Immediate Release Film Coating of an Acetaminophen Extended Release Matrix Tablet Containing a High Concentration of Polyethylene Oxide Water Soluble Resin

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PURPOSE

The purpose of this study was to investigate the feasibility of film coating (Opadry® II) on the physical appearance and drug release for a 40 mg acetaminophen (APAP, model drug) hydrophilic matrix tablet containing a high concentration of a low melting point polyethylene oxide resin (POLYOX™ WSR1105). The effect of accelerated stability on drug release was also investigated.

METHODS

Acetaminophen (APAP, used as model drug) 40 mg dose, extended release (ER) tablets (10 mm, 400mg, standard concave) were prepared by direct compression method using an instrumented Piccola 10 station rotary press at a compression force of 15kN.

All powders, except magnesium stearate, were passed through ASTM #16 mesh (1180 µm) and blended in a 16-quart V-blender (GlobePharma, USA) for 10 minutes. Magnesium stearate was then screened through ASTM #40 mesh (400 µm) and added to the powder mixture followed by blending for additional 2 minutes.

Table 1. Acetaminophen POLYOX ER Matrix Formulation

Material	% w/w	mg/tablet
POLYOX (WSR 1105 LEO NF) (International Flavors and Fragrances Inc., USA)	80	320
APAP (Covidien Mallinckrodt)	10	40
MCC (Microcel 102) (Blanver, Brazil)	8.95	35.8
Fumed silica (Aerosil 200, Evonik Industries, Germany)	0.5	2
Magnesium Stearate (Parchem,USA)	0.5	2
BHT (Parchem,USA)	0.05	0.2

POLYOX ER matrix tablets were coated to 4% theoretical weight gain (WG) in a 24” side-vented pan (Labcoat II, O’Hara, Canada) using 1.2 mm spraying gun (Schlick, Germany) with plough baffles and 6.5” spray gun to bed distance.

Two sets of conditions were used for HPMC (hypromellose) based Opadry II, with bed temperature at 40/42°C and 40/50°C +/- 1 for PVA-based Opadry II. Process time was about 90 min for HPMC-based coating and 60 min for PVA-based coating.

The coating dispersion were prepared and continuously mixed throughout the coating process using a propeller mixer.

Coating process parameters are listed in Table 2.

Table 2. Coating Process Parameters

Coating system	HPMC-based Opadry II		PVA-based Opadry II	
	Run #1	Run#2	Run#3	Run#4
Batch size (kg)	15	15	14	14
Pan speed (rpm)	11-12	12	12	12
Inlet air temperature (°C)	52.3 – 57.8	47.9 - 51	61.1 –	48.7 – 53.1
Exhaust air temperature	42.1 – 44.3	40.3 – 40.9	49.5 –	41 – 42.5
Product temperature (°C)	41 - 43	39 -40	49 - 50	40 – 41
Airflow (cfm)	275	275	275	275
Atomization air pressure	25	25	25	25
Fan air pressure (psi)	30	30	30	30
Spray rate (g/min)	44.4	44.3	42.6	44.8
Process duration (min)	90	90	66	63
Solids content (%)	15	15	20	20

Compact mechanical strength was determined before and after the coating process. Breaking force values were obtained using a hardness tester (Erweka TBH300). Friability was determined using a friabilator (Electrolab EF-2); at 25 rpm and 4 minutes running test time.

Coated tablets were packaged in high-density polyethylene (HDPE) bottles containing cotton, desiccant and heat- sealed. Bottles were stored at 40°C/75% RH for 6 months. Samples were pulled at predetermined intervals and subjected to dissolution testing.

In vitro drug release was determined in a USP compliant bath using Apparatus II (paddles, with sinkers) operated at 100 rpm. The dissolution medium was purified water (1000 mL) at 37.0± 0.5°C.

The dissolution results generated were compared using the f^2 factor.[1, 2]

RESULTS

Despite the heat generated during 5 hours of compression cycle, no sticking was observed on the tablet punches. The inclusion of MCC may assist compression to reduce friction due to the low compaction pressures necessary to create compacts. Tablet weight uniformity (Table 3) was consistent with a relative standard deviation of less than 1%. Tablet hardness (Table 4) increased from 24.6 Kp for the uncoated tablets to 29.6 and 30.5 Kp for the HPMC and PVA based coated tablets, respectively.

Table 3. Physical Properties of Uncoated POLYOX ER Matrix Tablets, at Initial Time Point

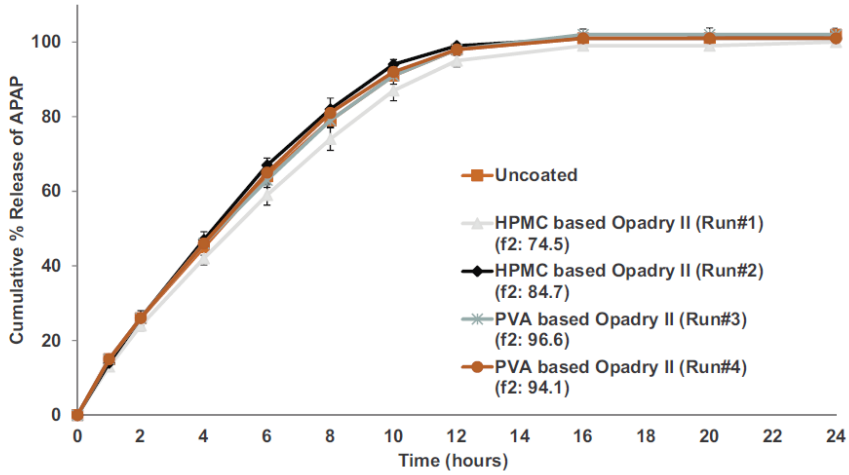
Tablet Compression Force 15 kN	0 min	60 min	120 min	180 min	240 min	298 min
Average weight (mg)	398.3	399.7	403.1	402.15	401.45	397.4
Weight RSD	0.96	0.92	0.50	0.65	0.81	1.00
Average thickness (mm)	5.74	5.76	5.78	5.74	5.73	5.59
Thickness RSD	0.53	0.56	0.33	0.47	0.44	0.63
Average hardness (Kp)	24.1	23.7	26.2	26.4	24.0	23.05
Hardness RSD	5.32	7.9	3.08	6.93	6.29	8.02

Table 4. Physical Properties of Film Coated APAP ER Matrix Tablets, at Initial Time Point

Product	Coating WG %	Bed temp.	Appearance	LOD (%)	Hardness (kp)	Tablet Thickness	Friability* (%)
Uncoated tablet	na	na	White, no defects	na	24.6	5.73	0.05
Run 1 – HPMC	3.56	41-43	No film coating defects, good appearance	0.94	29.6	5.95	0.00
Run 2 – HPMC	3.59	39-40		0.96	26.2	5.94	0.00
Run 3 – PVA	3.78	49-50		0.73	30.5	6.07	0.00
Run 4 – PVA	3.87	40-41		1.06	28	5.95	0.00

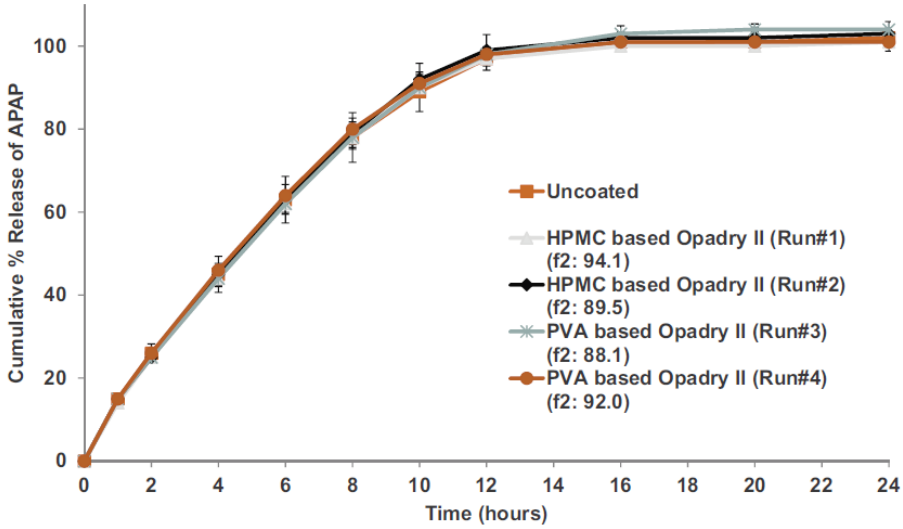
Figure 1, 2 and 3 show APAP release profiles at time zero; 3 mth and 6 mth (40°C/75% RH) accelerated stability condition for HPMC and PVA coated hydrophilic matrices. Similarity factors (f_2) were all greater than 70, indicating no significant change in dissolution performance with film coating formulation and time.

Figure 1. APAP Release Profiles from PEO Tablets - initial: (Dissolution Method: USP Apparatus II, at 100 rpm with Sinkers and in 1000 mL of Deionized Water at 37 ± 0.5°C)



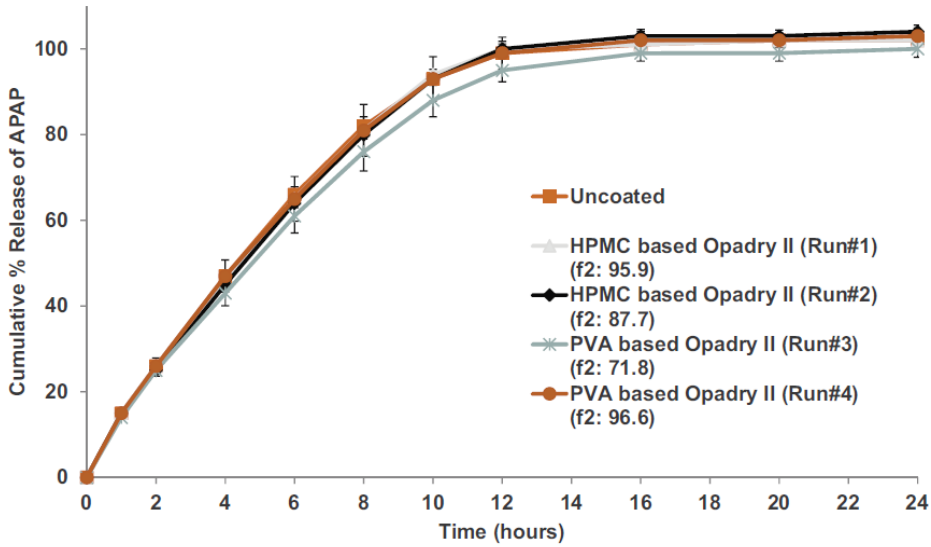
Opadry II film coating system had no impact on drug release profiles. Good similarity factor (f_2 > 50) was obtained for all coating process.

Figure 2. APAP Release Profiles from PEO Tablets - 3 months: (Dissolution Method: USP Apparatus II, at 100 rpm with Sinkers and in 1000 mL of Deionized Water at 37 ± 0.5°C)



Opadry II film coating system had no impact on drug release profiles at 3 months. Good similarity factor (f_2 > 50) was obtained for all coating process.

Figure 3. APAP Release Profiles from PEO Tablets - 6 months: (Dissolution Method: USP Apparatus II, at 100 rpm with Sinkers and in 1000 mL of Deionized Water at 37 ± 0.5°C)



Opadry II film coating system had no impact on drug release profiles at 6 months. Good similarity factor ($f_2 > 50$) was obtained for all coating process.

CONCLUSIONS

High POLYOX content based APAP (40 mg, model drug) extended release matrices were successfully manufactured without picking or sticking issues during long tableting run.

Drug release as well as aesthetics of the APAP matrices was not affected after application of aqueous film coating. Both coating systems, PVA-based and HPMC-based Opadry II resulted in good film coated tablets without any defects, and with minimal change in drug release profiles when coated at extremes of product bed temperatures, as recommended for these systems. All the coated formulae showed excellent stability after 6 mth storage at 40°C/75 % RH in HDPE containers.

REFERENCES

1. Moore J.W, & Flanner H.H., Mathematical comparison of dissolution profile, Pharm.Tech. 1996;20: 64-74
2. FDA, Federal Register. 1995;60: 61642

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