The Effect of Film Coating on the Stability of Extended Release Metformin Hydrochloride POLYOX™ Matrices

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Opadry® II / POLYOX™

Purpose

Polyethylene oxide (PEO) is prone to oxidation and thermal degradation at high temperatures, resulting in reduction of polymer viscosity and polymer chain cleavage during storage.[1] PEO degradation can be regulated by oxygen impediment, oxygen removal and/or other methods as mentioned in the literature.[1-3] The aim of this study was to investigate the effect of an Opadry® II film coating system on the stability of metformin HCl extended released (ER) polyethylene oxide (POLYOX™) matrix tablets at accelerated storage condition (40°C/75% RH). Tablets were pulled at pre-determined time points and evaluated for physical properties and drug release. The effects of filler and presence of desiccant were also evaluated in this study.

Methods

Materials and Formulations

The composition of metformin HCl formulations is shown in **Table 1**.[4] Metformin HCl was used as the model drug, POLYOX Coagulant as the release controlling agent, and StarCap 1500® and/or microcrystalline cellulose (MCC) utilized as a filler in this study.

Table 1. Composition of Metformin HCl ER Formulations

Ingredients	% Composition (w/w)		
	F1	F2	F3
Metformin HCl (Wanbury Limited, India)	50.0	50.0	50.0
POLYOX Coagulant (The Dow Chemical Company, USA)	20.0	20.0	20.0
StarCap 1500 (Colorcon Inc., USA)	29.0	-	14.5
Microcrystalline cellulose (Microcel 102SP, Blanver, Brazil)	-	29.0	14.5
Fumed silica (Aerosil 200, Evonik Industries, Germany)	0.5	0.5	0.5
Magnesium stearate (Akros Chemicals, Holland)	0.5	0.5	0.5
Total	**100.0**	**100.0**	**100.0**

Tablet Preparation and Film Coating

The API, POLYOX Coagulant, filler(s) and fumed silica were passed through an ASTM 30 mesh (600 µm), and then mixed in a 4 quart V blender (Patterson-Kelley Co., USA) at 25 rpm for 10 mins. Magnesium stearate was screened through an ASTM 40 mesh (400 µm) then added to the powder mixture, followed by blending for an additional 3 mins.

Matrix tablets (1000 mg) were compressed on a rotary tablet press (Piccola, RIVA, Argentina), using caplet shaped tooling (19.1 mm × 9.3 mm), at the compression force of 30 kN (compression pressure of 190 MPa).[4] Tablets were then coated with a PVA-based Opadry II film coating system to the theoretical weight gain of 4%, in a fully perforated coating pan (Labcoat I, O'Hara, Canada) fitted with a 10" pan without baffles. The film coating process parameters are shown in **Table 2**. Coated and uncoated matrix tablets were then packed in HDPE bottles, with or without a desiccant, and stored in 40°C/75% RH stability chamber for 6 months.

Table 2. Coating Process Parameters

Process parameters	Values
Nozzle size (mm)	1.2
Pan charge (g)	600
Pan speed (rpm)	20
Inlet air temperature (ºC)	65-69
Exhaust air temperature (ºC)	48-53
Product temperature (ºC)	42-45
Air volume [cfm / (m^3/hr)]	130 / 218
Atomization pressure (psi / bar)	15 / 1.0
Pattern air pressure (psi / bar)	20 / 1.4
Spray rate (g/min)	12-13
Coating time (min)	10

Tablet Characterization and Drug Release

At each pre-determined time interval: tablet weight, breaking force, diameter and thickness were measured with an automated Multicheck tablet tester (Erweka, Germany). Tablet friability was also measured using a VanKel friabilator at 100 revolutions, 25 rpm (Varian Inc., USA). Drug release testing was performed using USP Apparatus II (VK 7000, Varian, USA) with sinkers at 100 rpm in 1000 mL of deionized water at 37 ± 0.5°C. Drug release was detected at a wavelength of 233 nm using a UV visible spectrophotometer (Agilent 8453, Agilent Technologies, USA) fitted with quartz flow cells of 1.0 mm path length.

Data Analysis and Model Fitting

The release exponent (n) and release rate constant (k) were calculated by fitting the dissolution data to the Power Law equation:[6]

$$Q = k \times t^{n} \qquad \text{Equation (1)}$$

where Q is the fractional amount released at time t, k is the kinetic constant, and n is the release exponent. In addition, the similarity factor (f_2) was calculated by comparing the dissolution curves obtained at a given stability interval versus time zero results.[5]

Results

Physical Properties of Matrices

The physical properties of the ER metformin matrices at time zero are shown in **Table 3**. All tablets exhibited acceptable mechanical strength, low weight variation and low friability values.

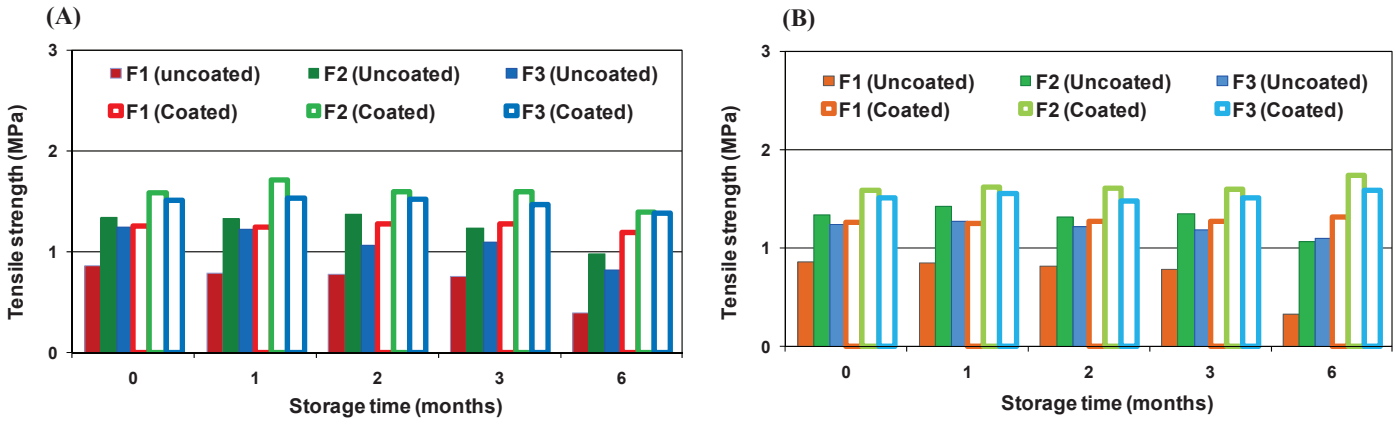
The tensile strength of metformin ER matrices is shown in **Figure 1**. At time zero, the mechanical strength of the tablets was in the range of 0.86-1.34 MPa (uncoated) or 1.26-1.59 MPa (coated). At 6 month time point, uncoated tablets exhibited loss of mechanical strength (0.40-0.98 MPa), while coated tablets had minimal change (1.32-1.73 MPa) when packed with a desiccant. The enhanced mechanical strength and stability of coated tablets was attributed to the Opadry II film coating and its excellent moisture and/or oxygen barrier characteristics. The mechanical strength loss of uncoated tablets might be explained by the elastic nature of POLYOX and small moisture uptake. No significant differences in tablet weight or thickness were observed for uncoated or coated PEO tablets.

Table 3. Physical Properties of Metformin HCl PEO Matrix Tablets at Time Zero (Compression force/ Pressure of 30 kN/ 190 MPa) (n = 20)

Formulation (Filler)	Opadry II Coating	Hardness (kp)	Tensile Strength (MPa)	Tablet Thickness (mm)	Weight Variation (%)	Friability* (%)
F1 (StarCap 1500)	No	10.40 ± 0.75	0.86 ± 0.07	6.76 ± 0.02	0.44	0.49
F2 (MCC)	No	15.70 ± 0.56	1.34 ± 0.05	6.56 ± 0.02	0.36	0.30
F3 (StarCap 1500+MCC)	No	14.30 ± 0.53	1.24 ± 0.05	6.47 ± 0.02	0.48	0.49
F1 (StarCap 1500)	Yes	15.90 ± 1.30	1.26 ± 0.10	7.03 ± 0.04	0.71	0.00
F2 (MCC)	Yes	19.50 ± 1.00	1.59 ± 0.08	6.85 ± 0.04	0.70	0.00
F3 (StarCap 1500+MCC)	Yes	18.30 ± 1.10	1.51 ± 0.09	6.94 ± 0.02	0.45	0.00

Note: * n = 10 for tablet friability testing.

Figure 1. Mechanical Strength of Metformin HCl ER Matrix Tablets (n = 20): (A) No Desiccant; (B) With Desiccant



Drug Release Profiles

Metformin HCl release profiles for uncoated and coated tablets are shown in **Figures 2-4**, respectively. Similar drug release profiles (f_2 > 50) were obtained for tablets at time zero and at 6 months regardless of filler choice or film coating. The Opadry II film coating system had no impact on drug release profiles (f_2 > 65). All formulations showed good data fitting to Power Law equation (R^2 > 0.99), and the release exponent (n) was in the range of 0.59-0.61 indicating drug release was mainly controlled by diffusion.[6]

Figure 2. Metformin HCl Release Profiles from PEO Tablets with StarCap 1500 as Filler (n = 6): (A) Uncoated, No Desiccant (f_2 = 65-85); (B) Coated, No Desiccant (f_2 = 72-73)

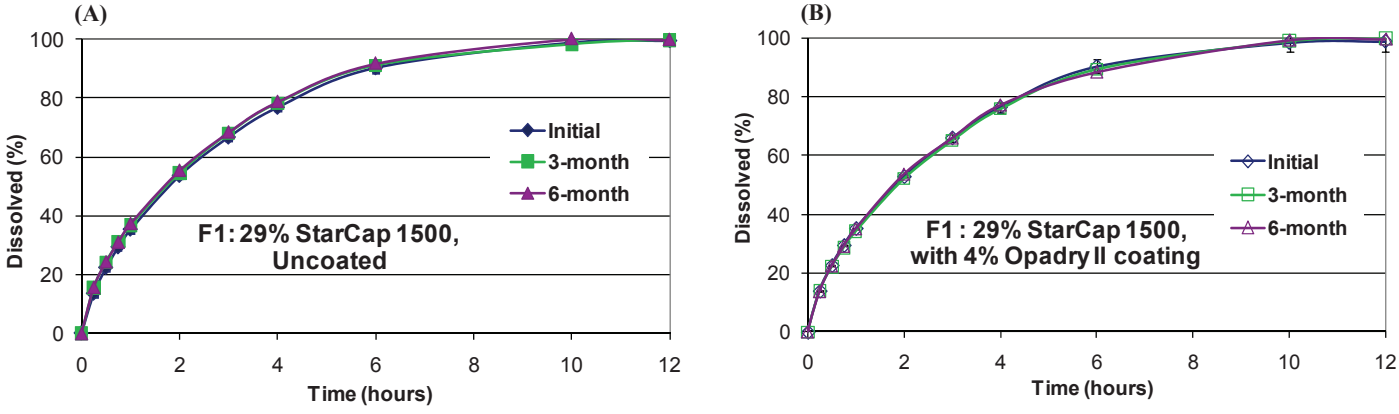


Figure 3. Metformin HCl Release Profiles from PEO Tablets with MCC as Filler (n = 6): (A) Uncoated, No Desiccant (f_2 = 67-78); (B) Coated, No Desiccant (f_2 = 53-79)

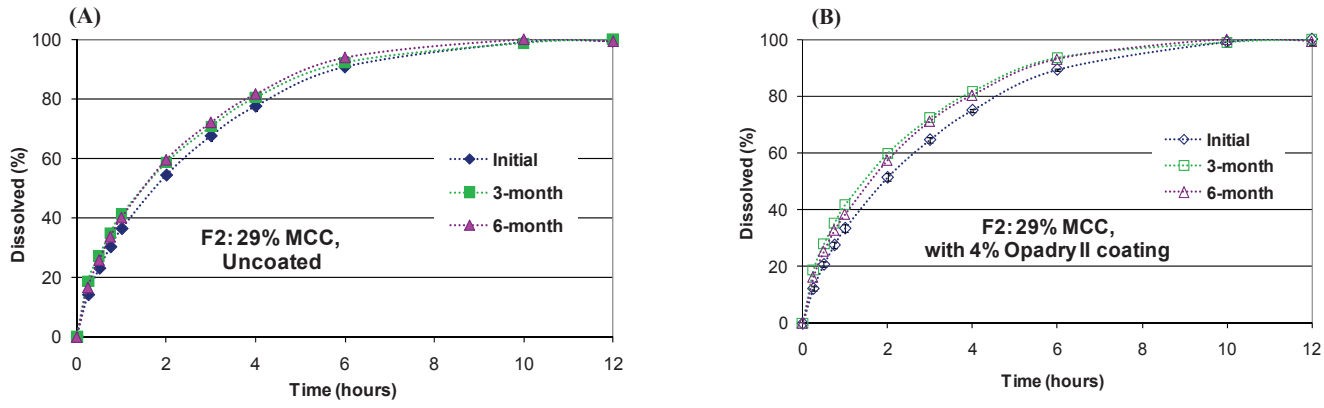
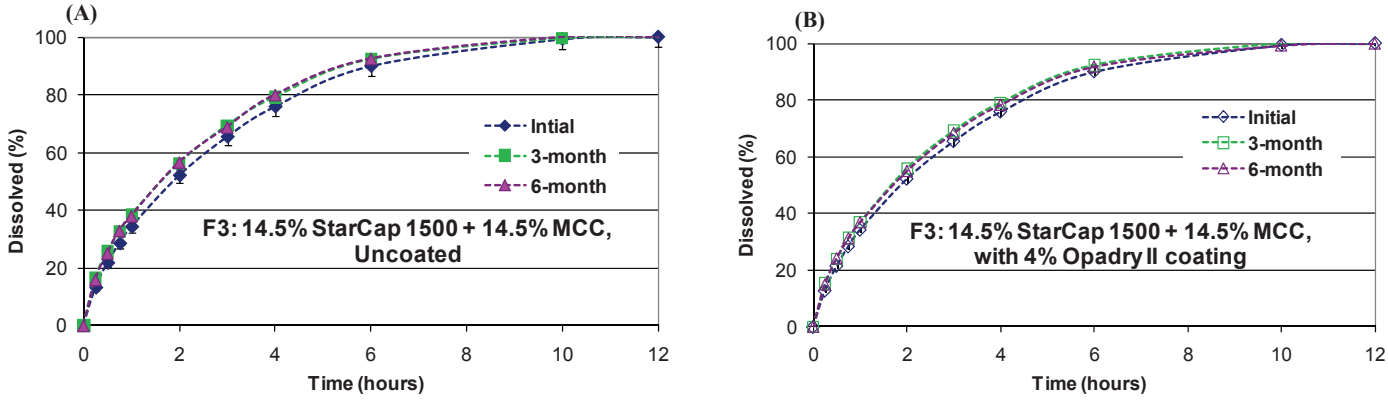


Figure 4. Metformin HCl Release Profiles from PEO Tablets with StarCap 1500 + MCC as Filler (n = 6): (A) Uncoated, No Desiccant (f_2 = 79-82); (B) Coated, No Desiccant (f_2 = 78-83)



Conclusions

The application of PVA-based Opadry II film coating system, at 4% weight gain on metformin HCl PEO matrices, significantly enhanced tablet stability and prevented loss of tablet mechanical strength during accelerated storage conditions. This is due to the excellent moisture/oxygen barrier of PVA based coating systems. The presence of a desiccant in the package provided additional protection and led to consistent mechanical strength values during storage. Drug release from the matrix tablets was not significantly affected by the presence of Opadry II film coating or various fillers. Similar drug release profiles were obtained for all evaluated matrices upon storage at an accelerated condition for 6 months.

References

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