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

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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 shown to fulfill the USP 37 dissolution requirements for furosemide tablets.

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

1. INTRODUCTION

The 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 always 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 in this direction. Moreover, such a method was shown to be consistent with the 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 by 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 through different individual units, where all the conditions/parameters are clearly defined and controlled. A prototype immediate release (IR) tablet was achieved by extruding and injecting a basic thermoplastic formulation, composed of an *in situ* synthesized model drug and polyethylene glycol (PEG), 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. Such techniques are widely employed within the plastics industry for large-scale production also of precision components. While the former is exploited to create items having a fixed, and in some cases complex, cross-sectional profile, the latter allows objects with a well-defined three dimensional shape to be manufactured. Over the last two decades HME and IM have found several applications in the pharmaceutical field, in particular for the manufacturing of modified-release drug products.[16,17] Egalet®, for instance, is a prolonged- and pulsatile-release delivery platform at an advanced development stage, which is obtained by double-injection molding. On the other hand, melt extruded formulations for prolonged release, intended either for oral administration or as inserts/implants, are currently on the market (*e.g.* Isoptin-SRE® and Nuvaring®). Moreover, HME has

successfully been applied to enhance the dissolution rate/bioavailability of drugs by promoting the formation of solid dispersions with thermoplastic carriers, and, again, a few products reached the marketplace (*e.g.* Kaletra® and Gris-PEG®).[18] With respect to IR dosage forms, starch-based injection-molded shells (Capill®) were proposed as an alternative to dip-molded gelatin capsules.[17] Furthermore, powders or granules derived from milling of extruded dispersions may be compressed to give IR tablets.[16] HME and IM are also mentioned by Eur. Pharm. 8.0[19], along with compression, as suitable techniques for the manufacturing of directly-shaped tablets. However, only a preliminary research paper published in the late '90s has preceded the one relevant to the integrated CM plant in describing the use of IM for the manufacturing of IR tablets within one single production step.[20] In these instances, polyethylene glycol (PEG) was considered as the sole thermoplastic vehicle without any broadening of the formulation study. As regards extruded products, it is only in very recent times that the dissolution performance of directly-shaped units has been taken into account.[21,22] 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. The use of these manufacturing techniques would also result in the possibility of carrying out solvent-free processes, overcoming mixing and/or compaction issues, patenting the obtained products and enhancing the relevant versatility in terms of size/shape. 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 formulation 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, Tokyo, Japan); hydroxypropyl methyl cellulose (HPMC; Methocel® E5, Colorcon, West Point, Pennsylvania); polyvinyl alcohol (PVA; Gohsenol®, Nippon Goshei, Hull, United Kingdom); polyvinyl alcohol-polyethylene glycol graft copolymer (KIR; Kollicoat® IR, BASF, Düsseldorf, Germany); polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (Soluplus®, BASF, Düsseldorf, Germany); metacrylic acid copolymer (Eudragit® E PO, Evonik, Darmstadt, Germany); corn starch (Ingredion, Westchester, Illinois); sodium starch glycolates (EXP, Explotab®; EXP_{CLV}, Explotab® CLV; VIV, Vivastar®; JRS Pharma, Rosenberg, Germany); vinylpyrrolidone-vinyl acetate copolymer (KVA; Kollidon® VA 64, BASF, Düsseldorf, Germany); deionized water (W); glycerol (GLY; Pharmagel, Lodi, Italy), polyethylene glycols (PEG; 400, 1500, 6000 and 8000, Clariant Masterbatches, Milan, Italy); talc (Carlo Erba, Milan, Italy); croscaramellose sodium (AcdiSol®, FMC BioPolymer, Philadelphia, Pennsylvania); low-substituted hydroxypropyl cellulose (L-HPC, ShinEtsu, Tokyo, Japan); sodium chloride (NaCl, Carlo Erba, Milan, Italy); sodium hydrogen carbonate ($NaHCO_3$, Carlo Erba, Milan, Italy); calcium carbonate ($CaCO_3$, Carlo Erba, Milan, Italy); citric acid (Carlo Erba, Milan, Italy); tartaric acid (Carlo Erba, Milan, Italy); furosemide (Metapharmaceutical, Barcelona, Spain).

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.[23] 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, Westborough, Massachusetts), 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, Duisburg, Germany) 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., Lecco, Italy). 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 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, Elk Grove, Illinois; n = 10) and thickness (digimatic indicator ID-C112X, Mitutoyo, Milan, Italy; n = 10). Digital photographs (Nikon D70, Nikon, Milan, Italy) and photomicrographs (SEM; Sigma, Zeiss, Munich, Germany; gold sputtering, 10 nm) of tablets not exposed to the aqueous medium and withdrawn at different times 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, North Brunswick Township, New Jersey; 1000 mL of distilled water or 1M HCl solution, 37 ± 0.5 °C, 100 rpm) and in a six-position disintegration apparatus (800 mL of distilled water or HCl 1M, 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 each inserted into a single basket-rack assembly. At pre-determined times 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, North Brunswick Township, New Jersey) under the following operating conditions: 900 mL of pH 5.8 phosphate buffer, 37 ± 0.5 °C, 50 rpm.[24] Fluid samples were withdrawn at fixed times 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 times 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 and some products already on the market, there is still much work to be done before they may be widely exploited for the preparation of directly-shaped IR tablets. In this respect, 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. [25] In this respect, HME and IM products may be critical because of a generally higher bulk density and lower porosity with respect to compressed ones of analogous composition (*e.g.* prolonged-release matrix systems, implants).[12,26,27] 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.[28-38] 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.[20] 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.[39-40] 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.

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 inherent 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 overcome when changing equipment and/or shape/size characteristics of items produced.

As far as the starch derivatives are concerned, they became 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.[30]

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.

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).

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.[27,41] 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 times (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.

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[42] (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.

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).[24]

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.[27,40,43-45]

All tablets, either placebo or containing the drug, were successfully prepared after minimal adjustments of process parameters (table 3). Only a 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 the difficulty of coping with excessive shear forces. 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.[44]

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.

Adjuvants that were 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 was obtained by HME and the other two by IM, fulfilled USP requirements for furosemide tablets.[24] In particular, when taking into account the contribution of the adjuvants to the improvement of disintegration and dissolution rate, effervescent excipients turned out to be more effective in molded rather than extruded tablets. During IM processing, wherein exposure to high temperatures is of shorter duration, 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 with, or in the case of HME tablets even better than, 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.

It was possible to identify a variety of suitable soluble and insoluble tablet-forming agents, able to give rise to consistent IR tablets starting from simple formulations, in some cases based on the polymer and plasticizer only, and showing appropriate behavior in aqueous medium. 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 USP 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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Figure 1: X-ray profiles of powdered Explotab® CLV and polymer-based sheets immediately after extrusion and after 6 months storage.

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

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.

Figure 4: Dissolution profiles of HPC- and EXP_{CLV}-based tablets containing furosemide.

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

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

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

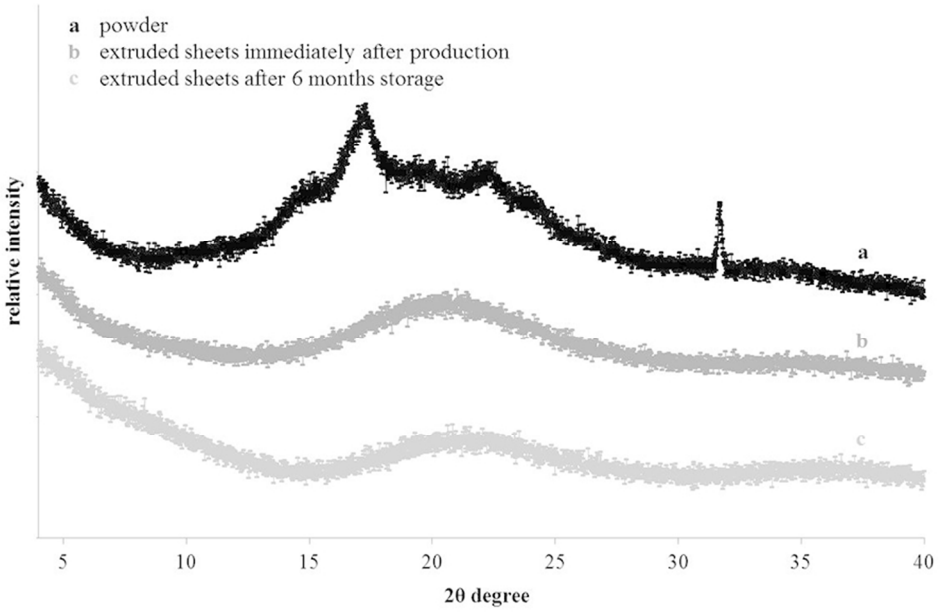
Table 3: composition and operative parameters used for the manufacturing of extruded and molded tablets based on EXP_{CLV} and HPC.

	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

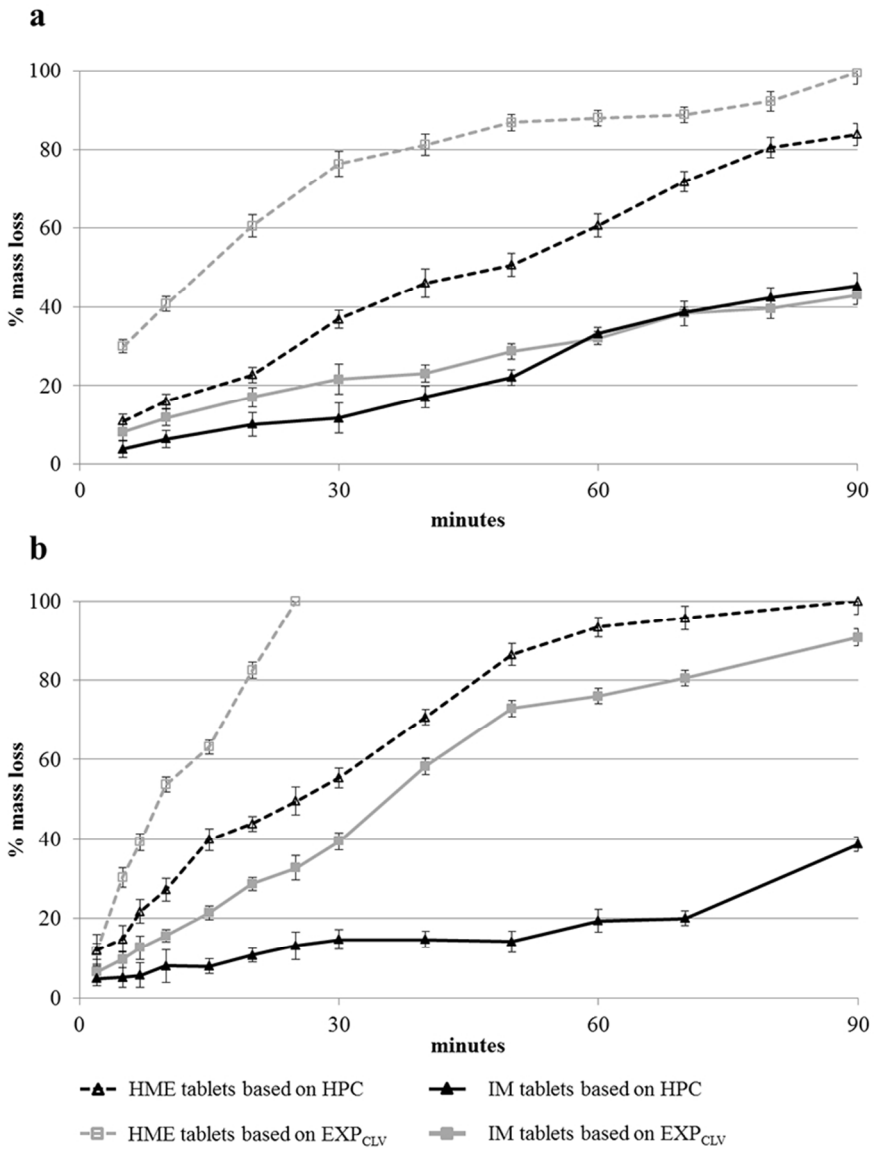
* maximum value obtained

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.

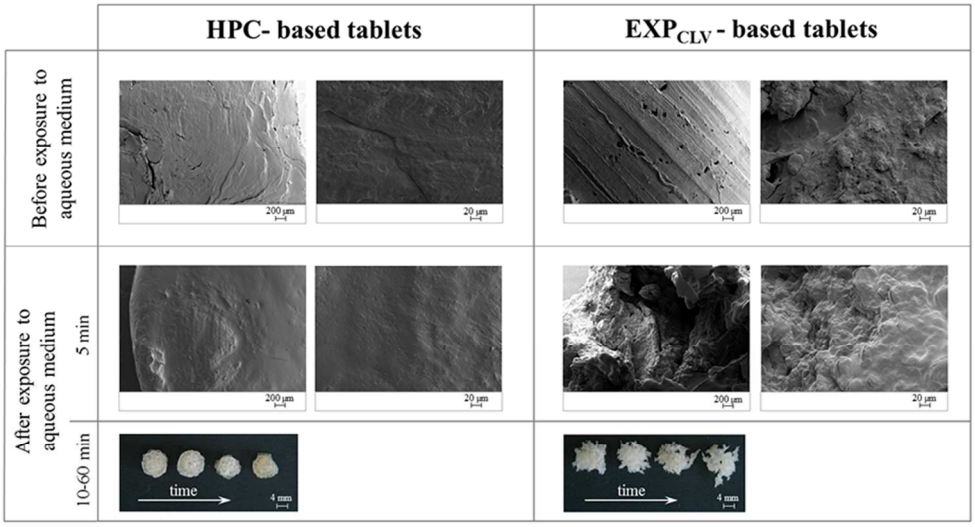
	Formulation				HME		IM	
	Polymer	Plasticizer (wt%)	Drug (20 %)	Adjuvant (30 %)	$\%_{20min}$ *(cv)*	$\%_{60min}$ *(cv)*	$\%_{20min}$ *(cv)*	$\%_{60min}$ *(cv)*
1a	HPC	PEG 1500 (10%)	Furosemide	-	7.02 *(11.05)*	28.93 *(6.42)*	1.47 *(3.15)*	4.47 *(6.44)*
1b				AcdiSol	6.56 *(9.10)*	24.25 *(10.46)*	6.13 *(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)*



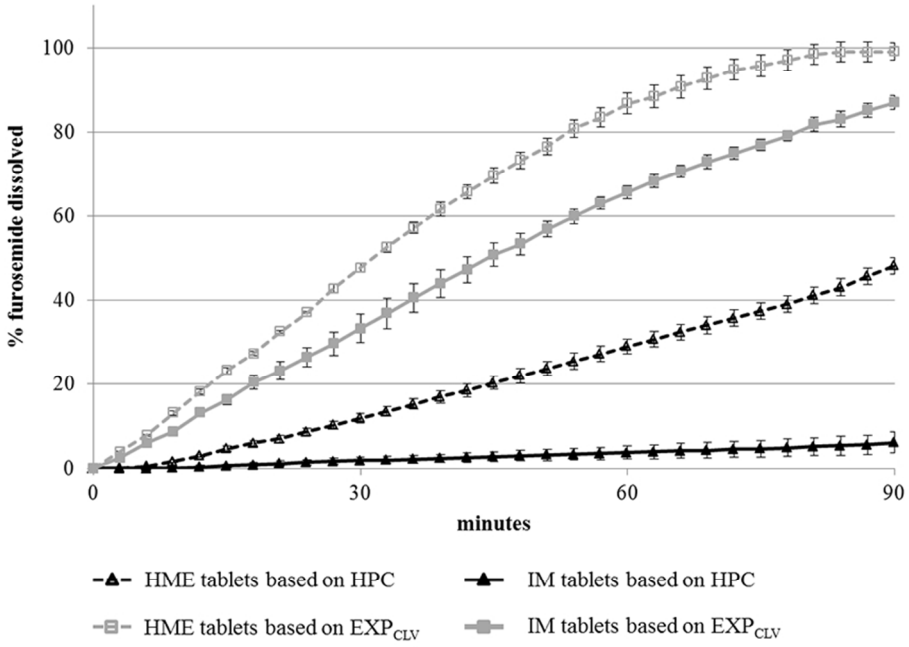
X-ray profiles of powdered Explotab® CLV and polymer-based sheets immediately after extrusion and after 6 months storage.
80x54mm (300 x 300 DPI)



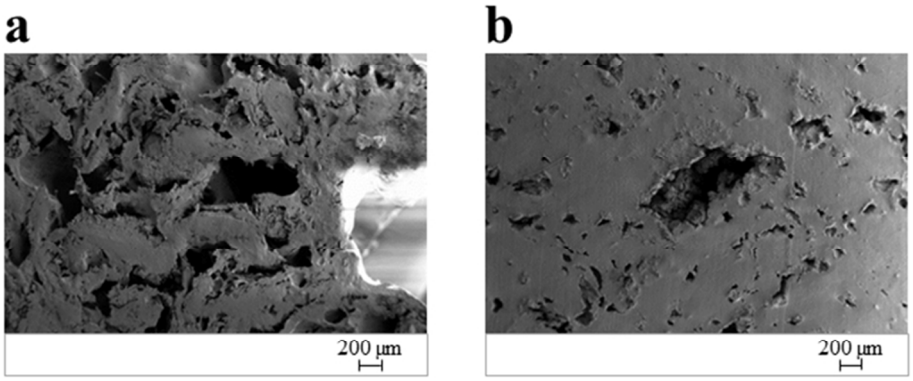
mass loss profiles of the HPC- and EXPCLV-based tablets performed in the dissolution (a) or disintegration (b) equipment.
80x98mm (300 x 300 DPI)



Digital photographs and photomicrographs of molded placebo tablets based on HPC and EXPCLV, before and after exposure to the aqueous medium. Digital photographs are referred to units tested in the dissolution apparatus.
160x95mm (300 x 300 DPI)



Dissolution profiles of HPC- and EXPCLV-based tablets containing furosemide.
80x56mm (300 x 300 DPI)



Photomicrographs of (a) HPC- and (b) EXPCLV-based placebo molded tablets containing 30% of NaHCO3 / tartaric acid.
80x36mm (300 x 300 DPI)