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Review

Injection Molding and its application to drug delivery

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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

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

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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 Fig. 1 a reciprocating screw machine is illustrated.

Fig. 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.

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