Stability Evaluation of Ethylcellulose Dry Powder Coated Metoprolol Tartrate Extended Release Multiparticulates

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AAPS
Poster Reprint 2017

Purpose

Ethylcellulose coating can be applied as an organic solution, aqueous dispersion or more recently as a dry powder for extended release (ER) applications. For dry powder coating applications, ethylcellulose particles are deposited onto the surface of multiparticulates (MP) using a plasticizer dispersion, eliminating the need for excessive solvent or water.[1, 2] Dry powder coated MP were cured at 45°C to ensure coalescence of the deposited ethylcellulose particles into a consistent barrier membrane. This study examined the stability of dry powder coated metoprolol tartrate (MT) ER multiparticulates developed using plasticizer combinations at two diff erent ratios. The consistency of drug release and potential microscopic changes in the fi lm morphology were evaluated.

Methods

Drug Layering

Metoprolol tartrate (MT) was layered onto sugar spheres (SUGLETS® PF011, #18-20 mesh; 850-1000 µm, Colorcon Inc., USA) using a hypromellose based Opadry® clear film coating (Colorcon Inc., USA) as binder at 70:30 drug:binder ratio (w/w), in a fluidized bed coater (Vector FL-M-60, Freund-Vector, USA). An additional 1% weight gain (w/w) seal-coat of the same coating was applied for mechanical protection of the drug layered beads. Drug loaded spheres were then screened through #16 mesh to remove agglomerates prior to barrier membrane dry powder layering. The composition of the drug layered MPs is shown in Table 1.

Table 1: Drug-Layered Multiparticulate Composition

Ingredients	Supplier	% w/w
Drug layer		
Metoprolol Tartrate	Polydrug, India	6.9
Suglets PF011 (Sugar Spheres NF 18/20)	Colorcon, USA	89.1
Opadry Clear (binder)	Coloron, USA	3.0
Seal-coat layer		
Opadry Clear	Coloron, USA	1.0
Total		**100**

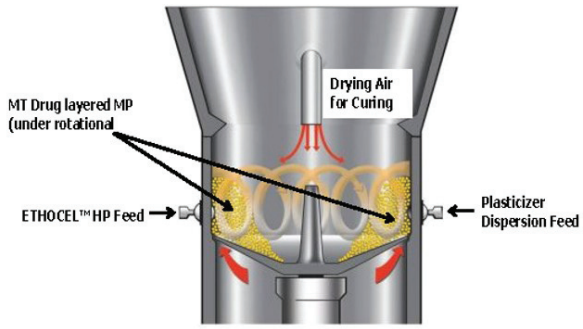
Dry Powder Coating of Ethylcellulose

MT drug layered beads were dry powder coated in a fluid-bed coater with rotor insert (Granurex, Freund-Vector) using a grade of ethylcellulose designed for this process (ETHOCEL™ HP, IFF, USA). In this process, ETHOCEL™ HP powder was metered through a twin screw, loss in weight feeder into the rotating bed of multiparticulates. Plasticizer combinations of oleic acid (OA) and dibutyl sebacate (DBS) at 75:25 w/w ratio were sprayed through a separate port at the opposite side of the powder addition port. The equipment and process is shown in Figures 1 and 2.

Figure 1: Fluid Bed Equipped with Conical Rotor Insert for Powder Coating*

(*Images courtesy of Freund-Vector Corporation, USA)

Figure 2: Representation of ETHOCEL™ HP Dry Powder Coating Process*



(*Images courtesy of Freund-Vector Corporation, USA)

ETHOCEL™ HP weight gain was kept constant at 20% w/w. Aqueous plasticizer dispersions were applied simultaneously at 40% and 50% w/w level (WRT polymer). Tables 2 and 3 show formulation of plasticizer dispersion and applied quantities of ETHOCEL™ HP and plasticizer dispersion to achieve 40% and 50% w/w polymer to plasticizer ratio, respectively.

Table 2: Plasticizer Dispersion Formulation

Ingredients	75:25 (OA:DBS) Ratio
	% w/w
Oleic Acid	30
Dibutyl Sebacate	10
DI Water	59.9
Polysorbate 80	0.1
Total	100

Table 3: Quantities of Ingredients for Dry Powder Coating

Ingredient	40% w/w Plasticizer Level	50% w/w Plasticizer Level
Drug layered MP (g)	2000	2000
ETHOCEL™ HP (g)	400	400
Plasticizer dispersion (40% w/w solids) (g)	400	500
% Plasticizer in the barrier membrane	28.6	33.3

The multiparticulates coated with ETHOCEL™ HP were dynamically cured in the rotor by raising product temperature 10°C above the plasticized (40% w/w WRT polymer) ETHOCEL™ HP glass transition temperature (35°C).[3] The process parameters for powder layering and curing phase are shown in Table 4. As a result of low glass transition temperature of plasticized ETHOCEL™ HP, the exposure to the accelerated stability condition (40°C/75% RH) may change the porosity of the film and subsequently change the drug release. Hence, this study evaluated drug release performance of the dry powder coated multiparticulates at plasticizer level of 40% and 50% w/w after storage at accelerated stability conditions. Additionally, scanning electron microscopy (SEM) image analysis was performed to examine and correlate the drug release changes to the film structure.

Table 4: Powder Layering Process Parameters

Parameter	Powder Layering Phase	Curing Phase
Rotor speed (rpm)	200	200
Inlet air volume (cfm)	<15	60 – 70
Inlet air temperature (°C)	20 – 22	80
Powder addition rate (g/min)	15	0
Liquid addition rate (g/min)	12-22	0
Product temperature (°C)	16 – 20	45 – 47
Slit air volume (cfm)	20	20
Process time (min)	30	0, 15, 30, 60

Drug Release Analysis

In vitro dissolution testing was conducted using USP Apparatus I (baskets) (Agilent Inc., USA) at 100 rpm in 1000 mL of purified water. Drug release was determined spectrophotometrically at a wavelength of 276 nm. Drug release data for all samples were compared using similarity factor (f_2).

Stability Study

Dry powder coated extended release MT multiparticulates were packaged in foil sealed HDPE bottles and stored at 40ºC/75% RH for 6 months. The samples were pulled at designated time intervals and characterized for any changes in drug release profi les and fi lm structure.

SEM Imaging

Samples of MPs were mounted and sputter coated with iridium using a Peltier cooled Sputter Coater EMS575X (Electron Microscopy Science, USA) for a total time of 60 seconds. Cross sections and surfaces of the MPs were evaluated in a Field Emission Scanning Electron Microscope (FE-SEM, Hitachi High Technologies America, Inc., USA). SEM images were obtained using an applied voltage of 10 kV and various working distances depending on sample height and thickness.

Results

Previous studies indicated that dry powder coating of ETHOCEL™ HP and 30% w/w plasticizer addition (with respect to polymer, equivalent to 23.1% w/w plasticizer level in the barrier membrane) provided immediate drug release due to porous film formation.[4] Use of 40% w/w plasticizer level enabled controlled release performance only after 30 minutes or higher duration of curing because of complete coalescence of deposited ETHOCEL™ HP particles in to a coherent controlled release film.

Although 40% w/w of plasticizer level and 30 minutes of curing provided controlled release initially, noticeably slower drug release was observed after 1 month exposure to accelerated stability (Figure 3). After an initial decline observed at 1 month, the drug release remained unchanged and stable up to 6 months. Increasing curing duration to 60 minutes at 40% w/w plasticizer level led to similar drug release (f_2 value > 73) up to 6 months of accelerated stability exposure (Figure 4).

Figure 3: Stability Drug Release Profiles of Metoprolol Tartrate Multiparticulates Coated Using 40% w/w Plasticizer Level and Cured for 30 Minutes (n=6)

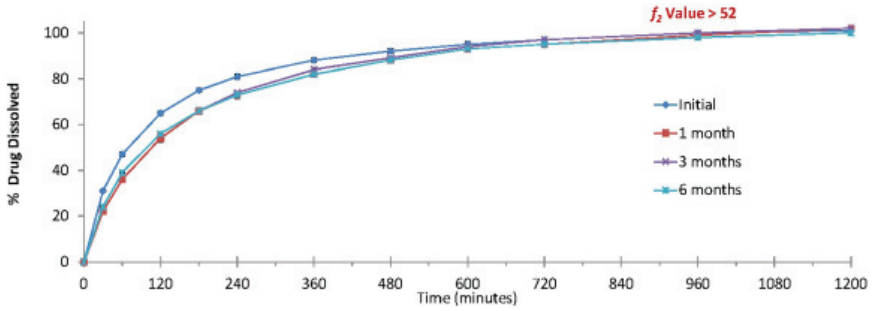
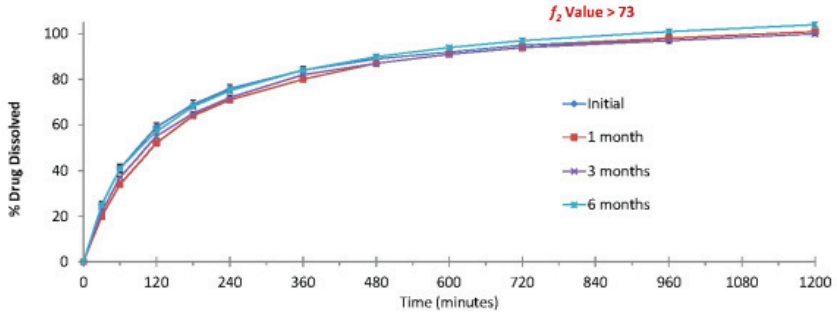
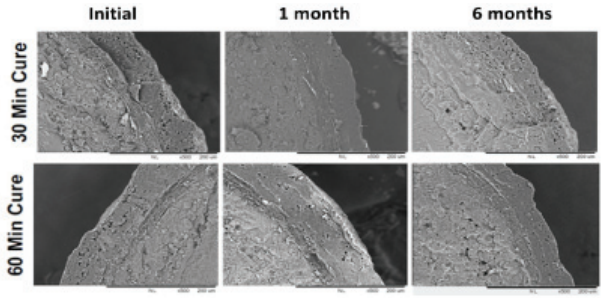


Figure 4: Stability Drug Release Profiles of Metoprolol Tartrate Multiparticulates Coated Using 40% w/w Plasticizer Level and Cured for 60 Minutes (n=6)



Examining the SEM images of the coated multiparticulates cross sections at 40% w/w plasticizer level after 30 and 60 minutes of curing suggested coherent film structure with some porosity. Reduction in film porosity after 1 month exposure of accelerated stability may have contributed to the slower drug release (Figure 5).

Figure 5: SEM Images of Metoprolol Tartrate Multiparticulates Coated Using 40% w/w Plasticizer Level and Cured for 30 and 60 Mins



ETHOCEL™ HP dry powder coating using 50% w/w plasticizer provided consistent and robust controlled drug release performance (f_2 value > 82) up to 6 months without any curing (Figure 6). Further reduction of ETHOCEL™ HP glass transition temperature at high plasticizer level (50% w/w) may contribute for complete coalescence of particle under the coating phase eliminating the need of any curing. Use of curing duration up to 60 minutes also resulted in consistent drug release (f_2 value > 66) for 6 months accelerated stability (Figure 7).

Figure 6: Stability Drug Release Profiles of Metoprolol Tartrate Multiparticulates Coated Using 50% w/w Plasticizer Level and No Curing (n=6)

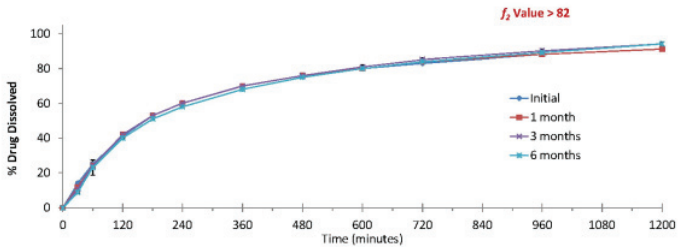
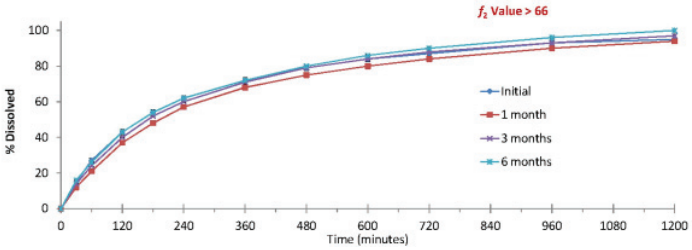
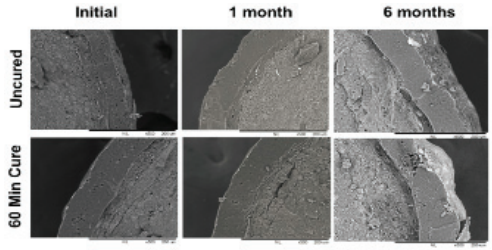


Figure 7: Stability Drug Release Profiles of Metoprolol Tartrate Multiparticulates Coated Using 50% w/w Plasticizer Level and Cured for 60 Minutes (n=6)



The SEM images of multiparticulate cross-sections at 50% w/w plasticizer level without curing and after 60 minutes of curing are shown in Figure 8. Use of 50% w/w plasticizer resulted in denser film structure compared to 40% w/w plasticizer level, with slower drug release from coated multiparticulates. Porosity of the film remained unchanged under the exposure of accelerated stability condition up to 6 months.

Figure 8: SEM Images of Metoprolol Tartrate Multiparticulates Coated Using 50% w/w Plasticizer Level and without Curing and with 60 Mins of Curing



Conclusions

The extended release metoprolol multiparticulates were successfully developed with a novel grade of ethylcellulose (ETHOCEL™ HP) using dry powder coating application. Stable and consistent drug release was observed under accelerated stability conditions through 6 months using 40% w/w plasticizer and 60 minutes of curing duration. Increase in plasticizer level to 50% w/w also provided stable drug release without any curing.

References

1. Pearnchob N, Bodmeier R., "Coating of pellets with micronized ethylcellulose particles by a dry powder coating technique", *International Journal of Pharmaceutics*. 2003; 268:1-11.
2. Terebesi I, Bodmeier R., "Optimised process and formulation conditions for extended release dry polymer powder-coated pellets", *European Journal of Pharmaceutics and Bio pharmaceutics*. 2010; 75:63-70.
3. Mehta RY, Folkenroth J, Grasman N, Cunningham CR, Missaghi S and Rajabi-Siahboomi AR., "Investigation of Plasticizer Selection for Extended Release Multiparticulates Using Powder Layering with Novel High Productivity Grade of Ethylcellulose", American Association of Pharmaceutical Scientists Annual Meeting, CO, USA (2016).
4. Mehta RY, Folkenroth J, Grasman N, Cunningham CR, Missaghi S and Rajabi-Siahboomi AR., "Influence of Plasticizer Level and Curing Duration on Performance of a High Productivity Grade of Ethylcellulose", Controlled Release Society Annual Meeting, MA, USA (2017).

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