Stability of a Sparingly Soluble BCS Class I API Ethylcellulose Coated Multiparticulate

ABSTRACT SUMMARY

The main objectives of this study were to: (1) examine long term stability; (2) determine curing effects; and (3) investigate the release kinetics of a sparingly soluble (12 mg/mL) BCS Class I API coated with an aqueous ethylcellulose dispersion. Drug release from coated multiparticulates was monitored during closed storage at 30°C/65%RH (long-term conditions) and 40°C/75%RH (accelerated conditions), both cured and uncured, for up to six months. In vitro dissolution studies revealed stable drug release at both storage conditions for the time periods examined. Formulation dependent curing was evident; however, once curing was complete, no further changes on stability were noted.

INTRODUCTION

Polymeric film coatings are commonly used to mask unpleasant tastes, to protect drugs against moisture and to control drug release from solid oral dosage forms.[1] Ethylcellulose, a water-insoluble polymeric film-forming material, is a popular polymer used for this purpose. The polymer can be applied either as an organic solution or as an aqueous colloidal dispersion (pseudo latex). Due to safety and environmental considerations and a lower viscosity at the same solids content, aqueous ethylcellulose dispersions are preferred.[2] While the use of aqueous ethylcellulose dispersions are advantageous from a toxicological and processing point of view, film formation and resulting storage stability can be critically affected by a continued post coating coalescence of the latex polymer particles. For this reason, the long term stability, predominantly under stressed conditions, is of particular interest.

EXPERIMENTAL METHODS

The following materials were obtained from commercial suppliers and used as received: SureSpheres® drug layering substrate (18/20 mesh nonpareil beads); Surelease® aqueous ethylcellulose dispersion; Opadry® complete film coating system (YS-1-19025-A), all from Colorcon, West Point, PA, USA. METHOCEL™ E6 premium cellulose ethers (hypromellose 2910) and talc were obtained from Dow-Wolff Cellulosics, Midland, MI and Luzenac, Greenwood Village, CO, respectively. All materials including purified water were reagent grade or higher. Drug loaded multiparticulates were prepared by layering a drug-binder suspension onto nonpareil beads using a fluidized bed coater (Vector VFC LAB3, Vector Corporation, Marion, IA) equipped with a Wurster insert to a target drug load of 30 mg/g.

For aqueous ethylcellulose coating, fractions of 500g of the drug layered beads were coated with three different Surelease products formulated with oleic acid (OA; E-7-19050), or in combination with medium chain triglycerides (MCT-OA; E-7-19010), or dibutyl sebacate (DBS-OA; E-7-7050), as plasticizers. Hypromellose was added to the aqueous ethylcellulose dispersion at a 90:10 ratio (w/w) to act as a pore-former, thereby enhancing drug release. The barrier membrane coating was applied at 15% dispersion solids content to a theoretical coating level of 10% weight gain (w/w based on core pellets) as outlined in Table 1.

Table 1. Coated API Bead Formula

Component	Quantities	
	(g)	(%)
Drug-binder		
18/20 Mesh Beads	6000	85.71
API	200	2.86
METHOCEL E6	100	1.43
Seal-coat		
METHOCEL E6	30	0.43
Talc	7	0.10
Ethylcellulose Barrier Membrane		
Surelease (25% Solids Content)	2280	8.14
METHOCEL E6	63	0.90
Top-coat		
Opadry	30	0.43
Total	7000.0	100.0

Both drug layering and barrier membrane film coating process parameters are listed in Table 2.

Table 2. Process parameters for drug layering and coating of drug layered beads.

Process Parameter	Drug Layering	Aqueous ethylcellulose dispersion, Surelease
Equipment	VFC Lab 3	Strea-1
Inlet Air Termperature (°C)	63 - 65	58 - 60
Oulet Air Temperature (°C)	40 - 42	38 - 42
Product Temperature (°C)	43 - 45	N/A
Spray Rate (g/min)	15	10
Atomizing Air Pressure (kg/cm^2)	1.4	1.5
Inlet Air Flow (m^3/hr)	70	100
Charge of Pellets (kg)	6.0	0.5
Nozzle Diameter (mm)	1.2	1.0
Column Height (cm)	2.0	1.0

In vitro drug release was determined using USP Apparatus 1, rotating basket method, (Varian VK7010, Cary, NC, USA) for twelve hours in 900 mL of USP pH 6.8 phosphate buffer at 37±0.5°C and 100 rpm for all samples (n=6). Sample media (1.5 mL) was collected into HPLC vials at designated time points. Samples were analyzed using HPLC (Waters Acquity), with a mobile phase of methanol:ammonium phosphate buffer: triethylamine (60:40:0.5), adjusted to pH 7.0 with phosphoric acid. The flow rate was 0.5 mL/min at 40°C, with detection at 220 nm. Run time was approximately one minute at an injection volume of 10 µL.
Dissolution profiles were compared using time to 50% drug release (t50), maximum drug release (%max), and similarity factor (f_2).[3] Post coating thermal treatment (curing) of coated pellets was investigated using a

temperature and humidity controlled chamber (ESPEC, SH-241, Hudsonville, MI). Curing conditions were 60°C/50%RH for 24 hours.

RESULTS AND DISCUSSION

Percent drug load (assay) achieved on nonpareil beads was high at 92% of target. Agglomeration was low at less than 1%. Coating process efficiencies (CPE) were also high with low recorded agglomeration for the barrier membrane coating step; greater than 96% CPE and less that 2% agglomeration for all coatings. Drug release from aqueous ethylcellulose dispersion coated multiparticulates remained stable through six-months storage at both long-term and accelerated conditions (Figures 1a and 1b) regardless of coating formulation.

Figure 1a. Influence of storage time and condition on in vitro drug release. Storage Condition: six-months 30°C/65%RH.

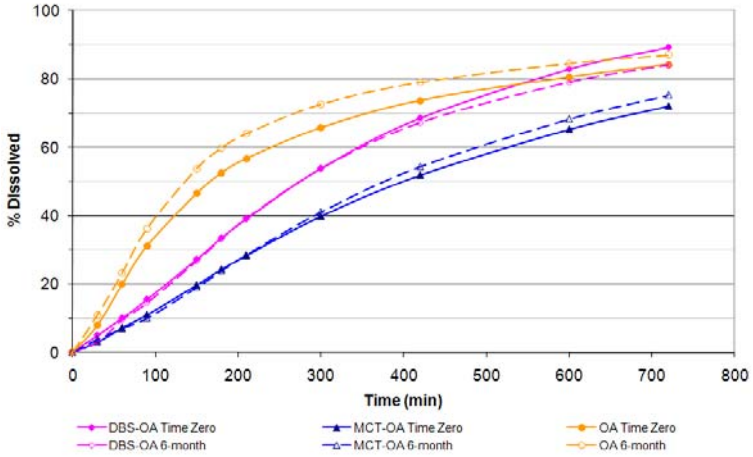
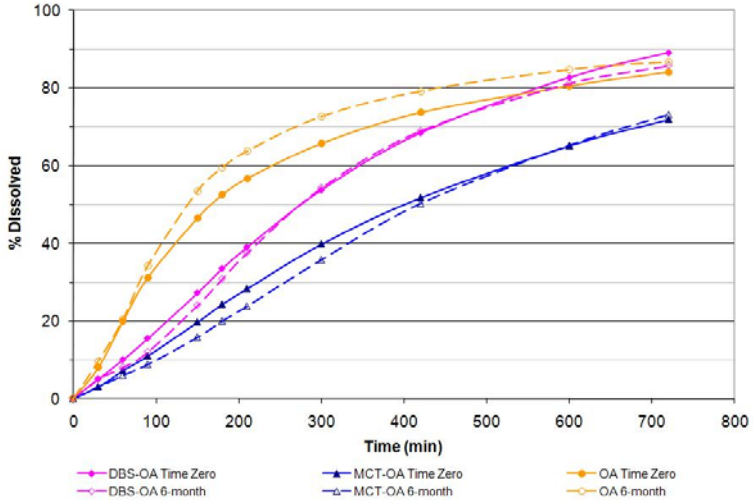
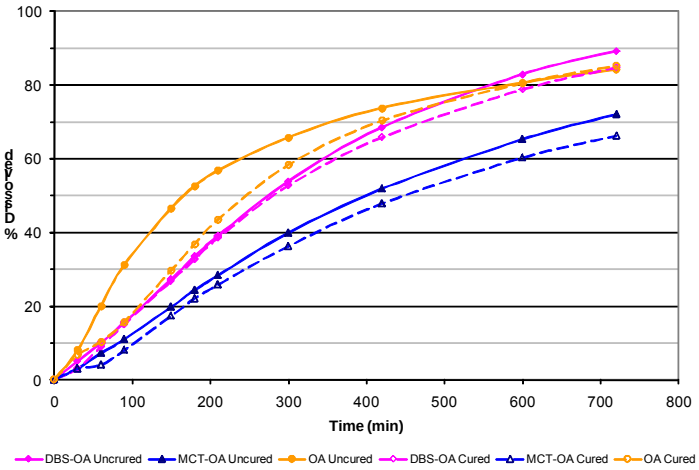


Figure 1b. Influence of storage time and condition on in vitro drug release. Storage Condition: six-months 40°C/75%RH.



Comparison of untreated (uncured) dissolution profiles using similarity factor gave f_2 values of 81, 85, 63 and 80, 76, 64 for samples (DBS-OA, MCT-OA and OA) stored for six months at ambient and stressed conditions, respectively. f_2 values for thermally treated (cured) samples stored for six months at both long-term and accelerated conditions ranged from 97 to 73 (profiles not shown). Drug release from beads subjected to a post coating thermal treatment, compared to untreated beads, did show some differences in rate and extent of release (Figure 2). The ethylcellulose formulation plasticized with DBS-OA showed minimal change in release (f_2 = 81) and was the most stable formulation studied. The MCT-OA and OA formulations both showed a slowing of drug release with f_2 values of 72 and 49 respectively.

Figure 2. Influence of coating and curing on in vitro drug release.



CONCLUSIONS

A stable ethylcellulose coated sparingly soluble BCS Class I API was formulated in an oral multiparticulate dosage form. Stable drug release was demonstrated over the time period studied at both long-term and accelerated conditions. In vitro drug dissolution studies revealed zero order or first order kinetic behavior dependent on barrier membrane coating formulation. Post coating thermal treatment of coated pellets did reveal changes in drug release indicating that additional coalescence of the ethylcellulose latex particles occurred, and was minimal with the DBS-OA variant. However, this change was formulation dependent, and no further changes were noted on stability.

Reprint of poster presented at Controlled Release Society Meeting, 2010.

Authors: Charles Vesey and Megan Koska

REFERENCES

1. Kranz, H., Gutsche, S., Evaluation of the drug release patterns and long term stability of aqueous and organic coated pellets by using blends of enteric and gastrointestinal insoluble polymers, International Journal of Pharmaceutics, 380, (2009), 112-119
2. Wesseling, M., Bodmeier, R., Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat®, or an organic ethylcellulose solution, European Journal of Pharmaceutics and Biopharmaceutics, 47, (1999), 33-38
3. Moore, J.W. and Flanner, H.H., Pharm. Tech., 20(6)(1996) 64-74