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Research paper

Tablet coating by injection molding technology – Optimization of coating formulation attributes and coating process parameters

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ABSTRACT

We developed and evaluated a solvent-free injection molding (IM) coating technology that could be suitable for continuous manufacturing via incorporation with IM tableting. Coating formulations (coating polymers and plasticizers) were prepared using hot-melt extrusion and screened via stress-strain analysis employing a universal testing machine. Selected coating formulations were studied for their melt flow characteristics. Tablets were coated using a vertical injection molding unit. Process parameters like softening temperature, injection pressure, and cooling temperature played a very important role in IM coating processing. IM coating employing polyethylene oxide (PEO) based formulations required sufficient room humidity (> 30% RH) to avoid immediate cracks, whereas other formulations were insensitive to the room humidity. Tested formulations based on Eudrajit E PO and Kollicoat IR had unsuitable mechanical properties. Three coating formulations based on hydroxypropyl pea starch, PEO 1,000,000 and Opadry had favorable mechanical (< 700 MPa Young's modulus, > 35% elongation, > 95×10^4 J/m^3 toughness) and melt flow (> 0.4 g/min) characteristics, that rendered acceptable IM coats. These three formulations increased the dissolution time by 10, 15 and 35 min, respectively (75% drug release), compared to the uncoated tablets (15 min). Coated tablets stored in several environmental conditions remained stable to cracking for the evaluated 8-week time period.

1. Introduction

Tablet coating is one of the most common pharmaceutical unit operations, providing benefits such as taste masking, odor masking, physical and chemical protection, product differentiation, and elegant appearance [1–6]. Achieving tailored drug release profiles and separation of incompatible drugs into separate coat and core formulations are other advantages of tablet coating. Tablet coating reduces dust generation and friction that can further decrease tablet friability and increase packaging speed [1,7–9].

The pharmaceutical industry borrowed the concept of sugar coating from the confectionary industry to coat tablets containing bitter drugs. Since sugar coating takes up to 5 days, needs stringent processing conditions, requires skilled labor and possesses a constant risk of mold and microbial growth; it is now mostly replaced by polymer film coatings with the first film-coated tablet marketed by Abbott Laboratories in 1954 [1]. The availability of various polymers and film coating equipment facilitated good reproducibility and batch to batch uniformity as well as ensured better process optimization and process control [7]. Film coating involving organic and aqueous solvent based polymer systems is the most commonly used tablet coating technology [5,7]. The organic solvents used can be expensive, flammable and toxic in nature [10]. Strict environmental regulations, possible safety hazards to the instrument operator, costly solvent recovery systems and the possibility of residual solvent in the final formulation further complicate the acceptability of organic solvents in coating [1,11]. Occupational Safety and Health Administration (OSHA) has recommended permissible concentration limits of organic solvent exposure for personnel [1]. The International Conference on Harmonisation (ICH) guidelines have recommended the use of non-organic solvent systems when possible and placed strict limits on residual solvents when they are used [7]. Unfortunately, aqueous coating systems require longer

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drying time and therefore higher energy costs. Some drugs are moisture sensitive and cannot be coated with aqueous systems. Aqueous based films are also more prone to aging and microbiological instability [12]. Both aqueous and organic based coating systems can also cause possible surface dissolution and drug migration [13]. This has led to the search of newer technologies that do not require organic or aqueous solvents. One such technology is dry coating where particles of coating material are directly layered onto the tablet surface with a simultaneous spray of liquid plasticizer and high temperature curing. This complicated procedure has sometimes rendered sticky films and inelegant film appearance [12,14]. Electrostatic dry powder coating has also been explored, which relies on the application of electric field for the deposition of the coating material. However, it needs uniform particle size of coating polymer with electrostatic properties and good compatibility of substrate and coating material and thus left researchers with fewer polymer options to choose from [12]. These dry coating technologies may also be difficult to run in commercial production.

In this era of modernization, the pharmaceutical industry is now shifting its stand from batch to continuous manufacturing [15]. In batch manufacturing, the final product is traditionally manufactured with several individual and separated sequence of batch-wise unit operations. This can result in inefficient and delayed processing with more chances of processing errors, defects in final product [16], and typically require a 14–24 months manufacturing cycle time. Continuous manufacturing is an uninterrupted processing technology that can be implemented to be a seamless flow of production. It reduces processing time and could provide more reliable products with smaller equipment footprint, less scale-up requirement and reduced production costs [17]. Regulatory agencies like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have strongly supported these initiatives. The FDA has recently approved two pharmaceutical products made by continuous manufacturing initiative [16]. Realizing the benefits of continuous processing, continuous tablet coating has also been explored with an aim to improve productivity and coating uniformity. Supercell™ fluid-bed coater, a quasi-continuous in-line tablet coater is one such type wherein coating is done in small batches with a few grams of tablets being coated [8]. The coater does not have a conventional rotating pan but the tablets are air fluidized and coated in a chamber. Additional coaters in series to match the tablet production rate would then make this process effectively continuous. Complete continuous film coating system (FastCoat™) has also been developed and studied [18]. In this system, tablets are first placed and tumbled to help their movement across the pan. Then, the tablets are heated and the coating solution is sprayed using spray guns until the targeted coating amount is achieved. Upon completing this step, coated tablets are transferred to the discharge side of the pan, uncoated tablets are simultaneously filled in the feed side of the pan and process continues. This technology claims to increase processing rate, decrease coating time, and improve coat uniformity. However, there could be material wastage during start-up and shut down process [19]. Also, the technology might be suitable mainly for large volume products. These quasi-continuous and continuous coating technologies do not address other inherent disadvantages of film coating process. Continuous tablet coating by injection molding (IM) could address the limitations experienced in other coating processes.

Injection molding (IM) technology involves the injection of molten thermoplastic polymers under high pressure, typically at elevated temperature into a precisely designed mold cavity. The polymers cool and solidify to form the solid product. To coat tablets with injection molding, a tablet core is placed inside the mold cavity. Molten polymer is then injected to form a thin layer on the surface of the tablet core. The polymer layer solidifies resulting in a coated IM tablet (details are in Section 2.2). IM can easily achieve thick coating, generally not achievable by other conventional coating processing and its potential should be explored. Clarke et al. [20] registered the use of injection molding process for coating a pharmaceutical tablet having an active ingredient in its core. However, this process doesn't lead to complete coating and leaves a few openings and orifices. Another patent was filed by Sowden et al. [21] utilizing IM for pharmaceutical tablet coating with at least one opening for modified release tablets. Similarly, McAllister et al. [22] described a process using injection molding compatible polymers to prepare capsule shells which could be filled with pharmaceutically active agent(s).

In recent years, flexible, continuous and easy to scale technologies like hot-melt extrusion (HME) and IM have been explored in the pharmaceutical industry to produce tablets in a continuous mode [23–25]. One of the earliest patent was filed by Speiser [26] discussing IM in pharmaceutical industry as a technique to produce oral pharmaceutical dosage forms. Egalet®, a pulsatile release drug delivery dosage form, has been formulated using IM [25]. West Pharmaceuticals has employed Targit® technology for site-specific drug delivery in the gastrointestinal tract. Targit® utilizes potato starch capsules prepared using injection molding technologies which are externally coated with pH sensitive polymers [27]. Even the European Pharmacopoeia 9.3 [28] lists HME and IM as suitable tablet manufacturing technologies. In our prior work, we used HME-IM to produce tablets on a fully integrated continuous manufacturing system [29]. Subsequent work on the HME-IM portion of the process, further improved the IM tableting technology [30,31]. Considering the suitability of this novel integrated HME-IM technology platform for continuous tablet core manufacturing and various advantages of the solvent free IM coating, the best end-to-end (powder to coated tablet) manufacturing could be achieved by coupling HME-IM integrated tablet manufacturing platform and IM coating. In other words, a final step to this integrated process would involve the addition of tablet coating polymer into the HME-IM system and injection molding coating step to coat the IM core tablets. IM coating can also be applicable to coat conventional powder compressed tablets.

To achieve the described continuous coated tablet manufacturing, IM coating is required to be thoroughly analyzed first as a separate technology by evaluating coating formulation attributes and IM process parameters. IM coating technology has not been explored in detail. This research had been divided into three parts with the final goal to evaluate the suitability of injection molding coating technology for pharmaceutical tablets. First, different coating polymer-plasticizer combinations suitable for IM coating were evaluated by tensile testing and melt flow analysis. Second, IM process parameters affecting the coating process were studied for the individual coating formulations. Third, the suitability and performance of IM coated tablets were confirmed by evaluating their long-term stability and dissolution analysis.

2. Materials and methods

2.1. Materials

Injection molded core griseofulvin (GF) tablets were formulated from Griseofulvin USP (Jinlan Pharm-Drugs Technology Co. Limited., Hangzhou, China), maltodextrin (Glucidex IT 12, Roquette America Inc. Geneva, IL), xylitol (Xylisorb® 90, Roquette America Inc., Geneva, IL) and anhydrous lactose (SuperTab 24AN, DFE Pharma, Paramus, NJ). Custom shaped polyetherimide (Ultem™ 1000, PEI) tablets were purchased from Proto labs (Maple Plain, MN). A wide variety of coating polymers were employed to coat these tablets and are listed here. Polyethylene oxide [PEO 100,000 (Polyox WSR N-10), PEO 300,000 (Polyox WSR N-750), PEO 1,000,000 (Polyox WSR N-12 K)] were obtained from the Dow Chemical Company (Midland, MI). Polyvinyl alcohol (PVA, Gohsenol™ EG-05 PW) was received from Nippon Gohsei (Osaka, Japan). Amino Methacrylate Copolymer-NF (Eudragit E PO) was acquired from Evonik (Darmstadt, Germany). Polyvinyl alcohol-polyethylene glycol graft copolymer, Kollicoat IR (Kollicoat) was procured from BASF (Ludwigshafen, Germany). Polyvinyl alcohol based co-polymer, Opadry 200 (Opadry) was acquired from Colorcon