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Predictability of Drug Release from Multiparticulate Systems Coated with an Aqueous Ethylcellulose Dispersion

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Abstract Summary

Ethylcellulose content of pellets of various size fractions coated with an aqueous ethylcellulose dispersion (Surelease®) was measured by a GPC/HPLC with a refractive index detector. A correlation between the actual and theoretical ethylcellulose weight gain on coated pellets were found. Larger beads had higher quantity of the polymer deposited on them, and exhibited slower drug release. Ethylcellulose weight gain on the pellets affected the onset of release but not equilibrium release rate.

Introduction

Ethylcellulose is one of the most widely used water-insoluble polymer in film-coating to achieve extended drug release. Historically, due to its solubility characteristics ethylcellulose has been applied in organic solutions to generate films of various permeabilities[1,2]. The quantity of polymer deposition or thickness of the functional film on the multi-particulates is the critical factor affecting the integrity of these systems as well as drug release rates. There have been some efforts to quantify actual weight gain or film thickness on barrier film coated pellets[3]. However, in most coating applications the amount of ethylcellulose coating that is added is usually based on theoretical weight gain. This method of quantification by weight is prone to variability since it assumes that all theoretical weight of polymer added is deposited on the product and the efficiency of coating is 100%.

The aim of this study was to analytically quantify ethylcellulose deposited on drug loaded Nu-pareils, coated with aqueous ethylcellulose dispersion (Surelease) to various theoretical weight gains. Chlorpheniramine Maleate (CPM), a highly water soluble drug (1 in 4), was used as the candidate drug in this study.

Experimental

Coating Process:

Four batches of sugar spheres (Nu-pareils) 14-18 mesh, 18-20 mesh, 20-25 mesh, and 30-35 mesh were drug loaded [CPM (37.5 mg/gm)] in the rotor unit of the Glatt GPCG-3 using PVP K30 as the binding agent. The corresponding bead sizes are 1000-1410 µm, 840-1000 µm, 710-840 µm, and 500-590 µm, respectively. The drug loaded beads were then coated with Surelease (diluted to 15% solids w/w) in the Wurster unit of the GPCG-3. During the coating of the different sized beads, the product bed temperature was maintained at 42.7±0.5ºC by controlling the inlet air temperature (59±2ºC). Samples were pulled every 4 percent weight gain from 1-20% weight gain of Surelease. The coating process parameters are shown in Table 1.

Table 1. Surelease Coating Process Parameters

Nu-pareil Sizes (mesh)	14-18	18-20	20-25	30-35
Inlet Air Temp (°C)	56.6	59.9	59.6	60.5
Product Temp (°C)	43.1	42.6	42.3	42.6
Exhaust Air (°C)	41.5	40.4	40.8	40.4
Fluid Delivery Rate (g/min)	24.5	24.3	25.0	24.0
Atomizing Air pres. (Bar)	2.0	2.0	2.0	2.0
Exhaust Flap Set (%)	60.0	60.0	60.0	60.0
Air Volume (Me=3/hr)	106.9	78.1	73.7	73.9
Air Velocity (m/s)	8.0	7.6	7.5	7.2

Drug Release Determination:

Chlorpheniramine Maleate (CPM) release from 1 gram of coated pellets in 1000 mL of deionized water was measured using a USP Apparatus I (baskets) method at 100 rpm (37±0.5°C). Drug release was detected using UV spectrophotometer at 267nm.

Ethylcellulose Content Evaluation:

Approximately 500 mg of coated beads were ground and the ethylcellulose was extracted into tetrahydrofuran after 30 minutes of shaking. The extracted samples were analyzed for ethylcellulose content by GPC/HPLC with a Waters refractive index detector using a Shodex KF-801 GPC column. Results were calculated from the area under the peak and reported as percent ethylcellulose content.

Results and Discussion

The system suitability and calibration curve (r^2=0.9999) for ethylcellulose content evaluation were determined. Figure 1 shows the refractive index detector output for selected standards and Surelease coated bead samples.

Figure 1. Chromatograms for Selected Ethylcellulose Standards and Surelease Coated Bead Sample

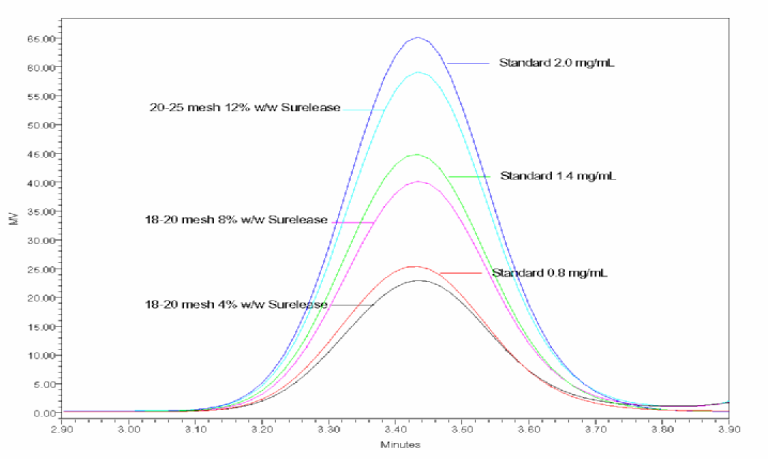


Figure 2 shows the actual ethylcellulose content of the Nu-pareils coated with Surelease against theoretical weight gain for various size fractions of pellets. There was a strong correlation between the actual and theoretical ethylcellulose content (r^2 = 0.9999). The relationship between the theoretical and actual ethylcellulose content is summarized in Equation 1.

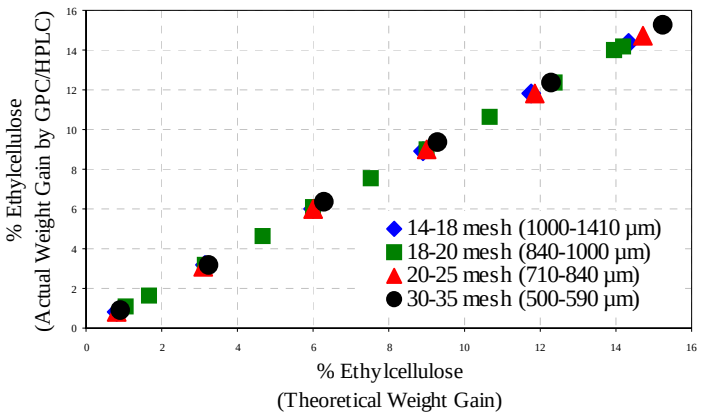
$$X_A = 1.0019 \bullet X_T + 0.0002 \qquad \textbf{(Equation 1)}$$

Where,

X_A = %Ethylcellulose [actual], and

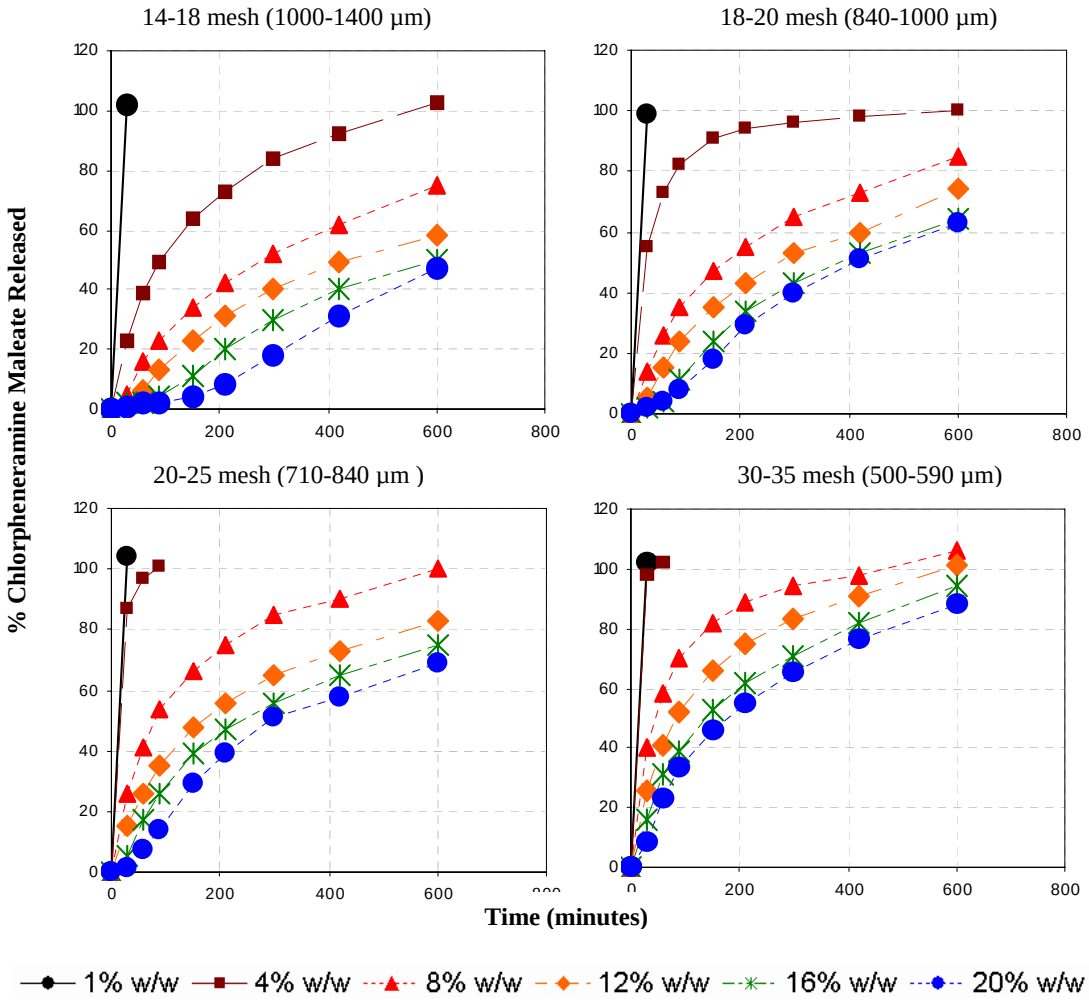
X_T = %Ethylcellulose [theoretical].

Figure 2. Correlation of Actual and Theoretical Ethylcellulose Content

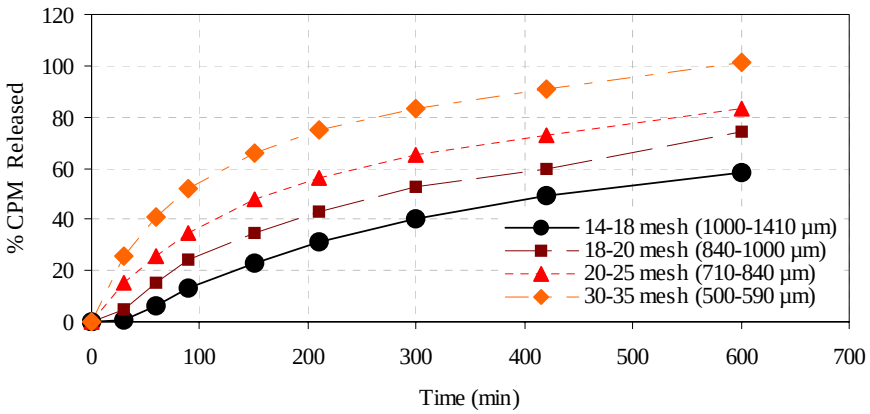


Release rate of CPM decreased with increasing Surelease applied and with increasing bead size. Figure 3 exhibits the drug release profiles from beads of various size fractions as a function of Surelease weight gain.

Figure 3. Release Profile of CPM from Beads Coated to Different Weight Gain of Surelease

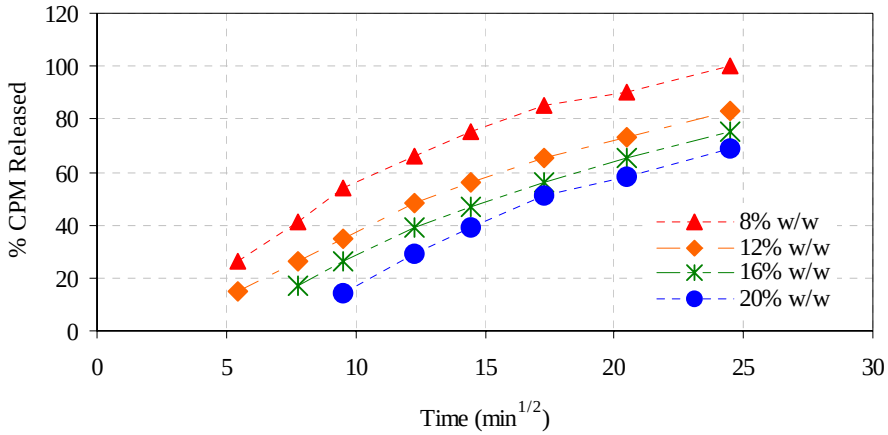


Decreasing the bead size increases the surface area available for polymer deposition, thereby reducing the thickness of the functional film. Larger beads due to lower total surface area, had a thicker film, and exhibited slower release of the drug (Figure 4).



Drug release was also plotted against the square root of time to determine the rate of CPM release. Representative square root of time release profiles for CPM from 20-25 mesh beads are shown in Figure 5.

Figure 5. Square Root of Time Release Profiles as a Function of Surelease Weight Gain for CPM from 20-25 Mesh Beads



Interestingly, Surelease weight gain affected the release profile of CPM, by affecting the onset of drug release. However, once drug release was initiated, the release profiles were similar irrespective of the amount of Surelease applied. In this case it appears that the initial lag time is more dependent on the thickness of the ethylcellulose film than the remaining release profiles. This phenomenon may be drug solubility, drug molecular weight dependent.

Conclusions

Analytical quantification of ethylcellulose on the coated pellets showed a strong correlation between the theoretical weight gain and the actual ethylcellulose on the pellets following a fluid bed coating process. This method may be used to validate process efficiency of an aqueous ethylcellulose dispersion coating system. This is also a powerful technique during formulation development to assist scale up of process parameters and achieving similar release profiles.

Drug release profiles from Surelease coated beads were dependent on the thickness of the functional film as well as the bead size. Adjusting the Surelease film thickness allowed altering the onset of drug release, followed by controlled release of the drug.

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