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Investigation of Venlafaxine HCl Release from Extruded and Spheronized Beads Coated with Ethylcellulose using Organic or Aqueous Coating Systems

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ABSTRACT SUMMARY:

Extruded and spheronized beads of venlafaxine HCl, were coated with aqueous dispersion or organic solution of ethylcellulose. Coated samples were exposed to various temperatures and relative humidity conditions. Drug release profiles indicated that the organic ethylcellulose applications resulted in a more robust coated system than the aqueous applications, for this formulation.

INTRODUCTION:

Drug release from coated multi-particulate (MP) dosage forms can be influenced by the choice of manufacturing process, the ingredients within the core formulation as well as the type of the coating system used. Ethylcellulose (EC) is a widely used water-insoluble polymer in extended-release (ER) film coating of MP formulations. It is applied either using an organic solution or an aqueous dispersion. It has been reported that the film strength of an EC coating from an organic solution differs from that of an aqueous dispersion, with the latter demonstrating a lower mechanical strength [(1)]. Even though the aqueous dispersions of ethylcellulose have been successfully used in the marketplace [(2)], the lower tensile strength of the aqueous EC dispersion films may ultimately impact the performance of some formulations. The objective of this study was to investigate the overall performance of an extruded and spheronized formulation containing venlafaxine HCl, a highly water soluble drug (572 mg/mL) [(3)], coated with ethylcellulose from organic or aqueous systems.

EXPERIMENTAL METHODS:

Preparation of the Coated Beads:

Extruded and spheronized beads of venlafaxine HCl were prepared at a particle size range of 0.85 – 1.7 mm, using a LCI extruder (MG-55) and LCI Marumerizer™ (QJ-400TG, USA) (Table 1). The beads were then coated with either an organic solution of EC (ETHOCEL™ Standard Premium 45 cp, Dow-Wolff Cellulosics) in a solvent mixture of methylene chloride and methanol, [63:37% w/w; applied at 3.85% solids content to a 6% weight gain (WG)], or an aqueous dispersion of EC (Surelease® E-7-19040), applied at 15% solids content to a 15% WG. Table 2 outlines the process parameters utilized for each coating system.

The coated beads were stored, open-dish, in various conditions, 60°C for 24 hours or 40°C/75% relative humidity (RH) for 1 week. If a decrease in drug release was observed (commonly known as "curing effect"), the beads were treated for an additional cycle to determine whether the system reached equilibrium.

Table 1. Formulation of Extruded and Spheronized Beads [(4)]

Ingredient	% w/w
Venlafaxine HCl (Cadila Pharmaceuticals, India)	37.3
Microcrystalline cellulose (MCC) (Avicel® PH101, FMC Corporation, USA)	62.2
Hypromellose 2208 (METHOCEL™ K3, Dow-Wolff Cellulosics, USA)	0.5
Total	100.0

Table 2. Process Parameters for Organic and Aqueous Coating Systems using a VFC-Lab 1 Flo-Coater®, (Wurster set-up, Vector Corporation, USA)

Process parameter	Organic ETHOCEL™	Surelease® E-7-19040
Batch size (kg)	1.0	1.0
Fluidizing air volume (cfm)	40	50
Inlet air temperature (°C)	52	62
Inlet air temperature (°C)	35	43
Atomizing air pressure (bar)	2	2
Spray rate (g/min)	15	7

Dissolution Study:

The treated and untreated beads were subjected to 24-hour dissolution testing to determine any potential change in their release profiles. Dissolution testing was performed in a USP compliant bath using apparatus I (baskets) at 100 rpm in de-ionized (DI) water. After dissolution testing, the beads were removed from the baskets and microscopic images were captured to study the surface and integrity of the coated beads, using a Leica S8 APO Stereomicroscope (Leica Microsystems Inc., USA).

RESULTS AND DISCUSSION:

Figure 1 shows the venlafaxine HCl release profiles of the untreated and treated beads coated with EC organically. The results indicate that exposure to high temperature and/or high humidity does not impact drug release from beads coated organically. In comparison, beads coated with the aqueous ethylcellulose dispersion, demonstrated a change in their release profiles when treated with high temperature and/or humidity (Figure 2). The aqueously coated beads showed a slower drug release when stored at 60°C for 24 hours. These beads were re-treated for a further 24 hours (Figure 2), after which drug release was faster.

Dissolution results for aqueous EC dispersion coated beads, when treated with high temperature and/or humidity showed an increase in drug release which is not a result of curing. This may be due to the formation of film defects caused by internal pressures generated by dissolved venlafaxine HCl (osmotic pressure)[5] and the swelling of the core (hydrostatic pressure)[6]. The combination of these effects can apply stress to the film layer leading to the formation of cracks upon storage and during dissolution testing.

Microscopic images of the beads after dissolution testing revealed a coherent film layer for EC films applied from organic solution, while the aqueous ethylcellulose films appeared to have some degree of film defects (Figure 3). This could be mainly due to the greater tensile strength of the EC film from the organic solution, which may better accommodate the dimensional changes of the core while exposed to the dissolution media.

Figure 1. Venlafaxine HCl Release Profiles from Extruded and Spheronized Beads Coated with EC in Organic Solution

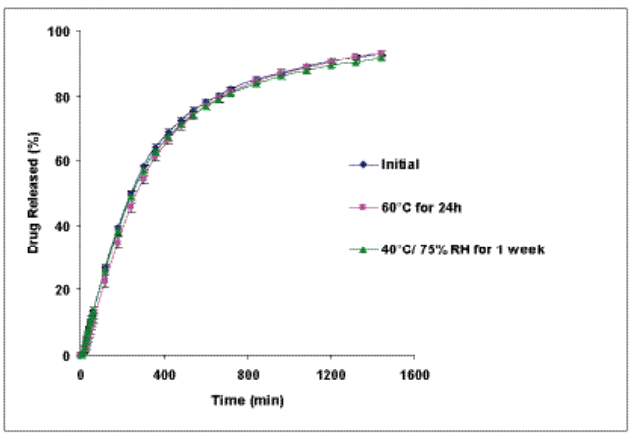


Figure 2. Venlafaxine HCl Release Profiles from Extruded and Spheronized Beads Coated with EC in Aqueous Dispersion

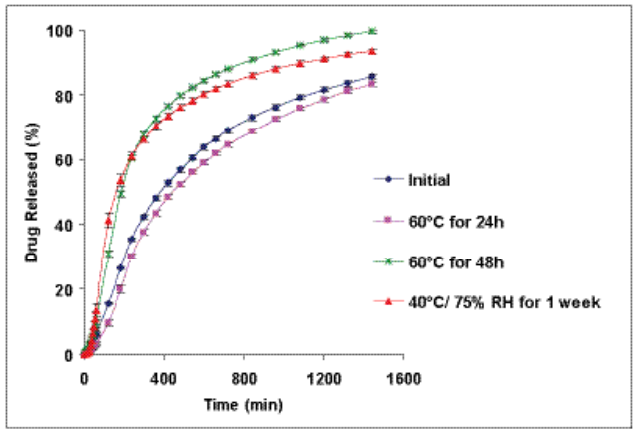
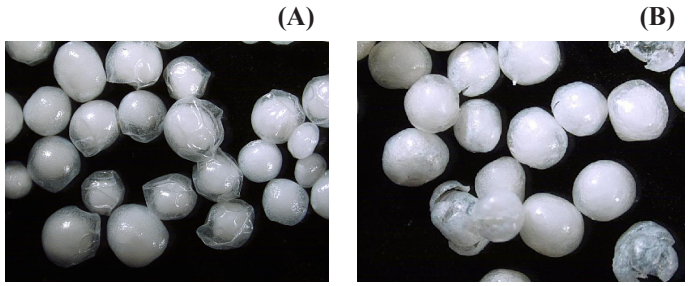


Figure 3. Microscopic Images of Beads coated with (A) EC in Organic Solution; (B) EC in Aqueous Dispersion, after Dissolution Testing



CONCLUSION:

Organic application of EC on venlafaxine HCl extruded and spheronized beads resulted in a consistent drug release. No significant effects were observed when treated with heat or heat and humidity. Application of an aqueous EC dispersion on the beads resulted in release profiles that were significantly affected by heat or heat and humidity treatment. This was related to the tensile strength of their respective films and the internal pressure generated during dissolution testing. Organic application of EC is therefore recommended for some challenging ER formulations such as extruded and spheronized venlafaxine HCl multi-particulates.

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