Influence of Plasticizer Level and Curing Duration on Performance of a High Productivity Grade of Ethylcellulose

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Purpose

Ethylcellulose coatings are commonly applied as an organic solution or aqueous dispersion to multiparticulates (MP) for extended release and taste-masking applications. Dry powder application of a high productivity grade of ethylcellulose (ETHOCEL™ HP) eliminates the need for large quantities of organic solvent or water from the coating process leading to a significant reduction in coating time[1]. In this process, plasticizer type, level and duration of curing are critical parameters[2,3]. Appropriate control of these parameters is important to ensure consistent coalescence and fusion of the deposited ethylcellulose particles into a continuous barrier membrane to achieve the desired drug release profiles. In this study, metoprolol tartrate was used as a model drug to investigate development of extended release (ER) multiparticulates using dry powder application of a high productivity ethylcellulose and suitable plasticizer combinations. The influence of plasticizer levels and curing duration on the drug release performance was investigated, and long term stability of the ER coated multiparticulates studied.

Experimental Methods

Drug Layering

Metoprolol tartrate (MT) was layered onto sugar spheres (#18-20 mesh; 850-1000 µm) (Suglets®, PF011 Colorcon Inc., USA) using a hypromellose-based Opadry®clear, Complete Film Coating System, (Colorcon Inc., USA) as binder at 70:30 w/w drug: binder ratio, in a fluidized bed coater (Vector FL-M-60, Freund-Vector, USA), followed by a 1% w/w seal-coat using the same Opadry system. Drug loaded spheres were then screened through #16 mesh to remove agglomerates, before application of the barrier membrane coating. The composition of the drug layered MPs is shown in Table 1.

Table 1: Multiparticulate Formulation

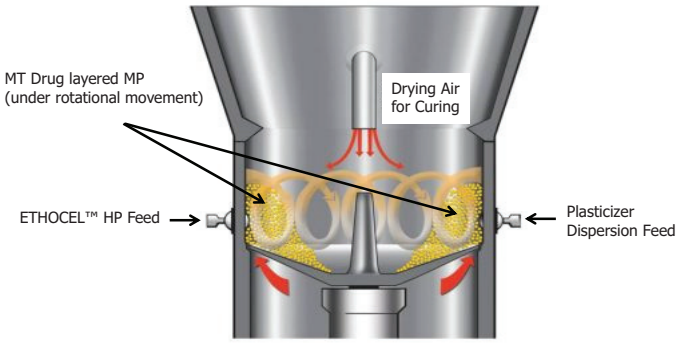
Ingredients	Supplier	% w/w
Drug Layer		
Metoprolol Tartrate	Polydrug, India	6.9
850/ 1000 Suglets (Sugar Spheres NF 18/20)	Colorcon, USA	89.1
Opadry Clear (binder)	Coloron, USA	3.0
Seal-coat Layer		
Opadry Clear	Coloron, USA	1.0
Total		**100**

Dry Powder Coating of Ethylcellulose

MT drug layered beads were dry powder coated in a fluid bed with rotor insert (Granurex, Freund-Vector) using ethylcellulose (ETHOCEL™ HP, International Flavors and Fragrances Inc., USA) and plasticizer combinations of oleic acid (OA) and dibutyl sebacate (DBS) at 75:25 w/w ratio. In this process, ETHOCEL™ HP powder was metered through a twin screw, loss in weight feeder into the rotating bed of multiparticulates. The plasticizer was 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 Dry Powder Coating*

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 30%, 40% and 50% w/w level (with respect to polymer) as the ethylcellulose powder was introduced into the rotor. Formulation of plasticizer dispersion and quantities of ethylcellulose and plasticizer sprayed to achieve 30%, 40% and 50% w/w polymer to plasticizer ratio are displayed in Table 2 and 3, 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

Ingredients	30% w/w Plasticizer Level	40% w/w Plasticizer Level	50% w/w Plasticizer Level
Drug layered MP (g)	2000	2000	2000
ETHOCEL™ HP (g)	400	400	400
Plasticizer dispersion (40% w/w solids) (g)	300	400	500

Plasticizer addition rate was adjusted to achieve desired ratio of polymer to plasticizer dispersion. Subsequently, multiparticulates coated with ETHOCEL™ HP were dynamically cured in the rotor by raising product temperature 5-10°C above the plasticized ETHOCEL™ HP glass transition temperature (35°C). Curing duration may affect the degree of coalescence of the deposited particles and subsequent porosity of the ethylcellulose film. This study examined the effect of curing for 15, 30 and 60 minutes and the influence on drug release. The process parameters for powder layering and curing phase are shown in Table 4.

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).

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.

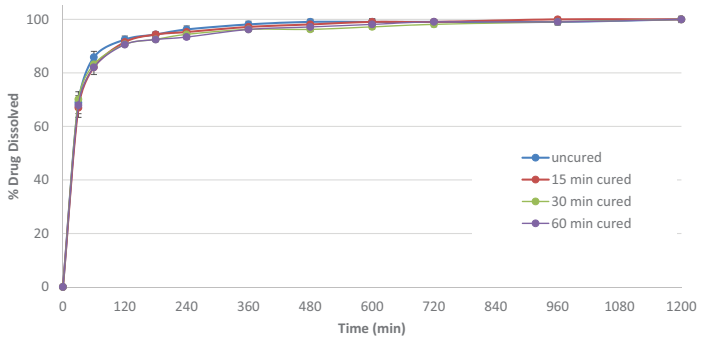
Stability Study

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 profiles.

Results

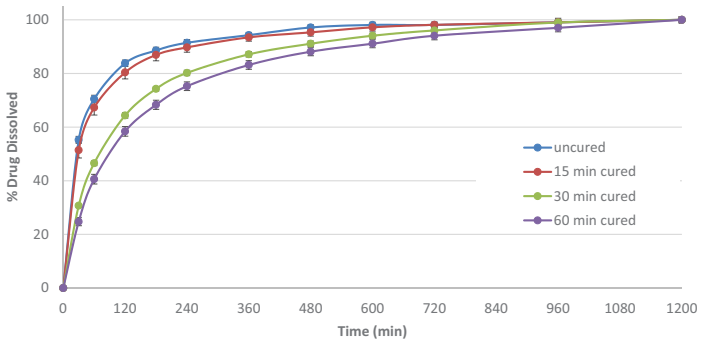
Use of 30% w/w plasticizer level resulted in immediate drug release at all curing durations (up to 60 minutes), suggesting incomplete coalescence and a porous barrier membrane formation (Figure 3).

Figure 3: Drug Release Profiles using 30% w/w Plasticizer Level and Different Curing Duration (n=6)



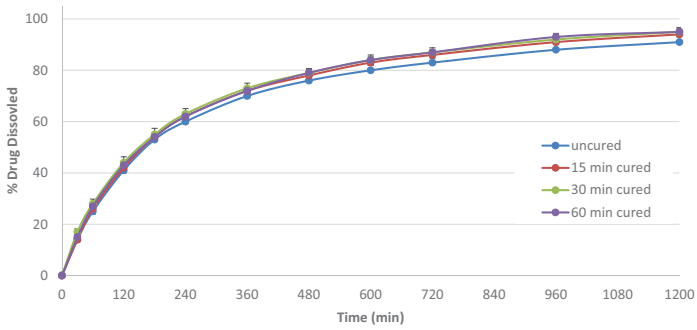
Increasing the plasticizer level to 40% w/w resulted in extended release of the drug when MPs were cured for 30 minutes or longer, indicating sufficient level of plasticization to achieve complete coalescence and dense film formation (Figure 4). The role of curing duration was equally important at 40%w/w plasticizer level to attain extended drug release functionality.

Figure 4: Drug Release Profiles using 40% w/w Plasticizer Level and Different Curing Duration (n=6)



As the plasticizer level increased to 50% w/w, drug release was further reduced even without the curing phase (Figure 5); this highlights the significance of plasticizer level to achieve extended drug release from dry powder coating with ETHOCEL™ HP.

Figure 5: Drug Release Profiles using 50% w/w Plasticizer Level and Different Curing Duration (n=6)



Influence of plasticizer levels and curing durations on ethylcellulose film structure was further evaluated using SEM images (Figure 6). Simultaneous spray of OA:DBS plasticizer dispersion ensured the adherence of ethylcellulose dry powder to the MP surface. However, porous film formation due to insufficient plasticizer level was observed at 30% w/w of plasticizer and this remained porous even after 60 minutes of curing. At 40% w/w plasticizer level, a noticeable difference in porosity between uncured and 60 minutes cured samples was observed, suggesting the influence of curing time on film coalescence and subsequent change of drug release profiles. Use of 50% w/w plasticizer level provided significantly dense film structure without any curing.

Figure 6: SEM Image of ETHOCEL™ HP Coated MT Multiparticulates

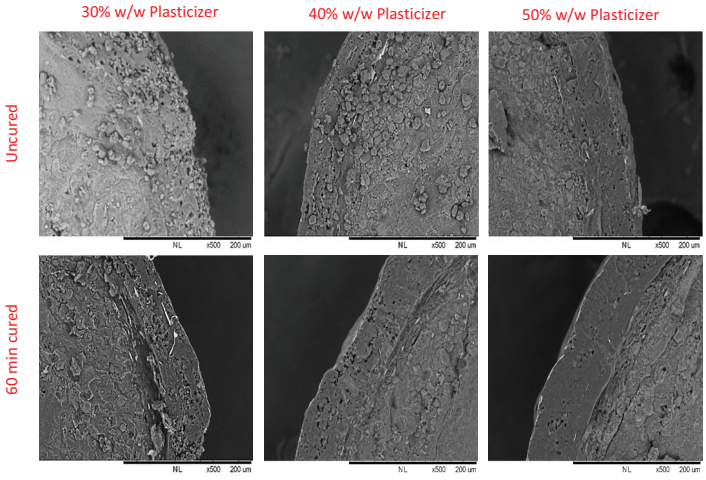
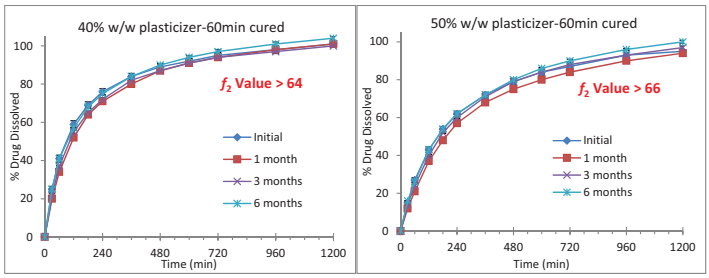


Figure 7: Drug Release Profiles using 40% w/w and 50% w/w Plasticizer Level with 60 min of Curing on Accelerated Stability (n=6)



Use of plasticizer levels higher than 40% w/w with 60 minutes of curing duration provided stable drug release from dry powder coating application of ETHOCEL™ HP. Coated MPs show similar drug release (f_2 values > 64 and 66) following accelerated stability for 6 months (Figure 7).

Conclusions

Dry powder coating with ETHOCEL™ HP resulted in successful development of metoprolol tartrate extended release multiparticulates. Plasticizer levels of 40% w/w or greater helps to achieve consistent barrier membrane formation with extended release profiles. The results indicated that curing durations should be optimized based on the plasticizer level to ensure extended drug release is achieved.

References

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