

The Influence of Pore Former Concentration and Coating Weight Gain on Drug Release from Multiparticulates Coated with Nutrateric[®], Nutritional Enteric Coating System

PURPOSE

Ethylcellulose (EC) is used as a film coating polymer in the pharmaceutical and nutritional industries to extend drug release, mask unpleasant tastes/odors, and improve product stability. EC is a water-insoluble, pH independent polymer which forms a non-eroding diffusional barrier¹. The permeability of EC films may be altered by the addition of pH dependent or pH independent polymers. For example, adding a nonionic polymer such as hypromellose to an EC coating increases film permeability causing increased drug release independent of the physiological pH range of the gastrointestinal tract. Conversely, adding acidic polymers decreases film permeability at low pH, preventing drug release in the stomach, yet increases film permeability at high pH, allowing drug release in the small intestine. The aim of this study was to investigate the influence of pH dependent pore former concentration and coating weight gain on drug release from multiparticulates coated with Nutrateric[®], nutritional enteric coating system. Nutrateric is a two component system comprised of an aqueous EC dispersion (Surelease[®], aqueous ethylcellulose dispersion) and a pre-formulated powder additive containing sodium alginate (NS Enteric[®], nutritional enteric component). The sodium alginate functions as a pH dependent pore former within the EC film to provide delayed release functionality.

METHODOLOGY

Sugar spheres, 18-20 mesh, Surelease E-7-19040, and NS Enteric 29Z19241 were obtained from Colorcon. Chlorpheniramine maleate (CPM, solubility 0.9 g/mL), polyvinylpyrrolidone (PVP, Povidone K30) and hypromellose (Pharmacoat 606, 6cP) were obtained from SigmaAldrich, BASF, and Shin-Etsu, respectively.

Drug Loading

Sugar spheres (850-1000 μ m) were drug loaded (CPM, 34.0mg/g) in the rotor unit of a Glatt GPCG-3 fluid bed using PVP K-30 as the binding agent. Drug loaded sugar spheres were then seal-coated with hypromellose (0.5% w/w theoretical weight gain (WG), 10% solids content).

Film Coating

The Nutrateric coating dispersions were prepared by dispersing the NS Enteric (10, 15, or 20% w/w) in water under low shear and mixing for 60 minutes. Surelease (90, 85, or 80% w/w) was added and mixed slowly for an additional 10 minutes. The solids content of the final dispersions was 10% (w/w). Nutrateric was

applied to theoretical weight gains of 15, 20, 25, and 30% (w/w) in the Glatt GPCG-3 using a Wurster coating configuration. Table 1 shows the final film coating compositions and theoretical weight gains for each coating trial. Table 2 shows the process parameters used to apply Nutrateric.

Table 1. Final Film Coating Compositions

NS Enteric™ (% w/w)	Surelease® (% w/w)	Final Solids Content (% w/w)	Theoretical Weight Gains (% w/w)
10	90	10	15, 20, 25, 30
15	85	10	15, 20, 25, 30
20	80	10	15, 20, 25, 30

Table 2. Coating Process Parameters

Coating Parameters for Nutrateric®	Glatt GPCG-3 Wurster Configuration
Charge (kg)	2
Inlet air temperature (°C)	65
Product temperature (°C)	46
Exhaust temperature (°C)	44
Fluid delivery rate (g/min)	25
Atomizing air pressure (bar)	2
Exhaust flap setting (%)	50
Air volume (m³/hr)	80
Air velocity (m/s)	7.5

Drug Release

Dissolution testing in a USP apparatus 1 (basket), with 1000 mL of 0.1N HCl for two hours followed by phosphate buffer pH 6.8 (1000 mL) at 37 ± 0.5°C and 100 rpm, was carried out for all samples (n=6). CPM absorbance was measured using a Cary 50 spectrophotometer at 265 nm.

RESULTS

All of the coated multi-particulates maintained integrity during the initial two hours in 0.1N HCl; no more than 5% of the drug was prematurely released from the formulations studied here. Drug release in phosphate buffer (pH 6.8) provided discriminating results as illustrated by the following dissolution profiles.

At 15% weight gain, 80% of the drug was released after 30 minutes in phosphate buffer regardless of the coating composition (Figure 1). At 20, 25, and 30% weight gains, 80% of the drug was released between 30 and 60 minutes in phosphate buffer when the coating compositions were 15:85 and 20:80% NS Enteric:Surelease. The 10:90% NS Enteric:Surelease composition at 20, 25, and 30% weight gains required two to three hours for 80% of the drug to be released (Figures 2-4).

Figure 1. Drug Release in Phosphate Buffer (pH 6.8) After 2 Hours in 0.1N HCl

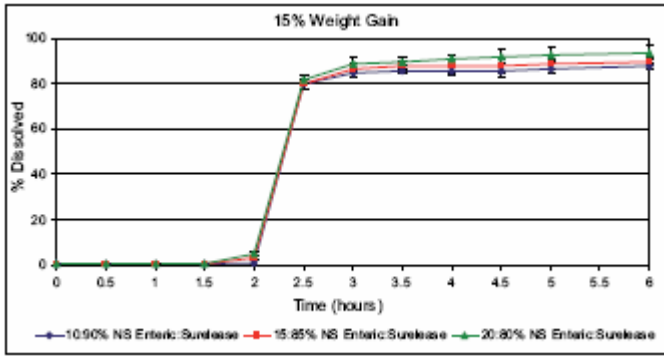


Figure 2. Drug Release in Phosphate Buffer (pH 6.8) After 2 Hours in 0.1N HCl

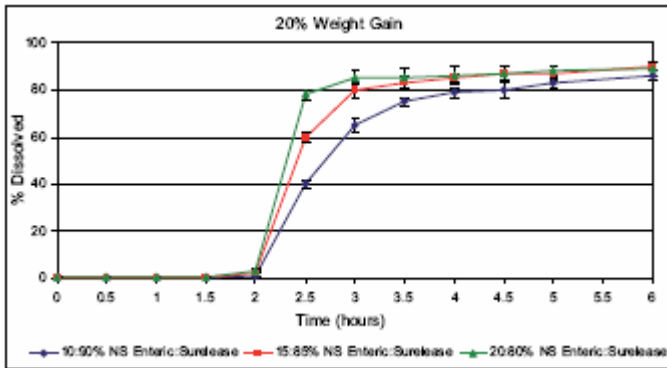


Figure 3. Drug Release in Phosphate Buffer (pH 6.8) After 2 Hours in 0.1N HCl

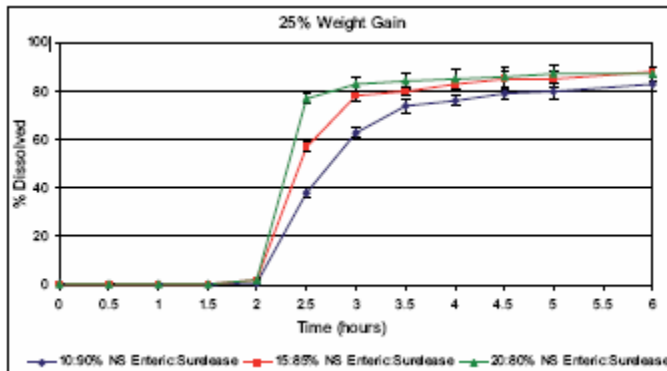
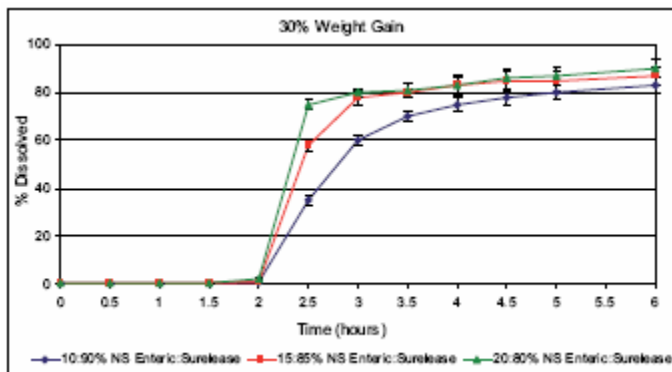


Figure 4. Drug Release in Phosphate Buffer (pH 6.8) After 2 Hours in 0.1N HCl



The lowest weight gain evaluated (15% w/w) released faster in phosphate buffer compared to higher weight gains (20, 25, and 30% w/w) when coated with 10:90 and 15:85% NS Enteric:Surelease compositions (Figures 5 and 6). Drug release rates were similar at each weight gain for the 20:80% NS Enteric:Surelease composition (Figure 7).

Figure 5. The Influence of Nutrateric Weight Gain on Drug Release from Multiparticulates Coated with 10:90% NS Enteric:Surelease

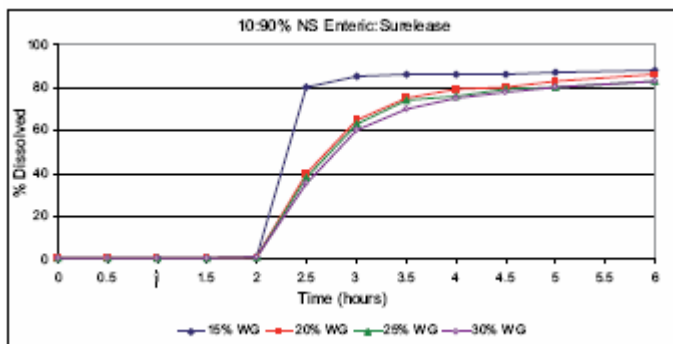


Figure 6. The Influence of Nutrateric Weight Gain on Drug Release from Multiparticulates Coated with 15:85% NS Enteric:Surelease

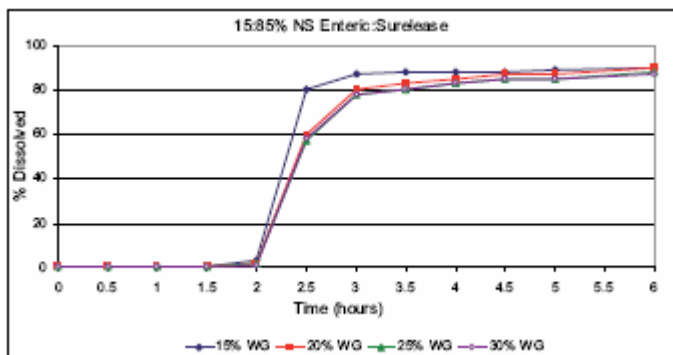
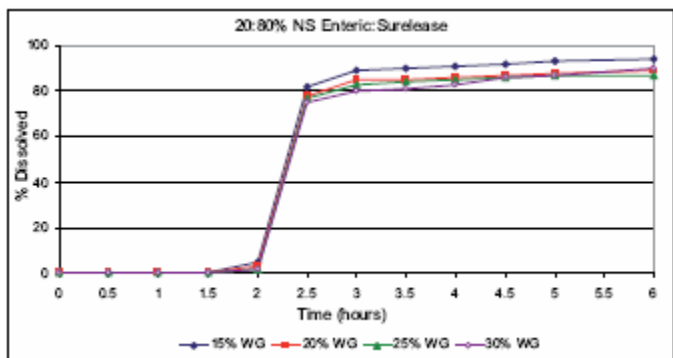
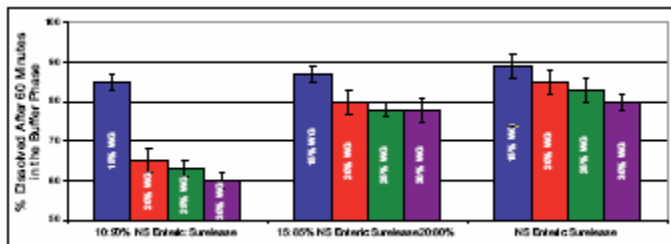


Figure 7. The Influence of Nutrateric Weight Gain on Drug Release from Multiparticulates Coated with 20:80% NS Enteric:Surelease



The percent of CPM dissolved after 60 minutes in phosphate buffer relative to coating weight gain and coating composition is shown in Figure 8. Following two hours in 0.1N HCl, drug release in phosphate buffer was slower from higher coating weight gains, as expected. Likewise, the higher the Surelease concentration, the slower the drug release in phosphate buffer.

Figure 8. CPM Release in Phosphate Buffer Relative to Weight Gain and Coating Composition



The sodium alginate component of NS Enteric functions as a pH dependent pore former within the Surelease film to provide delayed release functionality. The sodium alginate converts to alginic acid, upon exposure to 0.1N HCl and remain insoluble, providing acid protection as intended. After the media change to pH 6.8, alginic acid reverts to an ionized alginate, hydrates and provides increased drug release due to increased permeability of the film.

CONCLUSIONS

In this study, the combination of a pH dependent pore former and an aqueous ethylcellulose dispersion resulted in the desired delayed drug release profiles from multiparticulate systems. Coating level and pore former concentrations were tailored to alter the duration of the delay in drug release followed by rapid release in higher pH media.

REFERENCES

1. Agrawal, A., et. al., Pharm Sci Tech, Volume 4, (4) Article 60, 2003, 1-11.
2. Handbook of Pharmaceutical Excipients, Third Edition, American Pharmaceutical Association and Pharmaceutical Press, 2000.

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