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Assessment of hot-processability and performance of ethylcellulose-based materials for injection-molded prolonged-release systems: An investigational approach

F. Casati[a,1,2], F. Briatico-Vangosa[b,2], F. Baldi[c], A. Melocchi[a], A. Maroni[a], A. Gazzaniga[a], L. Zema[a,*]

[a] Dipartimento di Scienze Farmaceutiche, Sezione di Tecnologia e Legislazione Farmaceutiche "Maria Edvige Sangalli", Università degli Studi di Milano, Milano, Italy
[b] Dipartimento di Chimica, Materiali e Ingegneria Chimica "G. Natta", Politecnico di Milano, Milano, Italy
[c] Dipartimento di Ingegneria Meccanica e Industriale, Università degli Studi di Brescia, Brescia, Italy

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ABSTRACT

The present work focuses on application of an investigational approach to assess the hot-processability of pharmaceutical-grade polymers with a potential for use in the manufacturing of reservoir drug delivery systems *via* micromolding, and the performance of resulting molded barriers. An inert thermoplastic polymer, ethylcellulose (EC), widely exploited for preparation of prolonged-release systems, was employed as a model component of the release-controlling barriers. Moldability studies were performed with plasticized EC, as such or in admixture with release modifiers, by the use of disk-shaped specimens ≥ 200 μm in thickness. The disks turned out to be a suitable tool for evaluation of the dimensional stability and diffusional barrier performance of the investigated materials after demolding. The effect of the amount of triethyl citrate, used as a plasticizer, on hot-processability of EC was assessed. The rate of a model drug diffusion across the polymeric barriers was shown to be influenced by the extent of porosity from the incorporated additives. The investigational approach proposed, of simple and rapid execution, holds potential for streamlining the development of prolonged-release systems produced by micromolding in the form of drug reservoirs, with no need for molds and molding processes to be set up on a case-by-case basis.

1. Introduction

The exploitation of hot-processing techniques, based on the extrusion and molding of polymeric materials, is currently one of the most appealing goals of the pharmaceutical industry, especially with respect to its potential for improving the bioavailability of poorly-soluble drugs, achieving new drug delivery targets and enabling continuous manufacturing (Melocchi et al., 2015; Tiwari et al., 2016; Vynckier et al., 2015; Zema et al., 2012). Moreover, 3D printing of dosage forms, which is supporting the advent of personalized therapy, can also be performed by extrusion, as in the case of fused deposition modeling (FDM) (Genina et al., 2016; Goyanes et al., 2015; Melocchi et al., 2016; Norman et al., 2017). In this respect, injection molding (IM) and 3D printing by FDM were recently proposed for the manufacturing of new drug delivery systems (DDSs) in the form of capsular devices, which may represent an advantageous alternative to traditional reservoir systems, *i.e.* drug-containing cores surrounded by a release-controlling barrier, generally applied by film-coating (Gazzaniga et al., 2011; Macchi et al., 2015; Melocchi et al., 2015; Zema et al., 2013a,b). In fact, capsule shells can be manufactured separately and then filled with different types of drugs/drug formulations, governing the release performance mainly on the basis of the design and composition of the shell itself (*e.g.* gastric resistance, delayed/pulsatile or prolonged release, colon targeting). One of the main reasons that still limit the use of hot-processing techniques in the drug delivery area is the lack of information about the thermal, rheological and stability characteristics of melts resulting from pharmaceutical formulations and of methods for the evaluation of their processability (Aho et al., 2015).

Ethylcellulose (EC) is a non-toxic insoluble polymer that has widely been used for the production of prolonged-release dosage forms, both as reservoir systems and monolithic devices, where the active ingredient is dispersed within the polymer. It is well known that slowing down the release of drugs, thus sustaining their plasma concentrations over time, may be related to major improvements in the therapy efficacy and

* Corresponding author.
E-mail address: lucia.zema@unimi.it (L. Zema).
[1] IMA S.p.a. – IMA Active Division, Ozzano dell'Emilia, Bologna, Italy.
[2] These authors contributed equally to the work.

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patient compliance (*e.g.* avoidance of peak-trough concentration profiles and of multiple administrations, reduction of the overall drug dose) (Lin and Chien, 2013). Depending on the duration of release, these systems can be suitable for different routes of administration. For instance, parenteral implants/inserts (*e.g.* injectable, auricular, ocular, vaginal) are able to deliver their contents for days up to several months, whereas formulations intended for the oral route release the drug conveyed within 12/24 h, consistent with the gastrointestinal transit. EC has shown to be extrudable, and several monolithic DDSs based on this polymer have been manufactured by hot melt extrusion (HME) and FDM as well as IM, the latter techniques allowing finished 3D-shaped items to be fabricated with greater detail precision and versatility in terms of size (miniaturization) and geometry (Bar-Shalom et al., 2003; Feng et al., 2016; Kempin et al., 2017; Mehuys et al., 2004; Quinten et al., 2009, 2011; Verhoeven et al., 2006, 2009; Vynckier et al., 2014; Zema et al., 2012). More recently, the possibility of attaining EC filaments intended for 3D printing by FDM was also demonstrated (Melocchi et al., 2016; Yang et al., 2018). In the present work, an investigational approach was proposed for time- and cost-effective assessment of the micromolding (μIM) processability of EC-based materials and prediction of behavior of the relevant molded barriers. For this purpose, screening specimens in the form of disks were employed. Indeed, the simple geometry of such a model, which was conceived and exploited for previous rheological, mechanical and barrier performance studies of polymeric materials of pharmaceutical interest, would make the analysis of the process and of its effects on the final product easier and faster to carry out (Melocchi et al., 2016; Zema et al., 2013b; Treffer et al., 2015). Demonstration of EC processability by μIM and its in-depth understanding may ultimately promote development of new DDSs fabricated by this technique. Particularly, the polymeric materials under investigation would be intended for the manufacturing of insoluble barriers, such as the capsule shell or the coating of a dosage form. Such barriers would allow biological fluids to permeate, thus bringing the drug contained within an inner compartment into solution and the dissolved drug molecules to diffuse through.

2. Materials and methods

2.1. Materials

Ethylcellulose, EC (Ethocel™ Std. 100 FP premium; Dow, US-MA): particle size ≤ 150 μm, mean particle size 30–60 μm; ethoxyl content 48.0–49.5% wt; the viscosity of 5% solution in 80% toluene and 20% alcohol (25 °C; Ubbelohde viscometer) 90–110 mPa·s; molecular weight not provided by the producer. Triethyl citrate, TEC (Aldrich, D). Polyvinyl alcohol-polyethylene glycol graft copolymer, KIR (Kollicoat® IR; BASF, D): MW ≈ 45,000 Da; d_{50} = 23 μm and d_{90} = 55 μm. Low-substituted hydroxypropylcellulose, LHPC (L-HPC NBD 020; Shin-Etsu, J): d_{50} = 42.6 μm and d_{90} = 91.1 μm; hydroxypropoxy content 14%. Blue dye-containing preparation (Kollicoat® IR Brilliant Blue; BASF, D), acetaminophen (Rhodia, I).

2.2. Methods

2.2.1. Preparation of materials

Plasticized EC – Plasticized EC mixtures (ECTEC) containing 10, 20 and 25% by weight (% wt) of TEC (ECTEC10, ECTEC20 and ECTEC25, respectively), calculated on the dry polymer, were prepared by kneading (Baldi et al., 2016). EC powder was placed in a mortar and the liquid plasticizer was added dropwise under continuous mixing. The resulting mixture was left 12 h at room conditions (21 ± 5 °C, 55 ± 5% RH). Afterwards, aggregates were ground by means of a blade mill and the < 250 μm fraction was recovered.

Plasticized materials – Release modifiers, KIR or LHPC, previously dried in an oven (40 °C for 24 h), were added as powders to milled ECTEC20 in a 70:30, 50:50 and 40:60 wt ratio. Formulations ECTEC20:KIR (70:30), ECTEC20:LHPC (70:30), ECTEC20:KIR (50:50) and ECTEC20:KIR (40:60) were thus obtained, respectively. ECTEC20 and the release modifier were mixed in a mortar for less than 1 min; physical mixtures were stored in plastic bags under vacuum and used within 1 or 2 days.

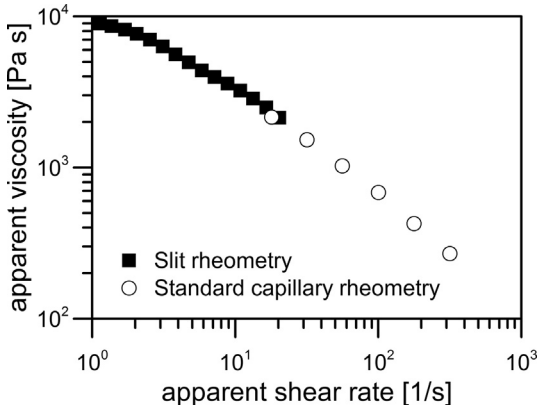

Fig. 1. Apparent viscosity *vs* shear rate curves at 175 °C for ECTEC20, measured through capillary rheometry (adapted from Baldi et al., 2016) and slit rheometry in the Haake™ MiniLab II microcompounder.

2.2.2. Rheological study

The flow behavior of neat and plasticized EC was evaluated by resorting to a slit capillary die (width 10 mm, height 1.5 mm, length 75 mm) integrated in the recirculation channel of Haake™ MiniLab II (Thermo Scientific™, US-MA) microcompounder, equipped with 2 conical screws (diameter 5/14 mm, length 109.5 mm) in counter-rotating configuration. Samples of 10 g were manually fed into the microcompounder. Data were collected at 165 °C and 175 °C. At each extrusion temperature, a series of measurements was carried out at screw rotation speeds from 10 to 200 rpm, acquiring data at 15 logarithmically-spaced points. For each speed, the difference in pressure between the exit and the entrance of the channel, ΔP, was monitored and recorded when a stable constant value was reached. The ΔP values *vs* revolution speed were then processed according to Yousfi et al., 2014, in order to obtain apparent viscosity curves. In Fig. 1 the results obtained by this procedure applied to ECTEC20 are compared with those from standard capillary viscosimetry tests performed on the same material (Baldi et al., 2016). Even if the overlapping of apparent shear rate ranges investigated by the two techniques is limited to one point, the overall trend seems to confirm the reliability of the measurements carried out in this work.

2.2.3. Moldability study

Micromolding (μIM) trials were carried out by a bench-top hydraulic press (BabyPlast 6/10P; Cronoplast S.L., S; Rambaldi S.r.L., I), equipped with a 10 mm piston and cooling circuit. 50 g samples were loaded into the μIM press hopper and extruded from the injecting unit as during a purge operation (air shot test) (Rosato and Rosato, 2000); the test was repeated under different operating temperatures.

Short shot test – ECTEC materials were processed by the μIM press equipped with a disk-shaped mold (diameter 30 mm) provided with a central gate and allowing to set different values of cavity thickness, *i.e.* 1000, 600, 400 and 200 μm. The molding process is pressure-controlled and based on two stages: the first-stage pressure (P_1) supports the filling of the mold cavity, while the second-stage one (P_2) leads to proper packing of the material until it solidifies (Rosato and Rosato, 2000). During short shot tests, the influence of the filling step on the melt progression throughout the mold was only considered, while P_2 was kept constant at the lowest setting conditions (Table 1).

Several injection tests at different P_1 values (10–100 bar, 10 bar