allowing the two halves to be matched (closed mold) or uncoupled (open mold). The clamping unit keeps the mold closed during injection. A clamping force exceeding the injection pressure is needed in order to prevent the mold from opening while the substrate is being injected and to retain the cavity pressure. The resulting gap would indeed hinder the accomplishment of the molded objects and/or cause the melt to squeeze out from the mold cavity (short shot and/or flash).

The mold temperature is controlled by a cooling system that normally utilizes water as the circulating fluid. After injection, the melt cools down and/or solidifies in the mold and, when sufficiently hardened, it can be ejected by pins located in the mobile half of the mold. In order to acquire its final mechanical characteristics, however, the molded object may require a curing treatment. The object can undergo changes in size with respect to the cavity image [24]. This is known as shrinkage and can occur inside the mold or after ejection (mold and post-mold shrinkage, respectively). On the other hand, warpage is a deformation that consists in the bending or twisting of the unit thus resulting in alterations of bi- and tridimensional shape; it can be considered as a non-uniform shrinkage.

IM machines are either single-stage, in which plastication and injection are carried out in the same cylinder by means of a reciprocating screw, or two-stage, wherein a plasticating screw feeds the melt into a holding/accumulator chamber [3]. The second stage (ram injection stage) involves the injection of the melt into the mold cavity. In Figure 1 a reciprocating screw machine is illustrated.

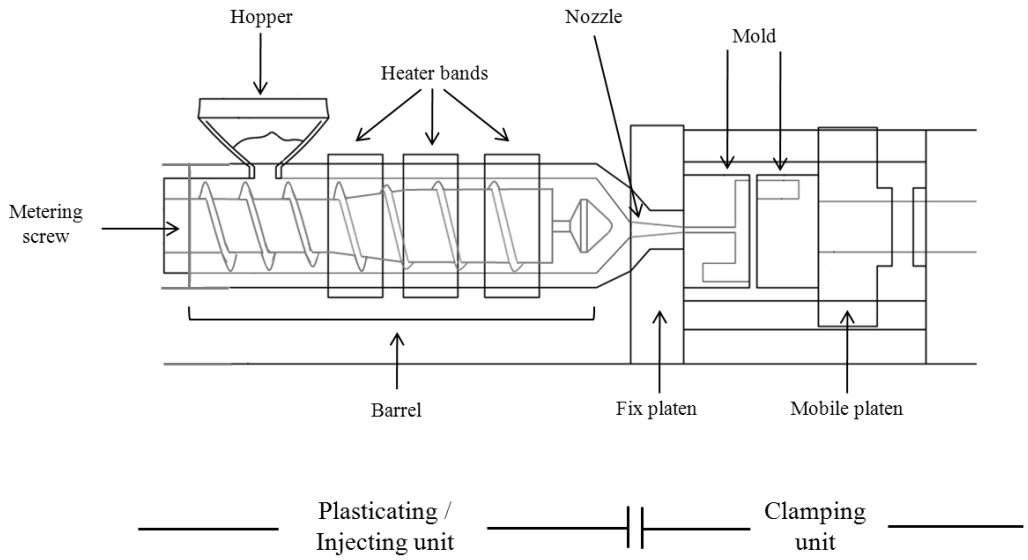
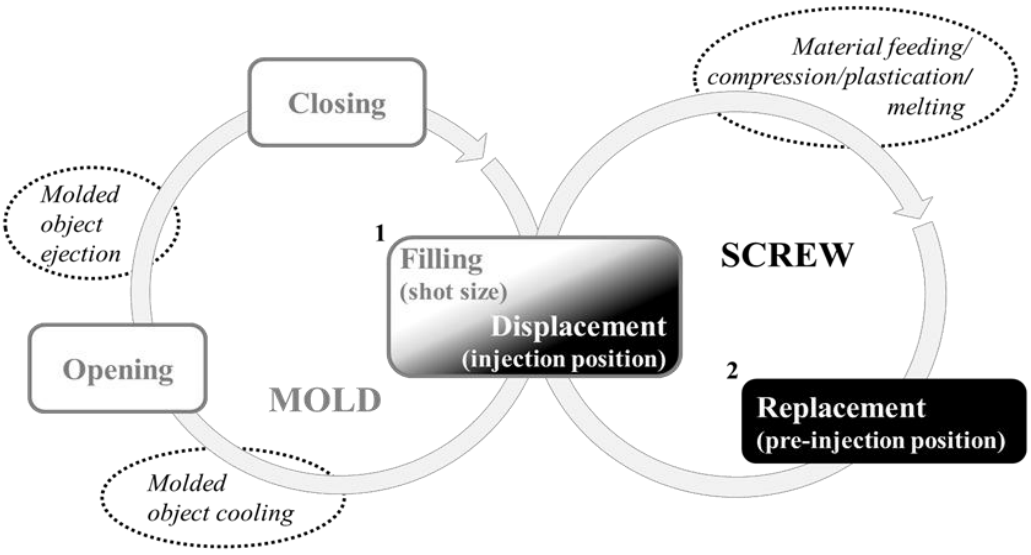


Figure 1: reciprocating screw machine (horizontal type).

Figure 2 shows an outline of an IM cycle in a reciprocating screw machine. The filling/opening/closing cycle of the mold synchronizes with the movement of the screw (that moves forward to the injection position and is pushed back to the pre-injection one). When the molded object is automatically ejected, the IM cycle starts again thus providing a continuous manufacturing process.



1. **Filling/Displacement:** the screw moves forward like a plunger, without rotating, to inject accurate amounts of molten material (shot size) into the mold trough the nozzle.
2. **Replacement:** the screw rotates and feeds the barrel with material (powder, particles or pellets) supplied from the hopper. In the barrel, this melts because of the high temperatures. A defined volume of molten material accumulates just before the nozzle (shot size) and pushes the screw back to the pre-injection position, ready for a new cycle.

Figure 2: IM cycle in a reciprocating screw machine.

In order to produce microparts or micro-structured parts, *i.e.* parts of few milligrams weight or with features where dimensions or dimension tolerances are in the micrometer range, respectively, special microinjection molding (μIM) machines were developed in the '90s [25,26]. The desired features of such machines encompass accurate metering and dosing, small shot size, high injection rate, short response time, small yet accurate clamping force, good stability and repeatability [27]. The main difficulties in the achievement of microparts were encountered for > 1 aspect ratios (*i.e.* ratio of total flow length to average wall thickness). μIM is not only a simple scale-down of classical IM. Indeed, the scale reduction of IM machine components (*e.g.* barrel length, screw/plunger and nozzle diameter, entire clamp unit, control equipment) alone was demonstrated not to be sufficient to ensure the accuracy of the metering size, limit the waste/degradation of polymer and prevent damage to molded parts during ejection. Moreover, the introduction of separate plasticating and injecting units along with a fine set-up of the process conditions were found necessary.

Some pharmaceutical applications of IM are based on the use of non-conventional equipment adapted from other techniques. Extruders, for example, can be employed for the plasticating phase. However, the material has then to be maintained under suitable temperature conditions and transferred into a different equipment for the injection phase. This two-step process might impair an advantageous IM feature, *i.e.* the possibility of automation.

3. Formulation aspects

Polymers, commonly thermoplastic (at least 90%), are the basic components of items produced by IM. Currently, the plastics industry supplies a wide variety of polymeric materials. Both amorphous (*e.g.* polyurethane, PU; PVC) and semi-crystalline (*e.g.* nylon; PE) polymers may be thermoplastic; they differ from each other in terms of behavior during the IM process and characteristics of the finished products (Table 1) [1].

Table 1: amorphous *vs* semi-crystalline thermoplastic polymers.

	Amorphous	**Semi-Crystalline**
IM behavior	soften on heating	melt on heating
	poor lubricity	good lubricity
IM product characteristics	limited and isotropic shrinkage	marked and anisotropic shrinkage
	high impact strength	low impact strength
	transparent	opaque

Because of the wide range of polymers available, the basic component can be chosen taking many different issues into account, such as the equipment, the time and costs of the process as well as the characteristics that the molded products should present depending of their final application. An improvement in the product characteristics may involve the use of extra components, sometimes very expensive and/or with critical processability. Hence, the formulation has to balance all aspects. In this respect, the most important categories of aids employed in the plastics industry are [3]:

- fillers (*e.g.* talc; mica), used in order to decrease the percentage of thermoplastic polymer, thus reducing the overall costs;
- reinforcements (*e.g.* graphite; glass fibers), generally added at 10-40% by weight to enhance properties such as mechanical strength and stiffness;
- colorants, organic (*e.g.* phtalocyanine; diazos) or inorganic (*e.g.* iron oxides; carbon black);
- agents limiting shrinkage and warpage (*e.g.* glass; carbon fibers);
- substances that may impart specific properties such as electrical conductivity (*e.g.* nickel; steel);
- plasticizers (*e.g.* dioctilphtalate for PVC) that improve the polymer melt flow index during the IM process/increase the product flexibility.

In order to help the ejection of the finished item from the mold, it is sometimes necessary to use mold release agents. These can be included in the injected mixture (internal lubricants, *e.g.* erucic and stearic amides used at 0.1-1%) or simply be applied to the mold cavity surface (external lubricants, *e.g.* silicone oils).

When applying IM technique to drug delivery, the formulation step may especially be challenging. Indeed, strict quali-quantitative limitations can be associated with the need for ensuring the quality, efficacy and safety requisites of drug products. These limitations are primarily dictated by the dose, physico-chemical characteristics and stability profile of the active ingredient, which cannot be modified. In particular, the operating temperatures could cause drug degradation phenomena to occur in-process or impair the overall stability of the product. Further aspects, such as the release pattern pursued, the tolerability and pharmaceutical acceptability of all excipients as well as the possibility of undergoing sterilization, are also to be considered.

The selected polymer is expected to fully or partly govern the release performance on the one hand, and possess on the other suitable melt flow index, thermal stability and behavior upon cooling. Moreover, depending on the design of the dosage form, certain challenging issues related to μIM might also be faced (*e.g.* injecting of minimal reproducible melting amounts). Indeed, microcomponents are defined as having typical exterior dimensions and wall thickness in the millimiter and micrometer ranges, respectively, as well as weight of hundred milligrams, which is consistent with values proper to drug products. Some other excipients may therefore need to be utilized in order to define not only the release pattern but also the processability of the polymeric component itself.

The application of IM to the production of dosage forms is still limited, and rather simple formulations have been described in the literature thus far. With reference to the previously reported classification, the following aids only have been identified in IM pharmaceutical formulations:

- reinforcements (*e.g.* microcrystalline cellulose, MCC; hydroxylapatite) [14,28];
- substances that may impart specific properties, added to modify the release performance (*e.g.* disintegrants; release modifiers; polymeric carriers for the formation of solid dispersions) [20-32];
- plasticizers used to lower the polymer glassy-rubbery transition temperature thus allowing the manufacturing process to be carried out at temperatures consistent with the drug and/or excipient stability (*e.g.* dibutyl sebacate, DBS; polyethylene glycol, PEG; glycerol) [28-33].

Excipients are often chosen based on literature data derived from techniques other than IM. For plasticizing purposes, for example, substances that are generally employed in film-coating processes are selected. Besides, internal and external lubricants are those used in

tableting (*e.g.* stearyl alcohol) and in the preparation of lozenges (*e.g.* vegetable oils), respectively.

By contrast, in some preliminary studies, silicone oils have been exploited as external lubricants, although these would be unsuitable for pharmaceutical use.

4. Applications

The exploitation of IM in the pharmaceutical area for the production of conventional dosage forms or Drug Delivery Systems (DDSs) is aimed at reducing the time and costs of manufacturing and/or improving the performance of drug products that are currently prepared by other techniques. Notably, only in a limited number of studies, actually innovative and unique design, composition and functional characteristics are described.

This article takes into account systems reported in the primary scientific literature and purposely omits all potential applications of the IM technique described in patents, which would require a separate discussion because of the high number and wide variety. All types of IM application reviewed herein along with their key formulation and manufacturing characteristics are summarized in Table 2.

Table 2: IM applications reviewed and relevant characteristics.

References	Product	Polymer	Formulation aspects	Equipment	Application
13, 16, 19, 34, 36, 39-44	Oral capsules	Potato starch Gelatin	Starch/water or gelatin/water mixtures (around 15% water content)	Horizontal injection molding machine (screw type)	Alternative system to gelatin dip-molded capsules
14	IR tablets	PEG 6000 PEG 8000	*Drug*: different active ingredients (dispersed/dissolved in the molten carrier) *Reinforcement*: MCC	Horizontal injection molding machine (screw type)	Alternative to immediate-release compressed tablets
29-32, 47	Oral non-disintegrating matrices	Wheat starch EC	*Drug*: model active ingredient (sodium benzoate); metoprolol tartrate *Plasticizer*: glycerol, DBS *Release modifier*: HPMC, L-HPC, xanthan gum, PEO *Reinforcement*: MCC *Mold release agent*: silicon based spray (external)	Horizontal injection molding machine (screw type) Twin-screw mini-extruder + lab-scale vertical injection molder	Alternative to compressed non disintegrating oral matrices
15, 17, 21, 48-51	Implantable matrices	PLA Polyanhydride copolymer PLC PLGA	*Drug*: valpreotide pamoato, gentamicine sulfate, fluconazole, praziquantel, 5-fluorouracil	Horizontal injection molding machine (screw type) Bench-top micro-molding machine (plunger type) Vertical injection molding machine Twin-screw mini-extruder + lab-scale vertical injection molder Homemade equipment	Alternative to current implants

52, 53	Intravaginal inserts	PLC Ethylene vinyl acetate	*Drug:* progesterone, davipirine	Horizontal injection molding machine Twin-screw extruder + injection molder (hydraulic or plunger-type)	Alternative to current intravaginal inserts
54-63	Oral multi-layer device	Impermeable shell: biodegradable polymers (*e.g.* EC) Plug/matrix: soluble/erodible polymers (*e.g.* PEO)	*Drug*: carvedilole, opioids (*e.g.* hydrocodone, morphine) *Plasticizers (shell)*: *e.g.* cetostearyl alcohol	Not specified	Double injected device for prolonged or pulsatile release
28, 65	Bi-layer device	Soy protein isolate	*Drug*: theophylline *Cross-linker*: glyoxal *Plasticizer*: glycerol *Reinforcement*: hydroxyl apatite	Twin-screw extruder + horizontal injection molding machine (screw type)	Co-injected device for controlled release
33, 72	Oral capsular device	HPC	*Plasticizer*: PEG 1500 *Mold release agent*: peanut oil (external)	Bench-top micro-molding machine (plunger type)	Functional container for pulsatile/colonic release
73	Oral magnetic depot capsular device	PLC Polycaprolactam PLC/starch	-	Homemade equipment	Magnetic driven container for site specific release

Dip-molding has extensively been used for the manufacturing of gelatin capsules for over a century and in this period it has undergone many improvements. However, it requires the use of 30% aqueous gelatin solutions maintained at 40 °C, which represent a good substrate for bacterial growth. Moreover, water needs to largely be removed by drying the molded items thus increasing the time and costs of production. Since the second half of the '90s, a thermoplastic processing technique for the molding of capsules was sought that would allow softened materials with a constant and low water content to be employed [16,19,34]. IM was therefore proposed also in view of the possibility of molding products with precise size, shape and closure characteristics. In addition, such a technique might be applied to materials that could not be processed by dip-molding. In this respect, starch was selected because it is a plant polymer that would overcome some common religious or dietary constraints and could especially be appealing for health (nutraceuticals) and food markets. Both gelatin and starch show a thermoplastic behavior under mechanical stress, in specific humidity and temperature conditions [34-38]. In particular, potato starch capsules with 0.4 mm wall thickness (Capill®) demonstrated an *in vitro* (disintegration time) and *in vivo* (bioavailability and scintigraphic data) performance comparable with that of marketed hard gelatin capsules [16,39]. Capill® was proposed in five different sizes (the same cap fits bodies with different lengths) and can easily be filled with a variety of formulations (solid or liquid) [40,41]. Generally, Capill® shell devices showed satisfactory technological characteristics in terms of dimension (height, length and wall thickness) consistency, suitable mechanical strength and smoothness of the surface. Capill®-based formulations were successfully proposed as the core for pH-sensitive coated DDSs [39,42]. In particular, by the Targit® technology [43,44], which relates to a starch capsule coated with a mixture of Eudragit® L and S up to different thicknesses, the authors claimed the possibility of targeting specific sites within the intestinal region (*e.g.* colon) through a combined pH- and time-dependent mechanism [45,46].

IM was also explored as an alternative technique for the preparation of conventional tablets [14] and oral prolonged-release matrix systems [29-32], implants [15,17,21,48-51] or intravaginal inserts [52,53], which are mostly manufactured by compression or HME at present.

The production of tablets by IM was preliminarily evaluated using solid PEGs as thermoplastic polymeric carriers and MCC as the reinforcement agent for immediate-release (IR) formulations [14]. The process was demonstrated to provide significant benefits, such as dust containment, good content uniformity even with low-dosed active compounds (< 1%) and poor influence of the particle size and shape of the drug on the physical properties of the

tablets. Stability and loading limitations, connected with the drug solubility in the molten polymer, were in few cases observed. According to the authors, although the estimated manufacturing rates would be lower than with conventional tableting, this might be outweighed by the reduced time, steps and costs needed to reach an industrial-scale production and by the continuous nature of the IM process.

Moreover, IM technique offers several possible advantages in the development of non-disintegrating prolonged-release drug delivery systems, such as the homogeneous embedding of drug particles within release-controlling polymer combined with the ability to yield and accurately define any possible shape of the device (*e.g.* round-shaped end to facilitate subcutaneous implantation [48]). With respect to biodegradable implants, the temperature conditions required by IM could be sufficient to sterilize the substrate material (autosterilization) with no need for other procedures that might alter the chemical and mechanical characteristics of the final product (*e.g.* γ-sterilization, ethylene oxide) [21]. Among prolonged-release DDSs, those produced by IM generally ensure a low porosity, great ability to maintain physical integrity (no disintegration/break) and effective control of release (very slow release rates obtained).

The use of wheat starch as the matrix former for oral prolonged DDSs was explored based on the thermoplastic properties shown by potato starch that were formerly exploited by the Capill® technology [47]. Ethylcellulose (EC) IM matrices, containing different hydrophilic polymers as release promoters, *e.g.* hydroxypropyl methylcellulose (HPMC) [29], low-substituted hydroxypropyl cellulose (L-HPC) [30], polyethylene oxide (PEO) [31] and xanthan gum [32], were also developed.

According to the their well-known thermoplasticity, some polymers were used to prepare biodegradable IM implants such as poly(L-lactide) (PLA) [21,48,49,51], poly(L-lactide-co-glycolide) copolymers (PLGA) [51], poly(ε-caprolactone) (PLC) [50]. Furthermore, a polyanhydride-based implantable system containing gentamicin sulfate for the treatment of osteomyelitis (Septacin™) was designed in the form of a string of five beads joined by four linkers having the same composition as the beads, and the relevant production-scale manufacturing was developed. *In vivo* data from infected animal models (rats and horses) demonstrated the ability of the implant to eradicate specific bacteria (Staphylococcus aureus) [15]. Moreover, a tolerability study conducted with surgically-treated patients showed that Septacin™ could provide high local drug concentrations at the implantation site while limiting the systemic levels.

As already mentioned, only a few applications of IM relate to delivery systems actually innovative in terms of design, composition and/or performance. In this respect, Egalet® is a new delivery platform for oral administration able to ensure a prolonged or pulsatile/delayed release of active substances [54-59].

In the prolonged-release configuration, this system is composed of a drug-containing hydrophilic/erodible matrix partially coated with an insoluble and impermeable polymeric layer (Figure 3a). The drug liberation can only occur from the two uncoated lateral surfaces and is driven by a diffusion/erosion-based mechanism. The release rate control (zero-order kinetics) is achieved by a restriction of the area in contact with aqueous biological fluids. By adding two erodible polymeric plugs at each open end, a lag phase prior to release can be obtained (Figure 3b). The duration of such a delay period can be modulated depending on the composition and thickness of the plugs. An active ingredient could also be included in the formulation of these plugs, thus enabling a repeated release of the same drug or distinct release pulses of different drugs (multi-therapy platform).

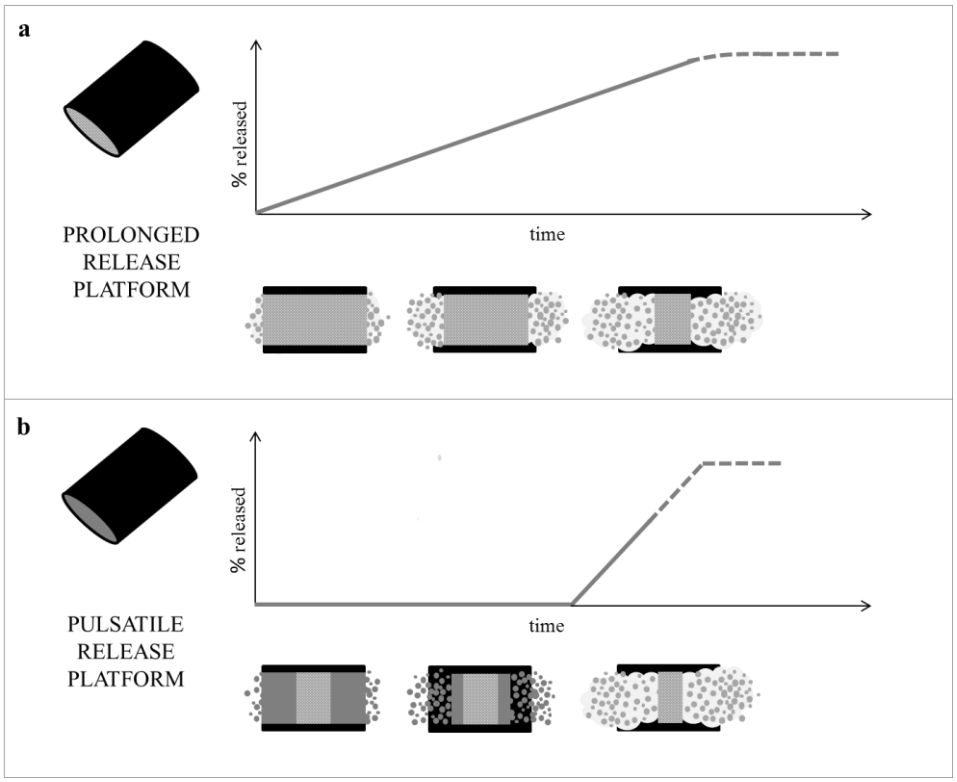


Figure 3: outline and expected release profiles of Egalet® [59].

The ability of the Egalet® technology to achieve zero-order release or selective delivery to the colonic region was demonstrated by γ-scintigraphic and pharmacokinetic studies [56,57,60]. In particular, the Egalet® ADPREM (Abuse Deterrent Prolonged Release Erodible Matrix) technology was developed for the administration of opioids (*e.g.* morphine; hydrocodone) to reduce the daily dosing frequency in patients under pain management therapy thus involving a lower risk of abuse [61,62].

The Egalet® release platforms are based on well-known materials, design and release mechanisms, yet they take advantage of IM for the preparation of multi-layer delivery systems within a single process (Egalet® technology). Such a process involves two subsequent injection phases into the same mold from two perpendicularly-positioned nozzles [63]. During the former phase, a plunger is placed in the center of the mold cavity, creating a gap between its own surface and the wall of the cavity. The coating material is injected into this space by the vertical nozzle and, as soon as it has cooled down, the plunger moves back. At the same time, the latter injection of the drug-containing core formulation is run. Finally, the plunger returns to the first injection position, thus favoring the ejection of the molded device.

By an innovative co-injection technique, Vaz and co-authors proposed a bi-layer delivery system based on soy protein [28,64,65]. This technique represents an evolution of traditional IM and likewise derives from the plastics industry where it was employed for the manufacturing of devices with a well-defined geometry and skin/core morphology [66]. It entails the sequential injection into the mold of skin and core materials from two different plasticating chambers through the same runner (Figure 4). This technique allows the core aterial to be completely encapsulated thus being potentially advantageous for the preparation of coated systems.

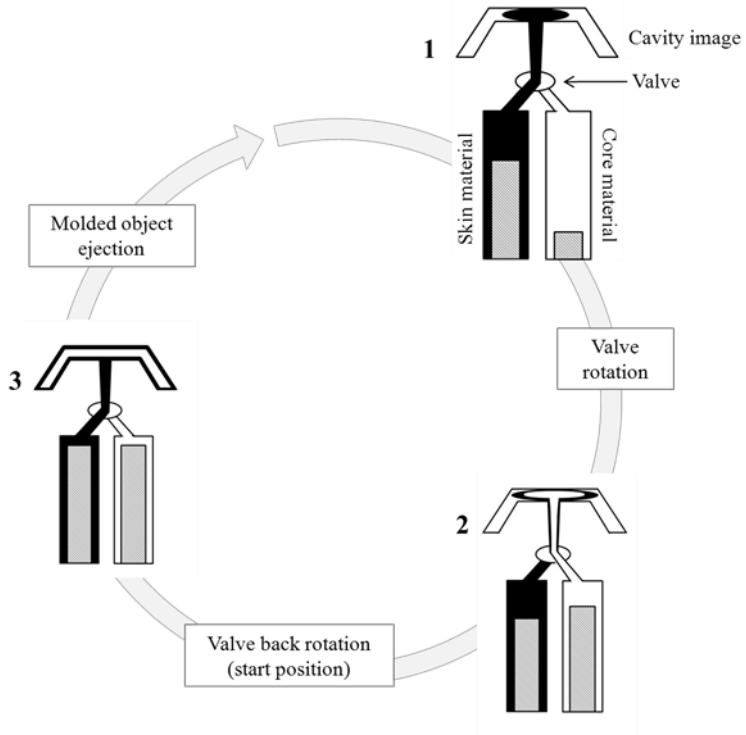


Figure 4: outline of a co-injection process [66].

Besides the general advantages offered by IM in terms of cost-effectiveness and industrial scalability, co-injection enables the simultaneous use of different materials to achieve a coated device in a one-step process without requiring further operations. Moreover, the coat layer thickness can precisely be defined irrespective of different shape characteristics. With respect to the release performance, the authors claimed the possibility of controlling the drug liberation by modulating the skin thickness and the cross-linking degree of the matrix-forming soy protein. In order to enhance the release control options, multi-layer systems could also be devised.

In the field of oral DDSs, the Chronotopic™ is a swellable/erodible device for pulsatile and/or time-dependent colonic release based on hydrophilic cellulose derivatives [67-71]. The duration of the lag phase prior to release depends on the thickness and composition of the functional cellulosic barrier applied to the drug-containing core. By pharmacokinetic and γ-scintigraphic studies, the Chronotopic™ was proved able to provide lag phases consistent with chronotherapy and colon targeting purposes. By employing the IM technique, a different configuration of the system was proposed based on separate container shells and drug fillings [33]. Such a shell device (Chronocap™) thus represents a functional container intended to convey differing formulations and release a variety of bioactive compounds following programmed lag phases. The peculiar advantages of the Chronocap™ would lie in the

possibility of undergoing an independent pharmaceutical development regardless of the final contents and the scalability of the relevant manufacturing process. Capsular shells with nominal thicknesses of 300, 600, 900 μm prepared from various hydroxypropyl cellulose (HPC) grades exhibited satisfactory technological properties and performance (Figure 5, Table 3). In particular, mechanical resistance was demonstrated to be comparable with that of hard gelatin capsules or even higher. Capsule shells filled with a tracer drug formulation showed reproducible *in vitro* lag phases followed by an immediate drug release caused by breakage of the shell. Lag times were dependent on the HPC grade and the shell wall thickness. In a preliminary *in vivo* evaluation, Klucel® LF-based systems were proved to yield delayed salivary levels of the conveyed model drug as a function of the shell thickness, with a linear correlation between *in vivo* and *in vitro* lag times [72].

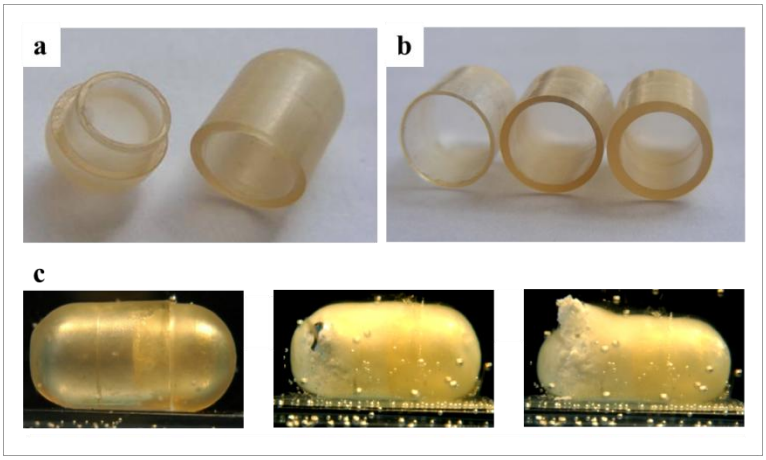


Figure 5: Klucel® LF-based Chronocap™ devices: (a) cap and body, (b) bodies with differing nominal thicknesses (300, 600 and 900 μm) and (c) morphological changes in aqueous fluid [33].

Table 3: key characteristics of Klucel® LF-based Chronocap™ devices with differing nominal thicknesses [33] and [72].

Nominal thickness μm	**Thickness μm (CV)**	**Elastic modulus N/mm² (CV)**	**$t_{10\%}$ *in vitro* min (CV)**	**$t_{10\%}$ *in vivo* min (CV)**
300	346 (12.30)	2.672 (15.04)	29.3 (22.2)	75.0 (13.6)
600	645 (13.20)	5.342 (15.72)	53.5 (10.6)	140.4 (16.2)
900	880 (4.64)	8.451 (3.44)	91.7 (3.16)	211.8 (20.1)

Polymeric capsules prepared by IM, the gastrointestinal (GI) transit of which would be externally controlled by means of a magnet, were also proposed [73]. Thanks to a small magnet placed inside the capsule, the system can be maintained in a specific site (*e.g.* the

stomach) for a defined period of time and, only after removing the external control magnet positioned on the skin in the concerned area, it can move on. The ability of magnetic depot preparations to increase the gastric residence time of solid dosage forms thus improving the bioavailability of drugs poorly absorbed in the lower parts of the GI tract was explored in animals and in humans using systems obtained by tableting or by filling commercially available capsules [74-76]. The use of IM allowed capsule-like shells with the magnet already inserted to be manufactured, and polymers with lower environmental impact to be screened.

5. Conclusions

In the present work, conventional and controlled-release dosage forms prepared by IM are reviewed. As it enables the manufacturing of 3D-shaped objects (monolithic, multilayer or coated ones) starting from polymeric formulations through a cyclic, automated process, this technique holds promise in terms of versatility (shape, dimensions, design and composition), patentability and industrial scalability of the obtained products. However, it may entail limitations related to the thermal stability of drug substances.

The overview of the scientific literature and of the drug products developed has pointed out two main fields for the application of IM, *i.e.* its use as an alternative manufacturing technique due to inherent economic advantages, and exploitation as a viable approach to novel DDSs. Moreover, it has been highlighted that there still is a great potential for capitalizing on this technique especially with regard to areas where new concepts are required, such as primarily the development of actively controlled miniaturized devices or biological electromechanical systems (BioMEMS) [77-80].

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Part II

The content of Part II has already been published in:

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GASTRORESISTANT CAPSULAR DEVICE PREPARED BY INJECTION MOLDING

Abstract

In the present work, the possibility of manufacturing by injection molding (IM) a gastro-resistant capsular device based on hydroxypropyl methyl cellulose acetate succinate (HPMCAS) was investigated. By performing as an enteric soluble container, such a device may provide a basis for the development of advantageous alternatives to coated dosage forms. Preliminarily, the processability of the selected thermoplastic polymer was evaluated, and the need for a plasticizer (polyethylene glycol 1500) in order to counterbalance the glassy nature of the molded items was assessed. However, some critical issues related to the physical/mechanical stability (shrinkage and warpage) and opening time of the device after the pH change were highlighted. Accordingly, an in-depth formulation study was carried out taking into account differing release modifiers potentially useful for enhancing the dissolution/disintegration rate of the capsular device at intestinal pH values. Capsule prototypes with thickness of 600 and 900 μm containing Kollicoat® IR and/or Explotab® CLV could be manufactured, and a promising performance was achieved with appropriate gastric resistance in pH 1.2 medium and break-up in pH 6.8 within 1 h. These results would support the design of a dedicated mold for the development of a scalable manufacturing process.

Contents

Keywords: injection molding, micromolding, capsular device, gastric resistance, enteric polymer, hydroxypropyl methyl cellulose acetate succinate.

1. Introduction

Preventing the chemical degradation of active principles in the acidic environment of the stomach and protecting the gastric mucosa from irritation phenomena induced by drug assumption are the two main reasons for conceiving gastro-resistant dosage forms [1]. Such formulations are also used to pursue selective release into particular regions of the intestinal tract, either to exploit favorable absorption sites or provide treatment for local diseases. Moreover, according to a time-dependent strategy, the colon can be targeted by enteric-coated pulsatile delivery systems able to provide lag phases starting on gastric emptying, with the coating dissolution, and lasting throughout the small intestinal transit time (SITT) [2-4].

Gastric resistance is generally obtained by means of polymers with pH-dependent solubility; the most widely employed are acrylic and metacrylic acid copolymers (*e.g.* Eudragit® L, S and FS), polyvinyl acetate phthalate (PVAP) and cellulose derivatives (*e.g.* cellulose acetate phthalate, CAP; hydroxypropyl methyl cellulose acetate succinate, HPMCAS) [5]. These are applied onto drug-containing solid cores (tablets, capsules, pellets, granules) using different techniques that can basically be distinguished according to the amount of solvent required, preferably water, and the role it would play in the coating process. Large amounts of liquid to be dried are in fact involved in the deposition of gastro-resistant layers from polymeric solutions or suspensions (film-coating technique) [6-9]. On the other hand, in order to avoid the use of water thus overcoming stability issues and drawbacks associated with the need for solvent removal, dry-coating techniques were proposed, such as conventional compaction-based processes (press-coating technique) [10-13]. More sophisticated approaches envisage the deposition onto core substrates of liquid (non-aqueous) or solid (powder blends) coating agents, and subsequent formation of a continuous layer by solidification/polymerization or heat-curing [14-17]. Despite the improvements in terms of process time, manufacturing costs and stability of the final product, the industrial scale-up and availability of suitable coat-forming agents still represent major limitations to a wider diffusion of dry-coating techniques.

In the case of enteric-coated products intended to release the active ingredient as soon as they are emptied from the stomach, a rapid disintegration/dissolution of the coating layer is expected. This is especially important when drugs having an absorption window in the upper part of the small intestine are dealt with [18]. It was recently highlighted that gastro-resistant systems can take up to 2 h for a complete exposure of the core to the intestinal fluids, thus potentially affecting the drug bioavailability and the efficacy of the therapy [19].

In coating processes an important role is generally played by the drug-containing core, the physical (shape, dimension, surface), technological (thermal resistance, hardness, friability, wettability, disintegration/dissolution tendency) and stability characteristics of which may constrain or even impair each of the above-mentioned techniques [20-23].

Based on the above-discussed premises, the possibility of preparing container-like enteric-soluble devices that could be filled and sealed after manufacturing would represent an innovative and advantageous alternative to the design of coated gastro-resistant dosage forms. In this respect, hollow HPMCAS or PVAP pipes were prepared by hot melt extrusion, manually filled with a model drug powder and heat-sealed at their open ends, thus providing enteric devices that showed promising results [24].

Injection molding (IM), which involves the injection of appropriately softened/melted materials into a mold wherein they are given a definite three-dimensional shape, was proven a viable technique in the preparation of capsular items composed of separately manufactured parts to be matched after filling with various formulations (powders, granules/pellets, semi-solids or liquids) through well-established processes [25]. The performance of such devices would depend on their composition and design features (morphology and thickness of the shell) only, in spite of differing characteristics of the conveyed drug and/or formulation, which could offer major benefits in terms of time and costs required for development. Moreover, they would be ready-to-use, *i.e.* easy to be filled for extemporaneous preparations. Molded capsular shells composed of potato starch (Capill®) were proposed to replace commercial gelatin or hydroxypropyl methyl cellulose capsules intended for immediate release (IR) [26,27]. More recently, IM was successfully employed to prepare a capsular pulsatile delivery device based on swellable/erodible polymers (hydroxypropyl cellulose, HPC) [28-30].

In the present work, the feasibility of IM in the preparation of HPMCAS-based capsules was explored with the aim of developing a gastro-resistant shell to be used as an innovative delivery platform for enteric dosage forms.

2. Materials and methods

2.1. Materials

Hydroxypropyl methyl cellulose acetate succinate (HPMCAS, AQUOT-LG®; Shin-Etsu, J); polyethylene glycol (PEG 1500; Clariant Masterbatches, I); sodium starch glycolate (Explotab® CLV; JRS, D) (d_{10} = 10 μm; d_{50} = 25 μm; d_{90} = 52 μm); polyvinyl alcohol-

polyethylene glycol graft copolymer (Kollicoat® IR; BASF, D) (d_{10} = 9 μm; d_{50} = 23 μm; d_{90} = 55 μm); dipotassium hydrogen phosphate anhydrous (K_2HPO_4; Carlo Erba, I) (d_{10} = 2 μm; d_{50} = 6 μm; d_{90} = 24 μm); sodium hydrogen carbonate ($NaHCO_3$; Carlo Erba, I) (d_{10} = 15 μm; d_{50} = 28 μm; d_{90} = 63 μm); acetaminophen (Atabay, TR) (d_{10} = 14 μm; d_{50} = 29 μm; d_{90} = 58 μm).

2.2. Methods

2.2.1. IM process

IM was performed by a bench-top micromolding machine (BabyPlast 6/10P, Cronoplast S.L.; Rambaldi S.r.l., I).

The polymeric formulations were prepared by co-grinding HPMCAS and PEG 1500 in a blade mill; blends containing release modifiers were obtained by mixing in turbula (Type T2C, WAB, CH) for 20 min. Prior to use, all materials except for PEG 1500 were kept in a ventilated oven at 40 °C for 24 h. In Table 1 the composition (%, by weight) of the molded polymeric formulations is reported.

Table 1: composition (% by weight) of molded formulations.

	Polymer	**Plasticizer**	**Release modifier**	
Code	**HPMCAS**	**PEG 1500**	**Explotab®CLV**	**Kollicoat®IR**
PEG15	87	13	-	-
PEG25	80	20	-	-
PEG35	74	26	-	-
EXP	60	15	25	-
EXPPEG35	55	20	25	-
KIR	60	15	-	25
1EXP2KIR	60	15	8.5	16.5
2EXP1KIR	60	15	16.5	8.5

Before processing, the behavior of the polymer and polymeric formulations when subjected to heating or IM was evaluated as follows.

Hot-plate experiment: 2-3 g of polymer/polymeric formulation was placed in an aluminum pan on a hot plate and heated under continuous manual mixing, while gradually increasing the temperature up to 200 °C. Samples were checked for overall aspect, color, texture and mechanical characteristics during heating and after cooling.

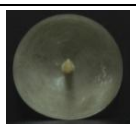
Air shot test: 50 g of polymer/polymeric formulation was loaded into the IM press through the hopper and expelled from the injecting unit as during a purge operation [31]. The test was repeated under different operating temperatures. Samples were checked for overall aspect, color and mechanical characteristics immediately after ejection and when solidified.

2.2.1.1. Manufacturing of molded items

50 g of polymeric formulation was loaded into the plasticating chamber of the IM press through the hopper and then conveyed by means of a first piston to the injecting chamber. By successively applying two distinct pressures, each for a defined period of time and at a selected rate, another piston (10 mm diameter) injected a specific amount of melt (charge) through a 1 mm diameter nozzle into the mold cavity (disk or capsular shape). Prior to product ejection, the mold was kept closed by applying a closing pressure to allow the injected melt to cool down and harden. The rate of each process stage was expressed as % of the maximum value.

Molded items were prepared by means of two different molds: *i)* a 30 mm diameter disk-shaped mold provided with a central gate, enabling the selection of differing thicknesses (200, 400, and 600 μm) and *ii)* a capsular mold with two cavities for the cap (8 mm height and 8 mm diameter) and the body (11 mm height and 8 mm diameter), respectively, each provided with a lateral gate, enabling the preparation of matching items within a single manufacturing cycle and the selection of differing shell thicknesses (300, 600, and 900 μm) [29]. The operating conditions were varied within different ranges of values according to whether disks or capsules were employed (Table 2). Molds were manually lubricated with peanut oil approximately every 15-20 units manufactured. The first unit obtained after this operation was discarded.

Table 2: IM operating conditions.

	Disk	**Capsule**
		
Plasticating chamber temperature, °C	120-160	140-165
Injecting temperature, °C	130-170	143-168
Nozzle temperature, °C	140-180	145-170
Charge, mm	4.5-11	6-20
First-injection pressure, bar	20-90	60-110
First-injection time, s	0.8	0.8-20
First-injection rate, %	40-90	5-85
Second-injection pressure, bar	15-70	35-65
Second-injection time, s	0.3	0.3-10
Second-injection rate, %	30-70	40-75
Cooling temperature, °C	15	15-25
Cooling time, s	2.5	10
Closing pressure, bar	60	60-90
Opening rate, %	20-40	40

2.2.2. Characterization of molded items

Molded items, *i.e.* disks and assembled capsule shells, were checked for weight (analytical balance BP211, Sartorius, D; n = 10) and thickness (digimatic indicator ID-C112X, Mitutoyo, J; n = 10). Digital photographs (Nikon D70, Nikon, J) of molded items were acquired, and photomicrographs were taken by scanning electron microscope (SEM; Sigma, Zeiss, D) after gold sputtering (10 nm). The characterization was performed immediately after ejection, except for photomicrographs, and after 24 h storage at ambient conditions (24 ± 2 °C/55 ± 5% RH). Photomicrographs of a few molded disks were also collected after incubation in unstirred pH 6.8 phosphate buffer at room temperature for 120 min and drying in a ventilated oven at 40 ◦C for 24 h.

2.2.2.1. Evaluation of gastric resistance performance

Disks: immediately after ejection disks were positioned on manually assembled cells modified from the extraction cells used in the dissolution test for transdermal patches (Ph. Eur. 7th ed.) (Figure 1). The reservoir compartment was loaded with an amount of a powder tracer (acetaminophen) ranging from 43 to 48 mg. The surface exposed to the

acceptor fluid was 177 mm^2. The test (n = 3) was performed in pharmacopoeial *apparatus* 2 (Dissolution System 2100B, Distek, US) at 100 rpm under the conditions of the Dissolution test for delayed-release dosage forms (Method B, USP 34) except for the medium volume (600 mL). Fluid samples were withdrawn at fixed time points and assayed spectrophotometrically at 254 nm (spectrophotometer lambda25, Perkin Elmer, US).

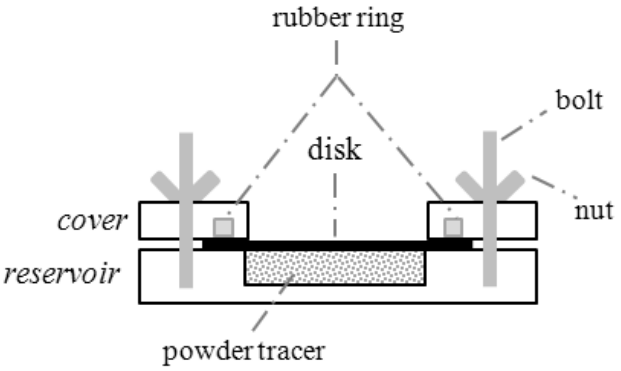


Figure 1: outline of the system for the evaluation of disk gastric resistance.

Capsular devices: each capsule body was manually filled with an amount of a powder tracer (acetaminophen) ranging from 86 to 92 mg and closed with a matching cap. The gastric resistance performance (n = 3) was evaluated in pharmacopoeial *apparatus* 2 (Dissolution System 2100B, Distek, US) at 100 rpm under the conditions of the Dissolution test for delayed-release dosage forms (Method B, USP 34). Fluid samples were withdrawn and assayed as above reported. Lag time ($t_{10\%}$), *i.e.* the time to 10% release in pH 6.8 phosphate buffer, was calculated from the release curves (n = 3) and reported as a detail in the figures together with the relevant coefficient of variation (CV).

3. Results and discussion

With the aim of developing a new injection-molded capsule-like container for enteric release, the relevant design and formulation features needed to preliminarily be assessed. The latter were indeed expected to fulfill a number of different requirements, such as the suitability for the oral route, versatility in terms of contents and possibility of filling through established industrial encapsulation processes. At the same time, the desired gastric resistance performance followed by a rapid disintegration/dissolution at intestinal pH values had to be ensured and merely depend upon the container device irrespective of the

conveyed formulation. Furthermore, the IM process should have been feasible and yield molded items with appropriate aspect, technological properties and physical/mechanical stability. As in the micromolding (μIM) technique, which is currently applied to the production of medical devices and miniaturized electronic parts, a specially devised press had to be employed, and the manufacturing was expected to be particularly critical in view of the need for meeting strictly controlled geometric as well as functional characteristics and maintain them over the shelf-life of the final formulation [32-37]. Besides, a strong impact of the operating pressure and thermal history of the material on the dimensional stability of the molded item had to be taken into account.

HPMCAS was chosen as the barrier-forming polymer because of its wide application as an enteric coating material and thermoplastic properties that were already exploited for hot melt extrusion (HME) [24]. Preliminarily, its softening/melting behavior following heating on hot plate or injection processing (air shot test) and its characteristics after solidification were evaluated, indicating the need for the addition of a plasticizer in order to counteract the glassy nature of the molded material. Among various plasticizers tested (triethyl citrate; dibuthyl sebacate; PEG 400, 1500, 6000 and 20000), PEG 1500 was selected based on the homogeneous aspect of the softened/molten raw materials and the improved mechanical characteristics of the solidified composite. Moreover, HPMCAS blends with PEG 1500 turned out to be the most easily processed by the IM press in use. The influence of the plasticizer on the processability of the polymeric formulation and the characteristics of the product was investigated in the 15-35% (with respect to the amount of polymer) range by means of two differing molds, *i.e.* a disk- and a capsule-shaped one, each allowing the nominal thickness of molded items to be varied within a relatively wide range (600, 400 and 200 μm or 900, 600 and 300 μm, respectively). The former allows the production of centrally gated circular disks (diameter 30 mm) especially suitable for the evaluation of dimensional changes. With respect to the capsule-shaped mold, though offering several advantages (*i.e.* production of capsule cap and body within the same cycle, possibility of varying the shell thickness), some limitations in the characteristics of the resulting items could be expected in view of the lateral position of the gate and presence of a mobile insert determining the width of the cavity [29].

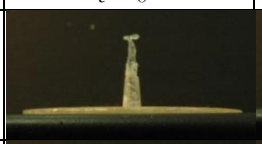
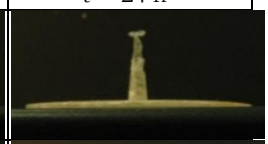
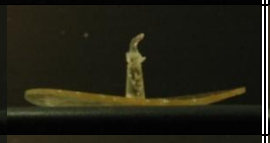
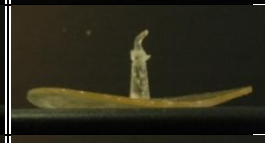
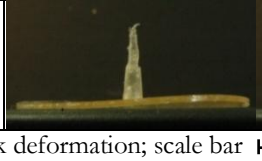
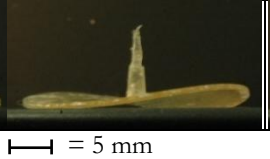
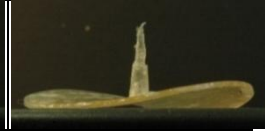
The amount of 15% of plasticizer turned out to be insufficient, not only on account of the poor flexibility shown by the molded items, but also because only 600 μm thick disks could be obtained and no capsular shells at all. Increasing the PEG 1500 content to 25% was already enough to easily manufacture disks up to 200 μm thickness and complete capsular

shells of 900 μm. Only with the highest amount of plasticizer tested, 600 μm capsules could be prepared.

When thermoplastics are processed by IM, the dimensions of the molded part change as the part cools. Often, these changes are referred to as either shrinkage or warpage and can be used to predict the appropriate mold geometry [38]. Although shrinkage is based on thermal contraction, other mechanisms may be responsible for dimensional changes after demolding (*e.g.* inherent stresses, crystallization, mechanical constraint). For example, if residual stresses created by variations in the cooling rate are strong enough to overcome the relevant structural integrity, the part will warp upon ejection from the mold. The control of shrinkage is particularly important in applications requiring tight tolerances. The wall thickness was shown to have a major influence on shrinkage that generally turns out increased for thicker parts, because of the variation in a series of parameters such as the holding pressure or the cooling and crystallization rates. In Table 3, differences between the thickness of disks and the width of the relevant mold cavity (600 μm) are reported along with digital photographs of the molded items immediately after ejection (t = 0) and over time (t = 3 and 24 h).

Molded HPMCAS disks were proven to increase in thickness immediately after demolding, and no significant influence ($p < 0.1$) of the amount of plasticizer on this parameter was found. On the contrary, a warp tendency of molded disks was noticed that could be related to the amount of plasticizer in the formulation. In fact, only for the items containing 15% of PEG 1500, bending was neither observed following demolding nor after storage. This allowed thickness measurements to be performed also 24 h after manufacturing.

Table 3: changes in thickness and aspect of 600 μm disks over 24 h from manufacturing.

Code	**Δ thickness** μm (CV)				
	t = 0	t = 24 h	t = 0	t = 3 h	t = 24 h
PEG 15	43 (7)	47 (8)			
PEG 25	55 (23)	nd			
PEG 35	35 (21)	nd			

nd = not determined because of disk deformation; scale bar ⟼ = 5 mm

As far as the gastric resistance of PEG25 and PEG35 formulations is concerned, the relevant capsular devices, irrespective of the shell thickness, remained intact in acidic fluid (pH 1.2) but they were unable to release their contents within 2 h in phosphate buffer pH 6.8.

These results pointed out some critical issues with respect to the goal of developing a delivery platform for enteric dosage forms based on HPMCAS capsules. In particular, the shrinkage/warpage tendency of the polymeric formulation and the need to shorten the opening time of the device had both to be taken into account. In the plastics industry, for the development of molded items, the design of a mold and the set-up of the melt composition as well as of the operating conditions would concomitantly be performed by trial and error once their requirements are defined (Figure 2). However, the inherent complexity of this approach would further be increased in the case of pharmaceutical products due to the need for fulfilling challenging requirements, such as a defined release behavior, and to the limited information available on the IM processability of the excipients involved (polymer and adjuvants). At this stage, it was accordingly decided to focus on a formulation study, and molded prototypes were used as screening tools for assessing the effectiveness of the gastric resistance performance. The thermal and rheological characteristics as well as mechanical stability of the selected formulation(s) will subsequently be evaluated in order to design the final mold.

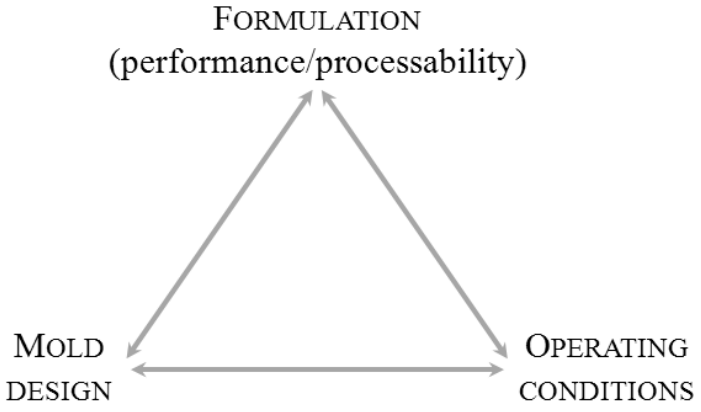


Figure 2: interrelated steps involved in the development of the molded device.

With the aim of enhancing the dissolution/disintegration rate of the capsular device at intestinal pH values, *i)* release modifiers, the channeling action of which could be attributed to the inherent solubility or swelling properties, and *ii)* buffering salts (dipotassium

hydrogen phosphate and sodium hydrogen carbonate), potentially suitable for increasing the microenvironmental pH of the surrounding fluids, were considered. The addition of soluble pore formers or disintegrants (*e.g.* polyvinylpyrrolidone and croscarmellose sodium, respectively) to film-coating suspensions of pH-responsive polymers was already suggested with the aim of improving the pulsatile release of drugs to the ileo-colonic region [39,40]. Moreover, a double coated enteric system consisting of an inner layer of Eudragit® L or S neutralized with organic acids and an outer conventional coating of the same polymer was recently proposed [18,41,42]. Such a device was subject to a fast and consistent disintegration after stomach emptying (around 30 min *in vivo* disintegration time).

The types and/or amounts of adjuvants were selected by preliminary heating and/or molding tests. In this respect, browning phenomena occurred at operating temperatures on polymeric samples containing either the phosphate or carbonate salt, thus pointing out possible stability issues for molded items. A polyvinyl alcohol-polyethylene glycol graft copolymer (Kollicoat® IR), generally employed as the film-forming polymer for immediate release coated dosage forms or as a binder in fast-dissolving tablets, was selected as the soluble pore former. Although characterized by a glassy-rubbery transition temperature (T_g) around 200 °C, when Kollicoat® IR was worked in admixture with plasticized HPMCAS, a homogeneous molded material was obtained already at the lowest operating temperatures. Among the disintegrants tested (starch and cellulose derivatives), sodium starch glycolate (Explotab® CLV) was shown to exert no negative impact on the processability of the polymeric substrate and rather improve the dimensional stability of molded items as expected from solid fillers [43]. As far as the polymer/plasticizer ratio in the polymeric formulations with the release modifiers is concerned, 25% of PEG 1500 with respect to the amount of HPMCAS was preferred because of the acceptable balance between processability of the polymeric substrate and dimensional changes of the product that was previously obtained.

Disks of 200, 400 and 600 μm containing 30% by weight of either the soluble pore former or the disintegrant selected were obtained, whereas in no case intact and complete capsular shells with thickness other than 900 μm were produced. The manufacturing of 200 μm disks with the KIR formulation was especially critical, thus providing brittle and often damaged items that could not withstand characterization. SEM photomicrographs helped highlight the surface and structure characteristics of molded items containing Kollicoat® IR or Explotab® CLV as compared with HPMCAS ones (Figure 3). In particular, solid

particles distributed throughout the cross-section of the disintegrant-containing item are clearly evident.

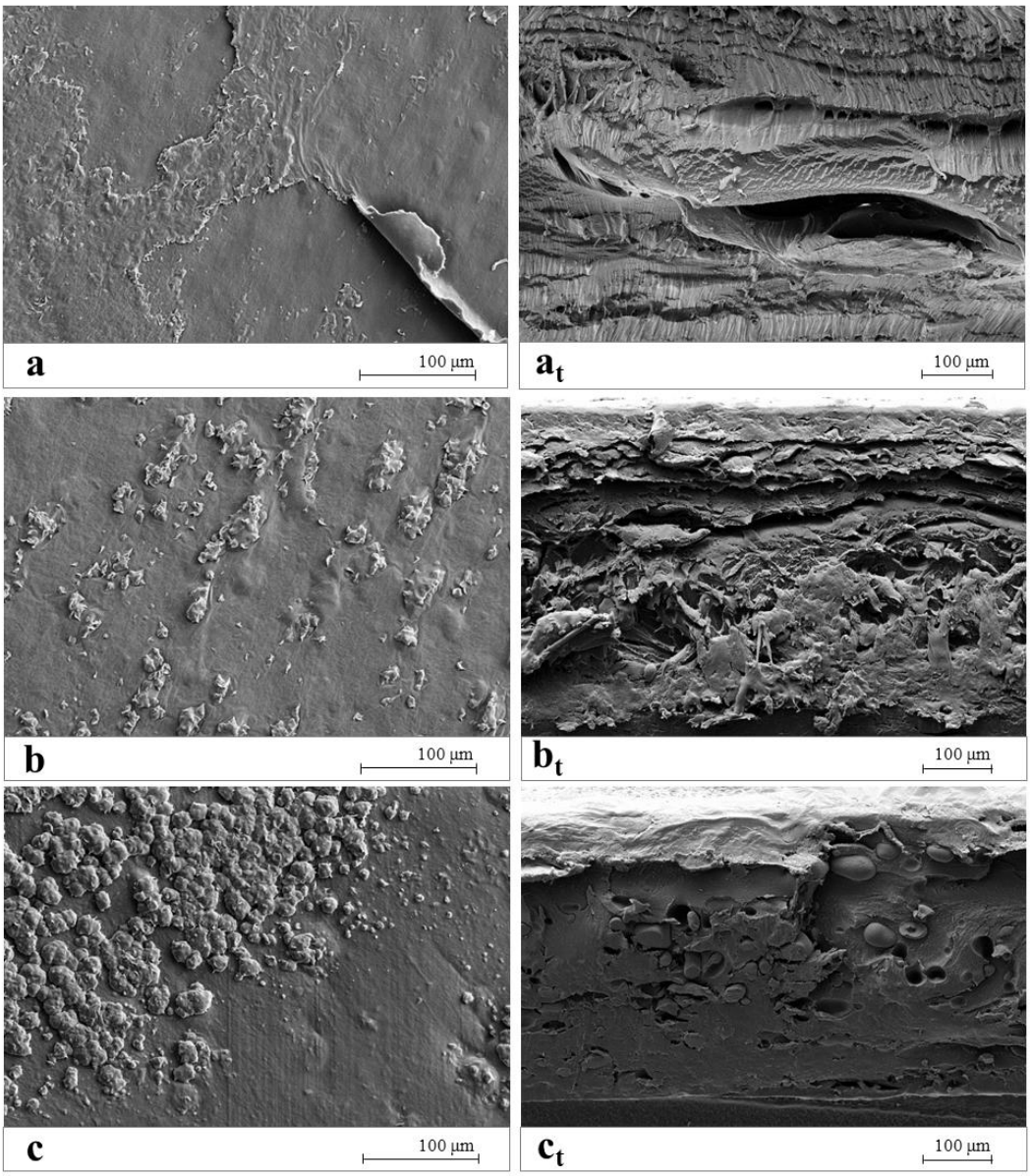


Figure 3: photomicrographs of the surface (a, b and c) and cross-section (a_t , b_t and c_t) of molded HPMCAS-based 400 µm disks, as such (a and a_t) or containing 30% by weight of a release modifier (Kollicoat® IR: b and b_t or Explotab® CLV: c and c_t).

In Figure 4 the release profiles of capsular devices containing a powder tracer and the relevant $t_{10\%}$ values in pH 6.8 buffer are reported.

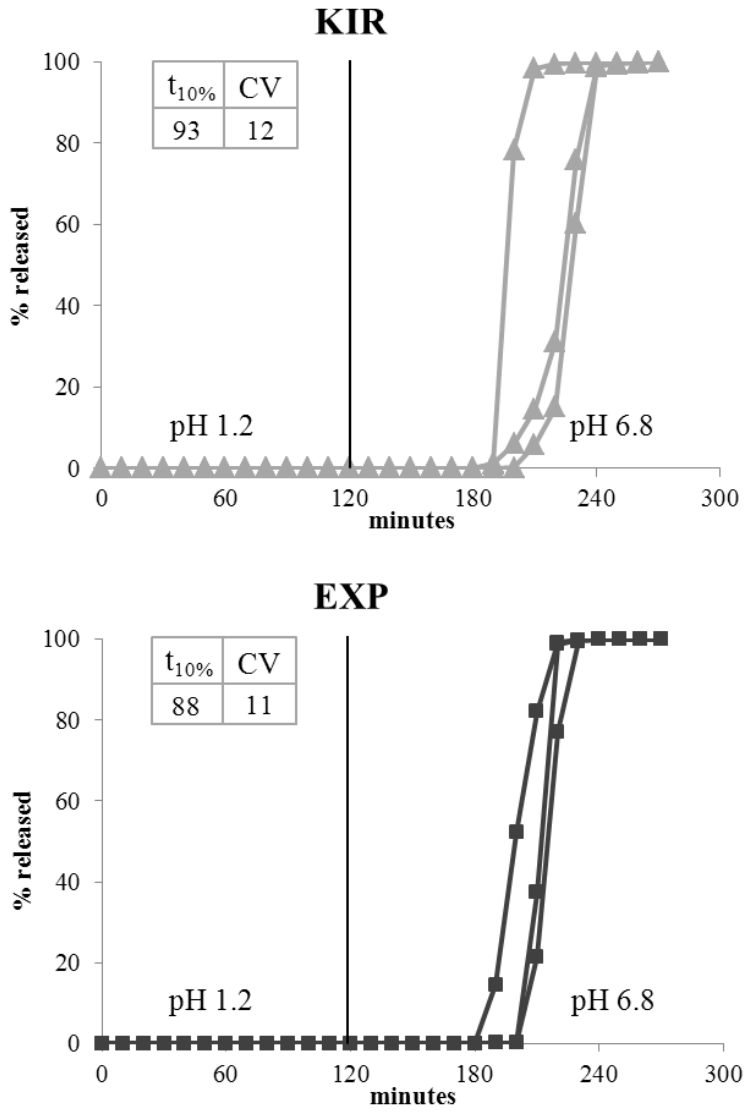


Figure 4: release profiles of 900 μm thick enteric capsular devices containing 30% by weight of a release modifier (top: Kollicoat® IR, bottom: Explotab® CLV); mean $t_{10\%}$ (min) in pH 6.8 buffer and relevant CV highlighted in tables.

Both the Kollicoat® IR- and Explotab® CLV-based capsular systems were demonstrated able to withstand the acidic medium (pH 1.2) for 2 h, confirming that the release modifiers were efficiently embedded in the molded polymeric matrix. In pH 6.8 buffer a lag time of about 1.5 h prior to the break-up of capsular devices and release of the conveyed powder was observed, which was slightly shorter for the disintegrant-containing shell. Indeed, a minor diffusive release phase was shown by the capsular system with the soluble pore

former. In order to evaluate the influence of the polymeric barrier thickness, the molded disks made of HPMCAS blends with Kollicoat® IR and Explotab® CLV were used. For this purpose, a testing method analogous to the compendial dissolution test for transdermal patches was set up. The amount of tracer assayed in the acceptor fluid, which was separated from the donor powder reservoir by molded disks of differing thicknesses (Figure 1), was plotted *versus* time (Figure 5).

As in the release profiles of capsules, a lag time prior to the rupture of the polymeric barrier was observed. Only in the case of the EXP formulation, $t_{10\%}$ values showed a tendency to decrease when reducing the thickness of disks to 200 μm. Indeed, a small amount of tracer was recovered in the acidic medium when one of the 200 μm disks was tested thus pointing out the possible existence of a thickness threshold for gastric resistance failure. The polymeric barrier containing Kollicoat® IR confirmed a less prompt break-up, with an initial diffusive release phase. Moreover, in the case of 400 μm disks, $t_{10\%}$ values obtained from the disintegrant-containing formulation were significantly ($p < 0.1$) lower as compared with those relevant to the KIR one, thus indicating that a more efficient mechanism would promote the polymer disintegration/dissolution in pH 6.8 buffer. The overall results obtained from capsular devices and disks containing pore formers indicated that the erosion of the HPMCAS matrix would in any case be triggered by the pH change, as this allows the medium to reach the adjuvants incorporated. Afterwards, the soluble polymer Kollicoat® IR may aid the solvent penetration only, while the disintegrant could also promote the formation of cracks in the polymeric barrier thereby reducing its resistance to rupture [40]. The latter hypothesis was confirmed by photomicrographs of partially eroded molded items (*i.e.* disks exposed to pH 6.8 buffer for 120 min and dried before being analyzed) (Figure 6). In fact, the disintegrant particles embedded in the polymeric matrix seem to be located within hollows that are larger than the dried particle itself and show tears on their edges. Such hollows and relevant tears may have formed because of the swelling of Explotab® CLV upon exposure to the aqueous fluid.

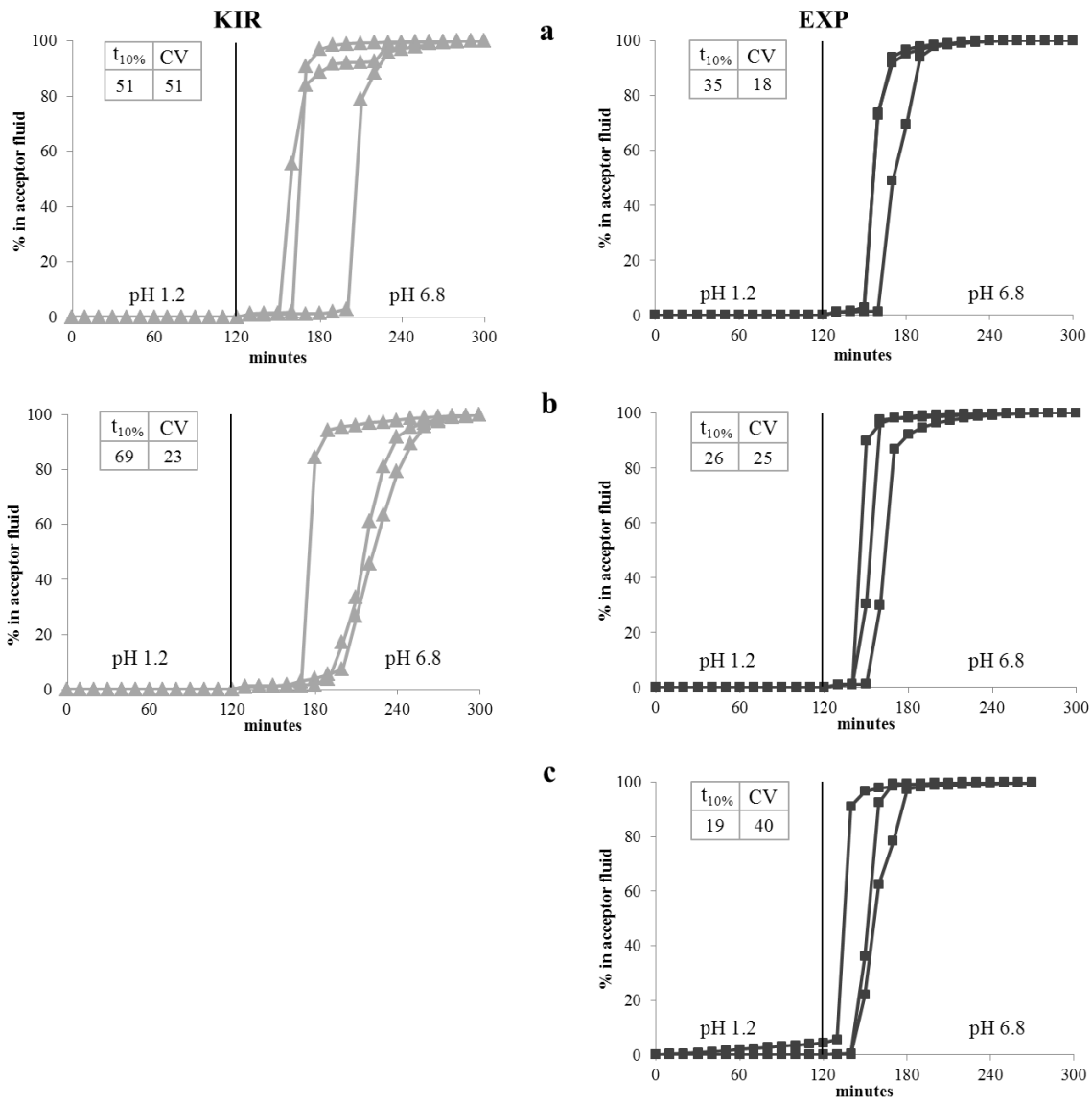


Figure 5: amount (%) of tracer in the acceptor fluid separated from the donor compartment by molded HPMCAS disks of differing thicknesses (600, 400 and 200 μm for a, b and c, respectively) containing 30% by weight of a release modifier (Kollicoat® IR on the left and Explotab® CLV on the right) *versus* time profiles; mean $t_{10\%}$ (min) in pH 6.8 buffer and relevant CV highlighted in tables.

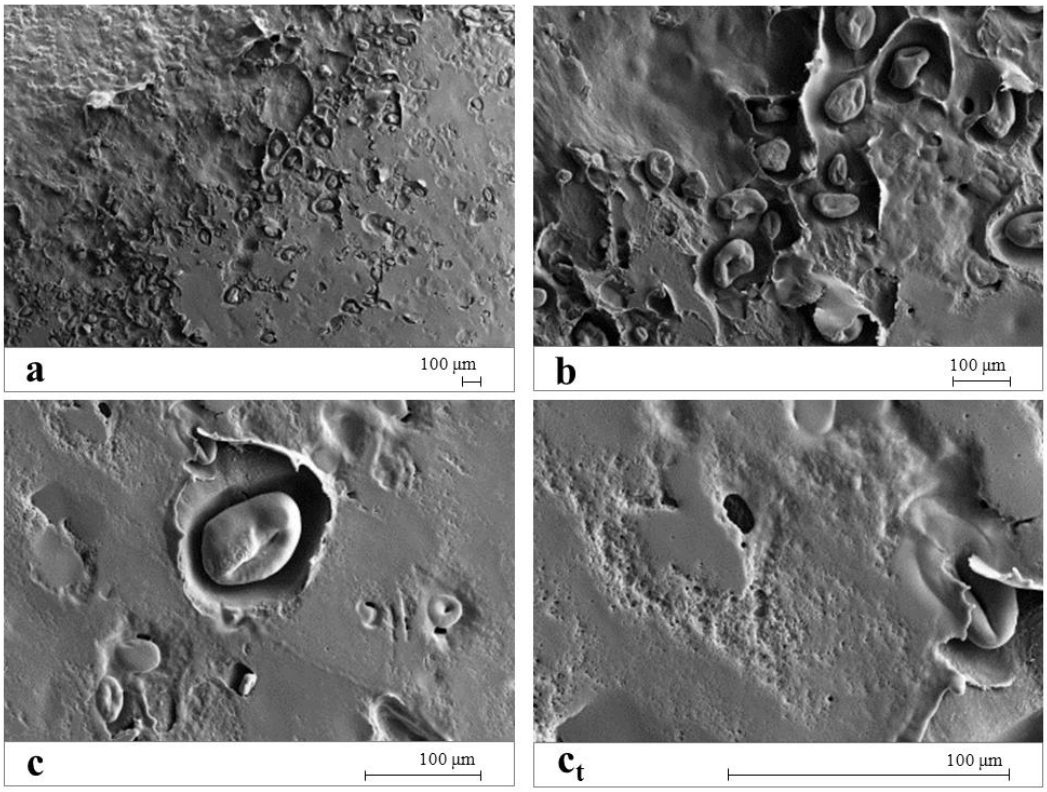


Figure 6: photomicrographs at different magnification (110, 400, 800, 2000x for a, b, c, and c_t , respectively) of the surface of HPMCAS-based 400 µm disks containing 30% of Explotab® CLV after exposure to pH 6.8 buffer; c_t is a detail from photomicrograph c.

According to the above discussed mechanisms, the ability of the soluble pore former to increase the extent of solvent penetration could improve the efficiency of the disintegrant. In this respect, confirmatory results were preliminarily obtained comparing the performance of 900 µm thick capsular shells containing blends of Kollicoat® IR and Explotab® CLV (10% and 20%, respectively, and *vice versa*) (Figure 7) with that of shells based on a single component (Kollicoat® IR or Explotab® CLV). Indeed, devices prepared from the 2EXP1KIR formulation in which 10% of the disintegrant was replaced with the soluble polymer showed the shortest lag time. On the contrary, only 10% of disintegrant in the shell composition seemed not enough to establish the cracking mechanism.

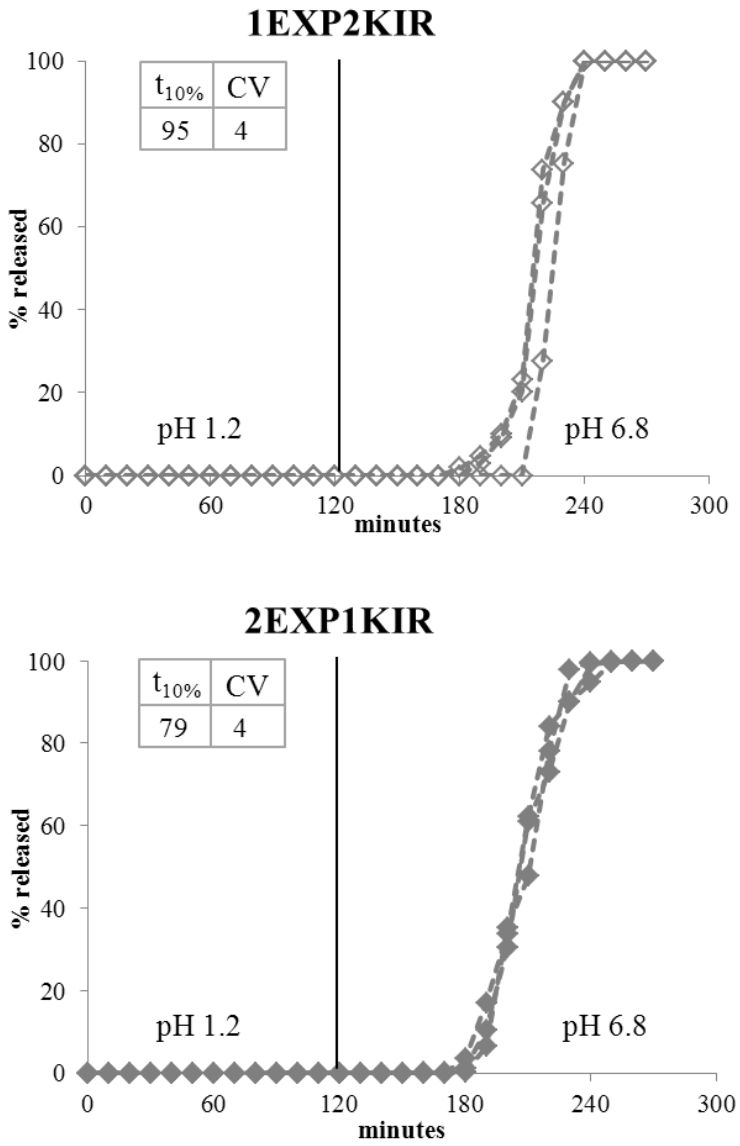


Figure 7: release profiles of 900 μm thick enteric capsular devices containing 30% by weight of a mixture of release modifiers (top: 10% Explotab® CLV and 20% Kollicoat® IR, bottom: 20% Explotab® CLV and 10% Kollicoat® IR); mean $t_{10\%}$ (min) in pH 6.8 buffer and relevant CV highlighted in tables.

In order to undertake the development of gastric resistant container-like devices, the impact of the shell thickness on the release performance needed to be more in-depth investigated. Therefore, some attempts were made at improving the IM processability of adjuvant-containing HPMCAS formulations. As expected, by adjusting the polymer to plasticizer ratio (increasing the amount of PEG 1500 to 35% on dry polymer), thinner capsular shells of 600 μm were manufactured containing 30% of Explotab® CLV. The relevant devices showed adequate resistance in the acidic medium and, in pH 6.8 buffer, a lag phase of less than 1 h, *i.e.* reduced of approximately 40% as compared with that

provided by thicker capsules containing the same amount of Explotab® CLV (Figure 8). Thus, the possibility of obtaining an earlier break-up by decreasing the shell thickness was confirmed, and this could represent the proper approach to the achievement of the desired release behavior.

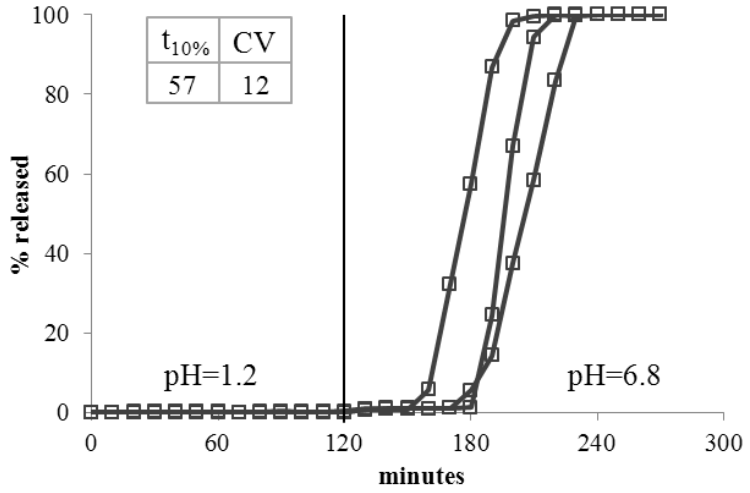


Figure 8: release profiles of 600 μm thick enteric capsular devices containing 30% by weight of Explotab® CLV; mean $t_{10\%}$ (min) in pH 6.8 buffer and relevant CV highlighted in tables.

4. Conclusions

The use of capsular containers suitable for conveying different types of drug formulations and determining the relevant release performance was recently proposed; for the manufacturing of such devices, IM technique was exploited because of the advantages it would offer in terms of versatility (dimensions, composition and shape or shape details), scalability and patentability of the relevant products. In this work, the development of enteric soluble capsules based on HPMCAS was approached. The feasibility of the manufacturing process with a polymeric formulation containing a plasticizer and a release modifier or mixtures of different types of release modifiers (a soluble pore former and a disintegrant, *i.e.* Kollicoat® IR and Explotab® CLV, respectively) was assessed. This basic composition showed promising results with respect to a possible fine tuning of the thickness and mechanical characteristics of the capsule shell. The formulation-based approach undertaken was therefore effective in assessing the main requirements of the molded capsular device. Accordingly, the development process would be worth pursuing by the design of a dedicated mold and set up of suitable operating conditions while finalizing the formulation parameters.

Acknowledgments

The support of Consortium TEFARCO Innova and Regione Lombardia, Fondo Sociale Europeo is gratefully acknowledged.

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- Appendix-

The content of this chapter has already been published as:

Zema L., Loreti G., Melocchi A., Macchi E., Del Curto M.D., Foppoli A., Gazzaniga A., Preliminary *in vivo* evaluation of a gastroresistant capsular device prepared by injection molding, Transactions 40th CRS Annual Meeting and Exposition, Honolulu, 21st-24th July 2013.

PRELIMINARY *IN VIVO* EVALUATION OF A GASTRORESISTANT CAPSULAR DEVICE PREPARED BY INJECTION MOLDING

Abstract

The *in vivo* release performance of a gastroresistant capsular device based on HPMCAS and prepared by injection molding (IM) was preliminarily evaluated in volunteers with respect to conventional enteric coated dosage forms. IM capsule prototypes demonstrated promising results in terms of opening time after entering the small intestine.

1. Introduction

A gastroresistant capsular device prepared by injection molding (IM) was recently proposed [1]. The feasibility of the manufacturing process with hydroxypropyl methyl cellulose acetate succinate (HPMCAS) as the thermoplastic polymeric component was assessed. By improving the basic formulation with a plasticizer and channeling agents (soluble polymers and/or disintegrants), promising results were obtained with respect to *in vitro* performance and fine tuning of the thickness as well as mechanical characteristics of the capsule shell.

In the present work, a preliminary *in vivo* evaluation of 600 μm thick HPMCAS capsules containing 30% (w/w on the plasticized polymer) of Explotab® CLV was carried out. For this purpose an assembled gastroresistant system was devised, consisting of an enteric-coated HPMC capsule filled with both fenazon powder and an acetaminophen-containing HPMCAS molded unit (Figure 1). The external capsule would dissolve after gastric emptying thus releasing its contents: the appearance of fenazon and acetaminophen in biological fluids would indicate the opening of the assembled system and of the HPMCAS unit, respectively.

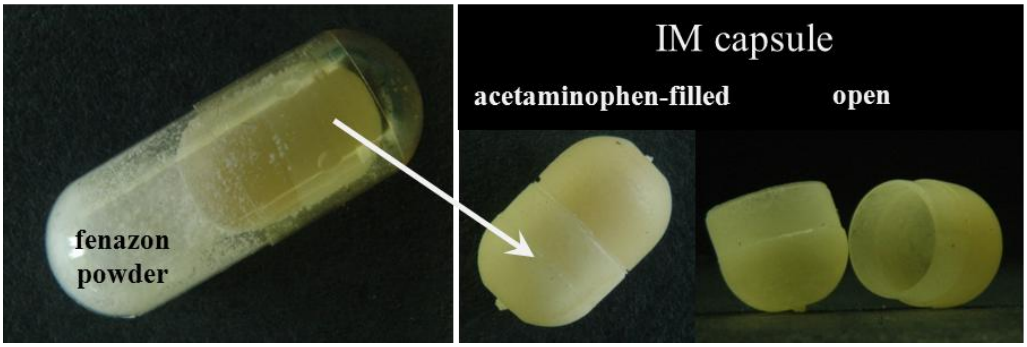

Figure 1: assembled gastroresistant system and HPMCAS molded capsule.

2. Materials and methods

2.1. Materials

HPMCAS (AQUOT-LG®; Shin-Etsu, J); polyethylene glycol (PEG 1500; Clariant Masterbatches, I); sodium starch glycolate (Explotab® CLV; JRS, D); metacrylic acid copolymer (Eudragit® L 30 D-55; Evonik, D); acetaminophen (Atabay, TR); fenazon (ACEF, I); HPMC capsules sizes 000 and 2 (V-Caps®, Capsugel, B).

2.2. Methods

2.2.1. System preparation

IM gastroresistant (IMGR) capsules: co-milled blends of HPMCAS and PEG 1500 were mixed with Explotab® CLV (55:22:23 ratio) in Turbula (Type T2C, WAB, CH), dried in a ventilated oven (40°C, 24 h) and transferred into the IM press (BabyPlast 6/10P, Chronoplast, Rambaldi, I). Previously set process conditions were adapted to the use of a different mold [1,2]. Each capsule was manually filled with 150 mg of acetaminophen and sealed with a HPMCAS alcoholic solution.

Coated gastroresistant (CGR) capsules: size 2 HPMC capsules, filled with 100 mg of fenazon and sealed with HPMC aqueous solution, were coated up to a 10 mg/cm^2 coating level with Eudragit® L 30 D-55 (LDCS Hi-coater equipped with a 1.3 L capacity perforated pan, Freund-Vector corporation, US; inlet temperature: 30 °C, air pressure: 12 psi; pan speed:18 rpm; rate of spraying 2 g/min).

Assembled gastroresistant (AGR) systems: size 000 HPMC capsules were filled with one IMGR capsule, together with 100 mg of fenazon powder, and dip-coated with an alcoholic solution of HPMCAS.

2.2.2. *In vitro* evaluation

Systems were tested in *apparatus* 2 USP35 (Dissolution System 2100B, Distek, US) according to the Dissolution test for delayed-release dosage forms (Method B, 100 rpm). Fluid samples were withdrawn and assayed spectrophotometrically. Time to 10% release in pH 6.8 ($t_{10\%}$) was calculated from the release curves.

2.2.2. *In vivo* evaluation

Two different studies were carried out involving 9 healthy volunteers (age 26-61 years, weight 53-87 kg). In the 1st study the AGR system was administered to 6 subjects; in the 2nd

one an IMGR and a CGR capsule were co-administered to 3 subjects. Systems were ingested with 250 mL of water. Saliva samples were collected at predetermined time points and immediately frozen; acetaminophen and fenazon were selected because they can be assayed in saliva. After defrosting, each sample was centrifuged at 4000 rpm for 15 min. 1 mL of supernatant was transferred into 10 mL plastic tubes along with 1 mL of $Ba(OH)_2$ 0.3 M and 1 mL of $ZnSO_4$ 0.3 M. 100 µL of theophylline monohydrate 0.2 mg/mL were added as the internal standard. After mixing by vortex for 30 s, samples were centrifuged at 4000 rpm for 15 min. Acetaminophen and fenazon were simultaneously assayed by gradient RP HPLC (Waters Co., US) using a µBondapack™ Phenyl, 150 x 3.9 mm 125 Å column (Waters Co., US) heated at 30 °C. Acetate buffer (pH 5±0.1) and CH_3CN were employed as the mobile phase at a flow rate of 1 mL/min ($t_{0\text{-}7min}$ = 95 : 5; $t_{7\text{-}10min}$ = 70 : 30; $t_{10\text{-}15min}$ = 95 : 5 v:v). Detection: spectrophotometer λ 245 nm. The concentration of acetaminophen and fenazon was determined from the tracer to internal standard peak area ratio. Data were processed by means of Breeze™ software (Waters Co., US).

3. Results and discussion

All systems showed the expected *in vitro* performance (Figure 2): fenazon release from CGR capsules and AGR systems occurred few minutes after pH change, whereas a 40-50 min longer latency was observed for IMGR capsules that could be attributed to the shell characteristics, mainly their thickness [1].

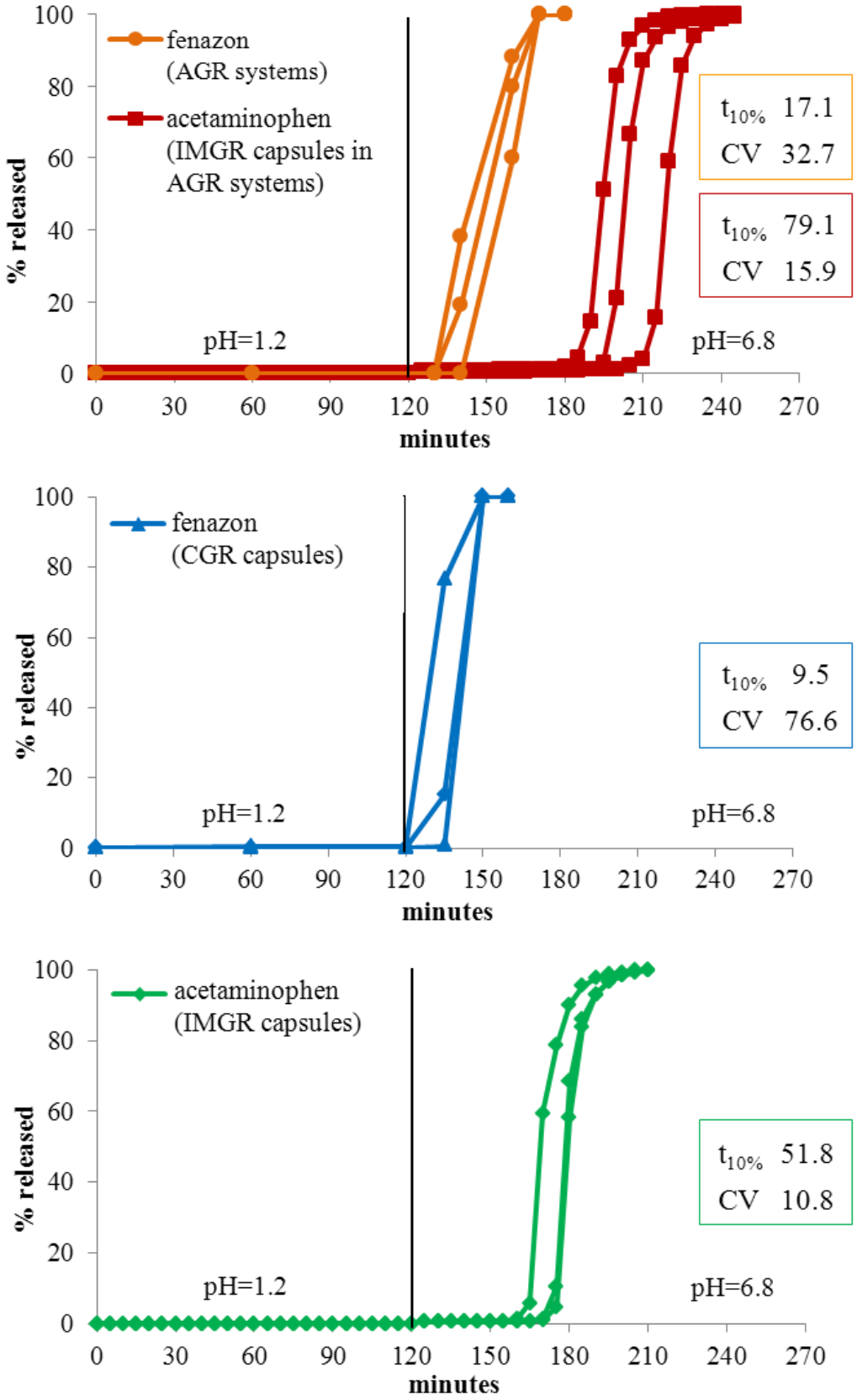

Figure 2: *in vitro* release profiles of AGR, CGR and IMGR systems (top to bottom).

As far as the *in vivo* studies are concerned, the time of first detection in saliva of acetaminophen or fenazon, contained in each administered dosage form, was used to define the relevant opening time (see examples in Figure 3 and Figure 4). Based on data obtained following administration of the AGR system, a mean opening time of 117 min (CV 43.9) after fenazon appearance was calculated for the IMGR capsule, which was assumed as the time to disintegration/dissolution of the latter. In the subsequent *in vivo* study, the performance of molded HPMCAS (IMGR) capsules was compared with that of conventional enteric-coated ones (CGR). On coadministration of the two systems, acetaminophen release from IMGR capsules on average occurred only 35 min after fenazon release from CGR ones (Table 1).

The overall results obtained seem to be in agreement with data reported in the literature relevant to gastroresistant dosage forms, generally indicating up to 2 h for their complete disintegration/dissolution in the human small intestine [4].

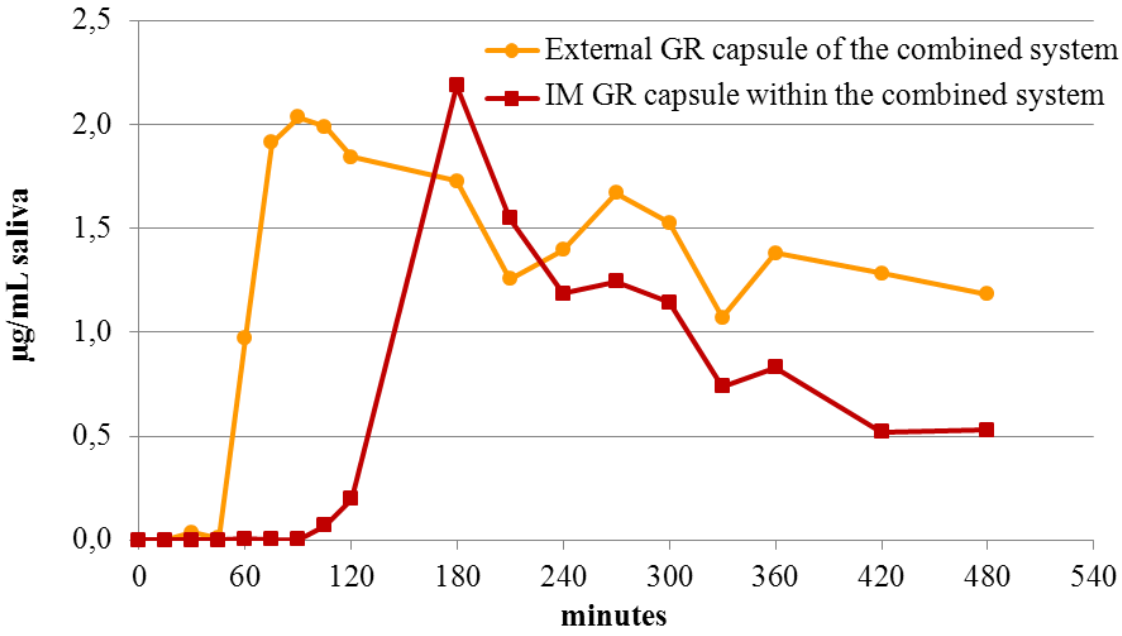

Figure 3: saliva concentration profiles following administration of the AGR system (subject #2).

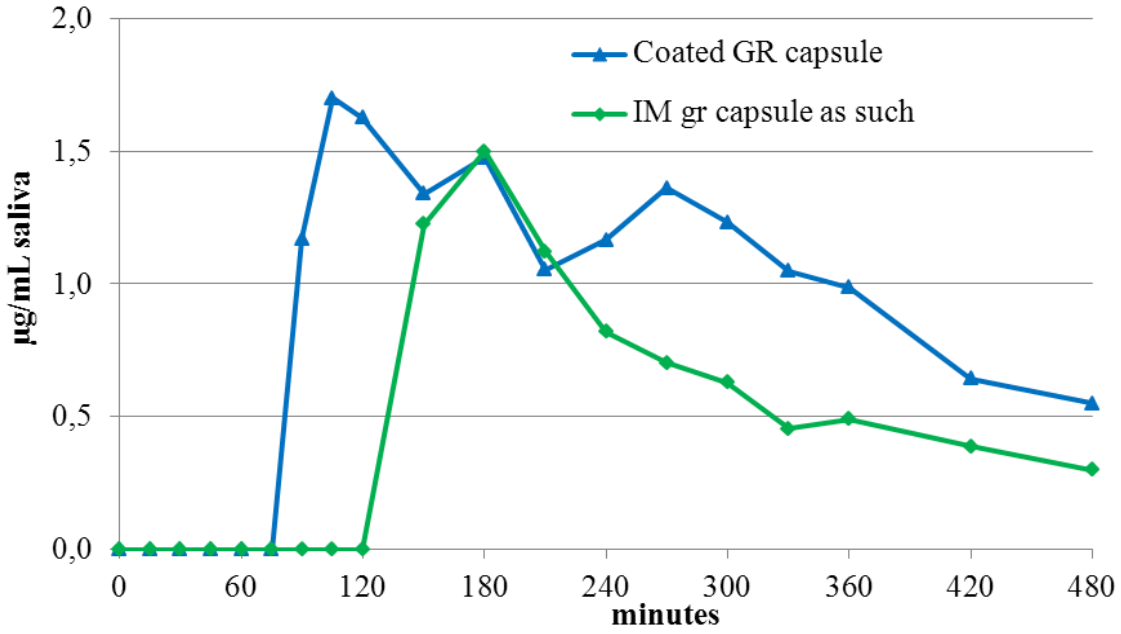

Figure 4: saliva concentration profiles following coadministration of CGR and IMGR capsules (subject #9).

Table 1: *in vivo* data of CGR and IMGR capsules.

opening time, min (CV)		**Δ min**
CGR capsules	**IMGR capsules**	
160 (42.3)	195 (35.3)	35

4. Conclusions

An IM gastroresistant capsular device, suitable for conveying different types of drug formulations, was evaluated *in vivo*, demonstrating the ability to release its contents in the intestine. Promising results were obtained in terms of opening time (*i.e.* an only 35 min longer latency as compared with conventional enteric-coated capsules), especially in view of the thickness of the prototypes employed.

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Part III

- Chapter I -

The content of this chapter has already been published in:

Loreti G., Maroni A., Del Curto M. D., Melocchi A., Gazzaniga A., Zema L., Evaluation of hot melt extrusion technique in the preparation of HPC matrices for prolonged release, Eur. J. Pharm. Sci. 52: 77-85, 2014.

EVALUATION OF HOT MELT EXTRUSION TECHNIQUE IN THE PREPARATION OF HPC MATRICES FOR PROLONGED RELEASE

Abstract

The aim of the work was to explore the potential of hot melt extrusion (HME) for preparing hydroxypropyl cellulose (HPC)-based prolonged-release matrices intended for oral administration. For this purpose, compressed and extruded systems, either composed of polymer only or containing different amounts of a model drug (theophylline or ketoprofen), were compared. The overall morphological/physical changes of the systems following interaction with water indicated that the manufacturing process would not exert a major influence on the swelling behavior of the polymeric matrices. On the other hand, the release rate was generally higher from HME systems probably due to an increase of the drug dissolution rate, which is in agreement with the relevant DSC data (loss of drug cristallinity). However, the technological characteristics of the matrices and the maximum drug load were demonstrated to depend on the mode of interaction of the active ingredient with the molten polymer. In this respect, the formation of a composite material from ketoprofen and HPC, when mixed in specific ratios, was supposed to explain the differences observed between compressed and extruded systems in terms of morphological characteristics, hydration/swelling and release. The obtained results support the possibility of exploiting the advantages offered by HME technique, above all the potential for continuous manufacturing, in the preparation of prolonged-release swellable matrices based on a cellulose derivative.

Contents

Keywords: hot melt extrusion, prolonged release, hydrophilic swellable matrices, hydroxypropyl cellulose, continuous manufacturing, tableting.

1. Introduction

Hot melt extrusion (HME) is a processing technique widely used to convert plastic raw materials into a product of uniform shape and density by heating and forcing them through a die, generally employing a rotating screw. Despite some limitations implied by the thermal stability of drugs and formulation aids as well as the need for thermoplastic carriers, the interest in HME has grown over the last 20-30 years in the pharmaceutical field. This can be ascribed to the inherent potential of such a technology for automation and development of solvent-free manufacturing processes [1,2]. Moreover, mixing and/or compaction problems that can be encountered with powder formulations would be overcome by HME, and the bioavailability of poorly soluble active ingredients could be enhanced due to the formation of solid phases with increased dissolution rate from molecular dispersions of the drug within the molten polymeric carrier. Further advances in the field of HME and molding techniques might be expected in the near future due to the consolidation of a continuous-manufacturing production model that could bring about significant economic benefits [3-6]. In this respect, a molding process was indeed selected for the preparation of tablets in the first "drug-manufacturing prototype" built up at the Novartis-MIT (Massachusetts Institute of Technology) Center for Continuous Manufacturing, which turns raw ingredients into finished drug products through six connected units of production [7].

Several research groups proposed HME for the preparation of single- and multiple-unit drug delivery systems, fast-dissolving or prolonged-release formulations, to be administered by the oral route or by the transdermal, transmucosal and transungual ones [8,9]. In the field of oral prolonged-release systems, different kinds of polymeric materials, either insoluble/inert (such as ethylcellulose or methacrylic acid copolymers) or hydrophilic/swellable (mainly polyethylene oxide) were investigated in order to produce matrices via HME [10-15]. As far as hydrophilic cellulose derivatives are concerned, which are broadly used to prepare tableted oral matrices owing to recognized advantages in terms of safety, versatility and low costs, their application was limited by the inherent thermal behavior. Indeed, the use of hydroxypropyl methylcellulose (HPMC), which is the most widely employed matrix-forming polymer, has proven challenging because of its narrow processing window, *e.g.* the difference between glassy–rubbery transition temperature (T_g) and degradation temperature [16]. The hydroxypropyl derivative (HPC), on the other side, was demonstrated to possess adequate thermoplastic properties and has extensively been used to prepare transdermal and transmucosal extruded systems although, at least so far, it

has not been evaluated in the manufacturing of orally-administered matrices by HME [17,18]. By the way, HPC is characterized by high plastic deformation during compaction but also by high elastic recovery after tableting, which might hinder its use as a compression filler [19]. Low molecular weight grades of this polymer were proposed as carriers in HME to attain solid dispersions of poorly soluble drugs [20]. Moreover, it has recently been proposed for the manufacturing of a pulsatile-delivery platform in the form of a capsular device prepared by injection molding [21,22].

Based on these premises, the aim of the work was to explore the potential of HPC as a thermoplastic carrier for monolithic matrix systems intended for oral prolonged release. In this respect, matrices prepared by HME were compared with directly compressed ones. The impact of the manufacturing process on the hydration, swelling and erosion rate of the polymer was studied by using pure polymeric systems, whereas its feasibility and the resulting release performance were evaluated taking drugs with different solubility and/or miscibility with the molten carrier into account.

2. Materials and methods

2.1. Materials

Hydroxypropylcellulose, HPC: regular and fine (X) grades, 250-300 μm and 80-100 μm average particle size, respectively (Klucel® GF and GXF; Ashland, US; Eigenmann & Veronelli, I); theophylline (Boehringer Ingelheim, I); ketoprofen (Cosma, I); cellulose acetate propionate (CAP 482; Eastman, US).

2.2. Methods

2.2.1. Powder characterization

Klucel® GF particle size was evaluated according to Ph. Eur. 7th ed. (7.6) (monograph 2.9.38 Particle-size distribution estimation by analytical sieving) in the 150-500 μm range; Klucel® GXF particle size was evaluated by means of an optical microscope (Axiolab, Zeiss, D). Powder d_{90} and d_{50} were calculated as reported in monograph 2.9.35 Powder fineness. The bulk and tapped density as well as compressibility of the powder were determined according to monograph 2.9.34 Bulk density and tapped density of powders, Method 1.

2.2.2. Matrix preparation

Pure-polymer and binary drug/polymer matrices with theophylline or ketoprofen content in the 5-70% or 5-40% range, respectively, were prepared by direct compression (DC) as well as hot melt extrusion (HME) after mixing the powders in Turbula (type T2A-Willy A, Bachofen, CH; 10 min). Powder samples of 150 mg were manually filled in a single-punch machine (Korsch, EKO, D; flat-faced punch, diameter 8 mm) and tableted at 35 kN. The compression force (FA) was measured during the process. HME was carried out in a single-screw extruder (Extrusiograph 19/25D, Brabender, D) equipped with a rod-shaped die (diameter 8 mm). Process parameters, processing time and torque values recorded while manufacturing pure-polymer matrices are reported in Table 1. Extruded products, stored at room temperature for 48 h, were cut into matrices with same nominal weight of the corresponding DC tablets by means of a bench-top saw.

Table 1: process and output parameters relevant to HME matrices.

Process parameters	Barrel temperature (°C)	150-155-160
Output parameters	Die temperature (°C)	150
	Screw speed (rpm)	15
	Processing time (min)	4-6
	Torque range* (N·m)	7-10

* work of the rotating screw needed to convey the material along the heated barrel

All systems were characterized for: weight (Crystal, Gibertini, I), diameter and thickness (digital micrometer CD-C112XB, Mitutoyo, J), crushing force (FC) (crushing tester TBH28; Erweka, D), surface wettability (contact angle test) and drug content. Cohesion index values were also calculated as $\frac{F_C}{F_A} \times 10^5$.

2.2.3. Release test

Drug release was evaluated by a dissolution Ph. Eur. 7th ed. *apparatus* 2 (Dissolution System 2100B, Distek, US) using 900 ml of deionized water at 37 ± 0.5 °C and 50 rpm; throughout all tests sink conditions were maintained. Drug concentration in the release medium was determined by spectrophotometer (lambda25, Perkin Elmers, UK) at λ_{max} of 272 and 260 nm for theophylline and ketoprofen, respectively (n = 6, bars in figures indicate standard

deviation). Prior to release testing, matrices were manually coated on all surfaces except for one base with an impermeable film of CAP (15% w/v acetone solution) [23].

2.2.4. Interaction with aqueous fluids

Water uptake and residual dry polymer of matrices immersed in unstirred water at room temperature were evaluated over 6 h (n = 3). Systems glued on a glass holder were immersed in 100 mL of deionized water, removed after predetermined time periods, gently blotted and weighed. In the case of drug-containing matrices, the amount of theophylline or ketoprofen released in the medium was spectrophotometrically determined (D_{rel}). Final dry weights were also determined after maintaining samples in an oven at 60 °C for 48 h. Two parameters were calculated, the % water uptake and the % residual dry polymer, according to the following equations:

$$\%\, water\ uptake = \frac{W_w - W_d}{W_w}\ x\ 100$$

where W_w is the weight of the wet sample on withdrawal, W_d is the weight of the sample after drying;

$$\%\, residual\ dry\ polymer = \ 1 - \frac{W_i - W_d\ \ - D_{rel}}{W_i - D_{load}}\ \ x\ 100$$

where W_i is the initial weight of the sample, D_{rel} is the amount of drug released, D_{load} is the nominal drug content.

The progression of swelling and erosion fronts was determined on coated matrices maintained under the same conditions as for the release test. Samples (n = 3) were recovered from the immersion fluid at predetermined time points. The position of the fronts was determined by means of a 0.01 mm-calibrated penetrometer (Dial Thickness Gage 7305, Mitutoyo, J) provided with a 0.3 mm diameter pin.

2.2.5. Thermal analysis

Powder and extruded samples were characterized by differential scanning calorimetry (DSC 2010, TA instruments, US) from 30 to 350 °C at 5 °C/min, N_2 purge 70 mL/min.

2.2.6. SEM analysis

Photomicrographs of gold-sputtered (10 nm) samples were collected by a scanning electron microscope (SEM; Sigma, Zeiss, D).

3. Results and discussion

3.1. Pure-polymer matrices

In order to explore the influence of the manufacturing technique on the performance of hydrophilic swellable matrices, pure polymeric systems prepared by DC and HME were preliminarily considered. A high molecular weight HPC was selected as the matrix-forming agent. Particularly, two different commercial types of the polymer were available, a regular particle size Klucel® GF (KGF) and a fine one (KGXF). Thus, their flowability and compaction tendency were evaluated as they could have impacted on the selected manufacturing processes (Table 2).

Table 2: physico-technological properties of HPC type KGF and KGXF (s.d. values in brackets).

	d_{50} μm	d_{90} μm	Bulk density g/mL	Compressibility index %	Cohesion index
KGF	290	490	0.39 (0.01)	19 (1)	292 (11)
KGXF	82	164	0.22 (0.02)	29 (2)	508 (15)

The poor flow characteristics (compressibility index in the 26-31 range; Ph. Eur. 7th ed. 2.9.36 Powder flow) of KGXF could indeed negatively influence both the tableting process, impairing the weight uniformity of the resulting matrices, and the continuous/automatic filling of the extruder. With regard to the compaction properties, coherent tablets where obtained with both polymer types by the application of relatively high compression forces (>25 kN) only. These presented a smooth and gloss surface as well as a tendency to deformation instead of breaking when undergoing the crushing test, thereby confirming in the case of Klucel® GF the same plastic behavior shown upon tableting by other HPC grades with a different molecular weight [19]. In the photomicroghaps of DC matrices, two different areas can be distinguished, an external packed layer and an internal core exhibiting a pore network (Figure 1a and b). In both areas, and especially in the external one, partially molten aggregates of polymer particles can be observed, which are particularly evident in the KGXF system (Figure 1b).

Moreover, consistent with a presumably wider area exposed, the fine polymer grade displayed a higher cohesion index, and the relevant tableted products showed a lower porosity. Therefore, DC matrices were finally prepared with KGXF by manually filling the tableting machine to overcome the problems connected with the poor flowability of the powder, while the coarser material was preferred for the extrusion process. Only with KGF, by adjusting the operating parameters, continuous manufacturing of cylindrical extrudates based on pure polymer could indeed be performed, with no need for any adjuvant.

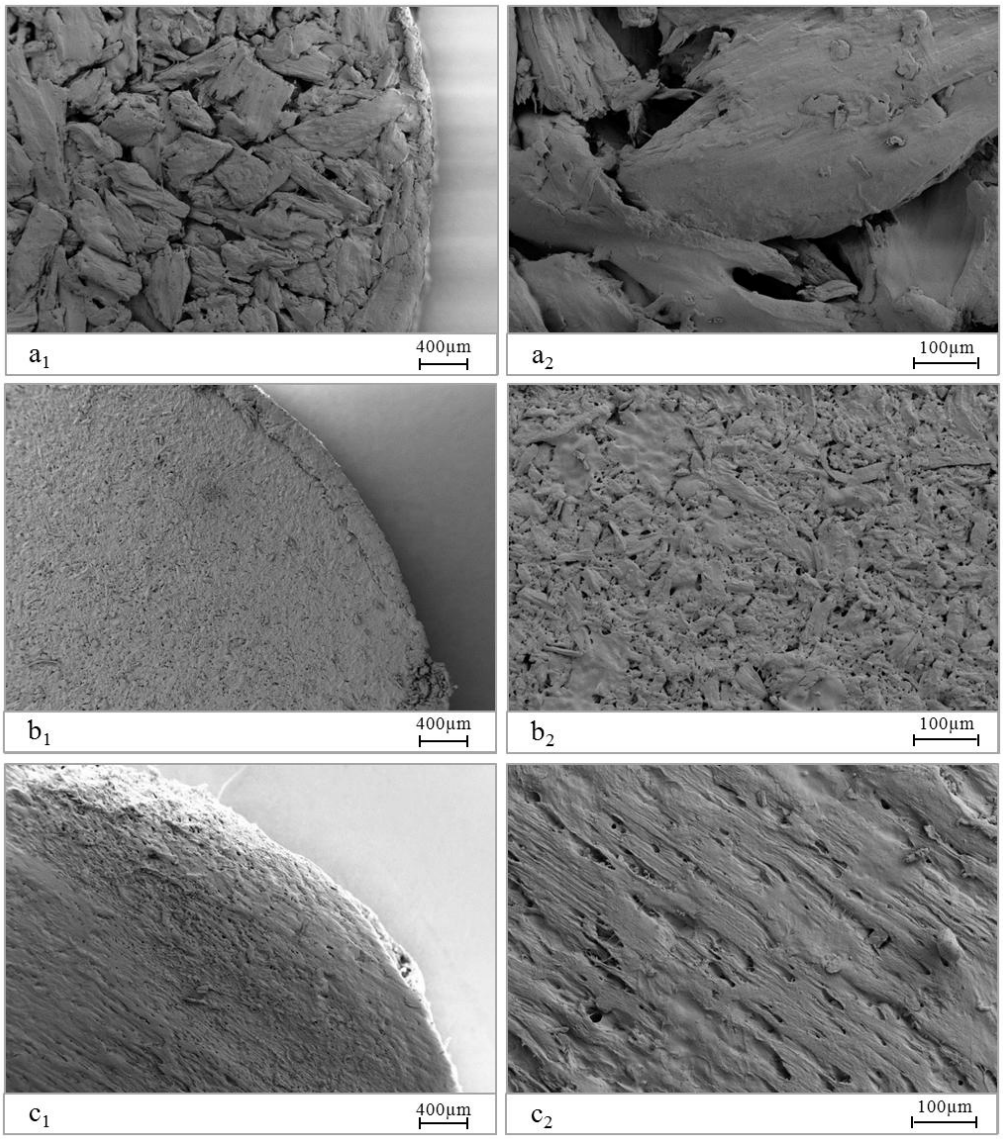

Figure 1: photomicrographs of pure polymer matrices: (a) KGF- and (b) KGXF-based DC systems, (c) KGF-based HME systems, at 100x (a_1, b_1, c_1) or 500x (a_2, b_2, c_2) magnification.

Pure-polymer matrix systems were characterized in terms of physical properties and behavior in aqueous fluids, *i.e.* water uptake/solvent penetration, swelling, dissolution/erosion and wettability. The relevant data are reported in Table 3 and Figure 2.

Table 3: physico-technological properties of pure polymer matrices (s.d. values in brackets).

	Diameter mm	Thickness mm	Density g/cm³	Crushing force N	Contact angle °
DC	7.99 (0.01)	2.92 (0.06)	0.88 (0.02)	166 (9)	47 (2)
HME	8.01 (0.06)	2.90 (0.01)	1.05 (0.10)	-	49 (3)

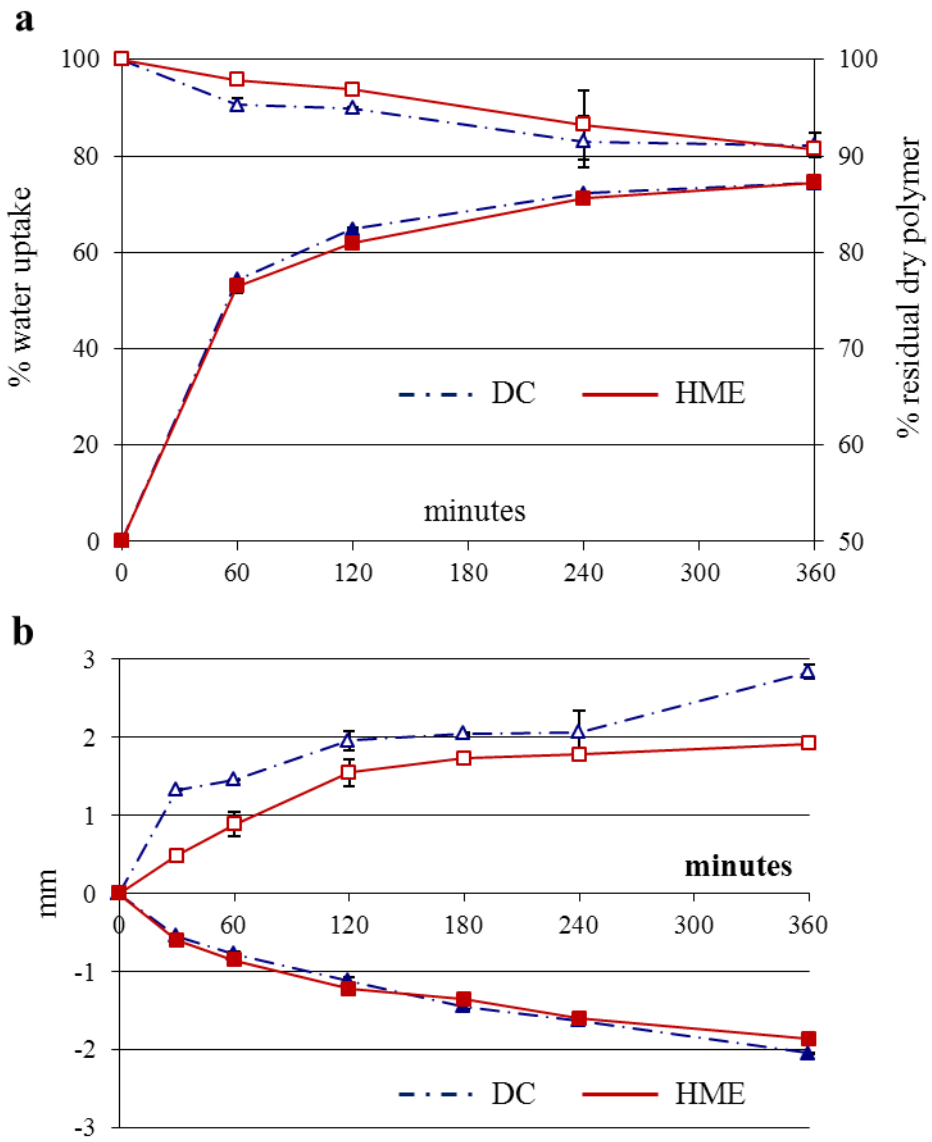

Figure 2: water uptake (■; ▲) and residual dry polymer (□; Δ) profiles (a), and swelling (■; ▲) and erosion (□; Δ) front profiles (b) of HPC matrices manufactured by DC (dotted lines) and HME (solid lines).

HME systems showed higher bulk density values, close to the true density of the pure polymer (1.15 g/cm^3). No particles of the coarse starting polymer could be distinguished in the photomicrograph of the extruded product, which also exhibited a lower porosity as compared with both the DC systems (Figure 1c). During the crushing strength test, HME units got deformed thus hindering the evaluation of the hardness characteristics.

DC and HME polymeric matrices had very similar wettability.

In the case of hydrophilic swellable matrices based on HPMC, it is well known that differences in the dry polymer particle size may only affect the initial hydration rate and thereby impact on the burst release phase, especially with very soluble drugs. Accordingly, in spite of the difference in porosity, the HPC matrices prepared by DC and HME showed an analogous behavior in contact of interaction with aqueous fluids, as pointed out by very similar water uptake, dry mass loss and solvent penetration (swelling) front profiles (Figure 2).

3.2. Drug-containing matrices

In order to evaluate the release performance and the influence of drug load, DC and HME systems containing increasing amounts of an active ingredient were prepared. Theophylline and ketoprofen were chosen as model molecules as they are characterized by melting points markedly above or below the HPC extrusion temperature, respectively (271.9 °C for theophylline and 95.8 °C for ketoprofen). The ability of ketoprofen to form solid solutions with low molecular weight grades of HPC on HME processing was already demonstrated as the drug and the polymer were found miscible [24]. Ketoprofen was confirmed to act like a plasticizer for KGF, progressively lowering the torque value recorded up to 1-3 N m as a function of concentration. On the other hand, a maximum load of 40% could be achieved still maintaining an acceptable mechanical resistance of the extrudate. At the highest drug load, the operating temperatures needed to be decreased below 100 °C. Ketoprofen-containing HME matrices were all transparent with no evidence of dispersed particles, as shown by the relevant photomicrographs (Figure 3a). However, while the extrudate with the 5% load appeared quite similar to the extruded polymer as such (Figure 3a$_1$), the aspect of the sample containing 40% of drug was very different, presenting an exfoliated surface split into thin flakes (Figure 3a$_2$).

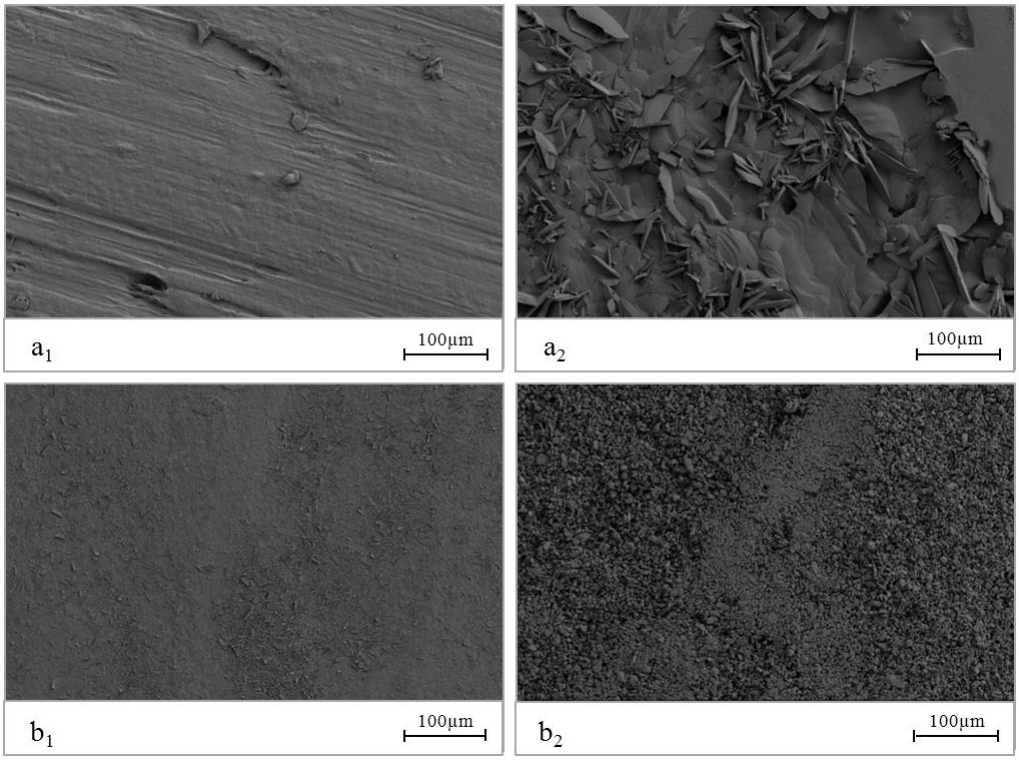

Figure 3: photomicrographs of HME matrices containing (a) ketoprofen, 5 (a_1) or 40% (a_2), and (b) theophylline, 5 (b_1) or 70% (b_2).

With respect to the HME matrices containing the high-melting model drug, products loaded up to 70% were obtained with no need for changing the operating conditions set for the pure polymer, thus suggesting a lesser ability of theophylline to plasticize the polymer. The matrices turned opaque already with 5% of this drug, and the matt appearance progressively increased with the loaded amount suggesting that theophylline would remain suspended in the polymeric carrier. The presence of solid particles was confirmed by SEM analysis (Figure 3b). However, as in the case of ketoprofen, a tendency of the torque value to diminish during the extrusion of drug-loaded materials was noticed, which could indicate a partial solubilization of theophylline in the molten polymer. In thermograms of HME formulations containing decreasing amounts of theophylline, from 70% to 5%, a progressive reduction of the drug melting peak and shift towards lower temperatures was observed, pointing out a gradual loss of crystallinity possibly due to drug–polymer interactions (Figure 4) [24]. On the other hand, the drug melting peak was evident in none of the thermograms of ketoprofen-based HME formulations. With the low-melting model drug, modifications of the area and position of the peak were observed when changing the processing technique irrespective of the drug content. By way of

example, thermograms relevant to formulations containing 20% of ketoprofen processed by mixing, tableting or HME are reported (Figure 5).

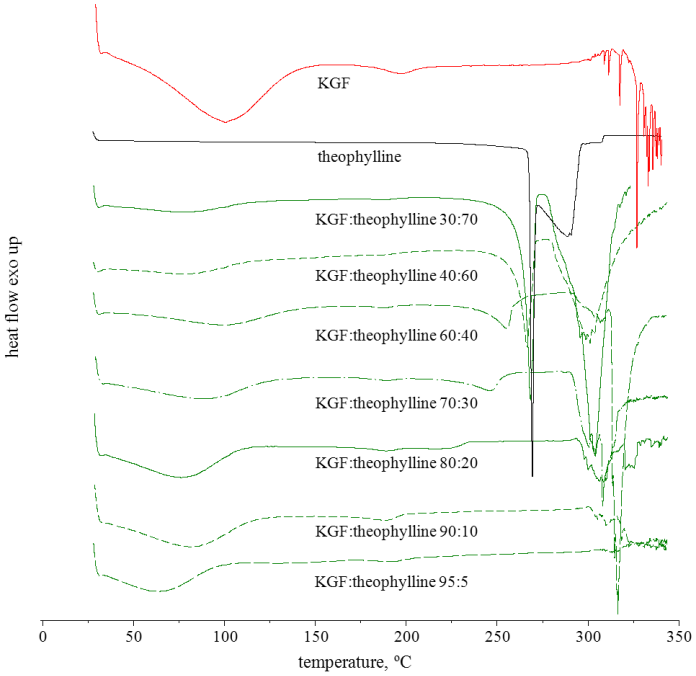

Figure 4: DSC thermograms of KGF, theophylline and HME matrices containing differing amounts of theophylline (5-70%).

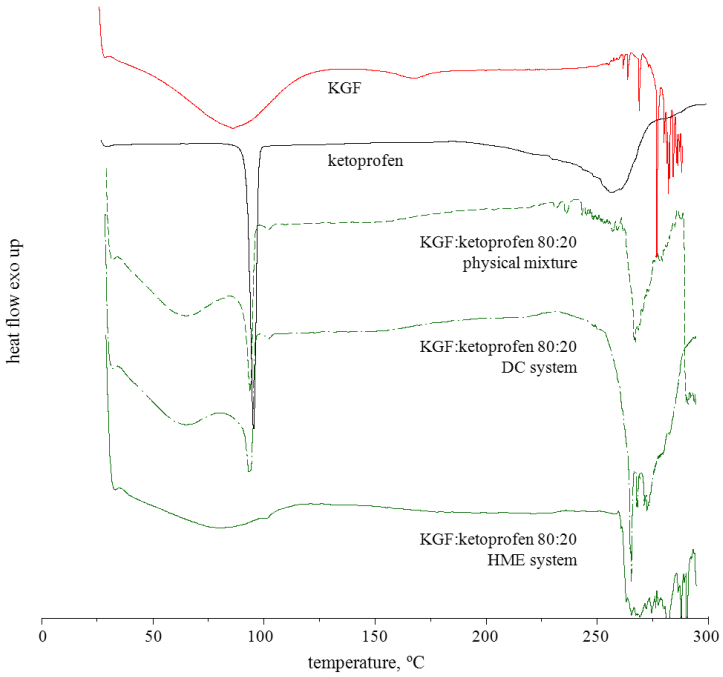

Figure 5: DSC thermograms of KGF, ketoprofen and formulations containing 20% of drug processed by differing techniques.

The drug content of HME systems was found >97% of the nominal load for all formulations except for those with 60% and 70% of theophylline, for which it turned out <95%. This result was attributed to the poor conveying and mixing ability of single-screw extruders and might be improved by changing the using equipment (twin-screw extruder).

As far as the DC products are concerned, they needed to be manufactured manually and showed not fully satisfactory mechanical characteristics. In particular, the matrices containing theophylline exhibited lower mechanical resistance as compared with pure-polymer ones, whereas the crushing strength of ketoprofen-containing systems was not determinable because deformation occurred. In this respect, it might thus be hypothesized that the increase in the micro-environmental temperature brought about by compaction could lead to the softening/melting of ketoprofen thereby resulting in plasticization of the polymeric matrix.

Moreover, the polymer compaction was hindered by the presence of both model drugs. These findings support the need for identifying alternative manufacturing techniques for prolonged-release matrix systems based on HPC.

Subsequently, the behavior in contact with aqueous fluids (formation and evolution of a gel barrier) and the drug release performance of DC and HME matrices were comparatively evaluated. The profiles of water uptake, dry polymer loss and swelling as well as erosion fronts of systems containing the smallest and the largest amounts of drug are reported in Figure 6 and Figure 7. The position of swelling and erosion fronts was not measured for extruded products with ketoprofen loads $\geqslant$30% as the relevant glassy portion did not withstand penetration of the pin device used for the experiment.

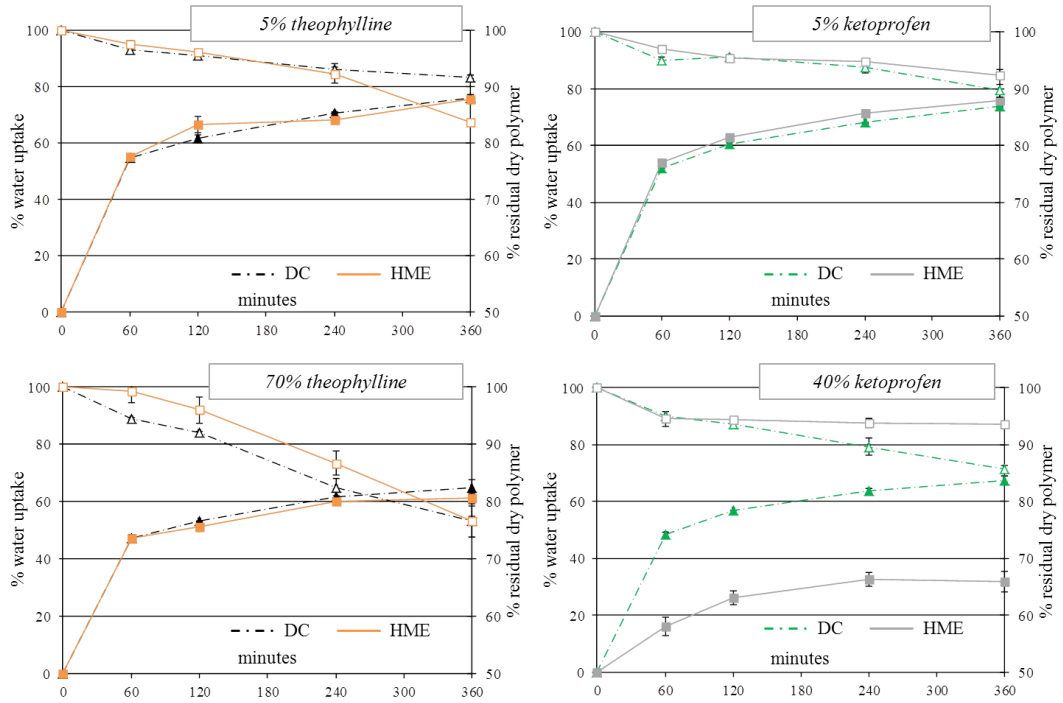

Figure 6: water uptake (■; ▲) and residual dry polymer (□; Δ) profiles of HPC matrices manufactured by DC (dotted lines) and HME (solid lines) containing differing percentages of drug.

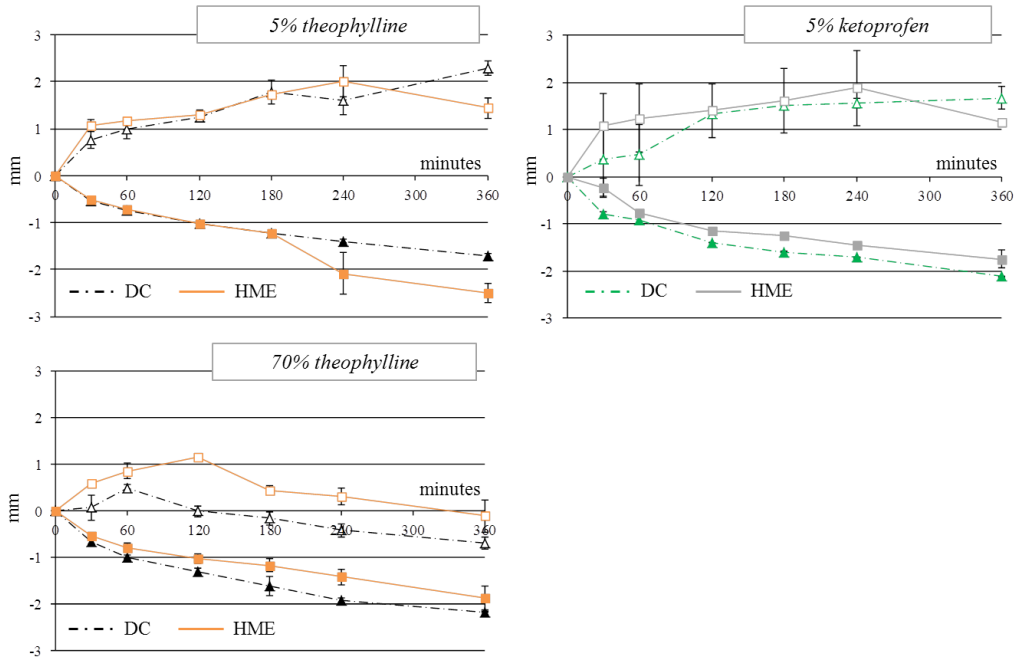

Figure 7: swelling (■; ▲) and erosion (□; Δ) front profiles of HPC matrices manufactured by DC (dotted lines) and HME (solid lines) containing differing percentages of drug.

With regard to matrices with a 5% drug load, DC and HME systems showed quite a similar behavior, which was in turn not different from that of the pure polymer. On the other hand, a faster dry polymer mass loss and a reduced gel thickness (distance between the erosion and the swelling front) were noticed in the case of systems with 70% of theophylline. These results could be attributed to the formation of a less resistant and/or continuous gel barrier due to the relatively small amount of swelling polymer. Notably, the impact of polymer erosion turned out more evident for the DC systems. Ketoprofen-based HME systems with ⩾30% drug loads showed a very low water uptake as compared with all the other formulations and particularly with the corresponding DC matrices (maximum water content of 30% after 6 h with 40% drug load HME systems *vs* almost 70% with DC ones). Moreover, no gel barrier was observed on the surface even though the position of the solvent penetration front could not be estimated as previously mentioned. Also based on the morphological aspect of ketoprofen systems with ⩾30% drug loads (Figure $3a_2$), the formation of a new solid phase, in which the hydrophilic nature of the cellulosic polymer was countered by the poor water solubility of the active ingredient, was supposed to take place, promoted by the interaction of the softened polymer chains with the molten drug. Such a hypothesis, however, needs to be supported by further investigation.

The release profiles of DC and HME systems containing increasing amounts of the two model drugs are reported in Figure 8 and Figure 9, respectively.

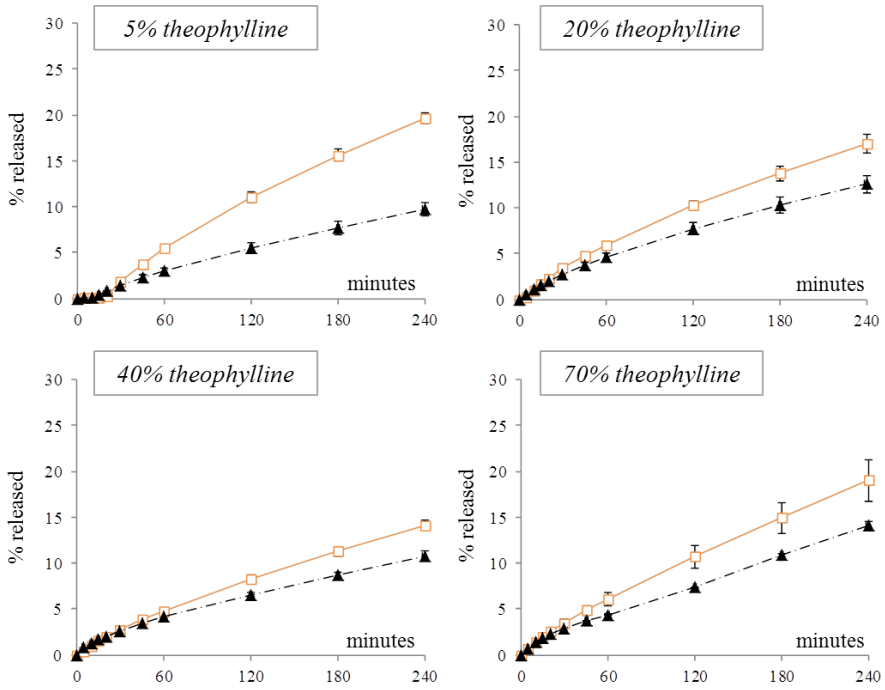

Figure 8: release profiles of DC (dotted lines) and HME (solid lines) matrices containing differing percentages of theophylline.

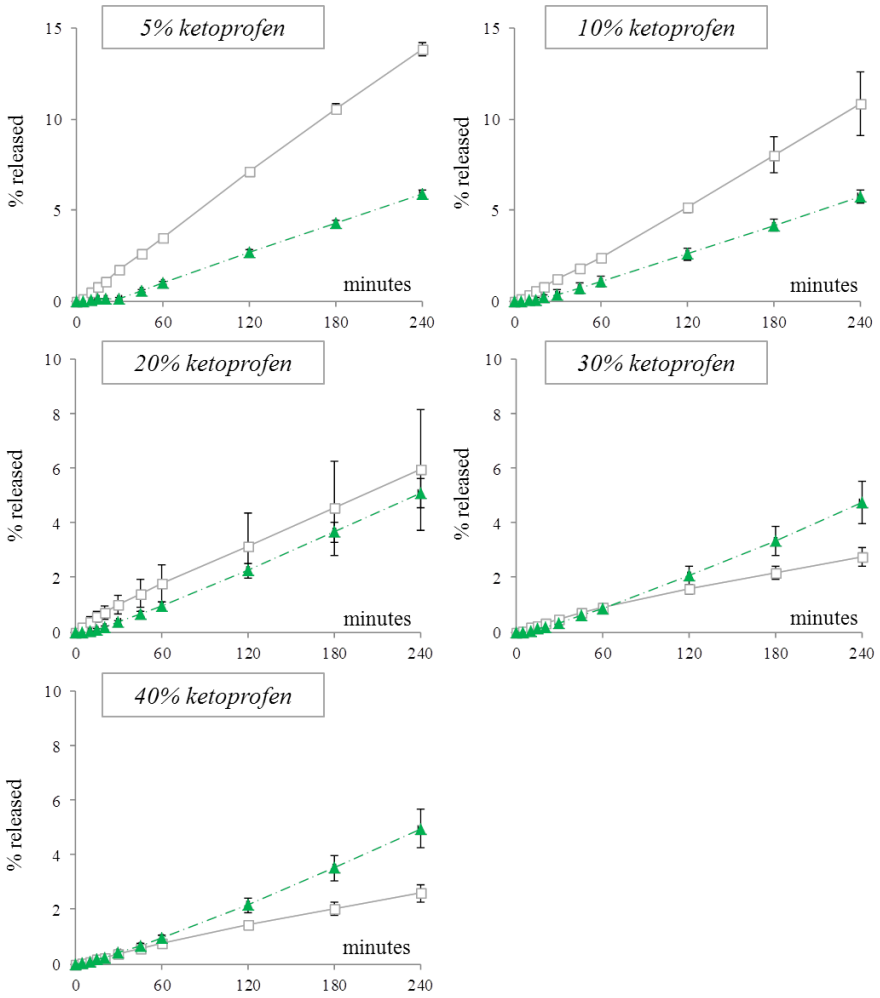

Figure 9: release profiles of DC (dotted lines) and HME (solid lines) matrices containing differing percentages of ketoprofen.

HME matrices for prolonged release are generally described as low-porosity systems able to ensure a strict control of drug release. Thus, they are used in subcutaneous, ocular or vaginal delivery where especially extended release phases are required (>24 h). Nevertheless, the sole comparison found between HME and DC systems refers to inert ethylcellulose (EC) oral matrices for which the main factor determining the rate of release is indeed porosity [25]. In the case of hydrophilic polymers, it was demonstrated that the entanglement of swollen macromolecular chains gives rise to meshes of relatively small size and, more importantly, independent of the initial porosity of the glassy matrix [26-28]. In this study, the drug release rate was generally higher from HME devices than from DC ones of analogous composition, practically independent of the model drug employed and the relevant content. Because hydration, swelling and erosion/dissolution processes were demonstrated only marginally influenced by the manufacturing technique, this trend was

attributed to the dissolution rate of the drugs in the microenvironment within the swollen matrix. Following extrusion, in fact, a loss of crystallinity was observed with both drugs, which could account for an increase in their dissolution rate and, therefore, in the apparent solubility gradient across the gel barrier driving drug release. On the contrary, in the case of ketoprofen-based systems containing 30% and 40% of drug, the release profiles of DC and HME matrices were superimposable for about 1 h whereas a marked decrease in the release rate from HME systems and a reverse order of the release patterns became afterwards evident. However, such a difference could once again be ascribed to the drug that might have promoted, by melting, the previously discussed increase in hydrophobicity of the matrix system and consequent slowing down of solvent-driven processes, *i.e.* hydration/swelling of polymeric chains and dissolution of drug particles.

4. Conclusions

As HPC was demonstrated critical in terms of compaction properties, the identification of an alternative technique for the preparation of oral prolonged-release matrices based on such polymer was considered of interest. In particular, because of its thermoplasticity, the use of HME, which has recently received attention especially due to its potential for continuous manufacturing, was investigated. Promising results were obtained as regards key aspect such as process feasibility (*e.g.* continuous manufacturing with no need for adjuvants, working temperatures in the 100-150 °C range, drug loads up to 70%) and technological characteristics (*e.g.* very low porosity, evidence of drug/polymer interaction, increase in the microenvironmental apparent solubility of the drug). The impact of the melting temperature of the active ingredient on the process conditions and the characteristics of the extruded products was highlighted. The overall results indicated that HME would be an advantageous technique for the manufacturing of swellable prolonged-release matrices, worthy of further investigation and wider application.

Acknowledgments

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- *Chapter II* -

The content of Part III, Chapter II has already been submitted for publication in:

Melocchi A., Loreti G., Del Curto M.D., A. Maroni, Gazzaniga A., Zema L., Evaluation of hot melt extrusion and injection molding for continuous manufacturing of immediate release tablets, J. Pharm. Sci., submitted.

EVALUATION OF HOT MELT EXTRUSION AND INJECTION MOLDING FOR CONTINUOUS MANUFACTURING OF IMMEDIATE RELEASE TABLETS

Abstract

The exploitation of hot melt extrusion and injection molding for the manufacturing of immediate release (IR) tablets was preliminarily investigated in view of their special suitability for continuous manufacturing, which represents a current goal of pharmaceutical production because of its possible advantages in terms of improved sustainability.

Tablet-forming agents were initially screened based on processability by single-screw extruder and micromolding machine as well as disintegration/dissolution behavior of extruded/molded prototypes. Various polymers, such as low-viscosity hydroxypropylcellulose, polyvinyl alcohol, polyvinyl alcohol-polyethylene glycol graft copolymer, various sodium starch glycolate grades (*e.g.* Explotab® CLV) that could be processed with no need for technological aids, except for a plasticizer, were identified. Furthermore, the feasibility of both extruded and molded IR tablets from low-viscosity hydroxypropylcellulose or Explotab® CLV was assessed. Explotab® CLV, in particular, showed thermoplastic properties and a very good aptitude as a tablet-forming agent, starting from which disintegrating tablets were successfully obtained by either techniques. Prototypes containing a poorly soluble model drug (furosemide), based on both a simple formulation (Explotab® CLV and water/glycerol as plasticizers) and formulations including dissolution/disintegration adjuvants (soluble and effervescent excipients) were demonstrated able to fulfill the USP 37 dissolution requirements for furosemide tablets.

Contents

Keywords: tablet, extrusion, formulation, oral drug delivery, polymers, continuous manufacturing, injection molding, Explotab® CLV, Nisso HPC SSL.

1. Introduction

Pharmaceutical industry is considered one of the most dedicated to innovation, as the total expenditure on research and development over US $ 100 billion could confirm [1]. However, only marginal attempts at improving the manufacturing efficiency have been reported, even though this has been highlighted as a very promising area of interest, especially with respect to the sustainability of dosage form development and manufacturing [2]. Traditionally, medicines have ever been manufactured through a batch method, in which materials are charged before the start of the process and discharged at the end. The final dosage form is obtained stage by stage over a series of workstations. This approach has been exploited for decades and it allows all regulatory requirements to be fulfilled. However, it does not offer adequate flexibility in responding to demand changes. As a consequence, in the last ten years the interest in the potential application of continuous manufacturing (CM) to the pharmaceutical field has been growing [3-6]. CM consists in producing/processing, without interruption, materials generally maintained in motion and undergoing chemical reactions or mechanical/heating treatments. Nowadays, this method is largely used in oil refining and production of paper as well as chemicals, where continuous commonly means operating 24 hours per day, 7 days per week with infrequent maintenance shutdowns, such as semi-annual or annual. According to the Food and Drug Administration (FDA), continuous processing has the potential for improving product quality and the industry is encouraged to truly consider a shift to it. Moreover, such a method was shown consistent with FDA's efforts towards quality by design implementation. Advantages related to CM are undeniable. It could reduce the time and costs of development simply by avoiding the moving of materials among facilities, limiting the stored amount of hazardous chemicals thus improving sustainability, overcoming the need for stopping, re-configuration and testing between batches as well as that for scaling up. In fact, transfer from pilot-plant to full-production scale could be accomplished just increasing the process time or making more lines work in parallel. Thanks to the restrained dimensions of the equipment required, a further increase of process efficiency could be achieved through a better exploitation of the manufacturing area.

Although many examples of continuous pharmaceutical processes that are run in a batch mode (*e.g.* blending, granulation, drying, tableting) have been reported [7-12], the first end-to-end (*i.e.* from drug synthesis to dosage form production) integrated CM plant was only very recently proposed [13-15]. Such a plant involves the flow of components trough different individual units, where all the conditions/parameters are clearly defined and

controlled. A prototype tablet intended for immediate release (IR) was achieved by extruding a basic thermoplastic formulation of an *in situ* synthesized model drug, followed by its injection into a properly shaped mold. Hot-processing techniques, such as hot melt extrusion (HME) and injection molding (IM), would especially be suitable for fulfilling the needs of CM. The use of these manufacturing techniques would also result in the possibility of carrying out solvent-free processes, overcoming mixing and/or compaction issues associated with powder formulations, increasing the bioavailability of poorly soluble drugs by the formation of solid dispersions/solutions and the patentability of the obtained products as well as the relevant versatility in terms of size and shape [17,18]. HME and IM are also mentioned in the pharmacopoeial monograph relevant to tablets (Eur. Pharm. 7th ed.). Only a preliminary research paper published in the late '90s, however, has preceded the above quoted CM study [16]. So far, polyethylene glycol (PEG) was considered as the sole thermoplastic vehicle without any broadening of the formulation study.

Therefore, the use of hot-processing techniques for the production of IR tablets still needs to be explored. In particular, an attentive formulation set-up is required to offset the poor porosity that is typical of extruded/molded items and may impair a prompt drug dissolution. Because IR tablets represent the top-selling dosage form in the pharmaceutical market, their CM would indeed be a remarkable accomplishment and could open the way for many other products. Based on these premises, the aim of the present work was the evaluation of polymeric components and the identification of formulations strategies for the achievement, by HME and IM, of solid units having acceptable IR characteristics (high disintegration/dissolution rate), thus strengthening the use of these innovative techniques and ultimately supporting progress in CM within the pharmaceutical field.

2. Materials and methods

2.1. Materials

Hydroxypropyl cellulose (HPC; Nisso SSL, Nisso, J); hydroxypropyl methyl cellulose (HPMC; Methocel® E5, Colorcon, US); polyvinyl alcohol (PVA; Gohsenol®, Nippon Goshei, UK); polyvinyl alcohol-polyethylene glycol graft copolymer (KIR; Kollicoat® IR, BASF, D); polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus®; BASF, D); metacrylic acid copolymer (Eudragit® E PO; Evonik, D); corn starch (Ingredion, Westchester, US); sodium starch glycolates (EXP, Explotab®; EXP_{CLV}, Explotab® CLV; VIV, Vivastar®; JRS Pharma, D); vinylpyrrolidone-vinyl acetate copolymer

(KVA; Kollidon® VA 64, BASF, D); deionized water (W); glycerol (GLY; Pharmagel, I), polyethylene glycols (PEG; 400, 1500, 6000 and 8000, Clariant Masterbatches, I); talc (Carlo Erba, I); croscaramellose sodium (AcdiSol®; FMC BioPolymer, US); low-substituted hydroxypropyl cellulose (L-HPC; ShinEtsu, J); sodium chloride (NaCl; Carlo Erba, I); sodium hydrogen carbonate ($NaHCO_3$; Carlo Erba, I); calcium carbonate ($CaCO_3$; Carlo Erba, I); citric acid (Carlo Erba, I); tartaric acid (Carlo Erba, I); furosemide (Metapharmaceutical, E).

2.2. Methods

2.2.1 Characterization of materials

Hot-plate experiment: 2-3 g samples of polymer/polymeric formulation were placed in an aluminum pan on a hot plate and heated under continuous manual mixing, while gradually increasing the temperature up to 200 °C. Samples were checked for overall aspect, color, texture and mechanical characteristics during heating and after cooling.

Air shot test: 50 g samples of polymer/polymeric formulation were loaded into the IM press through the hopper and expelled from the injecting unit as during a purge operation [19]. The test was repeated under different operating temperatures. Samples were checked for overall aspect, color and mechanical characteristics immediately after ejection and after cooling.

X-Ray diffraction: X-ray diffractograms were collected with a X'pert Pro MPD diffractometer (Panalytical, US), using Cu-Kα radiation (λ=1.5418 Å). The generator voltage and current were set at 45 kV and 40 mA, respectively and the 2 - theta scanning range was from 4 to 40° (step size 0.0083556°, scan speed 0.053907 °/s). Powder samples and extruded/molded samples of uniform thickness were analyzed.

2.2.2 Manufacturing of extruded and molded units

Tablet-forming polymers, except for PEGs, were kept in a ventilated oven at 40 °C for 24 h prior to use. Plasticized polymeric formulations were prepared by mixing or granulating polymers in a mortar with the selected solid or liquid plasticizer, respectively; the amount of plasticizer was expressed as weight % (wt%) on the dry polymer. Adjuvants and/or drug were added to plasticized formulations by mixing in a mortar; the amount of the added component was expressed as wt% on the final formulation. As far as starch and starch derivatives are concerned, final formulations to be processed by IM were prepared by

extrusion through a 4 mm rod-shaped die (see HME process). Only for the EXP_{CLV}-based formulations containing effervescent adjuvants, the latter were added after extrusion, in order to limit their early contact with water and exposure to high temperatures.

HME process: HME was carried out by a single-screw extruder (Extrusiograph 19/25D, Brabender, D) equipped with rod-shaped (diameter 4 or 8 mm) or ribbon-shaped (thickness 1 mm) dies. Process parameters (barrel T_1-T_2-T_3 and die T_4 temperatures, screw rate) and torque values were recorded. Rods of 4 mm in diameter were manually cut into pellets and then processed by IM; rods of 8 mm in diameter rods were cut into tablets (thickness 4 mm) by a bench-top saw. Rods of 30 mm in diameter disks were die-cut from extruded sheets.

IM process: IM was performed by a bench-top micromolding machine (BabyPlast 6/10P, Cronoplast S.L.; Rambaldi S.r.l., I). Materials were loaded through the hopper into the plasticating chamber of the IM press by means of the loading plunger and then conveyed to the injecting chamber. By successively applying two distinct pressures, the injection pressure P_1 (maintained for 2.5 sec) and the holding pressure P_2 (maintained for 1.5 sec), both at a selected rate (r_1 and r_2, respectively) expressed as a percentage of the maximum one, a second plasticating plunger (10 mm diameter) moved 7-16 mm forward thus injecting specific amounts of formulation through a 1 mm nozzle into the mold cavity. Molded items were prepared by way of two different molds: *i)* a disk-shaped mold of 30 mm in diameter and 1 mm in thickness provided with a central gate; *ii)* a cylindrical mold of 8 mm in diameter and 4 mm in height provided with a central gate. Prior to product ejection, the mold was kept closed (2.5-15 sec at 15 °C) and the formulation was allowed to cool down and harden. The disk-shaped mold was manually lubricated with vegetable oil approximately every 20 manufactured units; the first disk obtained after this operation was discarded.

2.2.3 Characterization of extruded and molded units

HME and IM units were checked for weight (analytical balance BP211, Sartorius, US; n = 10) and thickness (digimatic indicator ID-C112X, Mitutoyo, J; n = 10).

Digital photographs (Nikon D70, Nikon, I) and photomicrographs (SEM; Sigma, Zeiss, D; gold sputtering, 10 nm) of tablets not exposed to the aqueous medium and withdrawn at different time points during the mass loss test were acquired; samples dried in a ventilated oven at 40 °C for 24 h were evaluated.

Mass loss test: the mass loss test on extruded and molded placebo units (disks and tablets) (n = 3) was carried out in both a USP37 dissolution *apparatus* (*apparatus* 2, Dissolution System Distek Inc. 2000, US; 1000 mL of distilled water or 1N HCl solution, 37 ± 0.5 °C, 100 rpm) and in a six-position disintegration *apparatus* (800 mL of distilled water or HCl 1N, 37 ± 0.5 °C, 31 cycles/min). Samples to be tested by dissolution apparatus were inserted into a polyethylene net (5 mm mesh for disks and 2 mm mesh for tablets). Tablets to be tested by disintegration *apparatus* were inserted each into a single basket-rack assembly. At pre-determined time points samples were withdrawn and oven-dried (40 °C) to constant weight. Percentage mass loss was calculated with respect to the initial sample weight. Times to 10 and 80 % mass loss (t_{10} and t_{80}, respectively) were obtained from mass loss data and the difference between the two values (t_{80-10}) indicated mass loss rate.

Dissolution test: the drug dissolution test (n = 3) was performed by USP37 *apparatus* 2 (Dissolution System Distek Inc. 2000, US) under the following operating conditions: 900 mL of pH 5.8 phosphate buffer, 37 ± 0.5 °C, 50 rpm, according to "Furosemide Tablets" USP37 monograph. Fluid samples were withdrawn at fixed time points and assayed spectrophotometrically (274 nm). At the end of the test (90 min), the total amount of drug dissolved was determined after vortex mixing (10 min). The percentage of furosemide dissolved at each time point was calculated with respect to the final dissolved amount. Dissolution parameters were statistically compared by umpired 2-tail t-student test, accounting for heteroscedasticity. The differences were considering significant with $p < 0.05$.

3. Results and discussion

HME and IM are well established processing techniques in the plastics industry. Despite the number of applications proposed in the scientific literature, there is still much work to be done before they may widely be exploited in the pharmaceutical industry, especially in the case of IM. Not only problems related to the processability of pharma-grade materials (rheological/thermomechanical behavior and stability), but also limitations associated with the active ingredient (dose, physical-chemical characteristics and stability) and the drug product requirements (release profile, physical characteristics and stability, route of administration, compliance) should be taken into account. In this respect, as no formulation approaches have been described for the manufacturing of IR tablets by HME or IM, the first objective of the present work was the identification of pharma-grade

polymers suitable for being processed and able to lead to products having the desired performance. Such polymers should not be considered merely as conventional fillers because they represent the thermoplastic components essential to the achievement of the final dosage form, *i.e.* the tablet-forming agents. The dissolution of the active ingredient should start as soon as IR formulations come in contact with biological fluids, and the dissolution rate should primarily depend on the physical-chemical properties of the drug while not being limited by the dosage form characteristics (Eur. Ph. 8th ed., Dosage Forms, Glossary). In this respect, HME and IM products, which generally show higher bulk density and lower porosity with respect to compressed ones of analogous composition (*e.g.* prolonged-release matrix systems, implants), may turn out critical [12,20,21]. A screening of traditional fillers, either soluble or insoluble, known for their thermoplastic properties and already proposed for hot-processing, was therefore undertaken.

3.1. Screening of tablet-forming agents

The possibility of using polymers as tablet-forming agents in HME and IM would depend on the processing temperatures and the rheological properties of the melt as well as the thermal/mechanical stability of the obtained products that has a great impact on the versatility of tablets in terms of shape, dimensions and drug loads. In this respect, based on the need for the material to be extruded/injected through thin gaps, which involves higher shear stresses, sheets and disk prototypes were employed in order to discriminate the behavior of different polymers.

Soluble polymers used as carriers for solid dispersions prepared by HME (HPC, HPMC, PVA, KIR, KVA, Soluplus, Eudragit E) and thermoplastic starch were initially considered [22-32]. Also polyethylene glycols (PEG 6000 and 8000), which were the only polymers already proposed for the manufacturing of tablets by IM, were taken into account for comparison purposes [16]. In addition, the ability of starch derivatives employed as disintegrants for solid dosage forms (EXP, EXP_{CLV}, VIV) to behave like thermoplastic starch does when processed in the same way, *i.e.* in admixture with plasticizers, under thermal and mechanical stresses, and to maintain hydration/swelling properties, was investigated.

As a preliminary step, hot-plate and air shot tests were performed to determine or confirm the working temperatures of the selected polymers and assess whether plasticizers were needed or not [33-34]. The choice of the type and amount of plasticizer as well as the identification of parameters to be used for the evaluation of HME and IM processability,

were then accomplished through the preparation of extruded sheets (1 mm in thickness) and molded disk-shaped prototypes (1 mm in thickness and 30 mm in diameter), respectively (Table 1). The HME processability of materials under investigation was evaluated based on morphological (uniformity of shape and thickness) and mechanical characteristics of extruded sheets. On the other hand, IM processability was rated according to the aspect (integrity and thickness) and mechanical characteristics of the molded disks as well as the possibility of their automatic ejection at the end of a molding cycle, thus providing a continuous manufacturing process.

Table 1: polymeric formulation and operating parameters used for the manufacturing of extruded sheets and molded disks.

Formulation		**Process conditions and performance**									
		HME				**IM**					
Polymer	Plasticizer (wt %)	T_1-T_2-T_3-T_4 *°C*	Screw rate *rpm*	Torque* *N m*	Processability[a]	T_1-T_2-T_3 *°C*	P_1 *bar*	r_1 *%*	P_2 *bar*	r_2 *%*	Processability[b]
PEG 6000	-	65-60-60-55	50	1	-	65-60-55	15	20	10	15	-
PEG 8000	-	65-65-60-55	50	1	-	65-60-55	15	20	10	15	-
HPC	PEG 1500 (10%)	95-100-110-115	15	9	+	110-115-125	40	30	30	20	+
HPMC	PEG 400 (50%)	*nd*	*nd*	*nd*	*nd*	130-140-150	30	50	20	40	-/+
KVA	PEG 1500 (10%)	140-150-155-145	30	5	-/+	140-145-150	30	20	20	15	-
KIR	GLY (15%)	150-140-150-140	25	10	+	130-135-150	50	40	30	20	+
PVA	GLY (20%)	140-150-160-150	20	7	+	160-170-180	40	40	30	30	+
Soluplus	PEG 1500 (15%)	90-95-100-120	40	5	-/+	130-140-150	40	30	30	20	-/+
Eudragit E	TEC (10%)	145-155-160-150	60	10	-/+	150-155-160	50	40	40	30	-/+
Starch	W (15%) / GLY (10%)	75-90-110-95	55	7	-/+	125-110-125	40	50	30	40	-/+
EXP	W (20%) / GLY (20%)	60-70-100-90	85	8	-/+	90-125-120	30	50	20	45	-/+
EXP_{CLV}		60-70-100-90	85	9	-/+	90-125-130	30	50	20	45	-/+
VIV		60-70-100-90	85	10	-/+	90-125-130	30	50	20	45	-/+

*maximum value obtained

[a]HME processability: "-" no sheet obtained; "-/+" incomplete sheet with non-uniform thickness/extreme brittleness; "+" complete sheet with uniform thickness and suitable mechanical properties

[b]IM processability: "-" broken/deformed disks; "-/+"not-automatically disks ejected/ extremely brittle; "+"automatically ejected disks with suitable mechanical properties

"nd" not determined; the extrusion process failed

A series of promising tablet-forming agents was identified that could be processed by HME and IM with no need for technological aids, except for plasticizers that both decreased the working temperatures and counteracted the glassy nature of the extruded/molded products. In this respect, hot-processing techniques would involve a remarkably limited number of excipients as compared with traditional tablet manufacturing by compression. PEGs only could be processed as such. However, they were characterized by very low melting points and viscosities at their working temperatures, which impaired the achievement of extruded sheets or any other item with own consistency. By IM, PEG products could be obtained because this technique envisages cooling and hardening inside a mold, nevertheless their original shape was not maintained over time. Some difficulties were also encountered in processing HPMC and Eudragit E by HME as well as KVA by both the techniques, although these may be overcame when changing equipment and/or shape/size characteristics of items produced.

As far as the starch derivatives are concerned, they demonstrated to become extrudable under thermal and mechanical stresses in the presence of water/glycerol mixtures, as already observed with starch. However, the amount of plasticizer and the rate of extrusion needed to be increased in order to process the starch derivatives. The relevant extruded products showed a marked and durable loss of crystallinity. By way of example, X-ray profiles of EXP_{CLV}-based samples immediately after extrusion and following six-months storage at ambient conditions (24 ± 2 °C, 55 ± 5% RH) are reported in Figure 1. It can be noticed that retrogradation or post-crystallization phenomena, typical of thermoplastic starch, did not occur in the case of sodium starch glycolate, at least within the considered period of storage [24].

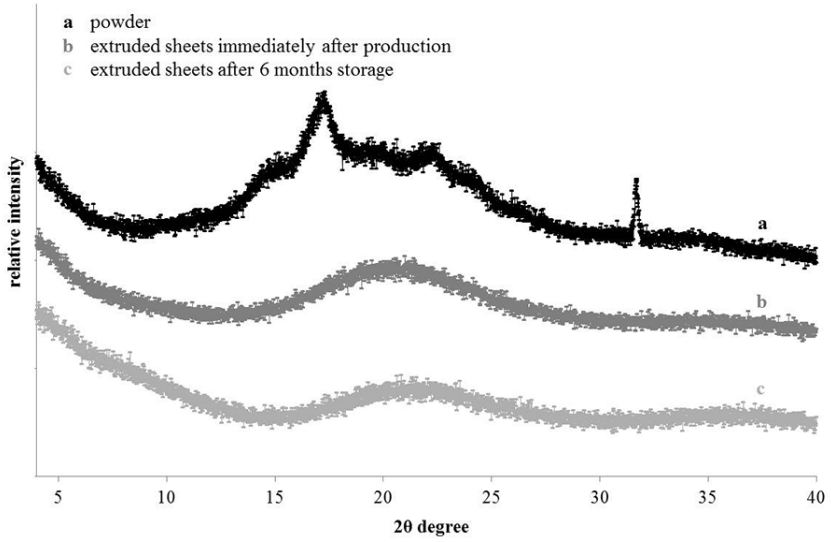

Figure 1: X-ray profiles of powdered Explotab® CLV and polymer-based sheets immediately after extrusion and after 6 months storage.

Disk-shaped prototypes, obtained by cutting the extruded sheets or by molding, were used to study the behavior of the polymeric formulations when in contact with aqueous fluids. Parameters calculated from their mass loss profiles are reported in Table 2.

Table 2: mass loss parameters (CV <5%), t_{10diss} (time to 10% of mass loss in the dissolution apparatus) and $t_{80\text{-}10diss}$ (difference between the time to 80 and 10% of mass loss in the dissolution apparatus), relevant to disk-shaped prototypes.

Formulation		**HME disks**		**IM disks**	
Polymer	Plasticizer (wt%)	t_{10diss} *min*	$t_{80\text{-}10diss}$ *min*	t_{10diss} *min*	$t_{80\text{-}10diss}$ *min*
PEG 6000	-	/	/	/	/
PEG 8000	-	/	/	/	/
HPC	PEG 1500 (10%)	< 5'	39' 24"	< 5'	21' 03"
HPMC	PEG 400 (50%)	-	-	< 5'	33' 47"
KVA	PEG 1500 (10%)	*nd*	*nd*	/	/
KIR	GLY (15%)	< 5'	26' 32"	< 5	28' 44"
PVA	GLY (20%)	10' 02"	> 60	< 5	40' 35"
Soluplus	PEG 1500 (15%)	7' 14"	46' 50"	8' 14"	> 60'
Eudragit E	TEC (10%)	*nd*	*nd*	< 5 *	26' 44" *
Starch	W (15%) / GLY (10%)	39' 20"	> 80	10' 07"	> 90'
EXP	W (20%) / GLY (20%)	< 5'	41' 43"	< 5'	48' 59"
EXP_{CLV}		< 5'	48' 49"	< 5'	39' 55"
VIV		< 5'	> 60'	< 5'	34' 28"

"/" neither extruded sheets nor complete disks obtained
"nd" not determined; no intact disks could be obtained by cutting
* mass loss test was performed in 1N HCl solution

Most of the samples lost at least 10% of the initial mass (t_{10diss}) in less than 10 min, in most cases within 5 min, and a further 70% ($t_{80\text{-}10diss}$) within about 60 min. Mass loss could be attributed to dissolution phenomena, predominant, as expected, in the case of samples based on soluble polymers, and mechanical erosion. The detachment of macroscopic fragments from the external surface of disks was evident with starch-derived disintegrants only. Differences between the mass loss performance of HME and IM disks with the same composition were not observed in spite of possibly different porosities. When present, such differences may fail to be highlighted owing to non-properly discriminating test conditions. Indeed, because disks were inserted into a polyethylene net, the access of water might be restricted and hydration/swelling phenomena, generally leading to the disintegration of solids, might consequently be limited. Moreover, fragments larger than the mesh size (> 5 mm) were not able to escape through the net, thus not being accounted as mass loss. Such issues were overcome when dealing with tablet products.

3.2. Placebo tablets

Two of the polymeric formulations that showed a good balance between HME/IM processability and fast mass loss performance, but a different dissolution/disintegration behavior, were selected for the manufacturing of tablets. HME and IM processes for the preparation of extrudates of 8 mm in diameter, subsequently cut into cylindrical items of 4 mm in thickness (*i.e.* final HME tablets), and molded tablets of the same size, respectively, based on HPC and EXP_{CLV} were set up (formulations 1a and 2a in Table 3). The manufacturing of placebo tablets, *i.e.* based on thermoplastic tablet-forming agents only, turned out to be less critical with respect to that of disks. In particular, IM tablets were obtained with no need for lubrication.

In order to better discriminate between the performance of differently prepared tablets, the mass loss test was carried out by both dissolution apparatus, with tablets inserted into a polyethylene net of 2 mm mesh, and disintegration apparatus, with tablets freely moving in the basket-rack assembly (Figure 2).

Table 3: composition and operative parameters used for the manufacturing of extruded and molded tablets based on EXP_{CLV} and HPC.

	Formulation				Process conditions							
					HME			IM				
	Polymer	Plasticizer (wt%)	Drug (wt%)	Adjuvant (30%)	T_1-T_2-T_3-T_4 *°C*	Screw rate *rpm*	Torque* *N m*	T_1-T_2-T_3 *°C*	P_1 *bar*	r_1 *%*	P_2 *bar*	r_2 *%*
1a	HPC	PEG 1500 (10%)	-	-	95-100-110-115	15	9	120-130-140	30	20	40	30
1b				AcdiSol	100-105-115-110	15	10	130-140-150	30	30	20	20
1c				L-HPC	100-105-115-110	15	10	130-145-150	30	30	20	20
1d				$NaHCO_3$	100-105-115-115	15	12	130-135-130	40	35	30	25
1e				$NaHCO_3$ / citric acid / $CaCO_3$	*nd*	*nd*	*nd*	130-135-130	50	40	40	30
1f				$NaHCO_3$ / tartaric acid	*nd*	*nd*	*nd*	130-135-130	40	40	30	30
1g				NaCl	95-100-110-115	15	18	130-135-130	40	40	30	30
1h				KIR	95-100-110-115	15	24	130-135-140	40	40	30	30
1i			Furosemide (20%)	-	90-100-115-115	60	14	100-120-130	30	50	20	40
1l				AcdiSol	90-100-115-115	60	19	100-120-130	30	40	20	30
1m				$NaHCO_3$ / tartaric acid	*nd*	*nd*	*nd*	130-135-130	40	40	30	30
1n				KIR	90-100-115-115	60	12	120-130-140	40	40	30	30
1o				NaCl	90-100-110-115	10	20	120-130-140	45	40	35	30
2a	EXP_{CLV}	W (20%) / GLY (20%)	-	-	60-70-100-90	65	9	100-130-140	50	20	40	30
2b				AcdiSol	60-70-110-90	40	20	90-130-120	40	40	30	30
2c				L-HPC	60-70-100-90	40	12	120-145-140	50	20	40	35
2d				$NaHCO_3$	60-80-100-90	40	11	110-120-130	40	30	30	20
2e				$NaHCO_3$ / citric acid $CaCO_3$	*nd*	*nd*	*nd*	110-120-130	40	40	30	30
2f				$NaHCO_3$ / tartaric acid	60-80-100-90	40	12	110-120-130	40	40	30	30
2g				NaCl	60-80-100-90	40	8	110-120-130	40	40	30	30
2h				KIR	60-90-110-90	40	8	110-120-130	40	40	30	30
2i			Furosemide (20%)	-	60-65-85-80	50	10	100-110-115	30	30	20	20
2l				AcdiSol	80-90-100-95	30	30	100-110-115	30	30	20	20
2m				$NaHCO_3$ / tartaric acid	80-90-100-95	30	25	100-110-115	40	40	30	30
2n				KIR	60-80-100-80	40	12	120-115-120	40	40	30	30
2o				NaCl	60-80-100-80	40	14	110-115-120	50	40	40	30

* maximum value obtained

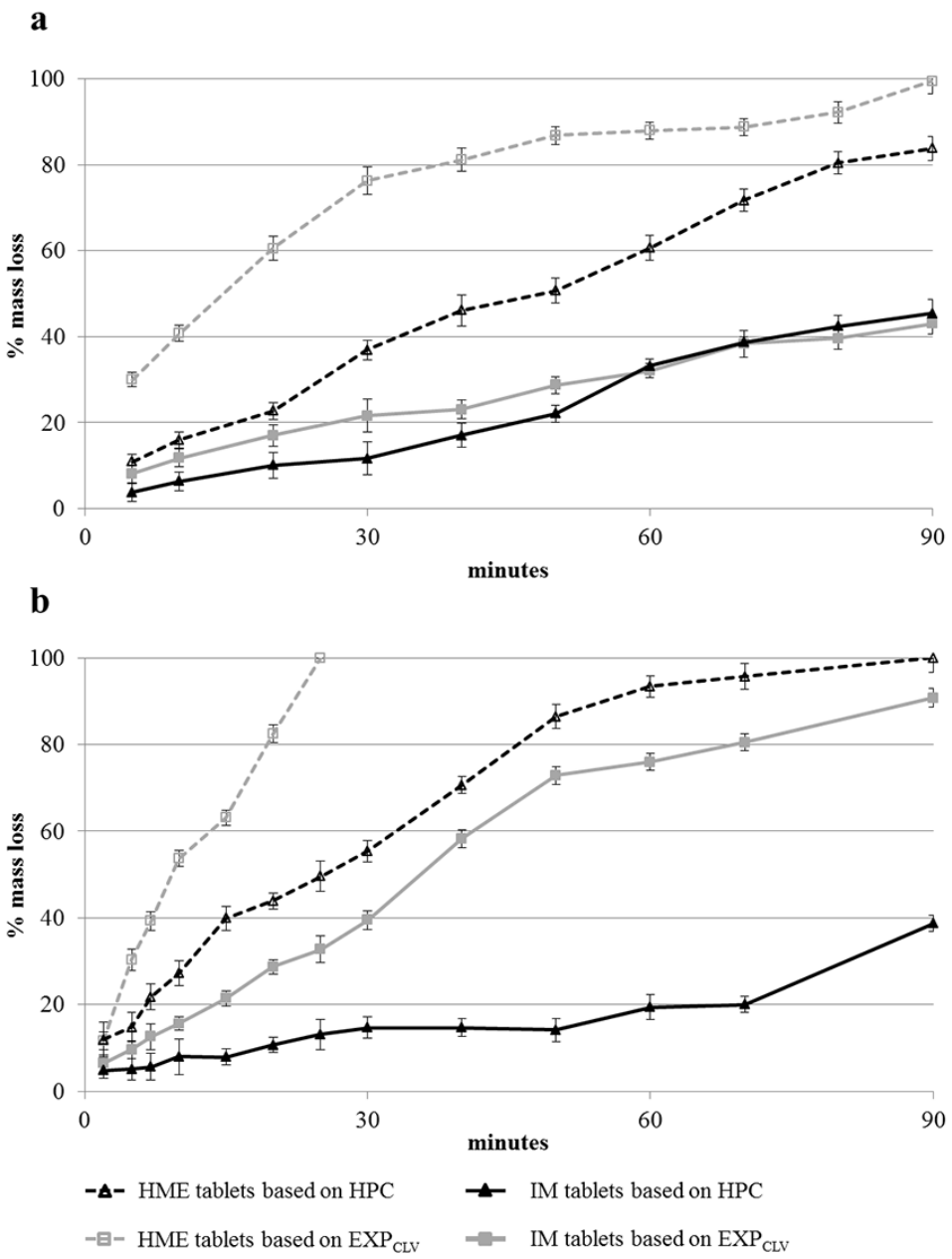

Figure 2: mass loss profiles of the HPC- and EXP_{CLV}-based tablets performed in the dissolution (a) or disintegration (b) equipment.

The mass loss rate of HME tablets turned out to be higher with respect to IM ones, irrespective of composition and test conditions. This could be due to possibly different surface and density characteristics of the products. Upon injection under high pressure into the mold cavity, in fact, a tight packing of polymer chains and a sudden cooling at the mold surface would take place, which may overall account for poor solvent penetration into the final item [21,35]. When tested by disintegration apparatus, all tablets except for the molded ones based on HPC showed an increase in mass loss over time. The mass loss increase was more evident with those materials which are known to possess an intrinsic ability to promote

disintegration (EXP_{CLV} vs HPC) or when tablet density could be assumed to be lower (extruded *vs* molded tablets). The different behavior of EXP_{CLV} and HPC formulations when exposed to the aqueous fluid was confirmed by the aspect of the tablets recovered. By way of example, in Figure 3 photographs of the molded tablets and photomicrographs of their surface, before and after exposure to the aqueous medium for different periods of time, are reported.

In the SEM images relevant to EXP_{CLV}-based tablets, cracks can be seen, already after 5 min of exposure to aqueous fluids, which could be attributed to the detachment of fragments. On the contrary, the surface of HPC tablets appears unchanged. Such findings are consistent with hypothesized mass loss mechanisms based on mechanical erosion or dissolution. This was confirmed by photographs of samples at successive time points (10-60 min in the dissolution *apparatus*), which pointed out a progressive reduction in volume of the HPC tablets without any notable change in their shape, thus supporting the occurrence of dissolution phenomena. On the other hand, it was evident that EXP_{CLV} tablets underwent a process of deaggregation.

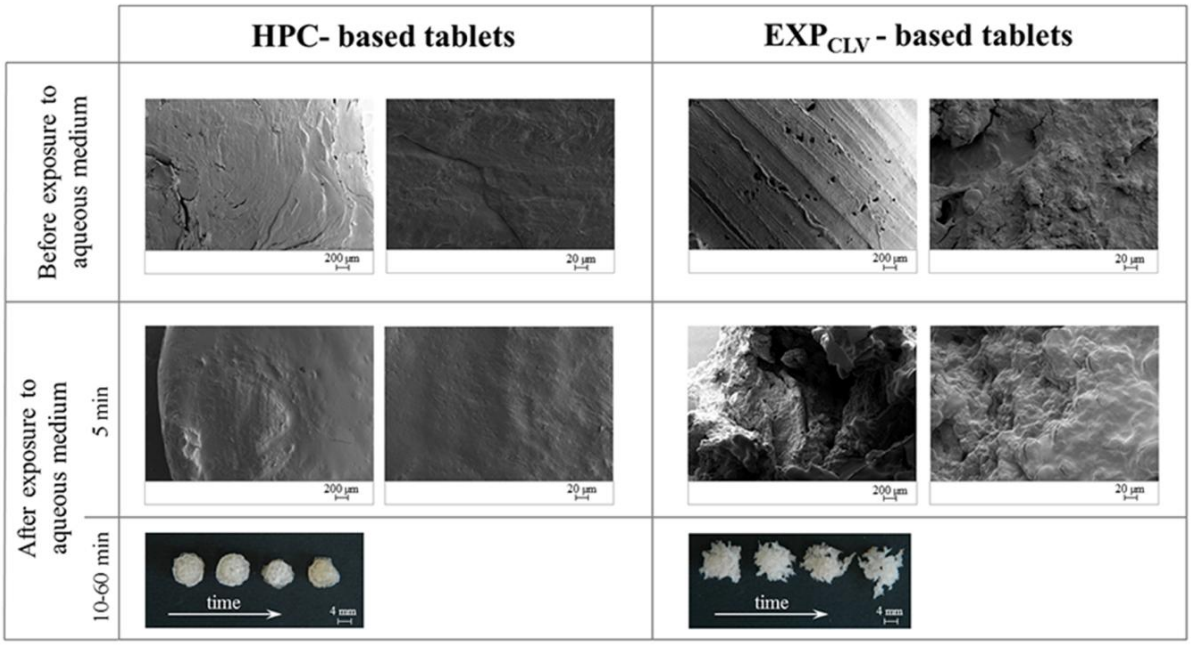

Figure 3: digital photographs and photomicrographs of molded placebo tablets based on HPC and EXP_{CLV}, before and after exposure to the aqueous medium. Digital photographs are referred to units tested in the dissolution *apparatus*.

3.3. Drug containing tablets

In order to further evaluate the potential for immediate release of the thermoplastic tablet-forming agents, a model drug, challenging in terms of dissolution properties, was selected. Tablets containing 20% of furosemide [36] (class IV of the Biopharmaceutics Classification System; T_m = 206 °C) were prepared by both HME and IM. Process conditions and dissolution profiles are reported in Table 3 (formulations 1l and 2l) and Figure 4, respectively.

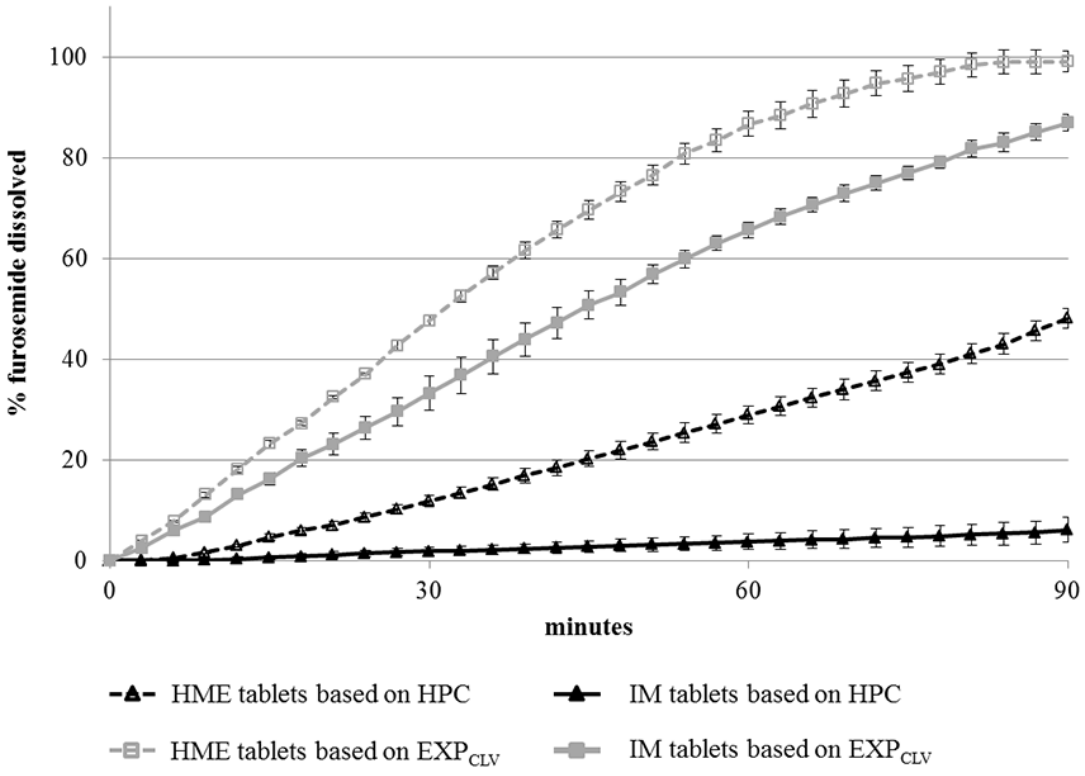

Figure 4: dissolution profiles of HPC- and EXPCLV-based tablets containing furosemide.

Dissolution results from furosemide-containing tablets were in agreement with mass loss from placebo ones. In fact, drug dissolution rate turned out higher in the case of extruded tablets and EXP_{CLV}-based formulations as compared with molded and HPC-based ones, respectively. The HPC-based formulations gave rise to non-disintegrating matrices from which drug liberation would occur through the swollen polymer. On the contrary, thermoplastic EXP_{CLV} was confirmed to be a very promising filler that would enable the manufacturing of disintegrating tablets by the investigated hot-processing techniques. Indeed, extruded prototypes having the simplest formulation (*i.e.* polymer/plasticizer/drug) fulfilled the requirements of USP 37 for IR furosemide tablets (*i.e.* not less than 80 % of furosemide dissolved in 60 min).

The use of dissolution/disintegration adjuvants was also attempted in order to enhance the rate of drug liberation. The possibility of adding soluble (NaCl, KIR), effervescent ($NaHCO_3$, $CaCO_3$, citric and tartaric acids) and disintegrant (AcdiSol, L-HPC) excipients to HPC and EXP_{CLV} formulations was investigated [21,34,37-39].

All tablets, either placebo or containing the drug, were successfully prepared after minimal adjustments of process parameters (Table 3). Only few HME manufacturing processes relevant to placebo formulations containing citric acid or tartaric acid and $CaCO_3$, in admixture with $NaHCO_3$ (formulations 1e, 1f, 1m and 2e), failed because of too high shear forces to deal with. When tablets containing effervescent excipients were successfully prepared, an internal porous structure was observed, especially in the case of HPC-based molded samples (Figure 5). This could be attributed to the evolution of CO_2 gas resulting from the thermal decomposition of sodium bicarbonate in the softened polymer [38].

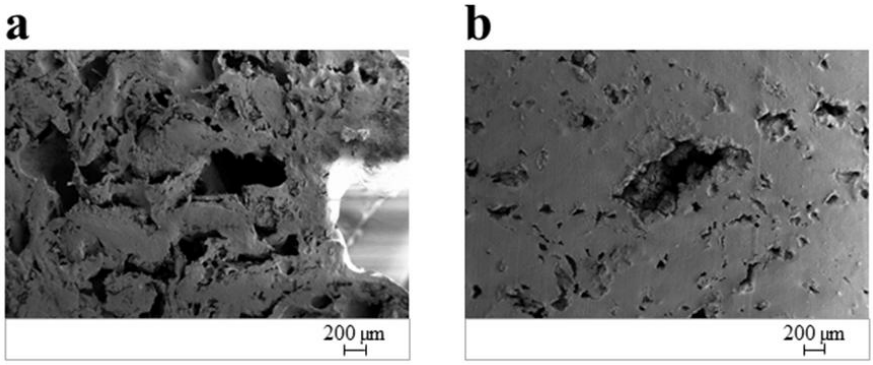

Figure 5: Photomicrographs of (a) HPC- and (b) EXPCLV-based placebo molded tablets containing 30% of $NaHCO_3$ / tartaric acid.

Dissolution parameters, *i.e.* the percentages of furosemide dissolved after 20 and 60 min ($\%_{20min}$ and $\%_{60min}$, respectively), relevant to adjuvant-containing tablets and reference products based on HPC and EXP_{CLV} only are reported in Table 4.

Table 4: percentage of furosemide dissolved after 20 and 60 min ($\%_{20min}$ and $\%_{60min}$, respectively) from HPC- and EXP_{CLV}-based tablets containing dissolution/disintegration adjuvants.

	Formulation				HME		IM	
	Polymer	Plasticizer (wt%)	Drug (20%)	Adjuvant (30%)	$\%_{20min}$ *(cv)*	$\%_{60min}$ *(cv)*	$\%_{20min}$ *(cv)*	$\%_{60min}$ *(cv)*
1a	HPC	PEG 1500 (10%)	Furosemide	-	7.02 *(11.05)*	28.93 *(6.42)*	1.47 *(3.15)*	4.47 *(6.44)*
1b				AcdiSol	6.56 *(9.10)*	24.25 *(10.46)*	6.13 *(9.1)*	18.37 *(1.41)*
1e				$NaHCO_3$ / tartaric acid	-	-	12.95 *(7.92)*	39.13 *(3.05)*
1f				KIR	10.04 *(7.04)*	34.65 *(4.29)*	2.88 *(0.33)*	22.03 *(12.86)*
2a	EXP_{CLV}	W (20%) / GLY (20%)	Furosemide	-	32.45 *(1.10)*	86.76 *(2.96)*	23.09 *(9.70)*	65.64 *(2.40)*
2b				AcdiSol	6.97 *(14.36)*	28.22 *(22.62)*	5.84 *(9.44)*	17.26 *(6.23)*
2e				$NaHCO_3$ / tartaric acid	27.93 *(0.86)*	74.93 *(0.46)*	51.58 *(11.25)*	99.8 *(4.57)*
2f				KIR	45.97 *(7.32)*	100.00 *(3.00)*	38.77 *(9.65)*	100.00 *(7.90)*

Adjuvants that were demonstrated able to increase the mass loss of HPC tablets (data not shown) generally improved the furosemide liberation, mainly from IM products. In particular, the best performance was obtained with the molded tablets containing $NaHCO_3$ and tartaric acid (> eight-fold amount of furosemide dissolved after 60 min as compared with 1a reference formulation). Indeed, these tablets not only showed a porous network but also a residual effervescent activity when in contact with the aqueous fluids, which could account for improved dissolution. A different behavior was observed in the case of formulations containing disintegrants. While mass loss of placebo products was increased by the latter adjuvants, AcdiSol slightly improved the dissolution rate of furosemide from molded tablets only. Moreover, the disintegrant did not significantly affect ($p > 0.05$) drug dissolution parameters of HME units.

EXP_{CLV} was confirmed an advantageous filler for the preparation of IR tablets by HME and IM. Indeed, three relevant formulations, one of which obtained by HME and the other two by IM, fulfilled USP requirements for furosemide tablets. In particular, when taking into account the contribution of the adjuvants to the improvement of disintegration and dissolution rate, effervescent excipients turned out more effective in molded rather than extruded tablets. During IM processing, wherein exposure to high temperatures lasts shorter, thermal decomposition of sodium bicarbonate and resulting CO_2 evolution would less likely occur. Accordingly, a residual effervescence ability might have been maintained thus aiding the

disintegration of tablets in contact with aqueous fluids. The addition of the soluble adjuvant KIR resulted in enhanced drug dissolution rate, and this effect was comparable or, even better in the case of HME tablets, with that of effervescent-containing products. Unlike all other EXP_{CLV}-based tablets, neither placebo nor drug-loaded KIR-containing ones gave rise to visible residues after the relevant exposure to aqueous fluids. Such a behavior was considered worth being further investigated. Finally, in the presence of AcdiSol, the rate of furosemide dissolution from both extruded and molded EXP_{CLV}-based products was decreased. The ability of the disintegrant to promote mass loss of placebo units in aqueous medium was thus not reflected in an enhanced drug dissolution rate. This already occurred with HME HPC-based tablets containing the same adjuvant. In this respect, the presence of salts in the buffer medium might account for a lower amount of water available for the hydration/swelling of EXP_{CLV} and/or AcdiSol. Indeed, the dissolution rate of furosemide increased when the test was performed under the mass loss experimental conditions, *i.e.* water instead of phosphate buffer as the medium, and 100 instead of 50 rpm: $\%_{20min}$ 21.32 (CV 1.89) and $\%_{60min}$ 69.16 (CV 3.36) for HME EXP_{CLV}-based tablets; $\%_{20min}$ 40.20 (CV 3.81) and $\%_{60min}$ 92.63 (CV 1.21) for IM EXP_{CLV}-based tablets.

4. Conclusions

The possibility of manufacturing tablets with potential for IR by HME and IM techniques, which could advantageously fulfill the needs of CM, may help progress of this emerging production mode in the pharmaceutical industry. Accordingly, a broad screening of pharmaceutical grade polymers was carried out aimed at evaluating the relevant suitability as tablet forming agents. Their selection was based on the polymer processability by both techniques and the disintegration/dissolution aptitude of the extruded/molded items obtained. The dissolution performance of extruded and molded tablets containing the poorly-soluble drug furosemide as a challenging tracer molecule was also investigated.

A variety of suitable tablet-forming agents, soluble and insoluble, able to give rise to consistent IR tablets starting from simple formulations, in some cases based on the polymer and plasticizer only, and showed appropriate behavior in aqueous media were identified. Sodium starch glycolate (*i.e.* Explotab®, Explotab® CLV and Vivastar®), in particular, was demonstrated to be processable as a thermoplastic polymer and led to items with an intrinsic tendency towards disintegration that was rather unexpected in view of the low inherent porosity of extruded/molded products. Moreover, formulation strategies based on the use of soluble, disintegrant and effervescent adjuvants to promote tablet disintegration and drug

dissolution were successfully set up. Explotab® CLV-based units with different composition, prepared by both HME and IM, turned out to comply with the USP 37 dissolution requirements for furosemide thus pointing out an interesting application potential of these techniques for the production of IR tablets, which may ultimately be exploited for continuous manufacturing.

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Conclusions

A PhD research project was undertaken aiming at investigating the possibility of transferring injection molding (IM)/micromolding (μIM) techniques to the pharmaceutical field for the manufacturing of drug products. With the main objective of identifying new potential areas of investigation, the overall information relevant to IM technology and its pharmaceutical applications already described in the scientific literature as well, were reviewed [Part I]. Hence, conventional dosage forms, *i.e.* immediate release tablets, and drug delivery systems (DDSs), *i.e.* gastroresistant capsular containers and hydrophilic swellable matrices, were successfully developed [Part II and III].

Since the ability of pharmaceutical polymers to undergo IM/μIM processes turned out poorly considered in the literature and, more generally, the identification of suitable materials was highlighted as a critical point in the development of molded drug products, a working procedure for a systematic evaluation of polymeric materials/composites was outlined within the research project. Pharmaceutical-grade polymers, either alone or in admixture, and polymeric composites with processing (*e.g.* plasticizers, reinforcements, lubricants) as well as functional (*e.g.* soluble and insoluble fillers, disintegrants, effervescent excipients) aids were evaluated leading to the construction of an extensive practical background. This work also helped to identify the need for developing a multidisciplinary approach to the problem based on thermal and rheological characterization of materials, engineering design of molds and set-up of processes as well as performance and stability evaluation of molded products. This knowledge has opened the way for scientific collaborations in the mechanical engineering and polymer science areas. Moreover, the experience gained from the research project, and in particular that derived from the evaluation of the feasibility of molded tablets with potential for immediate release, was profitably exploited during a nine-month internship at the Novartis-MIT Center for Continuous Manufacturing. The Center stems from a 10-year research collaboration between Novartis and the Massachusetts Institute of Technology (MIT), which is aimed at replacing the pharmaceutical industry conventional batch-based production mode with a continuous manufacturing one involving processing, without interruption, of materials generally maintained in motion and undergoing chemical reactions or mechanical/heating treatments. The research activity carried out at MIT is not included in my thesis because of confidentiality issues.

As mentioned, IM/μIM are known to involve the use of molds specifically devised for one single item/material. Therefore, any change in the design and/or composition of dosage forms may require the development of new molds and manufacturing processes. In this

perspective, the real-time prototyping capabilities of three dimensional (3D) printing technology could turn out especially useful to speed up the screening of formulations and their transition to manufacturing as well as the identification of design characteristics of the device that could be critical for the performance. In fact, starting from a 3D model or other electronic data, such a technology allows solid objects of almost whatever shape to be manufactured. In particular, the fused deposition modeling (FDM) technique, which is based on the use of thermoplastic filaments, could prove suitable for achieving prototypes of IM/μIM products. Accordingly, some preliminary steps forward in coupling the design and the development of new devices by FDM 3D printing and in their scale up to industrial manufacturing by IM/μIM have been undertaken and are giving interesting insight.