Stability of Six Model Drug Products Coated with PVA-Based Opadry® II

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Purpose

Consistent drug release during prolonged storage is an essential requirement for a robust drug product. Film coatings are often applied to improve aesthetics and/or enhance stability, therefore, the film coating should not introduce any incompatibilities or affect drug release significantly. The purpose of this study was to investigate the influence of PVA-based Opadry® II high performance film coating systems on stability and release of immediate release formulations containing six model drugs, after storage at accelerated conditions.

Methods

Six model actives having varying solubility (freely to practically insoluble) were chosen for the study. Tablet formulations were developed for each active that provided suitable tablet properties for film coating (**Table 1**).

Table 1. Model Actives Solubility and Uncoated Tablet Properties

Active	Dosage strength (mg)	Solubility (mg/mL)	Total Tablet Weight (n=20) (mg) (%RSD)	Breaking Force (n=20) (kp) / (MPa)	Friability (%)	Disintegration Time (min.) in 37°C H_2O (min – max)
Montelukast Sodium	10	100	200.6 (0.74)	8.1 / 1.99	0.14	1.8 - 3.0
Lamivudine	150	70	293.5 (0.55)	8.8 / 1.64	0.03	0.25 - 0.58
Donepezil Hydrochloride (HCl)	10	33	282.9 (0.85)	12.1 / 1.12	0.00	2.0 - 3.0
Tolterodine Tartrate	2	12	81.5 (0.89)	6.0 / 2.5	0.00	1.35 - 2.4
Quetiapine Fumarate	100	3.29	258.3 (1.28)	8.5 / 1.94	0.04	3.6 - 3.9
Aripiprazole	10	<0.1	96.3 (1.82)	6.3 / 2.87	0.02	1.1 - 2.1

The uncoated tablet formulations and manufacturing methods are listed in **Tables 2-7**.

Table 2. Montelukast Sodium - Direct Compression Formulation

Ingredients (Manufacturer)	Formula	
	Percentage	mg / Tablet
Montelukast Sodium (Sun Pharma Industries Limited)	5.20	10.40*
Lactose, Monohydrate NF (316 Fast Flo, Foremost Farms)	61.20	122.40
Co-processed Mixture of Corn Starch/Pregelatinized Starch (StarCap 1500®, Colorcon)	30.60	61.20
Croscarmellose Sodium (Solutab Type A, Blanver)	2.00	4.00
Colloidal Silicon Dioxide NF (Cab-O-Sil M-5P, Cabot)	0.25	0.50
Magnesium Stearate NF (Hyqual, Mallinckrodt)	0.75	1.50
Total	100.00	200.00
*10.4 mg Montelukast Sodium Salt, which is equivalent to 10 mg of Montelukast Acid		

Table 3. Lamivudine - Direct Compression Formulation

Ingredients (Manufacturer)	Formula	
	Percentage	mg / Tablet
Lamivudine (Analytica Chemie Inc.)	50.85	150.01
Microcrystalline Cellulose NF (Microcel 102, Blanver)	36.86	108.73
Pregelatinized Starch NF (Starch 1500®, Colorcon)	11.79	34.79
Colloidal Silicon Dioxide NF (Cab-O-Sil M-5P, Cabot)	0.25	0.74
Magnesium Stearate (Mallinckrodt)	0.25	0.74
Total	100.00	295.00

Table 4. Donepezil HCl - Direct Compression Formulation

Ingredients (Manufacturer)	Formula	
	Percentage	mg / Tablet
Donepezil Hydrochloride (Vasudha Pharma Chem Limited)	3.58	10.00
Pregelatinized Starch NF (Starch 1500®, Colorcon)	47.96	134.30
Microcrystalline Cellulose NF (Microcel 102, Blanver)	47.96	134.30
Magnesium Stearate NF (Hyqual, Mallinckrodt)	0.25	0.70
Colloidal Silicon Dioxide NF (Cab-O-Sil M-5P, Cabot)	0.25	0.70
Total	100.00	280.00

Methods (cont'd)

Table 5. Tolterodine Tartrate - Direct Compression Formulation

Ingredients (Manufacturer)	Formula	
	Percentage	mg / Tablet
Tolterodine Tartrate (Fleming Laboratories)	2.50	2.00
Pregelatinized Starch NF (Starch 1500®, Colorcon)	48.50	38.80
Microcrystalline Cellulose NF (Microcel 102, Blanver)	48.55	38.84
Magnesium Stearate NF (Hyqual, Mallinckrodt)	0.20	0.16
Colloidal Silicon Dioxide NF (Cab-O-Sil M-5P, Cabot)	0.25	0.20
Total	100.00	80.00

Table 6. Quetiapine Fumarate - Wet Granulation Formulation

Ingredients (Manufacturer)	Formula	
	Percentage	mg / Tablet
Intragranular		
Quetiapine Fumarate USP (Mega Fine Pharma (P) Limited)	46.05	115.12*
Pregelatinized Starch NF (Starch 1500®, Colorcon)	15.00	37.50
Microcrystalline Cellulose NF (Microcel 101, Blanver)	32.70	81.75
Hypromellose USP (METHOCEL™ ESLV, Colorcon)	3.00	7.50
Extragranular		
Colloidal Silicon Dioxide NF (Cab-O-Sil M-5P, Cabot)	0.75	1.87
Magnesium Stearate NF (Hyqual, Mallinckrodt)	2.50	6.25
Total	100.00	250.00
*Equivalent to 100 mg quetiapine base		

Table 7. Aripiprazole - Direct Compression Formulation

Ingredients (Manufacturer)	Formula	
	Percent	mg / Tablet
Aripiprazole USP (Sun Pharma Industries Limited)	10.53	10.00
Pregelatinized Starch NF (Starch 1500®, Colorcon)	29.22	27.76
Microcrystalline Cellulose NF (Microcel 102, Blanver)	60.00	57.00
Colloidal Silicon Dioxide NF (Cab-O-Sil M-5P, Cabot)	0.13	0.13
Magnesium Stearate NF (Hyqual, Mallinckrodt)	0.13	0.13
Total	100.00	95.00

The tablets were coated with pigmented, PVA-based Opadry II formulations applied at 20% solids concentration in a fully-perforated coating pan. The target coating weight gain (WG) was 3.0% for all active tablets, except for the aripiprazole which had a target WG of 4.0%.

The coated tablets were packaged in foil-sealed HDPE bottles and stored at 40°C / 75% RH for 3 and 6 months.

Dissolution testing of the initial uncoated tablets and coated tablets after 3 and 6 months storage was conducted using FDA recommended dissolution methods for each active compound (**Table 8**).

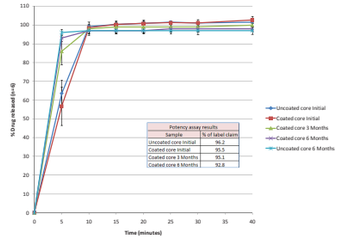
Table 8. FDA Recommended Dissolution Methods[1]

Active	USP Apparatus	Speed (RPM)	Medium	Volume (mL)
Montelukast Sodium	II (paddle)	50	0.5% SDS in water	900
Lamivudine	II (paddle)	50	DI Water	900
Donepezil HCl	II (paddle)	50	0.1N HCl	900
Tolterodine Tartrate	II (paddle)	50	Simulated gastric fluid without enzymes (pH 1.2)	900
Quetiapine Fumarate	II (paddle)	50	DI Water	900
Aripiprazole	II (paddle)	60	pH 1.2 USP Buffer (Hydrochloric Acid)	900

Results

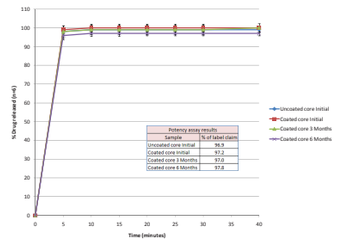
Initial dissolution results between the uncoated and coated active tablets in the study were very similar. All tablets (uncoated or coated) exceeded 80% drug release within the first 10 minutes of testing, irrespective of the active or storage time at 40°C / 75% RH (**Figures 1 – 6**).

Figure 1. Montelukast Sodium - Dissolution and Assay Results (40°C / 75% RH)



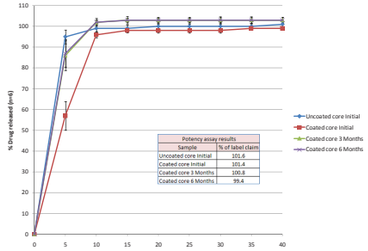
At the 5-minute dissolution time point, the initial uncoated and coated montelukast sodium dissolution profiles were almost identical, but showed slower drug release than the coated tablet samples after 3 and 6 months storage. The uncoated montelukast sodium tablets also showed faster drug release after 6 months storage. The difference in dissolution at the 5-minute time point between the initial and stored samples was consistent between the coated and uncoated tablets indicating no change related to the film coating itself. For all samples, >90% drug release was achieved at the 10-minute dissolution time point.

Figure 2. Lamivudine - Dissolution and Assay Results (40°C / 75% RH)



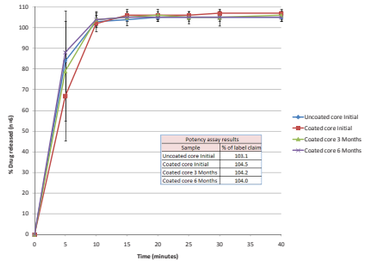
The lamivudine dissolution profiles were consistent between uncoated and coated tablet samples at all time points. The dissolution behavior for this active was consistent with the fast 30 second dis-integration time of the uncoated tablet.

Figure 3. Donepezil - Dissolution and Assay Results (40°C / 75% RH)



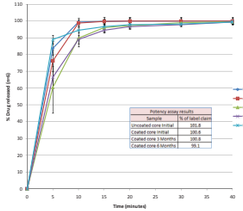
The initial coated donepezil tablets exhibited slower dissolution at the 5-minute time point compared to the uncoated tablets but at 10 minutes, greater than 90% of the drug was released. The dissolution profiles of the coated tablets after 3 and 6 months of storage were comparable to the initial uncoated tablets. For all samples, > 90% drug release was achieved at the 10-minute dissolution time point.

Figure 4. Tolterodine Tartrate - Dissolution and Assay Results (40°C / 75% RH)



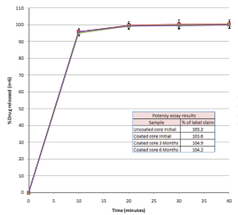
The tolterodine tartrate dissolution profiles were consistent between uncoated and coated tablet samples at all time points. High variation in drug release among the samples at the 5-minute time point was attributed to the 1.4 min. to 2.4 min. disintegration time of the uncoated tablets as well as the sparingly soluble nature of the drug.

Figure 5. Quetiapine Fumarate - Dissolution and Assay Results (40°C / 75% RH)



Some variation was seen between release rates of coated vs. uncoated samples both initially and after storage. The uncoated quetiapine fumarate tablets also exhibited slower drug release after storage than the initial sample. For all samples, > 80% drug release was achieved at the 10-minute dissolution time point.

Figure 6. Aripiprazole - Dissolution and Assay Results (40°C / 75% RH)



The aripiprazole dissolution profiles were consistent between uncoated and coated tablet samples at all time points. For all samples, > 90% drug release was achieved at the 10-minute dissolution time point.

For all actives in this study, the drug assay results were within specification at all time points. After 6 months storage, the coated tablets were also free of any visible defects such as odor, sticking or blocking.

Conclusions

The PVA-based Opadry II film coating formulations used in this study had no impact on drug release vs. the uncoated tablets. The Opadry II coatings provided protection at elevated temperature and humidity conditions and maintained the desired drug assay and drug release characteristics. This stability performance was demonstrated on a range of actives with varying solubility and chemical properties.

REFERENCES

1. US Department of Health and Human Services. FDA US Food and Drug Administration. Dissolution Methods Web site. http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Accessed January 13, 2010.