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Evaluation of Different Opadry® Film Coating Systems on Tablets Containing Amorphous Solid Dispersion of Itraconazole

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Introduction

Formation of amorphous solid dispersions (ASD) has been demonstrated to be effective in enhancing solubility of poorly soluble drugs. In our previous study, ASD form of itraconazole was successfully formulated into a robust tablet dosage form. It provided lower porosity and assumed lower risk of interaction with moisture. In addition to the aesthetic and functional benefits of film coatings, when applied to tablets containing ASD, this adds a moisture barrier to further stabilize the core formulation. As ASD is a thermodynamically unstable system, an amorphous form of the drug may recrystallize during processing and storage of the product. The resulting recrystallization affects drug solubility, dissolution and potentially chemical stability of the drug. The purpose of this study was to evaluate the effect of different aqueous Opadry® film coating systems on tablets containing ASD of itraconazole.

Methods

ASD of itraconazole (ITR) and hypromellose acetate succinate medium substitution (HPMCAS 912G) were prepared by hot-melt extrusion (HME) using a twin-screw extruder, in 1:3 ratio of drug: polymer. The feeding rate, screw speed and target processing temperature were set at 3-7 g/min, 100 rpm and 170°C respectively. The extrudates were then air-cooled, pelletized and milled (ZM 200, Retsch) into powder using a two-pass method (500 µm and 350 µm screen) at 18000 rpm. Milled extrudates (50% w/w) were mixed with StarTab® directly compressible starch (49.5% w/w), lubricated with magnesium stearate (0.5% w/w) and compressed on a rotary tablet press (Piccola 4×4 B/D) using 12.7 mm standard round concave tooling at 35 kN compression force and 37 rpm turret speed.

Four different aqueous Opadry® film coating systems (shown in Table 1) were applied at 4% w/w weight gain to the tablets, using a perforated coating pan (O'Hara Labcoat II) according to process parameters listed in Table 1. The tablets were cooled to room temperature in the pan before unloading, and then stored in double plastic bags with a desiccant. Tablets were then packed in 75 cc HDPE bottles (closed with screw cap and induction seal, with or without desiccants). Both uncoated and coated tablets were placed on accelerated storage condition at 40°C / 75% RH for up to six months.

The tablets at different stability time points (0, 1, 3, 6 month) were characterized for appearance, dimensions, hardness, disintegration time, moisture content and drug assay. Dissolution tests were performed in 1000 ml phosphate buffer pH 6.8 at 37°C using USP Paddle apparatus (Agilent) at 75 rpm. Tablet samples were collected using an autosampler and analyzed spectrophotometrically at 257 nm. Tablets at the start and end of stability study (0 and 6 month) were also characterized and compared using XRD, SEM, DSC, and FTIR to determine whether any evidence of crystallization occurred in the tablet formulations during the accelerated stability study.

Table 1. Coating Parameters Used for the Opadry Film Coating Systems

Coating System	Opadry amb II	Opadry II 85F	Opadry QX	Opadry HPMC-based
Solid Content (% w/w)	20	20	25	15
Pan Speed (rpm)	18-19	18-19	18-19	18-19
Air Volume (CFM)	160	160	160	160
Atomizing Air Pressure (psi)	15	15	15	15
Pattern Air Pressure (psi)	15	15	15	15
Spray Rate (g/min)	7-8	10-15	10-15	10-15
Inlet Temperature (°C)	57-63	53-63	54-58	56-59
Exhaust Temperature (°C)	41-47	43-47	37-44	44-47
Product Temperature (°C)	45-51	42-46	42-46	42-55

Results

Coating of ITR ASD Tablets

Four different aqueous Opadry film coating systems (Opadry amb II, Opadry II 85F, Opadry QX, and Opadry (HPMC based) were successfully applied to ITR ASD tablets (Figure 1). The coated tablets all showed good coating appearance and were free of any film defects. All coated tablets showed higher hardness compared to uncoated tablets (Table 2). The disintegration time (DT) of coated tablets were also more than the DT of uncoated tablets. There was no difference with Loss on Drying (LOD) of coated and uncoated tablets (Table 2), indicating the coating process did not introduce extra moisture to the core tablets.

Figure 1: Film Coated ITR-ASD Tablets using Different Opadry Systems at 6M and DE* Value

	Opadry amb II (4% WG)	Opadry II 85F (4% WG)	Opadry QX (4% WG)	Opadry (HPMC Based) (4% WG)
6M, 40°C/75% RH				
DE* (Compared to Initial)	0.23	0.58	1.14	2.24

Key: DE value < 3 indicates no visible change in color

Table 2: Accelerated Stability Data of Coated ITR ASD Tablets

Physical Properties	Time	A (Opadry amb II)	B (Opadry II 85F)	C (Opadry QX)	D (Opadry HPMC based)	E (Uncoated)
Loss on Drying (%)	0M	7.32 ± 0.08	7.13 ± 0.20	7.18 ± 0.22	7.25 ± 0.09	7.23 ± 0.09
	1M	7.96 ± 0.32	7.62 ± 0.29	7.63 ± 0.11	7.81 ± 0.28	7.51 ± 0.28
	3M	8.08 ± 0.28	7.88 ± 0.36	7.73 ± 0.18	7.71 ± 0.13	7.69 ± 0.01
	6M	8.10 ± 0.27	7.76 ± 0.35	7.80 ± 0.07	7.80 ± 0.07	8.06 ± 0.05
Assay (%)	0M	97.45 ± 1.03	98.54 ± 0.17	98.92 ± 3.11	100.98 ± 0.46	101.27 ± 0.97
	1M	98.24 ± 0.87	99.54 ± 0.61	98.67 ± 0.82	98.10 ± 2.40	102.18 ± 0.36
	3M	98.98 ± 0.46	98.12 ± 1.69	97.15 ± 0.16	100.54 ± 0.23	103.20 ± 0.08
	6M	98.33 ± 0.53	99.18 ± 0.94	99.59 ± 0.40	99.78 ± 1.34	101.92 ± 1.68
Disintegration time (seconds)	0M	84.33 ± 8.38	99.00 ± 14.23	74.17 ± 6.59	185.67 ± 21.53	48.00 ± 6.87
	1M	78.83 ± 8.06	97.00 ± 9.06	78.00 ± 7.62	170.00 ± 27.02	46.00 ± 3.23
	3M	76.33 ± 10.67	103.00 ± 8.85	82.83 ± 7.39	171.33 ± 30.99	48.67 ± 8.89
	6M	82.17 ± 6.27	108.83 ± 19.05	84.33 ± 5.72	168.33 ± 7.97	54.17 ± 11.58

Key: Appearance, weight and hardness testing passed

Stability Study

The color and appearance of all tablets were consistent after 6 months at 40°C/75% RH storage conditions (Figure 1). Drug release profiles at initial time point and 6-month time point showed similar release profiles for uncoated and coated tablets, irrespective of the coating system used in the study (Figure 2). Tablets stored at 40°C/75% RH in HDPE bottles without desiccant were analysed up to 6-month stability. All samples were found to be stable in accelerated storage condition. Similarity factor (f^2) values of all uncoated and coated tablets were higher than 50, which indicated all tablets were stable during the 6-month accelerated stability study (Table 3). To determine whether recrystallization of ITR occurred during the stability study, DSC, FTIR, SEM and XRD of crushed tablets at 6-month were performed. DSC, SEM, FTIR and XRD data did not show any presence of recrystallization in crushed samples of all formulations. Further, the whole (intact tablets) were evaluated for XRD. The coated tablets were either analyzed with intact coating or the coating were peeled off manually so the exposed tablet core could be evaluated. As shown in Figure 3, the peak at 2theta = 17.5° (characteristic fingerprint for ITR crystals) was observed on uncoated tablets on 6-month storage at 40°C/75% RH. However, this peak was not observed on the coated tablets (intact) or peeled tablet surface after 6 months storage. This data suggested some ITR on the surface of uncoated tablets did crystallize. However, the ASD form of ITR inside tablet formulation or on surfaces under the coating layers was not recrystallized.

Figure 2. Drug Release Profiles of Uncoated and Coated Tablets at Initial Time and 6 Months

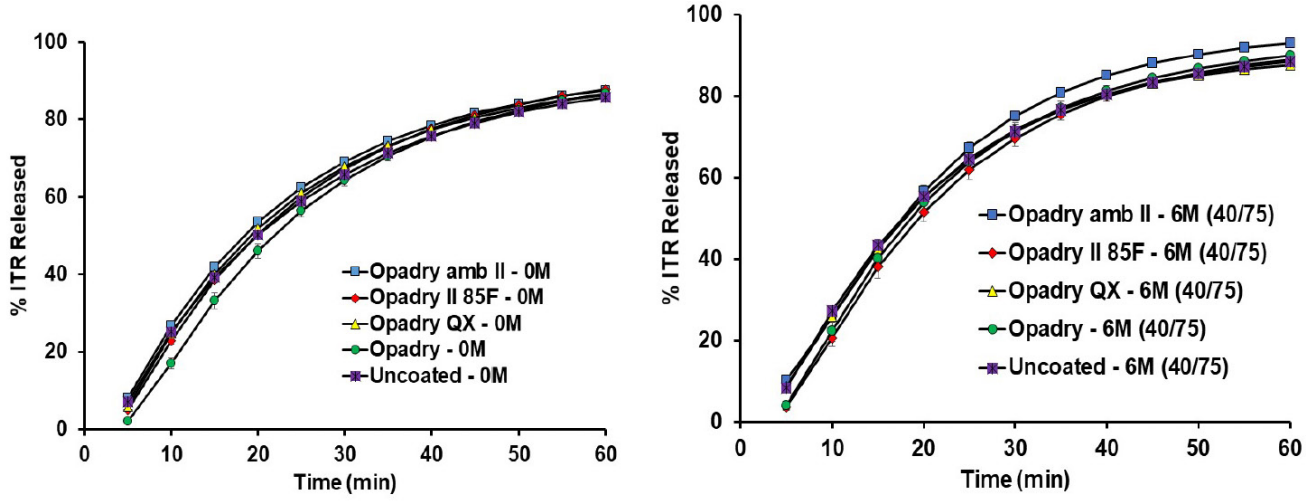
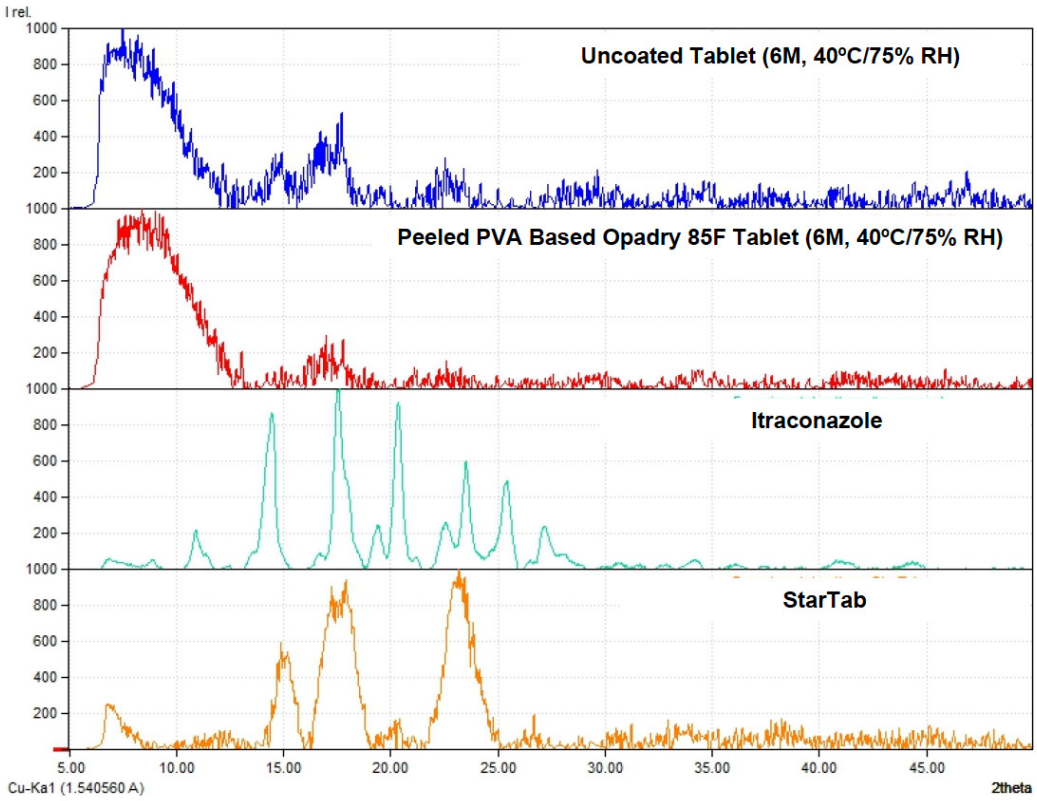


Table 3. Similarity Factor (f^2) Values at 40°C/75% RH)

	Formulation	0M	1M	3M	6M
A	Opadry amb II	Ref.	88.8	63.5	64.6
B	Opadry II 85F	Ref.	81.4	65.1	82.6
C	Opadry QX	Ref.	81.2	66.4	76.1
D	Opadry (HPMC Based)	Ref.	82.0	56.7	61.6
E	Uncoated	Ref.	96.2	57.8	68.1

Figure 3. XRD of Peeled Opadry 85F Coated Tablet and Uncoated Tablet



Conclusions

Four different Opadry coating systems were successfully applied to ITR ASD tablets at standard processing conditions. Dissolution data demonstrated all uncoated tablets were stable during 6-month accelerated stability study. Characterization techniques such as DSC, FTIR, SEM and XRD of crushed tablets at 6-month stability time point did not show presence of crystallinity of ITR, indicating that the amorphous dispersion of the drug was stable. The XRD of tablet surfaces indicated small recrystallization of ITR on the surface of uncoated tablets. The application of various Opadry film coating systems avoided recrystallization of ITR, which provided a significant benefit in improving the stability of ASD tablets.

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