Investigation of Plasticizer Selection for Extended Release Multiparticulates Using Powder Layering with Novel High Productivity Grade of Ethylcellulose

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Purpose

Ethylcellulose is a commonly used polymer in barrier membrane coating, applied organically or aqueously to develop extended release (ER) multiparticulate (MP) dosage forms. Recently, a novel grade of ethylcellulose, ETHOCEL™ HP, was developed that can be applied as a dry powder coating. This technology results in the elimination of large quantities of solvent or water during the application process and achieves a significant reduction in coating process times.[1] For dry powder coating, the plasticizer plays a key role in adhering, softening and coalescing the ethylcellulose particles to develop a consistent barrier membrane.[1,2] In this investigation, metoprolol tartrate (MT) multiparticulates were used for dry powder layering with ETHOCEL HP, using oleic acid and dibutyl sebacate (OA:DBS) as a plasticizer, and the influence of the plasticizer combinations on ethylcellulose glass transition temperature (Tg)) was evaluated.[3] In addition, the long term stability of the ER coated multiparticulates was studied.

Methods

Drug Layering

MT was layered onto sugar spheres (18-20 mesh; 850-1000 µm) (Suglets®, PF011 Colorcon Inc., USA) using a hypromellose-based Opadry® clear 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). This was followed by application of 1% w/w seal-coat using the same Opadry system. The drug loaded spheres were then screened to remove agglomerates before application of the barrier membrane coating. The composition of the drug layered MP is shown in Table 1.

Table 1. Multiparticulate Formulation

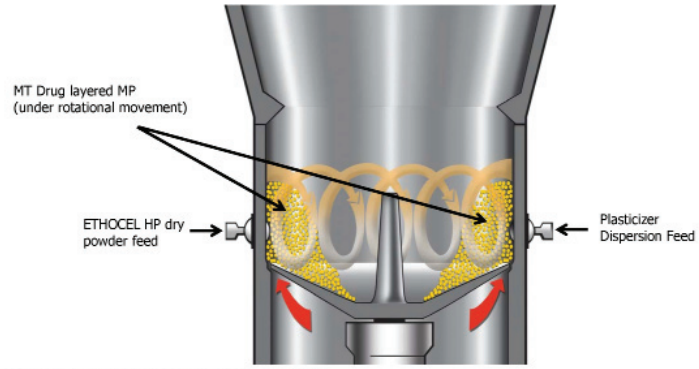
Ingredients	Supplier	% w/w
Drug Layer		
Metoprolol Tartrate	Polydrug, India	5.3
850/1000 Suglets (Sugar Spheres NF 18/20)	Colorcon, USA	69.8
Opadry Clear (binder)	Coloron, USA	2.3
Seal-coat Layer		
Opadry Clear	Coloron, USA	0.7
Barrier Membrane Layer		
ETHOCEL™ HP (ethylcellulose)	The Dow Chemical Company, USA	15.6
Plasticizer Combinations (Oleic acid: Dibutyl sebacate, OA: DBS, 50 :50) or (OA :DBS, 75 :25)	Croda Inc., USA (OA) and Vertellus Inc., USA (DBS)	6.3
Total		**100**

Dry Powder Coating of Ethylcellulose

The drug layered MP (2.0 kg) were dry powder coated in a fl uid bed equipped with rotor insert (Vector VFC-3 and Granurex GXR-35, Freund-Vector, USA) using ethylcellulose (ETHOCEL HP, International Flavors and Fragrances Inc., USA) and liquid plasticizer. 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 process is shown in Figures 1 and 2. The process parameters are shown in Table 2.

Figure 1. Fluid Bed Equipped with Conical Rotor Insert (Granurex, GXR-35) for Dry Powder Coating*

Figure 2. ETHOCEL HP Dry Powder Coating Process*



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

Table 2. 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	60 – 80
Powder addition rate (g/min)	15	0
Liquid addition rate (g/min)	15	0
Product temperature (°C)	16 – 20	45 – 47
Slit air volume (cfm)	20	20
Process time (min)	30	60

The OA: DBS plasticizer combination was applied at the ratios shown in Table 3. The weight gain of ETHOCEL HP and plasticizer level (with respect to polymer) were kept at 20% and 40% w/w, respectively. Plasticizers were dispersed in water at a 40% w/w level and applied to the batch simultaneously as the ethylcellulose powder was introduced. The coated MP were dynamically cured in the rotor for 1 hr at 80°C inlet temperature.

Table 3. Plasticizer Dispersion Formulation

Ingredients	50:50 (OA:DBS) ratio	75:25 (OA:DBS) ratio
	% w/w	% w/w
Oleic Acid	20	30
Dibutyl Sebacate	20	10
DI Water	59.9	59.9
Polysorbate 80	0.1	0.1
Total	100	100

Simultaneous spraying of the OA: DBS plasticizer combination dispersion ensured the adherence of ETHOCEL HP dry powder onto the MP surface. The deposited powder was converted into the dense film during the curing phase where the product temperature was raised 10ºC above the plasticized ETHOCEL HP glass transition temperature (35ºC) to achieve complete coalesce and dense film formation.

Drug Release Analysis

In vitro dissolution testing was conducted using USP Apparatus I baskets 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 factors (f_2).

Stability Study

The dry powder coated ER metoprolol tartrate MP 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.

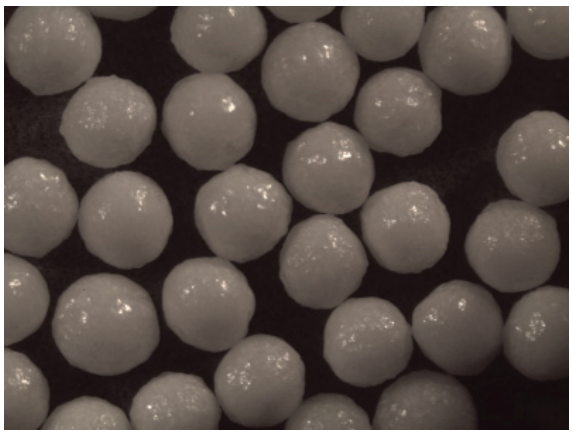
Glass Transition Temperature (Tg) Evaluation

To further understand plasticizer effects and to determine effective plasticizer levels, thermal analysis was conducted on cast films. A sample of ETHOCEL HP was dissolved in toluene: ethanol (80/20 w/w) solvent mixture at 10% w/w. Plasticizer combinations of OA:DBS at 50:50 or 75:25 ratio were added to the solvent mixture at 20, 30, 40 or 50 % w/w levels with respect to the weight of ETHOCEL HP . The solutions were allowed to mix overnight, then 5 gm of each solution was cast onto the aluminum pan to form a plasticized ethylcellulose film. Films were left to dry overnight, then removed and tested via DSC (DSC Q200, TA Instruments, USA) to measure glass transition temperature.

Results

After completion of the dry powder coating and curing process, the beads were free of any fines or agglomeration and exhibited a smooth and glossy surface (Figure 3).

Figure 3. Appearance of MP after Coating and Curing (10X magnification)



The dry powder ETHOCEL HP and plasticizer application process resulted in extended drug release at either plasticizer ratios. The drug release rates also remained consistent (f_2 values >68), through 6 months of accelerated storage conditions (Figures 4 and 5). The stability results indicated that complete coalescence of the ethylcellulose film was achieved during the powder layering process.

Figure 4. Metoprolol Tartrate Drug Release Profiles using Plasticizer Combination OA: DBS at 50:50 w/w (n=6))

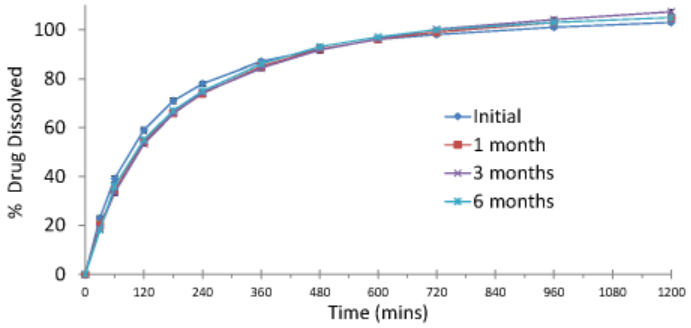
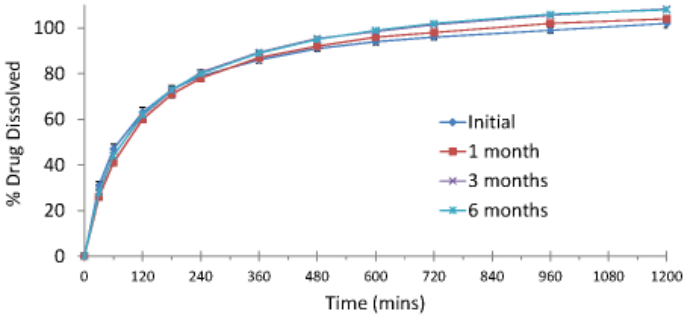


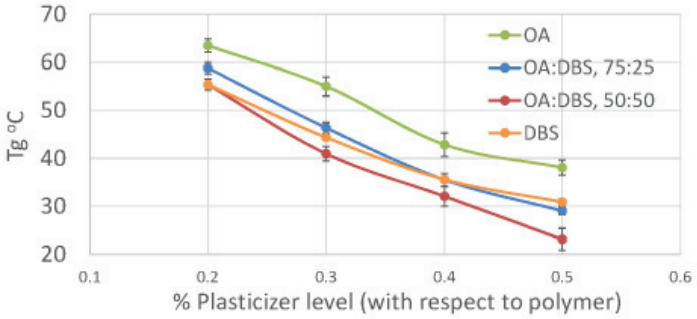
Figure 5. Metoprolol Tartrate Drug Release Profiles using Plasticizer Combination OA: DBS at 75:25 w/w (n=6)



Glass Transition Temperature (Tg) Evaluation

The cast film results confirmed that the 40% plasticizer level and composition used for the coating trials was sufficient to reduce the Tg¬ of the ethylcellulose below 40°C (Figure 6). This resulted in effective film coalescence at the curing temperature (45°C – 47°C) used in the process.

Figure 6. Glass Transition Temperature (ºC) versus Plasticizer Level (%)



Conclusions

ER metoprolol multiparticulates were successfully developed with a novel grade of ethylcellulose (ETHOCEL HP) using dry powder application and OA: DBS plasticizer combinations. Stable and consistent drug release was observed under accelerated stability conditions through 6 months. The OA: DBS combination resulted in similar Tg compared to when DBS is used alone as plasticizer; but offered an advantage of keeping each plasticizer content at acceptable levels i.e. below that reported in the FDA Inactive Ingredient Database (IID), while sufficiently plasticizing the polymer for coherent film formation.

References

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