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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

(Harleysville, PA). Hydroxypropyl pea starch (Readylycoat) was received from Roquette (Keokuk, IA). The plasticizers polyethylene glycol (PEG 400, PEG 1500) and glycerol were purchased from Sigma-Aldrich (St. Louis, MO), whereas acrylate based plasticizer (Eudragit NE 30D) was obtained from Evonik (Darmstadt, Germany). Potassium acetate, magnesium chloride, potassium carbonate and magnesium nitrate salts were purchased from Sigma-Aldrich (St. Louis, MO). Propylene glycol-water mixture (Dowtherm SR-1 35, The Dow Chemical Company, Midland, MI) was used as a coolant.

2.2. Methods

2.2.1. GF tablet manufacturing

An integrated HME-IM continuous tablet manufacturing platform was used to manufacture GF tablets. Formulation constituents, GF (drug), xylitol (plasticizer) and lactose (reinforcing agent) were used as received, whereas maltodextrin (polymer carrier) was dried to achieve the residual moisture less than 0.5%. Briefly, premixed blend of GF (10%), dried maltodextrin (54.4%), xylitol (32.6%) and lactose (3%) were fed through weight-in-loss feeder to the feed zone of the co-rotating intermeshing twin screw extruder (Nano 16, Leistritz, Somerville, NJ, USA). The feed flow rate was 80 g/hr, whereas the screw speed was maintained at 90 rpm and feed zone temperature was 8 °C. Formulation ingredients were mixed and sheared at elevated temperatures progressing with zone temperatures of 80 °C, 155 °C, 155 °C and 155 °C inside the extruder barrel. The extrudate, coming out from the extruder, was directly fed to the reservoir of the attached IM unit (MHS Hot Runner Solutions, Ontario, Canada). The IM unit could be divided into reservoir system and hot runner system (comprised of manifold and nozzles). The reservoir, manifold and nozzle temperatures were maintained at 150 °C, 145 °C and 135 °C, respectively. The extrudate progressed from the reservoir and hot runner systems to the mold cavities of the IM system and solidified at 45 °C for 30 s to form core IM GF tablets. Since the melting point of GF is very high (~220 °C), the employed processing conditions and polymer carrier maintained the stable crystalline nature of GF in the core IM tablets. The crystalline nature of the griseofulvin in tablet matrix was confirmed by X-ray diffraction analysis (supplementary material). Fig. 1a shows the resultant GF tablets.

2.2.2. PEI tablet manufacturing

Computer-aided design (CAD) model of the tablet (Fig. 1b) was provided to Proto Labs. This custom prototype manufacturer employed Computer Numeric Control (CNC) milling process to manufacture the required precise shaped PEI tablets having 10 mm diameter and 5.7 mm maximum thickness at the center.

2.2.3. Preparation of coating formulations

A vertical, co-rotating conical, miniature, twin-screw extruder (DACA instruments, Goleta, CA, Fig. 2a) was employed to prepare coating formulations. The screws with 14.5 mm diameter at the entrance and 5.5 mm at exit were enclosed in a heated jacket (Fig. 2b) having an exit port. Coating polymer and plasticizer in particular ratios were weighed, premixed and fed to the extruder through the feed port. The amount of this mixture (3–5 grams) was determined depending on the torque and the volume occupied in the extruder. The screw speed was set at 100 rpm for all coating formulations. The unique design of this extruder with a featured recirculation channel allowed recirculation and thorough mixing of polymer mixtures inside the extruder. After recirculating for 5 min, the output valve was opened and the extrudate was collected through the exit port (Fig. 2c). Extrudates having a well-mixed appearance and no scaling were chosen for further study. Extrusion was first tried at extruder temperatures near the polymer glass transition temperature and/or melting temperature reported in literature. Later, they were optimized depending upon the polymer-plasticizer combination and extrudate characteristics (Table 1). The extruder temperatures that provided extrudates without any visual phase separation, and scaling were used to prepare coating formulations.

2.2.4. Tensile testing

Specimens for the tensile testing of coating formulations were produced using a microinjector (DACA instruments, Goleta, CA, Fig. 3a). The instrument consists of a heated block that supports the conical, self-clamping mold and a heated barrel. The coating formulation extrudates obtained from the miniature twin-screw extruder were cut into small pieces. The barrel was then manually filled with these extrudate pieces. An injection piston, pneumatically driven by a bore cylinder forced the coating formulation from the barrel into the dog-bone shaped mold cavity (Fig. 3b). As a starting point, the temperature required to extrudate the coating formulation from the miniature twin-screw extruder was used as the barrel temperature. Then, the barrel temperature was further optimized (typically increased) to achieve a fully filled mold cavity at the selected barrel temperature. The mold temperature was maintained at 35 °C for all coating formulations. The optimized barrel temperature values required for the specimen preparations (Fig. 3c) of each coating formulation are provided along with their tensile properties (Table 2). The length, width and thickness of the test regions of the prepared specimens are 25 mm, 4 mm, and 1.5 mm respectively.

The tensile properties of the dog-bone specimens were studied using a universal testing machine (5967 Dual Column testing system, Instron, Norwood, MA), installed with a 1 KN capacity load cell. The specimens were fixed in place using serrated-faced metal grips. Specimens were

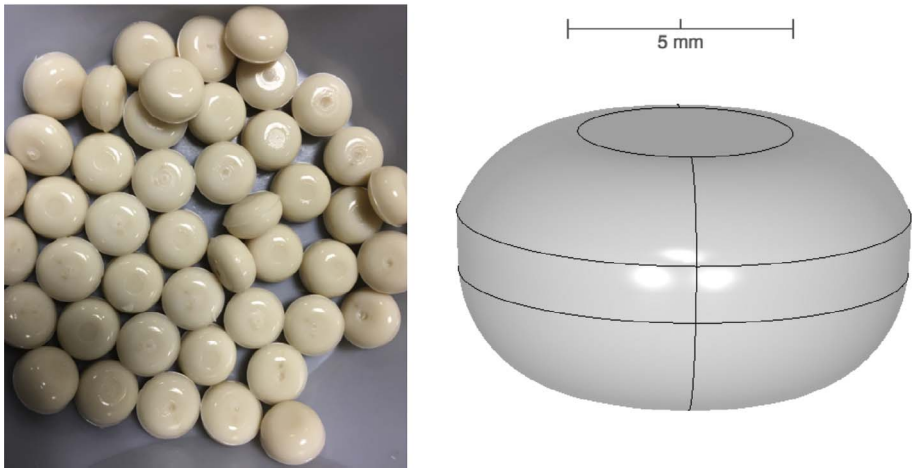

Fig. 1. (a) GF tablets (b) CAD model of the tablet shape.

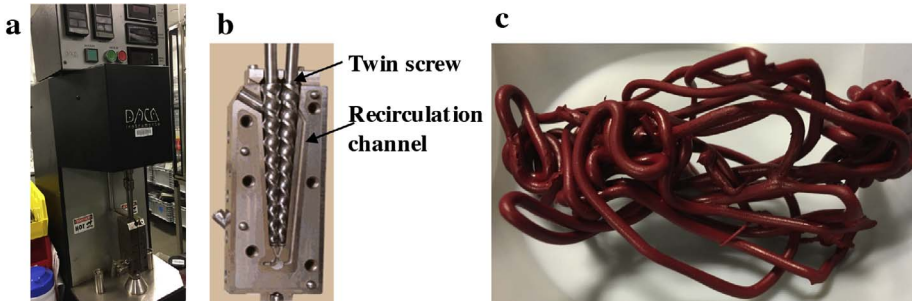

Fig. 2. (a) Miniature twin-screw extruder (b) twin-screws and recirculation channel and (c) an example of extrudate.

Table 1
Coating formulations and processing temperature used for their preparations.

Coating polymer	Plasticizer (% w/w)	Extrusion processing temperature (°C)
PEO 100,000	PEG 1500 (10%, 20%, 30%)	90,80,80
PEO 300,000	PEG 1500 (10%, 20%, 30%)	120, 115, 95
PEO 1,000,000	PEG 1500 (10%, 20%, 30%)	95, 95, 95
PVA	Glycerol (20%, 30%, 40%)	170, 170, 170
PVA	PEG 400 (10%, 20%, 30%)	180, 180, 180
PVA	PEG 1500 (20%)	190
Eudragit E PO	Eudragit NE 30D (10%, 20%, 30%, 40%)	100, 100, 100, 100
Kollicoat	PEG 400 (10%, 20%, 30%)	185, 170, 150
Kollicoat	PEG 1500 (20%)	180
Kollicoat	Glycerol (20%)	170
Opadry	Glycerol (20%, 25%, 30%)	165, 155, 150
Hydroxypropyl pea starch	Glycerol (30%)	100

Note: different ratios of plasticizer employed in the trials are provided in each row by providing its percentage value. Processing temperature values correspond to these polymer - percentage plasticizer combinations in same sequence (i.e., PEO 100,000 + 10% PEG 1500 coating formulation was processed at 90°C; PEO 100,000 + 20% PEG 1500 coating formulation was processed at 80°C and so on).

stored for at least 24 h in ambient conditions before the testing. Testing was conducted for at least 3 samples at ambient conditions at a strain rate of 50 mm/min. Instron's advanced video extensometer (AVE 2663-821) was used to measure the strain (elongation) of the test specimen more accurately by tracking the positions of two contrasting round marks (each near the end of the test regions). Stress-strain analysis was collected for each sample and major tensile parameters, like Young's modulus, percentage elongation at the break, toughness, tensile stress at break and tensile strength were analyzed.

2.2.5. IM tablet coating

Based upon tensile testing results, particular coating formulations were selected and GF and PEI tablets were coated using the MIT in-house built vertical injection molding machine. This machine had the following components: temperature controlled injection barrel with an orifice in the bottom part, an actuator controlled injection piston, top mold inserts with orifices, bottom mold inserts and a LabVIEW System Design Software (National Instruments, Austin, TX). Briefly, the temperature controlled injection barrel, maintained at particular temperature was first filled with the coating formulations. The coating formulation was heated for about 10 min to soften it. Two thermocouple heating bands attached at top and bottom part of the barrel maintained the set temperature. The tablets were coated in two steps (Fig. 4) and different pairs of mold inserts were used for each step. In total, 4 mold inserts (two pairs) were used in complete tablet coating. One insert for top halve and another insert for bottom halve (first pair) were used for

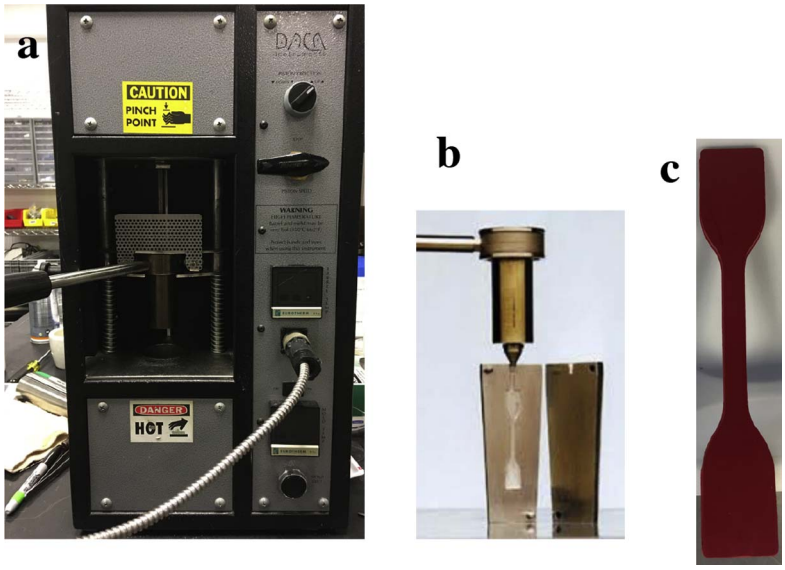

Fig. 3. (a) Microinjector (b) dogbone shaped mold cavity and (c) dogbone shaped specimen.

Table 2
Tensile properties of IM coating formulations.

Coating formulation	Microinjector barrel temperature (°C)	Tensile properties of coating formulations, measured at ambient conditions				
		Young's modulus (MPa)	Elongation (%)	Toughness (J/$m^3 * 10^4$)	Tensile strength (MPa)	Ratio - Tensile strength/ Young's modulus
PEO 100,000 + 30% PEG 1500	80	1209 (141)	2.14 (0.81)	22.9 (7.1)	15.73 (1.04)	0.013
PEO 300,000 + 10% PEG 1500	90–110	571 (39)	11.0 (2.9)	86.6 (17.3)	10.1 (2.0)	0.018
PEO 300,000 + 20% PEG 1500	90–110	517 (22)	15.2 (6.5)	126 (67)	11.7 (2.0)	0.022
PEO 300,000 + 30% PEG 1500	90–110	572 (41)	15.6 (6.2)	187 (73)	11.5 (1.0)	0.020
PEO 1,000,000 + 30% PEG 1500	90–110	656 (65)	51.6 (7.9)	370 (72)	11.29 (0.01)	0.017
PVA + 20% Glycerol	190	114 (22)	90.9 (14.6)	2724 (903)	42.4 (1.2)	0.372
PVA + 30% Glycerol	170	81.8 (4.9)	88.5 (3.6)	1440 (74)	21.3 (1.5)	0.260
PVA + 40% Glycerol	150	49.3 (4.4)	88.4 (14.2)	834 (200)	11.6 (1.0)	0.240
Eudragit E PO + 40% Eudragit NE 30D	125	2200 (302)	1.37 (0.13)	21.3 (4.2)	23.1 (1.7)	0.010
Kollicoat + 20% glycerol	> 150	157 (12)	5.31 (1.11)	16.0 (1.5)	5.0 (1.0)	0.032
Hydroxypropyl pea starch + 30% Glycerol	100–130	1.57 (0.20)	230 (19)	97.1 (26.4)	0.49 (0.12)	0.312
Opadry + 20% Glycerol	190	309 (56)	16.9 (2.9)	181.6 (30)	16.6 (3.5)	0.053
Opadry + 25% Glycerol	170	95.8 (5.2)	35.80 (0.85)	218 (20)	9.53 (0.31)	0.099
Opadry + 30% Glycerol	150	66.6 (5.2)	30.00 (0.42)	144 (10)	5.96 (0.45)	0.089
PVA + PEG 400*	~170	Chalky white product, incompatible plasticizer				
PVA + PEG 1500*	~170	Chalky white product, incompatible plasticizer				
Kollicoat + PEG 400*	> 150	Poor melt flow, product breaks apart, incompatible plasticizer				
Kollicoat + PEG 1500*	> 150	Poor melt flow, sticks in mold cavity, incompatible plasticizer				

Values in parenthesis indicate standard deviations.
* 10, 20 and 30% of PEG were used.

step 1. Later, half coated tablets had different dimensions compared to the uncoated tablets (discussed below) and therefore the mold inserts were changed for step 2 (third insert for the top halve and forth insert for bottom halve, making the second pair). These mold inserts were designed on the basis of the IM tablet shape, size and curvatures, with the aim to provide 300 μm coating thickness. The temperatures of mold inserts were maintained by the circulating liquid cooling system (coolant) in the molding halves. In step 1 (Fig. 4a), the tablet was placed inside the cavity of the mold inserts and the molding halves were closed. Next, injection piston applied pressure to the coating formulation and the applied piston pressure allowed the softened coating formulation to travel from the barrel to the mold insert and fill the available space between the tablet and top mold insert. The coating formulation solidified inside the mold cavities in 5–15 s and rendered a smooth coating layer attached to the tablet surface. The desired injection pressure, holding pressure, and holding time were controlled with the LabVIEW system design software. Injection pressure was applied by two different modes. The pressure regulated mode targeted to keep the pressure constant by fluctuating the piston position, which resulted in oscillation in pressure values around the target. The position regulated method held the piston in the defined position which allowed the pressure to decay. The typical decrease was about 13.8 MPa over 5–15 s (in Table 3, the higher value is the initial pressure which decayed to the lower value at the end of the cycle). Mold halves were opened and the step 1 coated tablets were collected. The solidified extra coating material (sprue) was manually removed, the mold inserts were changed, and tablet was flipped over and step 2 coating (Fig. 4b) was performed similar as step 1 to obtain fully coated IM tablet (Fig. 4c). Step 2 coats overlapped step 1 coats resulting in a coat thickness of 450 μm in the overlapping region.

Process parameters (barrel temperature, injection pressure, mold temperature, and cooling time) were optimized in the following way. Initially, the set point of the barrel temperature was selected to be the same as the miniature twin screw extruder temperature used to prepare the coating formulations. The barrel temperature was further optimized such that the complete tablet coating could be achieved at the lowest temperature and injection pressure values. Real time pressure profiles were evaluated each time to ensure the reproducibility of the pressure profiles. For example, Fig. 5 shows the closed-loop pressure response of the developed step 1 injection molding process of the coating formulation PEO 1,000,000 + 30% PEG on the PEI tablet. As shown in Fig. 5, the developed LabVIEW based pressure control strategy drove the system to the pressure setpoint with overshoot around 5.7% and then maintained the pressure against disturbances (leakage) for specific time (5 s hold time). This performance indicates the set point tracking capacity and robustness of the pressure control strategy. The closed-loop response for Step 2 was similar to that of the step 1. Mold temperature and cooling time were then optimized with the aim to minimize the difference between the barrel and mold temperatures. Table 3 lists the optimized process parameters employed for GF and PEI tablet coating by selected IM coating formulations.

Due to the limited flowability of the PVA coat formulation, tablets were coated by a compression molding method. Before closing the mold halves, material was injected to fully cover the top mold cavity of the upper mold insert. Mold halves were then closed and coating formulation present on the top mold cavity surface coated the tablet. Then, the mold inserts were changed and tablet was flipped over for step 2 coating. Barrel temperature and mold temperature were maintained at 180 °C and 35 °C, respectively. Mold halves were closed for 5–10 s (hold time).

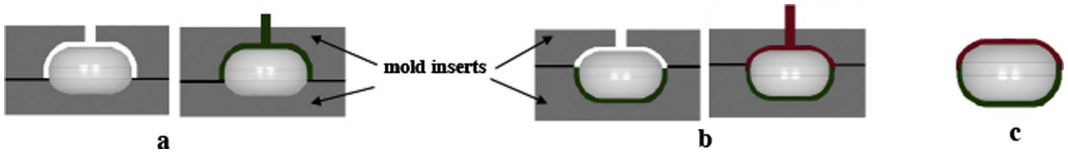

Fig. 4. (a) IM step 1 coating, (b) IM step 2 coating and (c) IM coated tablet.

Table 3
IM process parameters employed for GF and PEI tablet coating.

Process parameters	Coating formulations (polymer + plasticizer w/w)						
	Hydroxy-propyl pea starch + 30% glycerol	PEO 100,000 + 30% PEG 1500	PEO 300,000 + 30% PEG 1500	PEO 1,000,000 + 30% PEG 1500	Opadry + 20% glycerol	Opadry + 25% glycerol	Opadry + 30% glycerol
IM coating - GF tablets							
Injection pressure (MPa)	41–55	35–45	35–48	41–55	69–83	69–83	69–83
Barrel temperature (°C)	110	80	95	100–130	190–200	170–180	150–170
Mold temperature (°C)	35	35	35	35–55	40	35	35
Hold time (s)	5	5	5	5	15	15	5–10
IM coating - PEI tablets							
Injection pressure (MPa)	41–55	35–45	35–48	41–55	69–83	69–83	69–83
Barrel temperature (°C)	110	80	95	100	180	170–180	150–170
Mold temperature (°C)	35	35	35	35	35	35	35
Hold time (s)	5	5	5	5	15	15	15

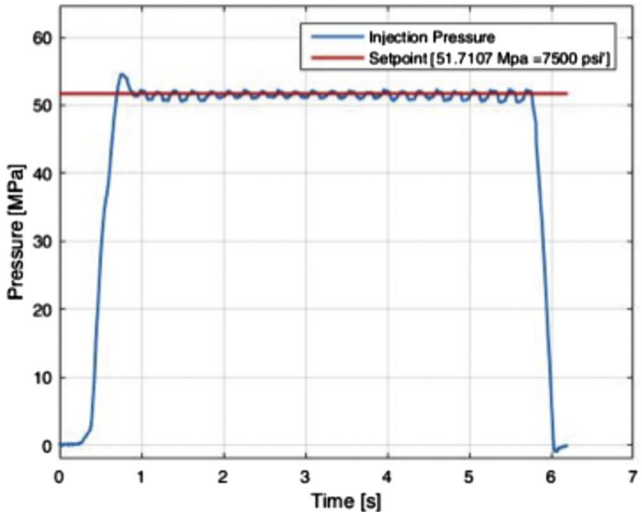

Fig. 5. The closed-loop pressure response of the step 1 IM process of the coating formulation PEO 1,000,000 + 30% PEG on PEI tablets.

2.2.6. Dimensional and weight gain analysis of coated tablets

The average weight (with standard deviation) of core and coated tablets were reported for at least five tablets. The core and coated tablet thickness and diameter were measured at least for five tablets using a force-controlled micrometer (Mitoyto, Japan) set to 0.5 N with a resolution of 0.001 mm.

2.2.7. Stability testing

Coated tablets were sealed using an induction sealer (Auto Jr, Enercon industries corporation, Menomonee Falls, WI) in high density polyethylene (HDPE 5502BN) pharmaceutical bottles. The bottles were stored in 19 °C/ < 10% RH; 19 °C/23% RH; 19 °C/33% RH; 19 °C/43% RH; 19 °C/53% RH; 25 °C/45% RH; 25 °C/60% RH and 30 °C/65% RH storage conditions and evaluated after 8 weeks to evaluate the coat stability. A chamber with dry gas purge was used to create 19 °C/ < 10% RH (typically 2–5% RH) storage condition. Controlled temperature and humidity chambers (LHU-133, Espec, Hudsonville, MI, USA) were used to provide 25 °C/45% RH, 25 °C/60% RH and 30 °C/65% RH storage conditions. Potassium acetate, magnesium chloride, potassium carbonate and magnesium nitrate saturated salt solutions were used to, respectively, provide 19 °C/23% RH, 19 °C/33% RH, 19 °C/43% RH and 19 °C/53% RH storage conditions.

2.2.8. Melt flow analysis

A melt flow analysis was conducted using the microinjector with some modifications in the original instrument. The injection barrel was heated to the temperature used to coat the tablets for that particular coating formulation. Extrudates of various coating formulations were cut and manually fed into the heated barrel until it was completely filled. The extrudate pieces were gently pushed down by wooden rod to reduce the voids between them and pack the barrel uniformly each time. The coating formulation was heated for about 10 min to soften it. A pressure of 4.1–4.3 MPa was applied by the injection piston onto the coating formulation residing in the heated barrel and the material coming out from heated barrel was then collected in a container. Typically, the melt flow test is conducted for 10 min and the result is reported in g/10 min (melt flow index). However, because of the high melt flow values of hydroxypropyl pea starch +30% glycerol and limitations in the total barrel volume, the melt flow test was conducted for 1 min for this particular formulation. For other studied formulations, the test was conducted for 5 min and result was converted to g/min units.

2.2.9. In vitro release testing

The method for *in vitro* release testing was based on the USP monograph for GF tablets (Dissolution test 1). USP apparatus II (paddle) dissolution tester (Agilent 708-DS, Agilent Technologies, Santa Clara, CA) was employed to evaluate the drug release from uncoated and coated GF tablets. The apparatus vessels were filled with 1000 mL of 40 mg/mL sodium lauryl sulphate. The paddle speed and solution temperature was maintained at 75 rpm and 37 ± 0.5 °C respectively. Samples were collected at specific time intervals, filtered through a 0.45 µm nylon filter, diluted if necessary and evaluated spectro-photometrically by a UV spectrophotometer (Lambda 35, PerkinElmer, Waltham, MA) at a wavelength of 291 nm. The average dissolution profile of three tablets were calculated.

3. Results and discussion

3.1. Preparation of coating formulations and tensile testing

The extrudability of each coating polymer, discussed in Table 1, was determined without plasticizer. Among these coating polymers, PVA, Kollicoat and Opadry required high processing temperatures

(> 180 °C) and they sometimes experienced thermal degradation in such stringent processing conditions. Also, very high mechanical energy was required (indicated by higher torque values, sometimes reaching the instrument limit – 6.2 N m), to extrude these polymers. For coating polymer PEO 100,000, the polymer alone could be extruded at low processing temperature (100 °C) but the product was very brittle in nature and it was clear that the polymer would not able to make a robust film layer to coat the tablets. Plasticizers are an additive commonly added to the coating polymers to improve flow and processability and reduce the brittleness of the coating polymer. The plasticizer interposes its molecules between the polymer chains and can also bond with the functional groups of the polymer chains [6,32]. Thus, it reduces the interaction between the polymer chains and increases the volume between them, imparting chain mobility and flexibility or distensibility. It was imperative to improve the processability of coating polymers and therefore plasticizers were added in the coating formulations.

Added plasticizer is required to be compatible and preferably miscible with the polymer, and so most of the selected plasticizers resemble the polymer's chemical structure and have the possible interaction capacity with the polymer. Shorter chain polymers (fewer monomers and overall lower M_w) can act as plasticizers. Short (Mw < 100,000) polyethylene oxide polymers, commonly known as PEG's, were selected as plasticizers for PEO. The hydroxyl-containing compound glycerol was used for most coating polymers (having a high hydroxyl ratio) and structurally similar Eudragit NE 30D was employed as a plasticizer for Eudragit E PO. Coating formulations were prepared with particular polymer-plasticizer combinations (Table 1) and further screened based upon the physical and visual appearance, uniformity, and scaling issue. Selected formulations (listed in Table 2) were analyzed for tensile properties. Stress vs. elongation (%) profiles of coating formulations are depicted in Fig. 6. Table 2 lists the calculated values of tensile properties, like Young's modulus, percentage elongation, toughness, and tensile strength (also called ultimate strength or ultimate tensile strength).

Young's modulus, also called the elastic modulus, is estimated from the slope of the linear region of the stress-strain profile where the formulation experiences elastic deformation. This fundamental material property shows the elasticity of the film with lower values corresponding to higher elasticity [33–36]. It evaluates the specimen resistance to the elastic deformation. The values are directly related to the interatomic bonding energy, with higher values corresponding to the stiffer and rigid film where it needs higher loads to deform elastically. Prima facie, it was hypothesized that the coating polymers having low values of Young's modulus should be good for IM coating. The employed methodology differentiated between the coating formulations, considering their capability to resist the deformation. The coating formulations containing PVA, Kollicoat, hydroxypropyl pea starch and Opadry had significantly lower Young's modulus values (Table 2) compared to the other coating polymers employed in the study. As plasticizer is generally expected to reduce the stiffness of the polymer [37], increase in plasticizer content decreased the Young's modulus values of coating polymers PVA and Opadry. However, there was no particular trend for PEO when the plasticizer (PEG) amount increased from 10% to 30%.

Coating formulations containing high molecular weight PEO (300,000 and 1,000,000), PVA, Opadry and hydroxypropyl pea starch had significant elongation in comparison with Eudragit E PO, Kollicoat, and PEO (100,000). The stretching or elongation is expected to be increased with an increase in molecular weight of the polymer and the plasticizer amount employed for the same polymer. There was an increase in percentage elongation with an increase in molecular weight of PEO. For Opadry and PEO (300,000), increasing the plasticizer amount further increased the percentage of elongation. However, for PVA, an increase in plasticizer amount did not change percentage elongation. For the studied coating formulations, PVA, Opadry, PEO and hydroxypropyl pea starch based formulations showed higher percentage elongation values (Table 2) when high plasticizer content was employed.

Tensile strength is the maximum force per unit area applied to the specimen. It is the maximum stress that a specimen can withstand before necking or cracking [33,34]. Plasticizers weaken the intermolecular forces between the polymer chains, which typically reduces the tensile strength and brittleness [6,37]. In case of PVA and Opadry, tensile strength was reduced with the addition of plasticizer as per the expectations. However, it was not the case for PEO-PEG system.

Toughness, the total area under the stress–strain curve, is a measurement of the energy absorption before failing [34]. Toughness indicates material's resistance to breakage. Toughness of the specimen depends on both the strength and ductility of the specimen. Based upon the results obtained, PVA, Opadry, PEO and hydroxypropyl pea starch based formulation showed higher toughness values (because of higher strength or ductility or the combination of both).

3.2. IM tablet coating

Based upon tensile testing analysis and values of the microinjector barrel temperature, the coating polymers in Table 3 were selected for IM coating. Eudragit E PO and Kollicoat based formulations had very low percentage elongation values. Also, Eudragit E PO based formulation was rigid and the Kollicoat based formulations required higher process temperatures and had severe sticking to the mold surface; therefore, they were not used further. For PEO 300,000 based formulations, PEO 300,000 + 30% PEG 1500 was chosen since it had improved mechanical properties compared to the PEO based formulation employing 10% or 20% PEG 1500. Addition of plasticizer increases the energy necessary to initiate the crack [38]. Plasticizer also decreases the Young's modulus and glass transition temperature of the specimen, effectively reducing the internal stress and decreasing the incidence of cracking [39]. PVA + 20% glycerol required > 190 °C processing temperature whereas PVA + 40% glycerol extrudates and specimens, stored in ambient conditions showed phase separation of glycerol from PVA in a week and therefore PVA + 30% glycerol was selected for coating.

IM is a very complex process which requires a sound understanding of IM process parameters and material attributes. Process optimization to ensure the final molded product robustness requires optimization of IM input variables such as barrel temperature, mold temperature, injection pressure and cooling time [40]. The barrel temperature is one of the most critical parameters to ensure proper flow of the material and therefore the IM product quality [41]. Another critical parameter is the injection pressure employed to inject the coating formulation from the barrel to the mold cavity. A pressure regulated mode was employed first. In order to keep the pressure constant (as discussed in Section 2.2.5), the fluctuations in pressure around the desired value caused deformation in the table cores. Therefore, a position regulated mode was developed to coat the tablets. In this mode, the decay in pressure during injecting/holding/cooling mode of the coating material in the mold cavity prevented any deformation to the core. This position regulated method was hence selected for carrying out the coating experiments. Low injection pressure could result in incomplete mold filling, whereas, high injection pressure could generate pressure induced stress [42] and flashing. Barrel temperature and injection pressure were therefore optimized with the utmost priority. Initially, the set point of the barrel temperature was the same as the miniature twin screw extruder temperature used to formulate the coating material. The barrel temperature was further optimized to achieve a complete tablet coat at the lowest temperature and injection pressure. Real time pressure profiles were evaluated each time to ensure the reproducibility of pressure profiles. Mold temperature and cooling time were then optimized with the aim to minimize the difference between the barrel and mold temperatures while not being excessively long. The quality of the

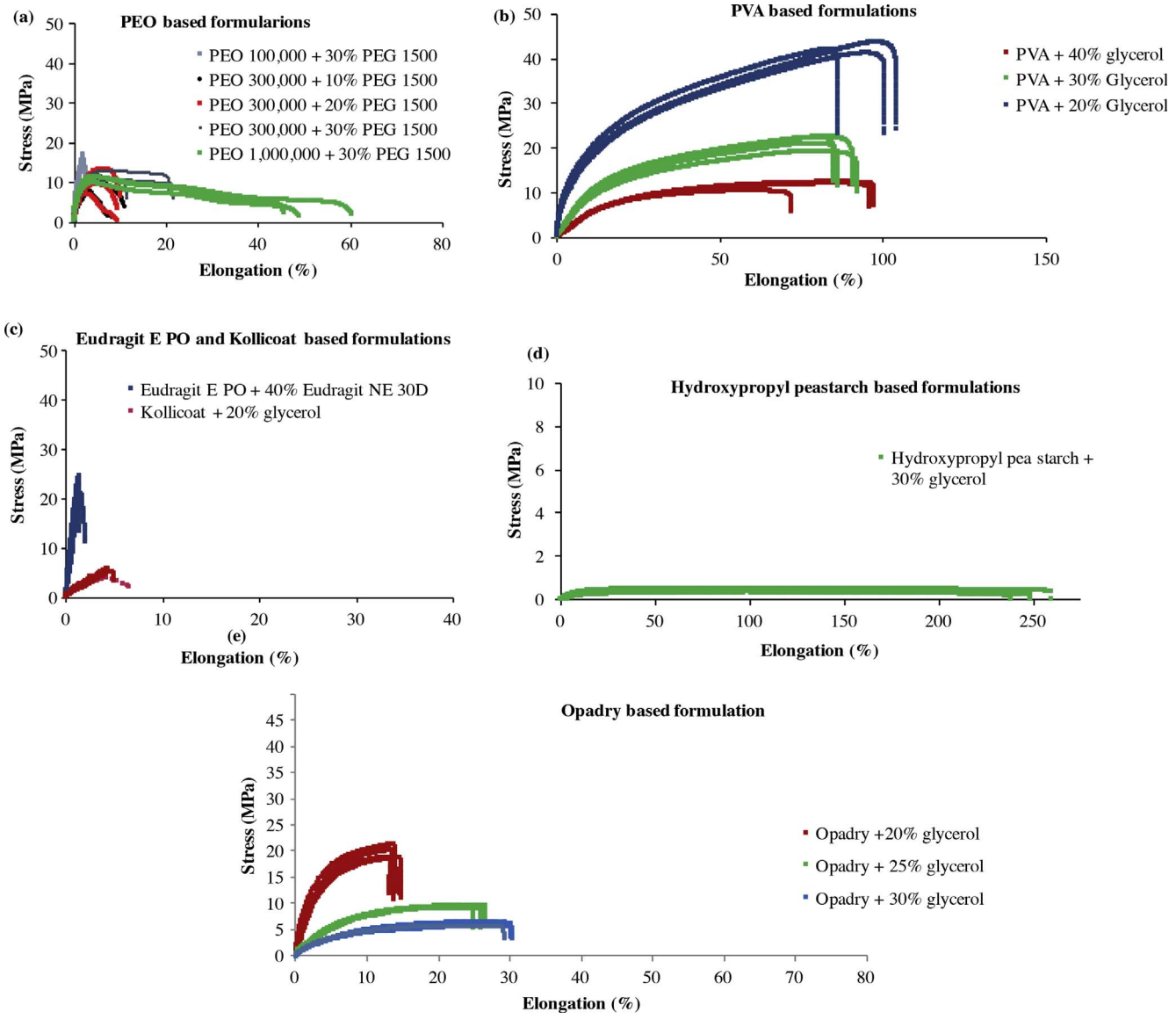

Fig. 6. Stress vs. elongation (%) profiles of (a) PEO, (b) PVA, (c) Eudragit E PO and Kollicoat, (d) hydroxypropyl pea starch and (e) Opadry based coating formulations.

Fig. 7. GF tablets coated with (a) Opadry 200, (b) GF tablets coated with hydroxypropyl pea starch and (c) PEI tablet coated with PEO 1,000,000 based coating formulations.

final product is greatly affected by the cooling stage of the injection molding cycle wherein a hot melted polymer is injected into the mold and allowed to stay until it solidifies [43]. Optimization of cooling time and the mold temperature plays an integral role for good coating. During the cooling stage, heat transfer also affects crystallization kinetics, shrinkage, and residual stresses and thereby impact the mechanical properties, surface clarity and geometric tolerance [44]. Therefore, considerable importance was given to these process parameters as well. Table 3 provides the optimized process parameters employed for IM coating. For the selected PVA formulation, high pressure and temperature were not sufficient enough to coat the tablet by IM. PVA based coating formulation was not flowing properly even at high temperature and pressure. Therefore, compression molding was used to coat the tablets for this formulation. The melt flow was analyzed for 4 coating formulations (discussed in the Section 3.4).

Hydroxypropyl pea starch, Opadry, and PEO based formulations provided uniform coating for both types of tablets, whereas non-uniform thick coating were obtained with PVA based coating formulation (due to the compression molding process). Room moisture was critical while coating tablets with PEO based formulations, particularly with PEO 1,000,000 + 30% PEG. In dry condition (19 °C, < 30% RH), PEO 1,000,000 + 30% PEG coated tablets cracked within an hour of

coating, for both types of tablets. When room humidity was higher than 30% RH, stable coats were obtained for PEI tablets. However, immediate coat cracking was sometime observed for GF tablets and it could be due to the pressure induced stress. Fig. 7 shows pictures of coated tablets.

In preliminary stability studies, tablets in sealed bottles were stored in various conditions: ambient (19 °C, 40–60% RH), 19 °C/ < 10% RH, 25 °C/45% RH and 30 °C/65% RH. Within 2 days, PEO 100,000 and 300,000 based coated formulations cracked in all storage conditions. GF and PEI core tablets did not have any dimensional instability and was therefore not the reason for this cracking. These 2 coating formulations had poor tensile properties compared to PEO 1,000,000. Also, the literature reports that an increase in the molecular weight of the polymer provides tougher coating with a decrease in the incidences of cracking as well as the crack propagation [38,39]. This could be the reason for the cracking of coats made from PEO 100,000 and 300,000 based formulations. In all the storage conditions, Opadry + 30% glycerol formulation experienced phase separation within 7 days with glycerol leaching out from the Opadry. Although Opadry + 20% glycerol formulation was stable at all storage conditions, the coat was not so smooth. Opadry + 25% glycerol was found to be stable as well as produced smooth coats. Tablets coated with PEO 1,000,000, hydroxypropyl pea starch and Opadry had stable coating without cracks (7 days, 3 storage conditions). The coating weight gain and dimensions of the tablets are provided in Table 4. The coating weight gain was higher for GF tablets in comparison with PEI tablets. This slight difference in weight gain could be due to the dimensional differences between PEI and GF tablets. It was also observed that the maltodextrin based GF tablets were bonded strongly with coating formulations. As per the mold design, the increase in tablet thickness was ~0.6 mm (2 * 0.3 mm coating on both sides of the tablet) and the increase in tablet diameter was ~0.9 mm (2 * 0.45 mm). Based upon these preliminary studies, tablets (PEI and GF) coated with hydroxypropyl pea starch and Opadry as well as tablets (PEI) coated with PEO 1,000,000 based formulations were stored in various stability conditions (listed in Section 2.2.7) and further evaluated.

3.3. Stability testing

Hydroxypropyl pea starch coated GF and PEI tablets did not show cracking for all storage conditions for 8 weeks. Opadry coated PEI tablets were also stable in all storage conditions. Opadry coated GF tablets were stable at and below 45% RH (19 °C and 25 °C). However, these tablets showed phase separation of glycerol from Opadry when stored above 45% RH. Apart from the storage temperature and humidity, GF core tablets had a critical role in this separation since the same phase separation was not observed for the PEI tablets. GF cores have moisture sensitive maltodextrin as polymer matrix and based upon our loss on drying experiments, these tablets have ~0.5% residual moisture content. Aggressive storage conditions and the tablet residual moisture induced this phase separation. PEO 1,000,000 based coats were stable with PEI tablets when stored at 19 °C/43% RH; 19 °C/53% RH; 25 °C/45% RH; 25 °C/60% RH and 30 °C/65% RH but cracked at lower humidity levels. Optimized processing and storage stability conditions suggest that PEO based formulations need a certain amount of moisture (acting as a plasticizer for the PEO) in the polymer coats to prevent cracking. (Note: a stability study of coated tablets, stored in open containers in different storage conditions, is provided in the supplementary material.)

3.4. Melt flow analysis

Melt flow analysis is an important quality control rheological parameter in the plastic industry which gives the critical data and interpretation about the suitability and processability of thermoplastic polymers for IM [45,46].

Table 4
Weight, thickness (t) and diameter (d) of coated tablets.

Tablet	Coating formulation	Coated tablet features					
		Weight (mg)	Weight gain (mg)	t (mm)	Increase in t (mm)	d (mm)	Increase in d (mm)
PEI (weight 460 ± 5 mg, thickness 5.70 mm, diameter 10.0 mm)	Opadry 200 + 25% Glycerol	597 ± 1	137	6.263 ± 0.019	0.563	10.928 ± 0.010	0.928
	Hydroxypropyl pea starch + 30% Glycerol	586 ± 1	126	6.264 ± 0.017	0.564	10.930 ± 0.014	0.930
	PEO 1,000,000 + 30% PEG 1500	570 ± 2	116	6.265 ± 0.013	0.565	10.997 ± 0.018	0.997
GF* (weight 523 ± 1 mg, thickness 5.67 mm, diameter 10.0 mm)	Opadry 200 + 25% Glycerol	679 ± 1	159	6.311 ± 0.019	0.611	10.930 ± 0.014	0.930
	Hydroxypropyl pea starch + 30% Glycerol	666 ± 2	143	6.322 ± 0.008	0.623	10.896 ± 0.019	0.896

* Data for PEO 1,000,000 + 30% PEG 1500 formulation is not provided as some tablet coating immediately cracked after the coating process.

Table 5
Melt flow analysis of coating formulations.

Coating formulation	Melt flow (g/min)	Temperature (°C)
Hydroxypropyl pea starch + 30% Glycerol	5.35 ± 0.14	110
Opadry 200 + 25% Glycerol	0.56 ± 0.09	170
PEO 1,000,000 + 30% PEG 1500	0.44 ± 0.05	130
Polyvinyl alcohol + Glycerol (30%)	0.11 ± 0.02	165

Coating formulations tested for their melt flow and the resultant melt flow values are tabulated (Table 5). Hydroxypropyl pea starch + 30% glycerol showed the highest melt flow followed by Opadry 200 + 25% glycerol and PEO 1,000,000 + 30% PEG 1500. PVA + 30% glycerol had significantly low melt flow values, suggesting the poor processability and confirming the reason of difficulties experienced during IM processing (despite exploring all the IM processing conditions). Thus, the melt flow test helped to predict, understand, and correlate processability of coating formulations for IM tablet coating application.

3.5. Discussion about coat stability and its relationship with tensile testing, melt flow analysis, and core formulations

Overall, the following 7 major observations were found from the coating experiments and stability studies and they can be correlated with the tensile testing, melt flow analysis and feasibility and capability of IM coating in pharmaceutical industry.

1. Coating formulations (for example, Opadry based) with good melt flow characteristics could coat the temperature and pressure sensitive maltodextrin based GF tablets even though the barrel temperature of the IM coating process was very high (170–180 °C). Good melt flow of the coating formulation compensated for the high processing temperature and the tablet was able to endure the effect of temperature and pressure did not deform.
2. Injection pressure should be controlled such that the pressure does not oscillate during the injection cycle. Oscillation caused the deformation of tablet cores whereas, unfluctuating pressure pattern eliminated core deformation when optimized pressure and temperature profiles were employed.
3. Typically, the formulations with lower Young's modulus (for example, hydroxypropyl pea starch and Opadry 200 based) provided suitable IM coating with stable coats. It has been reported that a low Young's modulus is advantageous in averting initiation and propagation of cracks [38]. For the accomplished research work, Young's modulus values of < 700 MPa were found to be suitable for IM coat stability.
4. Coating formulations with higher percentage elongation (> 35%) values were found to be more robust for IM coating.
5. Toughness was found to be a good indicator to look for in screening formulations for IM coating. Overall, formulations having toughness values higher than 95 x 10^4 J/m^3 (for example, Opadry, PVA, hydroxypropyl pea starch and PEO 1,000,000 based formulations) performed well in IM coating. The major exception was PEO 300,000 + 30% PEG 1500, which cracked after storage—lower ductility (elongation) could be the reason.
6. It is well known that the derived mechanical parameter, tensile strength/Young's modulus ratio indicates crack resistance and could predict cracking [34,39]. Based upon the requirement of the tough and elastic nature of the tablet coat, coating formulations having a high ratio of tensile strength/Young's modulus would resist the external forces and stresses and have a lower tendency towards the cracking. PVA, hydroxypropyl pea starch, and Opadry based formulations had high values compared to other coating formulations and these coating formulations were the most successful in IM coating.
7. Maltodextrin based GF tablets could be deformed at high injection pressure and would be sensitive to processing temperature, humidity, and pressure induced residual stress mainly because of the sensitive polymer matrix (maltodextrin) employed to formulate the IM tablets. To eliminate these confounding factors, temperature and pressure resistant, as well as moisture insensitive PEI tablets were employed in the study. PEO based coating formulation provided an acceptable and stable IM coating for PEI tablets and confirmed the feasibility of this formulation for IM coating. However, the coatings cracked when applied to maltodextrin based GF tablet, corroborating the fact that the core tablets play a critical role in successful IM coating.

For successful pharmaceutical tablet coating, a formulator can work on the basis of two approaches, minimize the internal stress of the system or accept these internal stresses and minimize the incidence of the defect by formulating "right" coating formulation that can absorb these stresses and survive. It seems we moreover applied the combined approach where we first selected the "right" coating formulations with the help of tensile testing and later prevented the coating defects (mainly cracking) by optimizing the IM processing. For researchers

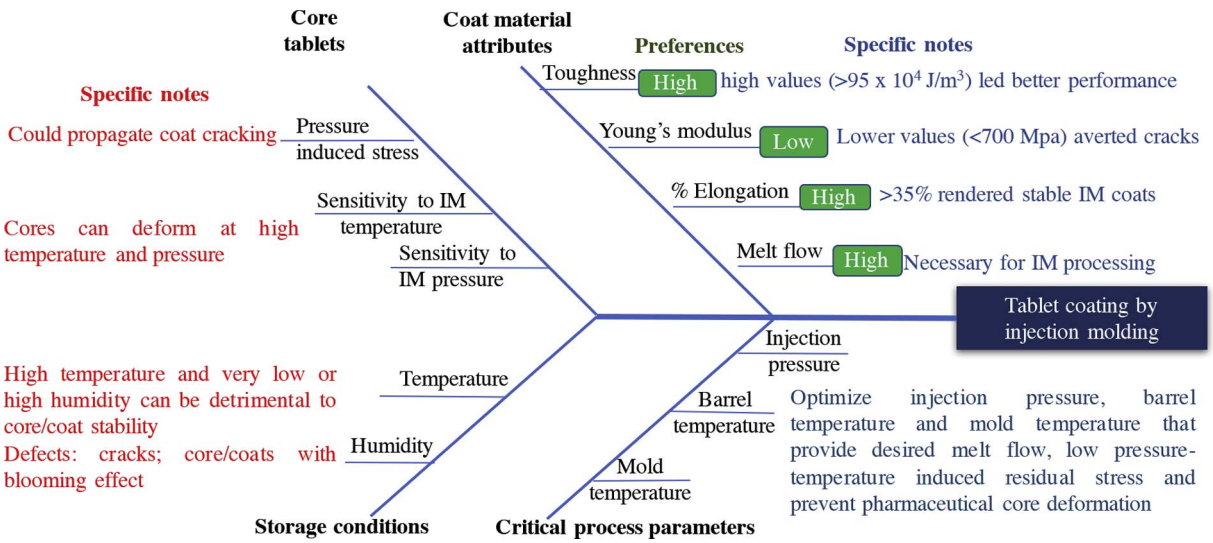

Fig. 8. A pictorial representation of coat material attributes, critical process parameters, influence of core tablets and storage conditions on tablet coating by IM process.

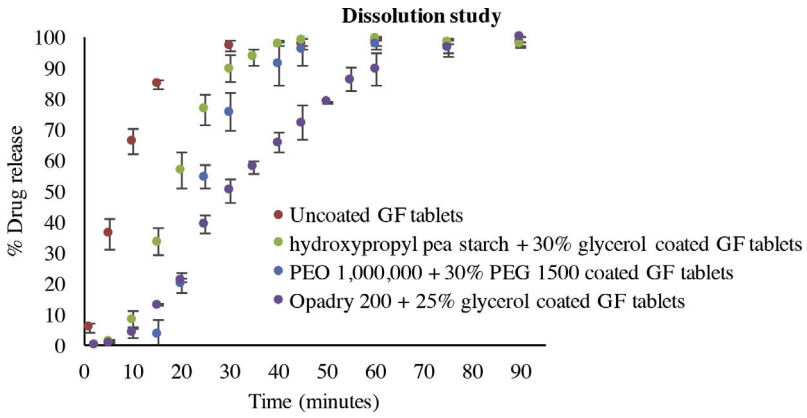

Fig. 9. *In vitro* dissolution study of uncoated and coated GF tablets.

working with IM coating, it is recommended that the tensile testing and melt flow analysis would be initially helpful to screen the coating formulation, followed by IM processing parameter optimization. Based upon this discussion, a pictorial diagram (Fig. 8) is drafted where all the observations (about material attributes, critical process parameters of IM process, influence of core tablets and storage conditions on IM coating) are compiled and visualized for better understanding.

Based upon the understanding achieved in this research work, players in continuous manufacturing area can develop a fully automated, end to end, integrated continuous pilot plant where the secondary product (tablet) manufacturing step could involve core tablet manufacturing by HME-IM integrated platform and IM coating of the cores (immediately after tableting) in the same IM unit of the integrated platform. Considering the manufacturing and easily achievable automation advancement in IM unit (for example, automations of coating steps - step1 coating, flipping the half-coated tablet, step 2 coating), the complete coating process can be achieved in 12–15 s. That means, depending upon the number of mold cavities, medium to large scale batch of IM coated tablets can be manufactured.

3.6. *In vitro release study*

In vitro dissolution study was conducted for tablets coated with hydroxypropyl pea starch + 30% glycerol, Opadry + 25% glycerol and PEO 1,000,000 + 30% PEG 1500 formulations. As shown in Fig. 9, > 75% drug was released from uncoated GF tablets in less than 15 min. Next, tablets coated with hydroxypropyl peastarch + 30% glycerol had a good immediate release profile with > 75% drug being released in ~25 min. Hydroxypropyl pea starch is a water-soluble polymer and an addition of glycerol as a plasticizer to hydroxyporpyl pea starch coating could help to further increase the water solubility. It has been reported in the literature that, as the concentration of glycerol in the pea starch formulations increase, more OH groups are available for hydrogen bonding and it increases the solubility of pea starch [47].

PEO 1,000,000 + 30% PEG 1500 also provided an immediate release profile for GF tablets (> 75% drug release in ~30 min). This could be attributed to good solubility of PEO in water and thereby helping the dissolution [48]. It also has a capacity to swell and erode when placed in the dissolution media [48].

Opadry + 25% glycerol required 50 min to dissolve > 75% of GF. The release was slower in comparison with hydroxypropyl pea starch and PEO based formulations. Chemically, Opadry is a PVA based polymer [49] and the solubility profile of PVA depends upon the degree of hydrolysis and molecular weight [50]. Since the label of Opadry only mentions it as a PVA based polymer and details could not be found about its hydrolyzation or molecular weight, the reason for this poor dissolution profile is difficult to justify. Also, the thick coat (300 μm thickness), obtained by IM coating, slowed down the drug release. A decrease in coating thickness would improve drug release of tablets coated by all coating formulations.

4. Conclusion

Material properties (Young's modulus, toughness, percentage elongation, and tensile strength/Young's modulus ratio), obtained from the stress-strain analysis helped in screening the coating formulations suitable for IM process. The melt flow characteristics of the coating formulations played a vital role in IM processing. Injection pressure, barrel temperature and mold temperature were identified as critical process parameters for IM coating and were evaluated in detail. Based upon this study, hydroxypropyl pea starch + 30% glycerol, Opadry + 25% glycerol and PEO 1,000,000 + 30% PEG were concluded as viable coating formulations for IM based tablet coating. These formulations possessed the mechanical and material properties required by IM processing, rendered stable coats and desired dissolution profile. The study serves as a model for product development with specifications of excipients in ranges within the designed acceptance space for optimal product performance.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejpb.2017.10.006.

References

[1] G.C. Cole, Introduction and overview of pharmaceutical coating, in: G.C. Cole, J. Hogan, M. Aulton (Eds.), Pharmaceutical Coating Technology, Taylor & Francis Ltd, London, 2002, pp. 1–5.
[2] S. Tanabe, H. Nakagawa, T. Watanabe, H. Minami, M. Kano, N.A. Urbanetz, Setting the process parameters for the coating process in order to assure tablet appearance based on multivariate analysis of prior data, Int. J. Pharm. 511 (1) (2016) 341–350.
[3] K. Knop, P. Kleinebudde, PAT-tools for process control in pharmaceutical film coating applications, Int. J. Pharm. 457 (2) (2013) 527–536.
[4] M. Klukkert, J.X. Wu, J. Rantanen, S. Rehder, J.M. Carstensen, T. Rades, C.S. Leopold, Rapid assessment of tablet film coating quality by multispectral UV imaging, AAPS PharmSciTech. 17 (4) (2016) 958–967.
[5] H.O. Ammar, M.M. Ghorab, L.A. Felton, S. Gad, A.A. Fouly, Effect of antiadherents on the physical and drug release properties of acrylic polymeric films, AAPS PharmSciTech. 17 (3) (2016) 682–692.
[6] L.A. Felton, J.W. McGinity, Influence of plasticizers on the adhesive properties of an acrylic resin copolymer to hydrophilic and hydrophobic tablet compacts, Int. J. Pharm. 154 (2) (1997) 167–178.
[7] S. Bose, R.H. Bogner, Solventless pharmaceutical coating processes: a review, Pharm. Dev. Technol. 12 (2) (2007) 115–131.
[8] C. Cahyadi, P.W.S. Heng, L.W. Chan, Optimization of process parameters for a

quasi-continuous tablet coating system using design of experiments, AAPS PharmSciTech. 12 (1) (2011) 119–131.
[9] H. Lin, Y. Dong, D. Markl, B.M. Williams, Y. Zheng, Y. Shen, J.A. Zeitler, Measurement of the intertablet coating uniformity of a pharmaceutical pan coating process with combined terahertz and optical coherence tomography in-line sensing, J. Pharm. Sci. 106 (4) (2017) 1075–1084.
[10] J.T. Heinämäki, A. Iraizoz Colarte, A.J. Nordström, J.K. Yliruusi, Comparative evaluation of ammoniated aqueous and organic-solvent-based cellulose ester enteric coating systems: a study on free films, Int. J. Pharm. 109 (1) (1994) 9–16.
[11] S. Muschert, F. Siepmann, Y. Cuppok, B. Leclercq, B. Carlin, J. Siepmann, Improved long term stability of aqueous ethylcellulose film coatings: importance of the type of drug and starter core, Int. J. Pharm. 368 (1–2) (2009) 138–145.
[12] M. Qiao, L. Zhang, Y. Ma, J. Zhu, W. Xiao, A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100–55, Eur. J. Pharm. Biopharm. 83 (2) (2013) 293–300.
[13] L.A. Felton, S.C. Porter, An update on pharmaceutical film coating for drug delivery, Expert Opin. Drug Deliv. 10 (4) (2013) 421–435.
[14] J. Hogan, T. Page, L. Reeves, J. Staniforth, Powder coating composition for electrostatic coating of pharmaceutical substrates, US Patent 20060280943A1, 2006.
[15] P.M. Desai, G.V. Vaerenbergh, J. Holman, C.V. Liew, Continuous manufacturing: the future in pharmaceutical solid dosage form manufacturing, Pharm. Bioprocess. 3 (5) (2015) 357–360.
[16] L. Yu, Continuous manufacturing has a strong impact on drug quality, 2016 (cited 2017 Apr 22); Available from: https://blogs.fda.gov/fdavoice/index.php/2016/04/continuous-manufacturing-has-a-strong-impact-on-drug-quality/.
[17] B. Van Snick, J. Holman, C. Cunningham, A. Kumar, J. Vercruysse, T. De Beer, J.P. Remon, C. Vervaet, Continuous direct compression as manufacturing platform for sustained release tablets, Int. J. Pharm. 519 (1–2) (2017) 390–407.
[18] C. Cunningham, F. Nuneviller III, C. Venczel, F. Vilotte, Evaluation of recent advances in continuous film coating technology in reducing or eliminating potential product losses 2009 [cited 2017 Apr 22]; Available from: https://www.colorcon.com/literature/marketing/fc/OpadryII/ads_opadry_II_eval_rec_adv.pdf.
[19] N. Thakral, S. Thakral, Continuous tablet coaters: developments, advantages and limitations, Innovations Pharm. Tech (2009) 70–73.
[20] A.J. Clarke, R. Glinecke, R. Raby, C.L. Li, L. Martini, Injection Molding process for the preparation of an oral delivery device for the pharmaceutically active ingredient, US Patent 20100221292 A1, 2010.
[21] H. Sowden, Modified release dosage form, US Patent 20060233881 A1, 2006.
[22] S.M. McAllister, R.K. Raby, Jr., A. Brown, A.J. Clarke, Pharmaceutical formulation, US Patent 7842308 B2, 2010.
[23] K. Eggenreich, S. Windhab, S. Schrank, D. Treffer, H. Juster, G. Steinbichler, S. Laske, G. Koscher, E. Roblegg, J.G. Khinast, Injection molding as a one-step process for the direct production of pharmaceutical dosage forms from primary powders, Int. J. Pharm. 505 (1–2) (2016) 341–351.
[24] A. Melocchi, G. Loreti, M.D.D. Curto, A. Maroni, A. Gazzaniga, L. Zema, Evaluation of hot-melt extrusion and injection molding for continuous manufacturing of immediate-release tablets, J. Pharm. Sci. 104 (6) (2015) 1971–1980.
[25] T. Quinten, T. De Beer, C. Vervaet, J.P. Remon, T. Quinten, Evaluation of injection moulding as a pharmaceutical technology to produce matrix tablets, Eur. J. Pharm. Biopharm. 71 (1) (2009) 145–154.
[26] P. Speiser, Injection-moulded oral medicament in solid form, US Patent 3432592A, 1969.
[27] P. Watts, A. Smith, TARGIT™ technology: coated starch capsules for site-specific drug delivery into the lower gastrointestinal tract, Expert Opin. Drug Deliv. 2 (1) (2005) 159–167.
[28] European Pharmacopoeia 9.3, Monographs on dosage forms: Tablets 01/2018:0478. pp. 4790–4792.
[29] S. Mascia, P.L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P.I. Barton, R.D. Braatz, C.L. Cooney, J.M.B. Evans, T.F. Jamison, K.F. Jensen, A.S. Myerson, B.L. Trout, End-to-end continuous manufacturing of pharmaceuticals: Integrated synthesis, purification, and final dosage formation, Angew. Chem. Int. Ed. 52 (47) (2013) 12359–12363.
[30] P.M. Desai, R.C. Hogan, D. Brancazio, V. Puri, K.D. Jensen, J.-H. Chun, A.S. Myerson, B.L. Trout, Integrated hot-melt extrusion - injection molding continuous tablet manufacturing platform: effects of critical process parameters and formulation attributes on product robustness and dimensional stability, Int. J. Pharm. 531 (1) (2017) 332–342.
[31] V. Puri, D. Brancazio, P.M. Desai, K.D. Jensen, J.-H. Chun, A.S. Myerson, B.L. Trout, Development of maltodextrin based immediate release tablets using an integrated twin-screw hot melt extrusion and injection molding continuous manufacturing process, J. Pharm. Sci. (2017) (in press).
[32] J.S. Boateng, H.N.E. Stevens, G.M. Eccleston, A.D. Auffret, M.J. Humphrey, K.H. Matthews, Development and mechanical characterization of solvent-cast polymeric films as potential drug delivery systems to mucosal surfaces, Drug Dev. Ind. Pharm. 35 (8) (2009) 986–996.
[33] F. Sadeghi, M. Shahabi, H. Afrasiabi Garekani, Comparison of physicomechanical properties of films prepared from organic solutions and aqueous dispersion of eudragit RL, DARU. J. Pharm. Sci. 19 (2) (2011) 100–106.
[34] H. Lim, S.W. Hoag, Plasticizer effects on physical-mechanical properties of solvent cast Soluplus® films, AAPS PharmSciTech. 14 (3) (2013) 903–910.
[35] R.J. Roberts, R.C. Rowe, The Young's modulus of pharmaceutical materials, Int. J. Pharm. 37 (1–2) (1987) 15–18.
[36] J.C. Kerridge, J.M. Newton, The determination of the compressive Young's modulus of pharmaceutical materials, J. Pharm. Pharmacol. 38 (12 S) (1986) 79P.
[37] J. Gutiérrez-Rocca, J.W. McGinity, Influence of water soluble and insoluble plasticizers on the physical and mechanical properties of acrylic resin copolymers, Int. J. Pharm. 103 (3) (1994) 293–301.
[38] R.C. Rowe, R.J. Roberts, The effect of some formulation variables on crack propagation in pigmented tablet film coatings using computer simulation, Int. J. Pharm. 86 (1) (1992) 49–58.
[39] R.C. Rowe, The cracking of film coatings on film-coated tablets—a theoretical approach with practical implications, J. Pharm. Pharmacol. 33 (1) (1981) 423–426.
[40] C. Fernandes, A.J. Pontes, J.C. Viana, A. Gaspar-Cunha, Modeling and optimization of the injection-molding process: a review, Adv. Polym. Technol. (2016), http://dx.doi.org/10.1002/adv.21683.
[41] J. Jeon, J. Gim, B. Rhee, The melt temperature variation in the barrel of injection molding machine, in: Annual Technical Conference - ANTEC, Conference Proceedings, 2016, Society of Plastics Engineers.
[42] W.F. Zoetelief, L.F.A. Douven, A.J. Ingen, Housz, Residual thermal stresses in injection molded products, Polym. Eng. Sci. 36 (14) (1996) 1886–1896.
[43] S.E. Everett, R. Dubay, A sub-space artificial neural network for mold cooling in injection molding, Expert Syst. Appl. 79 (2017) 358–371.
[44] B. Pignon, N. Boyard, V. Sobotka, D. Delaunay, Heat transfer analysis at high cooling rate on the surface of thermoplastic parts, Int. J. Heat Mass Transfer 106 (2017) 253–262.
[45] A.V. Shenoy, D.R. Saini, Melt flow index: More than just a quality control rheological parameter Part II, Adv. Polym. Tech. 6 (2) (1986) 125–145.
[46] J. Brooks, Failure analysis of a thermoplastic elastomer: melt flow index method provides critical data, Rubber World 253 (1) (2015) 42–43.
[47] B. Saberi, Q.V. Vuong, S. Chockchaisawasdee, J.B. Golding, C.J. Scarlett, C.E. Stathopoulos, Mechanical and physical properties of pea starch edible films in the presence of glycerol, J. Food Process. Preserv. 40 (6) (2016) 1339–1351.
[48] M. Rane, J. Parmar, S. Tiwari, A.R. Rajabi-Siahboomi, Application of polyethylene oxide in hydrophilic matrix tablets, Pharma Times 45 (3) (2013) 41–48.
[49] J. Teckoe, T. Mascaro, T.P. Farrell, A.R. Rajabi-Siahboomi, Process optimization of a novel immediate release film coating system using QbD principles, AAPS PharmSciTech. 14 (2) (2013) 531–540.
[50] X. Tang, S. Alavi, Recent advances in starch, polyvinyl alcohol based polymer blends, nanocomposites and their biodegradability, Carbohydr. Polym. 85 (1) (2011) 7–16.