Tablet Formulation Development of Amorphous Solid Dispersions with StarTab® Directly Compressible Starch as Filler

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Introduction

Hot melt extrusion (HME) has been demonstrated as an effective technology to enhance the solubility of poorly soluble drugs by formation of amorphous solid dispersions (ASD). Poorly soluble drugs such as itraconazole (ITR) may be hot melt extruded with polymers such as hypromellose acetate succinate (HPMCAS) to improve solubility as well as provide crystal inhibition property of polymer.[1] In order to develop a commercial dosage form, it is necessary to convert ASD into a final dosage form, such as tablets or capsules. Tablets are the most preferred dosage form by patients and offer benefits such as size, and very low porosity resulting in better moisture stability. Film coating tablets can further enhance stability during shelf-life of the product. ASD prepared by hot melt extrusion is extremely dense and after milling they may have good powder flow, which is important for tableting operation; however, the high density may affect their compression properties. The purpose of this work was to characterize a tablet formulation for ITR ASD, maintaining the enhanced solubility of ITR after compression.

Methods

ASD of itraconazole (ITR) and hypromellose acetyl succinate (HPMCAS 912G, DuPont) were prepared by HME using a twin-screw extruder (Pharma 11, Thermo Fisher Scientific), 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 one pass method (500 µm screen) or two-pass method (500 µm and 350 µm screen) at 18000 rpm. All the formulations were evaluated for their apparent solubility and dissolution. Tablets formulations were then developed using ASD milled by two-pass method.

Initial screening for formulation involved use of different fillers and two-pass milled extrudates of ITR – HPMCAS ASD at 50% w/w or 70% w/w loading in the tablet formulations. Tablet weight for 50% w/w and 70% w/w loading were kept at 800 and 571 mg respectively, with the dose of ITR maintained at 100 mg per tablet in all the formulations. Small blends of various formulas (Table 1), were prepared by mixing the ingredients (Table 1) in 60 cc screw-capped bottles for 10 minutes, and then magnesium stearate (passed through 60# mesh screen) added and blended for a further minute. The formulation blends were evaluated for density and moisture properties before being compressed at ~5000 psi (MTCM-1, GlobePharma). With dwell time maintained at 5 sec. 12.7 mm and 10 mm round, flat-faced tooling was utilized for 50% w/w and 70% w/w ASD loading formulations, respectively. The process flow of the formulations is shown in Figure 1. Tablet mechanical property and disintegration time (DT) in distilled water at 37ºC, were characterized. Dissolution tests were performed in 1000 ml phosphate buffer pH 6.8 at 37ºC using USP Paddle apparatus (Agilent) at 75 rpm. The samples were collected using autosampler and analyzed spectrophotometrically at 257 nm.

Two formulations, selected from preliminary work, were compressed on a Piccola rotary tablet press (Riva GB Ltd) using one set of 0.5” (12.7 mm) standard round concave B-tooling at 37 rpm turret speed, fitted with powder paddle feeder set at medium speed. Compression profiles were generated at compression force of 10-35 kN. Tablets were evaluated for physico-chemical properties, including disintegration and dissolution as described above. Tablets compressed at 35 kN compression force were put on accelerated stability at 40ºC / 75% RH for one month in HDPE bottles (open or closed with screw cap and induction seal). Tablets were analyzed for assay, physical properties and dissolution.

Figure 1: Process Flow for ITR-ASD Tableting

Table 1. Composition of ITR-ASD Tablet Formulations

Formula	A-50^	A-70#	B-50^	B-70#	C-50^	C-70#	D-50^	D-70^
Ingredients	**% w/w**							
Milled ITR-HPMCAS ASD *	50.00	70.00	50.00	70.00	50.00	70.00	50.00	70.00
Avicel PH 102 (MCC, DuPont)	24.88	14.88	23.88	13.88	33.17	19.83	-	-
StarTab® (Colorcon)	24.87	14.87	-	-	-	-	49.75	29.75
Fast Flo 316 (spray dried lactose, Foremost)	-	-	23.87	13.87	-	-	-	-
Starch 1500® (Colorcon)	-	-	-	-	16.58	9.92	-	-
Kollidon CL (crospovidone, BASF)	-	-	2.00	2.00	-	-	-	-
Magnesium Stearate	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

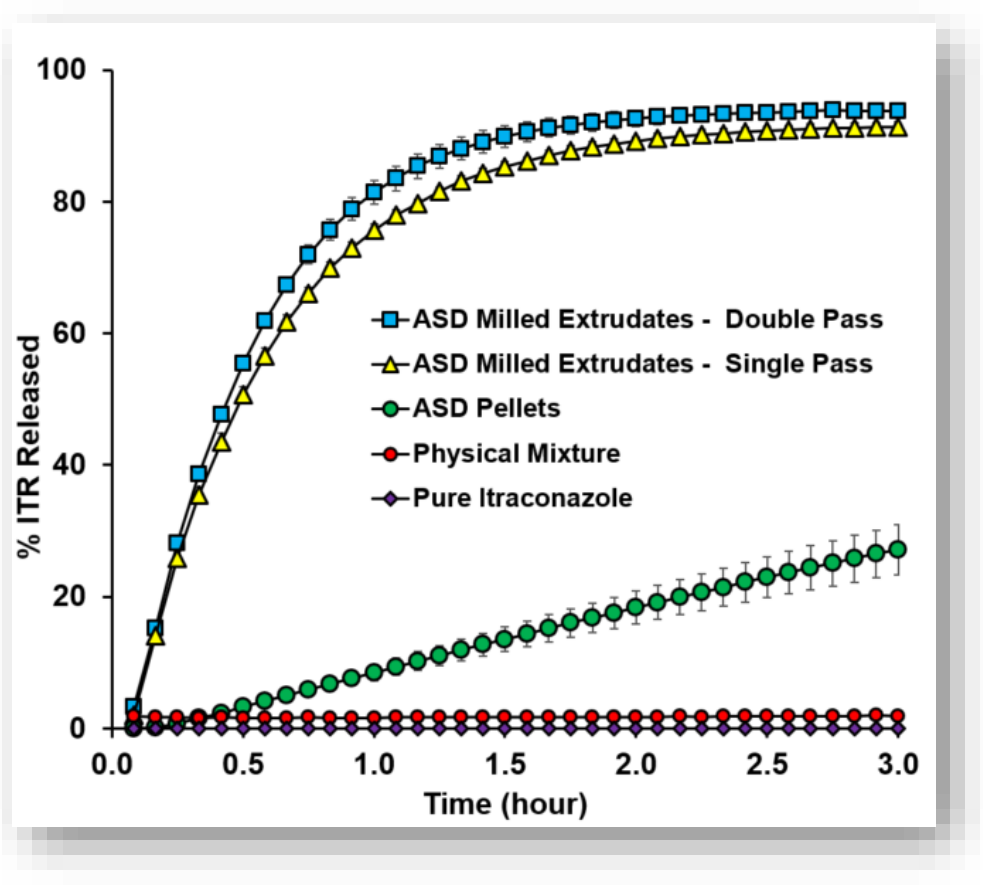
**400 mg of ITR-ASD was equivalent to 100mg of ITR; ^Final tablet weight was 800mg; #Final tablet weight was 571mg*

Results

Solubility Enhancement of ITR

ITR–HPMCAS amorphous solid dispersions prepared by hot melt extrusion showed significantly improved apparent solubility and dissolution rate of the drug, compared to its crystalline form or physical mixture of drug and HPMCAS (Figure 2). Dissolution rate of hot melt extrudate pellets was slow due to the large particle size of the pellets and low surface area. However, when the extrudates were milled, their dissolution rate significantly improved due to lower particle size and higher surface area. Extrudates milled using double-pass method gave mean particle size (d50) of 113 µm and higher drug dissolution rate at the end of 1 hour compared to extrudates milled using single-pass method, with mean particle size (d50) of 151 µm (Figure 2).

Figure 2. Effects of Milling on Dissolution of ITR from ASD



Tablet Formulation Screening

ITR-HPMCAS extrudates, milled using two-pass method, were selected for tablet formulation screening. Formulations containing StarTab or Starch 1500 did not require addition of superdisintegrant, since these excipients provide good disintegrant property. Powder blend and tablet properties of all formulation are shown in Table 2; all showed good powder flow. Formulations containing StarTab exhibited lower water activity compared to other blends. The low water activity indicates tightly bound moisture which is unavailable to react with other ingredients or cause re-crystallization of amorphous drugs, despite their high loss on drying. Tablets containing StarTab were also harder compared to other formulations. Formulations with 50% w/w ASD loading, were found to be optimal for further rotary press tableting based on mechanical strength.

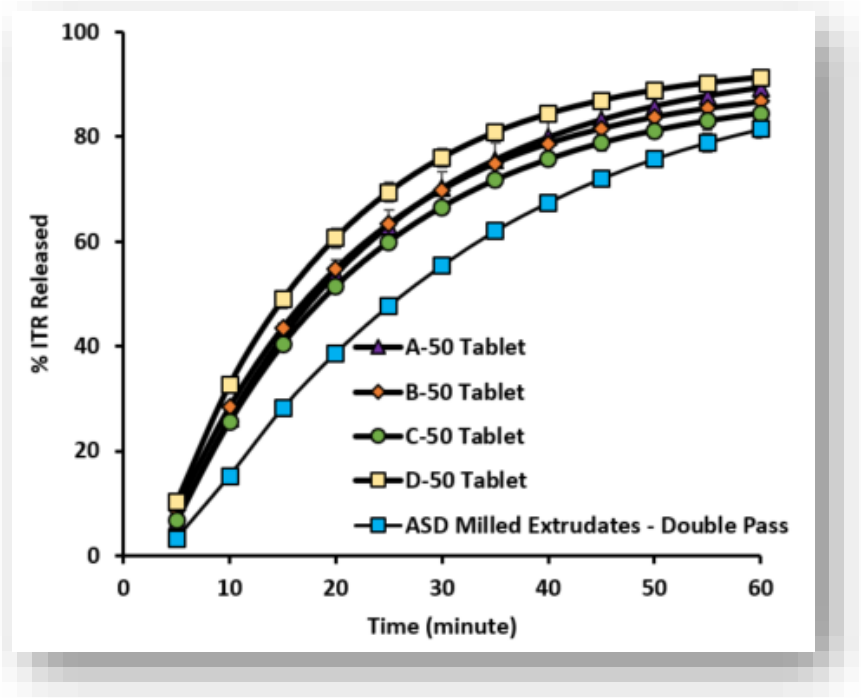
Table 2. Powder Blend and Tablet Properties

Formula	A-50	A-70	B-50	B-70	C-50	C-70	D-50	D-70
Powder Blend Property								
Bulk Density (g/mL)	0.53	0.56	0.47	0.49	0.48	0.53	0.60	0.58
Tap Density (g/mL)	0.66	0.67	0.64	0.67	0.62	0.68	0.70	0.71
True Density (g/mL)	1.39	1.35	1.40	1.35	1.40	1.35	1.39	1.35
Compressibility Index (%)	19.40	16.18	26.98	26.98	22.58	22.39	14.75	18.75
Hausner Ratio	1.25	1.20	1.36	1.37	1.29	1.28	1.17	1.22
LOD (%)	5.98	4.62	4.46	3.54	5.28	4.08	8.17	6.40
Water Activity (aw)	0.41	ND	0.43	ND	0.43	ND	0.41	ND
DVS at 25ºC/60% RH (%)	5.72	ND	3.15	ND	6.23	ND	7.92	ND
DVS at 25ºC/75% RH (%)	7.57	ND	4.40	ND	8.32	ND	10.02	ND
DVS at 25ºC/90% RH (%)	10.45	ND	6.42	ND	11.58	ND	13.24	ND
Tablet Property								
Tablet Weight (mg)	796.15	562.50	792.70	569.60	801.95	569.90	802.90	572.30
Hardness (kP)	32.70	18.60	17.90	9.40	16.00	9.10	20.70	15.70
Tensile Strength (mPa)	3.12	1.88	1.68	0.94	1.48	0.92	1.93	1.61
Disintegration Time (sec)	28.50	30.50	27.00	33.00	42.00	35.00	27.50	25.00
Dissolution at 1h (%)	89.34	88.39	86.72	85.86	84.47	83.86	91.27	90.45
Apparent Solubility at 3h (µg/mL)	94.08	91.11	89.14	88.60	89.19	88.51	93.76	93.83

ND = Not Determined

All tablets and milled extrudates exhibited more than 80% drug release in the first hour (Table 2, Figure 3). This can be attributed to the amorphous nature of ITR and decreased particle size. Drug release from all tablet formulations was faster than milled extrudates in first hour, due to better dispersion and wetting of the formulations. Similar dissolution profiles for the blends and tablets were obtained (data not shown). Drug release from 50% w/w ASD was faster than with 70% w/w ASD loading (Table 2).

Figure 3. Itraconazole Release Profiles from ASD Tablet Formulations



Rotary Tablet Compression

Based on the data from screening study, formulation D-50, which contained StarTab and ASD drug loading of 50% w/w, was selected for generating compression profiles on rotary tablet press. The compression profile data is summarized in Table 3. StarTab gave good tablet properties and dissolution (Figure 4). Tablets were also subjected to accelerated stability testing for 1M at 40ºC/75% RH in HDPE bottles (open or closed condition). Tablets stored in closed HDPE were found to be stable with respect to tablet hardness, dissolution (Table 4) and no detection of crystalline peak in the XRD (data not shown).

Table 3. Compression Data of ITR-HPMCAS ASD Tablet Formulation Containing StarTab, Compressed on Rotary Tablet Press

Tablet Properties	10kN	15 kN	20 kN	25 kN	30 kN	35 kN
Weight (mg)	806.10	809.30	810.10	810.30	810.30	812.00
Tensile Strength (mPa)	0.18	0.58	0.91	1.14	1.29	1.55
Hardness (kP)	2.50	7.10	10.60	13.00	14.60	17.30
Thickness (mm)	7.45	6.89	6.69	6.62	6.56	6.49
Disintegration Time (sec)	14.50	16.50	19.00	21.00	25.00	29.00
Friability (%)	> 1*	0.02	0	0	0	0
Ejection Force (N)	144.73	131.57	111.64	98.44	90.37	90.17

** Failed Friability*

Figure 4. Itraconazole Release from ITR-HPMCAS ASD Tablet Formulation Containing StarTab, Compressed on Rotary Tablet Press at Different Compression Force

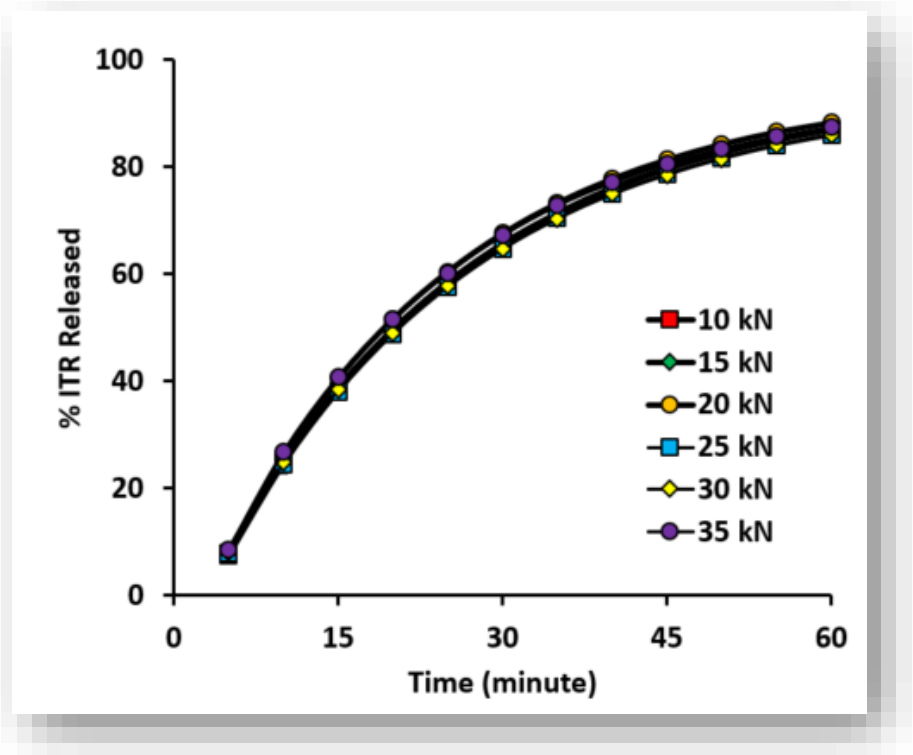


Table 4. Accelerated Stability Data for ITR-HPMCAS ASD Tablet Formulation Containing StarTab, Compressed at 35 kN Compression Force

Physical Properties	Initial	Open HDPE Bottle 40ºC/75%RH, 1M	Closed HDPE Bottle 40ºC/75%RH, 1M
Weight (mg)	812.00	840.97	815.27
Hardness (kp)	17.25	15.83	17.07
Tensile Strength (mPa)	1.55	1.30	1.48
Disintegration time in water (sec)	29.00	47.00	27.00
Assay (%)	101.28	99.55	101.00
Dissolution @ 1h (%)	87.40	84.13	88.59
f1 (similarity factor) ^	reference	16.1	3.7
f2 (dissimilarity factor) ^	reference	49.0	80.4
Apparent solubility @ 3h (µg/mL)	93.26	92.48	94.08

^Guidance for industry: Dissolution testing of immediate release solid oral dosage forms, FDA, CDER, 1997

Conclusions

A successful tablet formulation of ITR-HPMCAS amorphous solid dispersions was prepared using StarTab as a directly compressible excipient, while maintaining enhanced solubility of ITR. On evaluation of formulations containing 70% or 50% w/w amorphous drug loading, the formulations with 50% w/w ASD showed faster dissolution profiles. Formulations with StarTab, directly compressible starch, provided excellent flow and robust properties, i.e. weight uniformity, tensile strength, rapid disintegration time and excellent dissolution performance.

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