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Demonstration of pharmaceutical tablet coating process by injection molding technology

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ABSTRACT

We demonstrate the coating of tablets using an injection molding (IM) process that has advantage of being solvent free and can provide precision coat features. The selected core tablets comprising 10% w/w griseofulvin were prepared by an integrated hot melt extrusion-injection molding (HME-IM) process. Coating trials were conducted on a vertical injection mold machine. Polyethylene glycol and polyethylene oxide based hot melt extruded coat compositions were used. Tablet coating process feasibility was successfully demonstrated using different coating mold designs (with both overlapping and non-overlapping coatings at the weld) and coat thicknesses of 150 and 300 μm. The resultant coated tablets had acceptable appearance, seal at the weld, and immediate drug release profile (with an acceptable lag time). Since IM is a continuous process, this study opens opportunities to develop HME-IM continuous processes for transforming powder to coated tablets.

1. Introduction

Tablet coating is a popular pharmaceutical technique used to impart a variety of functionalities to a drug product such as product differentiation, protection from environment, taste masking, modified drug release, and enhanced mechanical integrity. Solvent-based spray coating is a widely-used process (McGinity and Felton, 2008). The popularity of this process notwithstanding, it has some important limitations. The use of aqueous/organic solvents and/or the long heat exposure times can adversely affect the product stability (Leane et al., 2013; Riedel and Leopold, 2005), increase process cost, and create environmental and safety hazards (Bose and Bogner, 2007). These limitations have spurred research on alternative solvent-free processes such as compression coating, dry powder coating, electrostatic spray powder coating, and photocuring coating (Bose and Bogner, 2007; Koeberle and Haack, 2013).

We briefly discuss these new advancements. First, the compression coating process has been implemented commercially and can be used to separate two incompatible ingredients in the same dosage unit. However, this process usually yields thick coats and has limited precision in accurately positioning the tablet core in the second compression step, which is important for reproducible formulation performance (Hariharan and Gupta, 2002; Ozeki et al., 2003a). A new approach—one-step dry-coated (OSDrC) tablet manufacturing system—-positions the tablet more precisely (Ozeki et al., 2003b). Second, dry powder coating and electrostatic spray powder coating processes involve dry powder deposit on the substrate followed by an added curing (temperature or IR based) step to complete the film formation process. However, often this process uses liquid plasticizers or wetting of substrate in the deposition step and it might be challenging to achieve a thick coat (Kablitz and Urbanetz, 2007; Qiao et al., 2010). Electrostatic spray coating has been used as a continuous coating process at the commercial scale (Reeves et al., 2001). Third, photocuring coating is specifically beneficial for temperature-sensitive products as it uses light energy for film formation and solidification, and lowers process cost (Wang and Bogner, 1995; Yang, 1993). Finally, other recent techniques such as hot melt spray coating and supercritical fluid coating do not require the curing step (Koeberle and Haack, 2013). But they have been only applied to particulate systems, and not yet to coating tablets.

In this study, we examine the application of the injection molding (IM) process to pharmaceutical tablet coating. IM is a novel process for drug delivery that has been applied to manufacture complex-shaped

Abbreviations: HME, Hot melt extrusion; IM, Injection molding; PEG, Polyethylene glycol; PEO, Polyethylene oxide

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products such as implants (Li et al., 2002; Zema et al., 2012), scaffolds (Teng et al., 2013), matrix tablets (Hemmingsen et al., 2011; Quinten et al., 2011), and single/multi component capsule shells (Gazzaniga et al., 1994; McAllister et al., 2010). But the application of IM to coating of tablets has been limited. One recent reference to the process is in a patent by Clarke et al. (2012). The patent applies the IM process to produce tablet coatings with one or more external openings. In this study powder-compressed core tablets were used as substrate with a range of coat materials (polymethacrylate copolymers, natural waxes, polyvinyl acetate, and hydroxylpropyl cellulose) and process conditions (temperature and pressure) that enabled the tablet to withstand the IM process without being deformed. Related inventions (Brown et al., 2012; McAllister et al., 2010) describe single/multiple compartment capsule shell dosage forms that were prepared by melt extrusion and IM processes. To the best of our knowledge, a complete tablet coating using the IM process, which is desired for most functional applications, has not yet been demonstrated.

IM coating is a promising technique that offers product differentiation and functionality, as precision coat molds can modulate shape and coat features. In addition, it obviates the use of solvent, provides thick coat with a minimal increase in core tablet exposure or process time, and reduces the likelihood of microbial contamination (Zema et al., 2012). Compared to other solvent-less technologies, IM has shorter processing times (no curing or drying required), is a continuous process, and can be scaled out (that is, coat molds can be parallelized). The potential challenges associated with IM-based tablet coating include the need to understand core tablet robustness for process conditions, identifying coat materials that have optimal melt processing properties, and investment in equipment and dedicated precision coat molds for each tablet type.

Our previous work used integrated hot melt extrusion-injection molding to convert powder to tablets (Puri et al., 2017). The tablets comprised a maltodextrin-xylitol matrix with 10% w/w griseofulvin. In this study, we coated these extrusion-molded "core" tablets (Fig. 1). Our aim was to develop an IM tablet coating process to achieve a target coat thickness of less than 500 µm with acceptable features (coat appearance, seal at the weld, and immediate release performance).

The results demonstrate successful application of the IM process for tablet coating. More broadly, the study provides a basis for refining the IM process and equipment to develop pharmaceutical coated formulations for wider applications.

1.1. Injection molding tablet coating process development

The IM process used for tablet coating on the vertically opening IM machine is illustrated in Fig. 1. Details of the equipment and molds (Supplementary Fig. S1), and process control (Supplementary Figs. S2 and S3) are provided in the Supplementary information S1. The "core" injection molded tablets had asymmetrical halves and a parting line.

Table 1
Summary of the three coat mold designs used in the IM tablet coating process.

Mold design	Tablet coat thickness (µm)	Coat thickness at weld (µm)	Weld type
Set 1	300	300	Non-overlapping
Set 2	300	500	Overlapping
Set 3	150	350	Overlapping

The tablet's appearance was similar to a cooking pot. Therefore, the top shallow half was called the "lid" and the bottom deeper half was called the "pot". In Step 1 of the process, the "pot" half of the tablet was coated followed by ejection. In Step 2, the half-coated tablet was inverted and the "lid" half of the tablet was coated. At the end of each step, the sprue on the coated side was manually cut.

The coat mold inserts for the targeted coat thickness were designed to complement the "core" tablet shape. The injection molded "core" tablet had varying radii of curvature. Therefore, the tablet images were captured on an optical comparator and imported into a LabVIEW program to obtain the "core" tablet drawings. Subsequently, the offset geometry of the targeted coated tablet was developed from which the coat mold inserts dimensions were derived.

Table 1 presents the three coat mold designs (non-overlapping and overlapping type) evaluated in this study. Fig. 2 shows the corresponding drawings of the tablet coat dimensions.

An important condition for process feasibility was that the core tablet should endure the coating process conditions (i.e., injection temperature and pressure) without deformation or degradation. Thus, the coat material and coating process parameters should be selected in view of the core tablet's mechanical strength and thermal stability. Many spray coat materials are amenable to melt processing (e.g. as matrix formers in hot melt extrusion (HME) tablets or as stabilizers in HME-based solid dispersions) (Maniruzzaman et al., 2012; Patil et al., 2016). Therefore, a wide range of coat materials can potentially be applied to the IM tablet coating process. Further the coat selection and optimization would be based on coat attributes of melt flow behavior (melt viscosity-pressure-temperature profiles) and the mechanical properties of the film coat (such as tensile strength, elastic modulus and toughness) (Rosato and Rosato, 2000) formed after the melt solidification process. In an extension of the current work, our research group evaluated different coat materials and the performance of IM coated tablets under storage (Desai et al., 2018).

Based on the above rationale, we selected polyethylene glycol (PEG 35,000, Sigma Aldrich) and polyethylene oxide (PEO, Polyox N10, Dow Chemical), water-soluble crystalline polymers with low melting temperature (about 66 °C) as model coating materials. These materials have film-forming properties and are amenable to molten processing at low temperatures (Jani and Patel, 2015). The coat compositions were produced by HME (described in supplementary information S1). The first

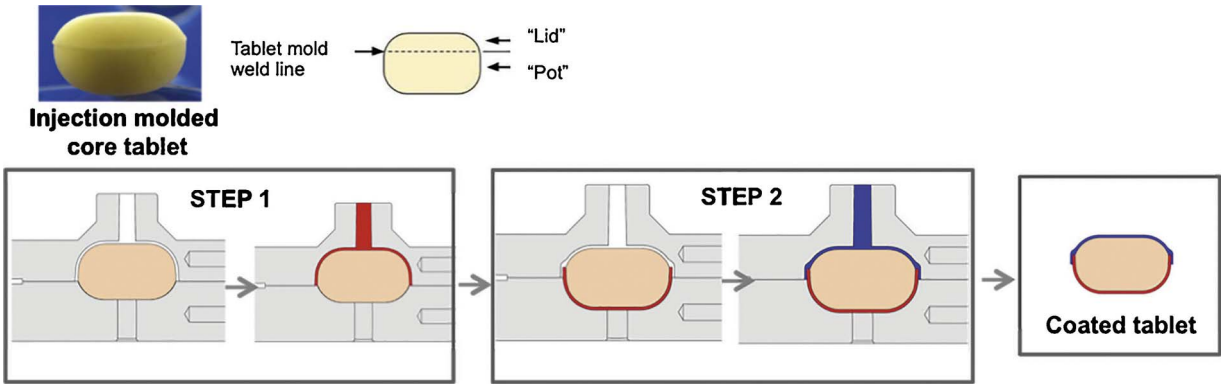


Fig. 1. Illustration of tablet coating process steps on the vertical injection molding machine.

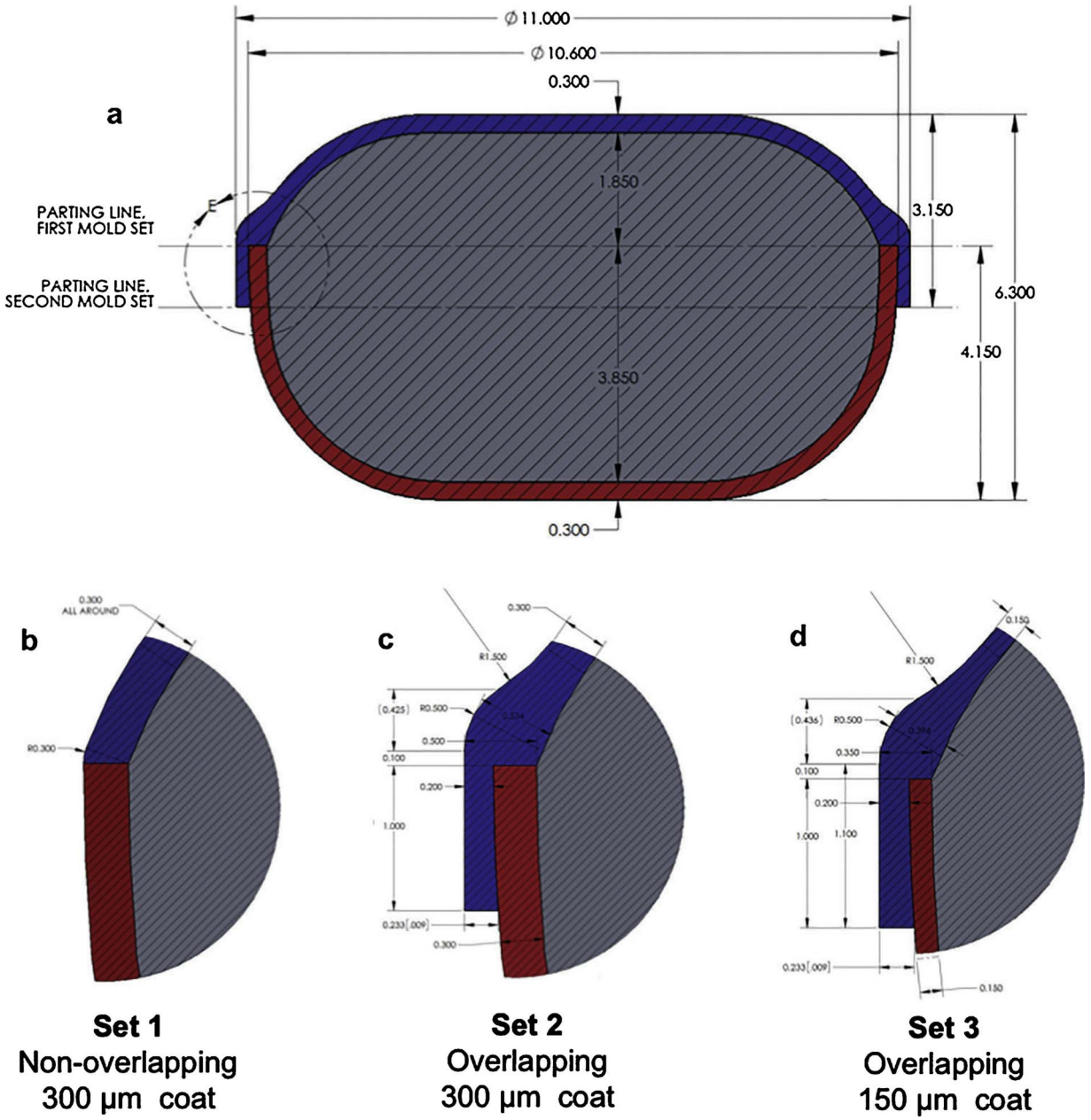


Fig. 2. (a) Drawing of a full coated tablet using the Set 2 coat mold design; b–d show the encircled region of coat dimensions for the three different mold sets. Grey: core tablet, Red: bottom coat and blue: top coat. Measurements are in mm (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

coat composition was a PEO-based formulation comprising PEO-PEG 1500 (71.5:28.5 w/w). The second coat composition was a PEG-based formulation comprising PEG 35,000-PEO (73.6:21.4 w/w). PEO-based coat composition was used for detailed assessment of the IM coating process.

2. Description of the first half tablet coating (step 1)

The melt extrusion trials for the PEO/PEG films indicated a working temperature of 90 ± 5 °C for producing a homogenous blend and an optimal melt flow. The IM films were verified for shrinkage or expansion behavior (details in supplementary information). Core tablets ingredients (griseofulvin and maltodextrin) were thermally stable for melt processing up to about 150 °C (Desai et al., 2017; LaFountaine et al., 2016; Puri et al., 2017; Zhou et al., 2008). Thus, IM coating process at 90 °C was acceptable with respect to thermal stability of the core tablet. The temperature threshold for mechanical deformation of the core tablet was determined to be about 100 °C. This was based on cumulative understanding of the glass transition pattern of the matrix (Puri et al., 2017) and observed mechanical strength of the core tablet in preliminary IM coating trials. Considering the optimal working range for both, the core tablet and the coat formulation, an injection temperature of 90 °C was selected for the process trials.

Fig. 3 lists the measurements and images of the half and full-coated tablets produced using different mold sets. The coat was smooth and adhered well to the core tablet. The coat thickness uniformity was checked for the "pot" half-coated tablets using a rapid screening technique of optical/polarized microscopy (Fig. 4a). The results corroborated the SEM observations (Fig. 4b) and fluorescence microscopy (Fig. S5 in Supportive information). A mild flash was observed at the parting line, which sometimes obstructed the microscopic coat thickness measurements. This flashing can be eliminated by using higher quality steel tooling manufactured to tighter specifications. The IM process parameters selected for the first and second half tablet coating are listed in

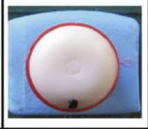
Features	Core tablet	Non-overlapping 300 µm coat		Overlapping 300 µm coat		Overlapping 150 µm coat	
		STEP 1 1st half coated (POT)	STEP 2 2nd half coated (LID)	STEP 1 1st half coated (POT)	STEP 2 2nd half coated (LID)	STEP 1 1st half coated (POT)	STEP 2 2nd half coated (LID)
Tablet weight (mg) (% w/w gain)	522.7 ± 6.4	599.2 ± 1.1 (14.6)	633.9 ± 1.8 (5.7)	596.8 ± 2.4 (13.6)	637.1 ± 1.6 (7.1)	559.8 ± 1.3 (7.1)	606.2 ± 1.9 (8.3)
Tablet diameter (mm)	9.95 ± 0.01	10.61 ± 0.01	10.61 ± 0.01	10.62 ± 0.02	11.02 ± 0.01	10.27 ± 0.02	10.71 ± 0.01
Tablet thickness (mm)	5.73 ± 0.02	6.00 ± 0.05	6.30 ± 0.01	6.03 ± 0.01	6.32 ± 0.02	5.87 ± 0.01	6.02 ± 0.02
	A	B	C	D	E	F	G
Tablet appearance							

Fig. 3. Measurements and images of coated tablets produced using non-overlapping and overlapping coat molds for the PEO coat formulation. Added black marks (3C and 3D images) helped orient measurements. Image 3G has an uncut sprue.

Table 2.

Effect of injection pressure: At an injection temperature of 90 °C, successful coating of the "pot" half of the tablet was achieved in the injection pressure range of 14-41 MPa. An injection pressure of 28 MPa was selected for further trials.

Effect of injection speed: Due to limitations of the in-house IM instrument, the injection pressure overshot initially and then plateaued at the set value (28 MPa). At an injection speed of 0.845 cm/s, the pressure overshoot reached ~48 MPa. However, at the maximum injection speed of 4.23 cm/s, the pressure spike hit ~98 MPa. The "pot" half coating was found to be complete at both speeds and no tablet deformation was observed (images B, D and F in Fig. 3)

Table 2
IM tablet coating process parameters. *There was an initial pressure spike as described in the text. .

Process parameters	Step 1: 1st half coat	Step 2: 2nd half coat
Injection pressure (MPa)	28*	165
Injection time (s)	2.5	4.0
Injection hold pressure (MPa)	28	165
Injection hold time (s)	2.5	3.0
Molten mass temperature (°C)	90	90
Mold temperature (°C)	30	30
Solidification time (s)	5.0	5.0
Injection speed (cm/s)	0.845	4.23

3. Description of the second half tablet coating (step 2)

The "pot" half-coated tablets with coat thickness in the range of nominal ± 50 µm were taken to Step 2, which involved coating the "lid" half and weld formation. The coalescence of the top molten mass with the bottom coat at the weld in the step 2 can be improved by using higher injection temperature, injection speed and bottom mold temperature. As discussed earlier, the upper limit of injection temperature was set at 90 °C. The injection speed of the instrument in step 2 was set at its maximum value of 4.23 cm/s. Further, the injection pressure was varied, keeping the bottom mold temperature low at 30 °C to enhance mechanical strength of the core tablet.

Effect of injection pressure: At an injection temperature of 90 °C, an injection pressure of less than 69 MPa was insufficient for the formed "lid" coating to adhere to the tablet. At the injection pressure of 110 MPa, the "lid" coating was achieved with an incomplete weld. Increasing the injection pressure to a range of 138–172 MPa yielded full-coated tablet and a complete weld.

A significantly higher injection pressure was used in Step 2 of the coating process for the following reasons. First, the non-overlapping mold (Set 1) provided minimal surface area for the top coat to weld with the bottom half. Second, when the molds were opened after coating, only the bottom mold moved down. This could cause the weld

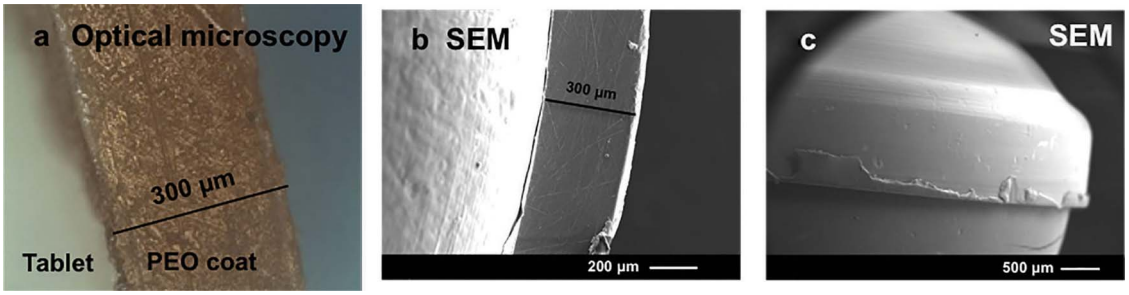


Fig. 4. (a) Optical microscopy and (b) SEM image of coat thickness measurement for a "pot" half-coated tablet placed "as is" under the microscope and on the SEM stub, respectively. (c) SEM image of weld region of a full-coated tablet, using the overlapping 300 µm coat mold (Set 2).

(if formed) to break, as the top coat experienced opposite forces i.e. the sprue in the top mold pulled the top coat upwards while the bottom tablet-half pulled the coat downwards. Third, the top coat had a shallow depth and thus had a greater tendency to separate as it did not extend to the tablet center region. In contrast, the bottom "pot" fit well in the bottom half mold and thus was unlikely to displace. Using overlapping molds (Set 2 and 3) improved the weld formation as there was increased contact area at the weld and the top coat formed a deeper cup.

Admittedly, the injection pressure in Step 2 can be reduced, which would minimize residual stress on the core tablet. But we were constrained to use high injection pressure due to limitations of the in-house machine that affected the weld formation. The injection pressure can be optimized by using a hot runner IM machine, appropriate part design (e.g. tapered sprue), improved mold design, higher quality and precision tooling, and better control of process parameters.

Tablet coating with the non-overlapping 300 µm coat mold (Set 1) produced a successful weld (image C in Fig. 3). However, the probability of variation was higher and in some cases microscopic gaps at the weld region were observed (Supplementary Fig. S4). In comparison, tablet coating with the overlapping 300 µm coat mold (Set 2) consistently yielded a complete weld of the two coat halves throughout the tablet diameter (image E in Fig. 3). SEM images showed that the coat at the weld region was smooth with no cracks (Fig. 4c).

The established IM process parameters (Table 2) were successfully used to achieve a 150 µm coat thickness using the Set 3 molds. The coat was visually thinner and had a complete seal at the weld (images F and G in Fig. 3). The PEO coated tablet showed about 15 and 22% weight gain for the 150 and 300 µm coat, respectively. Using the same IM process parameters, coated tablets were prepared with the PEG based coat formulation at 150 and 300 µm coat thicknesses.

During process parameter evaluation at each coating step, multiple samples of coated tablets were manually peeled off and the core tablets were examined for appearance (surface cracks and discoloration) and dimensions to confirm that there was no change. The SEM of a half-coated tablet surface showed no apparent differences from an uncoated core tablet surface. Further, no cracks were seen (Fig. 4b). Similarly, the coat on the full-coated tablets was peeled and the obtained core tablets were checked for dimension and surface changes. In this case, the tablet dimensions were within ± 10 um of initial "as is" core tablet dimensions and microscopic examination showed no surface cracks (Fig. 5a). An illustration of all measurement locations of coat thickness on the half and full-coated tablets (Fig. S6) is provided in the supplementary information. We cross-sectioned representative coated tablets using a sharp blade and examined the tablet core by SEM (Fig. 5b). No apparent differences were observed in the core microstructure compared to the untreated core tablets.

We would like to highlight that in the current study, only extrusion molded core tablets were used. It would be of interest to evaluate the impact of IM coating process on the microstructure of powder compressed tablets, as they may behave differently. The study by Clarke et al. (2012) described IM coating of powder compressed tablets and suggested operating conditions of injection pressure up to 6000 psi (41 MPa) and temperature in range of 25–300 °C, however changes in the core tablet microstructure were not discussed. We acknowledge this aspect warrants more evaluation to facilitate viability of the IM coating process technology. Modern imaging tools of X-ray microtomography (Lin et al., 2017b; Sinka et al., 2004; Tokudome et al., 2009; Wu et al., 2008; Zeitler and Gladden, 2009) and terahertz pulse (Ho et al., 2007; May et al., 2013; Zeitler et al., 2007; Zhong et al., 2011) can be employed to understand the effect of coating process on the core tablet microstructure and film characteristics.

Since the sprue was cut manually, the tablet coat thickness in the sprue region (circular region of 1 mm diameter) was slightly higher (about 50 µm) than the nominal tablet coat thickness. Since it was a small region of the tablet, it would not have a significant impact on the results. Further, the region surrounding the sprue was visually checked for cracks or defects. Sprue formation is a limitation of the cold runner IM equipment and can be overcome by using a hot runner IM equipment (Rosato and Rosato, 2000).

The coat dimension precision and reproducibility depends on equipment factors such as mold alignment, mold clamping, mold part tolerance, and robustness of tablet positioning in the mold. In this study, the core tablets were manually placed into the bottom mold and a single mold set was used for each type of coat design. The tablet coating was reproduced within target thickness ± 50 µm. Commercial IM machines employ tools to verify mold clamping and alignment, and automated part insertion and removal. Thus can provide process control and product accuracy at micron scale (Hyland, 2001; Surace et al., 2012).

4. Characterization of *in vitro* drug release of coated tablets

In vitro drug release testing of tablets was performed in aqueous sodium lauryl sulphate solution dissolution media (details provided in Supplementary data S1) for core and coated tablets (Fig. 6). Compared to the core tablets, PEO coated tablets of 150 and 300 µm coat showed an acceptable initial lag of about 5 and 10 min, respectively. The PEG coated tablets of both 150 and 300 µm coat displayed an initial lag of about 5 min followed by a similar drug release profile. For all coated tablets, the time taken for 80% of drug release was extended by no more than 5–15 min. These results confirmed successful application of IM coating process to yield immediate release coated tablets.

A coat thickness of 150–300 µm by IM process showed about

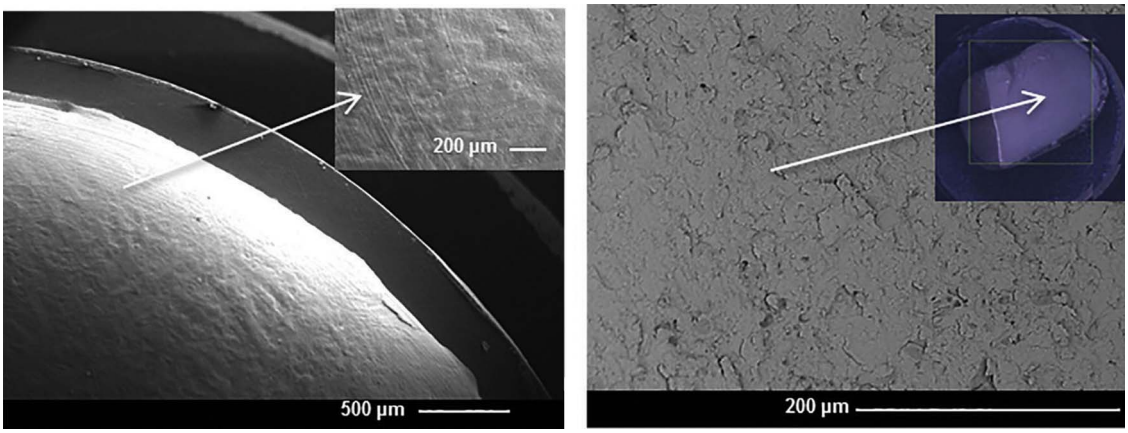


Fig. 5. SEM images of (a) surface of the core tablet after peeling the top coat of a full-coated tablet and (a) cross section of a full-coated tablet. The tablet coat was produced using the overlapping 300 µm coat mold (Set 2).

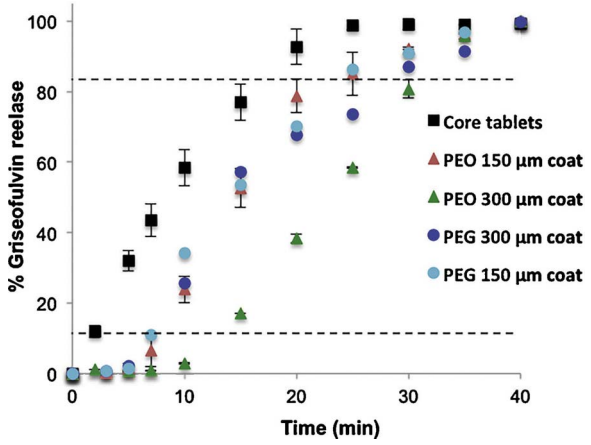


Fig. 6. Griseofulvin dissolution profiles for the core and coated tablets (n = 3, mean ± SD).

15–22% weight gain. Spray coating process for tablet coating has been reported to produce a wide range of coat thickness which differs based on coat material and weight gain. A recent publication by Lin et al. (2017b) provides comprehensive data of 22 coated tablet products using spray coating process for Opadry coat materials. A coat of 50 ± 15 µm thickness was achieved for multiple opadry compositions with tablet weight gain of 3–4% and coat thickness of 105 µm for about 10% weight gain for Eudragit E material. A Kollicoat SR30D sustained release coat (Lin et al., 2017a), by spray coating technique produced coat thickness of 280 µm by tablet weight gain of about 16% w/w. Compared to spray coating, coat porosity is likely to be lower in the IM process because the latter involves a deposit of molten material under pressure. The SEM image of PEO/PEG coat (Fig. 4b) showed a dense microstructure with no visible pores. Further, the initial dissolution lag and weight gain for IM coated tablets were comparable to the reported characteristics of two types of conventionally-used capsule shells. These are hard gelatin and non-gelatin shells manufactured using the dip molding method and starch-based shells (Capill®) made using the IM process (Chiwele et al., 2000; Gullapalli and Mazzitelli, 2017).

5. Conclusion

This study has demonstrated a novel application of the IM process technology to the coating of tablets. The coated tablets thus produced displayed acceptable appearance, seal at the weld, and drug release performance. Varying coating mold design and coat thickness improved the understanding of the extent of process feasibility. The study opens avenues for research on how IM process parameters impact coating features. From a formulation perspective, studies that explore different coating materials and assess performance on storage would be relevant.

More broadly, our study shows one instance of a potentially more widespread application of the IM process technology to the pharmaceutical industry. The technology has been used to develop micro-scaled products in the plastics and medical devices industries (Sammoura et al., 2007; Surace et al., 2012). The results in the current study provide a starting point to adapt the micro IM technology for developing coated tablets with micro-scaled features.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijpharm.2017.10.062

References

Bose, S., Bogner, R.H., 2007. Solventless pharmaceutical coating processes: a review. Pharm. Dev. Technol. 12, 115–131.
Brown A., Matthews W.M., Margestson D.M., McAllister S.M., Raby R.K., 2012. Pharmaceutical formulations. US Patent 8147871.
Chiwele, I., Jones, B.E., Podczeck, F., 2000. The shell dissolution of various empty hard capsules. Chem. Pharm. Bull. 48, 951–956.
Clarke A.J., Glinecke R., Raby R., Li C.L., Martini L., 2012. Injection molding process for the preparation of an oral delivery device for the pharmaceutically active agent. US Patent 8123509, 28 February.
Desai, P.M., Hogan, R.C., Brancazio, D., Puri, V., Jensen, K.D., Chun, J.-H., Myerson, A.S., Trout, B.L., 2017. 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, 332–342.
Desai, P.M., Puri, V., Brancazio, D., Halkude, B.S., Hartman, J.E., Wahane, A.V., Martinez, A.R., Jensen, K.D., Harinath, E., Braatz, R.D., Chun, J.-H., Trout, B.L., 2018. Tablet coating by injection molding technology – optimization of coating formulation attributes and coating process parameters. Eur. J. Pharm. BioPharm. 122, 25–36.
Gazzaniga, A., Sangalli, M.E., Giordano, F., 1994. Oral Chronotopic® drug delivery systems: achievement of time and/or site specificity. Eur. J. Pharm. Biopharm. 40, 246–250.
Gullapalli, R.P., Mazzitelli, C.L., 2017. Gelatin and non-gelatin capsule dosage forms. J. Pharm. Sci. 106, 1453–1465.
Hariharan, M., Gupta, V.K., 2002. A novel concept for the production of compression-coated tablets. Pharm. Technol. Eur. 14 46,48,50,52,54,56.
Hemmingsen, P.H., Haahr, A.-M., Gunnergaard, C., Cardot, J.-M., 2011. Development of a new type of prolonged release hydrocodone formulation based on Egalet® ADPREM technology using in vivo–in vitro correlation. Pharmaceutics 3, 73–87.
Ho, L., Müller, R., Römer, M., Gordon, K.C., Heinämäki, J., Kleinebudde, P., Pepper, M., Rades, T., Shen, Y.C., Strachan, C.J., Taday, P.F., Zeitler, J.A., 2007. Analysis of sustained-release tablet film coats using terahertz pulsed imaging. J. Contolled Release 119, 253–261.
Hyland, I., 2001. Robots used on plastic injection moulding machines. Ind. Robot: Int. J. 28, 104–112. http://dx.doi.org/10.1108/01439910110382657.
Jani, R., Patel, D., 2015. Hot melt extrusion: an industrially feasible approach for casting orodispersible film. Asian J. Pharm. Sci. 10, 292–305.
Kablitz, C.D., Urbanetz, N.A., 2007. Characterization of the film formation of the dry coating process. Eur. J. Pharm. Biopharm. 67, 449–457.
Koeberle, M., Haack, D., 2013. Solvent-free coating of traditional and user-friendly dosage forms. Pharm. Technol. 37, 32–34 52.
LaFountaine, J.S., Prasad, L.K., Brough, C., Miller, D.A., McGinity, J.W., Williams, R.O., 2016. Thermal processing of PVP- and HPMC-based amorphous solid dispersions. AAPS PharmSciTech 17, 120–132.
Leane, M.M., Sinclair, W., Qian, F., Haddadin, R., Brown, A., Tobyn, M., Dennis, A.B., 2013. Formulation and process design for a solid dosage form containing a spray-dried amorphous dispersion of ibipinabant. Pharm. Dev. Technol. 18, 359–366.
Li, L.C., Deng, J., Stephens, D., 2002. Polyanhydride implant for antibiotic delivery – from the bench to the clinic. Adv. Drug Deliv. Rev. 4, 963–986.
Lin, H., Dong, Y., Markl, D., Williams, B.M., Zheng, Y., Shen, Y., Zeitler, J.A., 2017a. 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, 1075–1084.
Lin, H., Dong, Y., Markl, D., Zhang, Z., Shen, Y., Zeitler, J.A., 2017b. Pharmaceutical film coating catalog for spectral domain optical coherence tomography. J. Pharm. Sci. 106, 3171–3176.
Maniruzzaman, M., Boateng, J.S., Snowden, M.J., Douroumis, D., 2012. A review of hot-melt extrusion: process technology to pharmaceutical products. ISRN Pharmaceutics 2012, 1–9.
May, R.K., Su, K., Han, L., Zhong, S., Elliott, J.A., Gladden, L.F., Evans, M., Shen, Y., Zeitler, J.A., 2013. Hardness and density distributions of pharmaceutical tablets measured by terahertz pulsed imaging. J. Pharm. Sci. 102, 2179–2186.
McAllister S.M., Raby R.K., Brown A., Clarke A.J., 2010. Pharmaceutical formulation. US Patent 7842308, 20 November.
McGinity, J.W., Felton, L.A., 2008. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, third ed. Marcel Dekker.
Ozeki, Y., Watanabe, Y., Inoue, S., Danjo, K., 2003a. Comparison of the compression characteristics between new one-step dry-coated tablets (OSDRC) and dry-coated tablets (DC). Int. J. Pharm. 259, 69–77.
Ozeki, Y., Watanabe, Y., Inoue, S., Danjo, K., 2003b. Evaluation of the compression characteristics and physical properties of the newly invented one-step dry-coated tablets. Int. J. Pharm. 267, 69–78.
Patil, H., Tiwari, R.V., Repka, M.A., 2016. Hot-melt extrusion: from theory to application in pharmaceutical formulation. AAPS PharmSciTech 17, 20–42.
Puri, V., Brancazio, D., Desai, P.M., Jensen, K.D., Chun, J.-H., Myerson, A.S., Trout, B.L., 2017. Development of maltodextrin-based immediate-release tablets using an integrated twin-screw hot-melt extrusion and injection-molding continuous manufacturing process. J. Pharm. Sci. 106, 3328–3336.
Qiao, M., Zhang, L., Ma, Y., Zhu, J., Chow, K., 2010. A novel electrostatic dry powder coating process for pharmaceutical dosage forms: immediate release coatings for tablets. Eur. J. Pharm. Biopharm. 76, 304–310. http://dx.doi.org/10.1016/j.ejpb.2010.06.009.

Quinten, T., De Beer, T., Almeida, A., Vlassenbroeck, J., Van Hoorebeke, L., Remon, J.P., Vervaet, C., 2011. Development and evaluation of injection-molded sustained-release tablets containing ethylcellulose and polyethylene oxide. Drug Dev. Ind. Pharm. 37, 149–159.

Reeves L.A., Feather D.H., Nelson D.H., Whiteman M., 2001. Electrostatic application of powder material to solid dosage forms. WO Patent 2001043727 A1. 21 June.

Riedel, A., Leopold, C.S., 2005. Degradation of omeprazole induced by enteric polymer solutions and aqueous dispersions: HPLC investigations. Drug Dev. Ind. Pharm. 31, 151–160.

Rosato, D.V., Rosato, M.G., 2000. Injection Molding Handbook, 3rd ed. Springer, New York.

Sammoura, F., Kang, J., Heo, Y.-M., Jung, T., Lin, L., 2007. Polymeric microneedle fabrication using a microinjection molding technique. Microsyst. Technol. 13, 517–522.

Sinka, I.C., Burch, S.F., Tweed, J.H., Cunningham, J.C., 2004. Measurement of density variations in tablets using X-ray computed tomography. Int. J. Pharm. 271, 215–224.

Surace, R., Trotta, G., Bellantone, V., Fassi, I., 2012. The micro injection moulding process for polymeric components manufacturing. In: Volosencu, C. (Ed.), New Technologies - Trends, Innovations and Research. InTech, pp. 65–90.

Teng, P.-T., Chern, M.-J., Shen, Y.-K., Chiang, Y.-C., 2013. Development of novel porous nasal scaffold using injection molding. Polym. Eng. Sci. 53, 762–769.

Tokudome, Y., Ohshima, H., Otsuka, M., 2009. Non-invasive and rapid analysis for observation of internal structure of press-coated tablet using X-ray computed tomography. Drug Dev. Ind. Pharm. 35, 678–682.

Wang, J.Z.Y., Bogner, R.H., 1995. Solvent-free film coating using a novel photocurable polymer. Int. J. Pharm. 119, 81–89.

Wu, C.-Y., Hancock, B.C., Mills, A., Bentham, A.C., Best, S.M., Elliott, J.A., 2008. Numerical and experimental investigation of capping mechanisms during pharmaceutical tablet compaction. Powder Technol. 181, 121–129.

Yang, D.B., 1993. Direct kinetic measurements of vinyl polymerization on metal and silicon surfaces using realtime FT-IR spectroscopy. Appl. Spectrosc. 47, 1425–1429.

Zeitler, J.A., Gladden, L.F., 2009. In-vitro tomography and non-destructive imaging at depth of pharmaceutical solid dosage forms. Eur. J. Pharm. Biopharm. 71, 2–22.

Zeitler, J.A., Shen, Y., Baker, C., Taday, P.F., Pepper, M., Rades, T., 2007. Analysis of coating structures and interfaces in solid oral dosage forms by three dimensional terahertz pulsed imaging. J. Pharm. Sci. 96, 330–340.

Zema, L., Loreti, G., Melocchi, A., Maroni, A., Gazzaniga, A., 2012. Injection molding and its application to drug delivery. J. Controlled Release 159, 324–331.

Zhong, S., Shen, Yao-Chun, LouiseHob, K., May, R., AxelZeitler, J., MikeEvans, F., Taday, P., Pepper, Michael, Thomas Rades, C., Gordon, K., Müller, Ronny, Kleinebudde, Peter, 2011. Non-destructive quantification of pharmaceutical tablet coatings using terahertz pulsed imaging and optical coherence tomography. Optics Lasers Eng. 49, 361–365.

Zhou, D., Zhang, G.G.Z., Law, D., Grant, D.J.W., Schmitt, E.A., 2008. Thermodynamics, molecular mobility and crystallization kinetics of amorphous griseofulvin. Mol. Pharm. 5, 927–936.