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Formulation and Characterization of a Compacted Multiparticulate System for Modified Release of Water-Soluble Drugs—Part II Theophylline and Cimetidine

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The purpose was to investigate the effectiveness of an ethylcellulose (EC) bead matrix and different film-coating polymers in delaying drug release from compacted multiparticulate systems. Formulations containing theophylline or cimetidine granulated with Eudragit® RS 30D were developed and beads were produced by extrusion–spheronization. Drug beads were coated using 15% wt/wt Surelease® or Eudragit® NE 30D and were evaluated for true density, particle size, and sphericity. Lipid-based placebo beads and drug beads were blended together and compacted on an instrumented Stokes B2 rotary tablet press. Although placebo beads were significantly less spherical, their true density of 1.21 g/cm^3 and size of 855 μm were quite close to Surelease®-coated drug beads. Curing improved the crushing strength and friability values for theophylline tablets containing Surelease®-coated beads; 5.7 ± 1.0 kP and 0.26 ± 0.07%, respectively. Dissolution profiles showed that the EC matrix only provided 3 h of drug release. Although tablets containing Surelease®-coated theophylline beads released drug fastest overall ($t_{44.2\%}$ = 8 h), profiles showed that coating damage was still minimal. Size and density differences indicated a minimal segregation potential during tableting for blends containing Surelease®-coated drug beads. Although modified release profiles >8 h were achievable in tablets for both drugs using either coating polymer, Surelease®-coated theophylline beads released drug fastest overall. This is likely because of the increased solubility of theophylline and the intrinsic properties of the Surelease® films. Furthermore, the lipid-based placebos served as effective cushioning agents by protecting coating integrity of drug beads under a number of different conditions while tableting.

Keywords multiparticulate system; modified release; hydrophobic matrix; ethylcellulose; extrusion–spheronization

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INTRODUCTION

Creating a multiparticulate, modified release dosage form containing a water-soluble drug involves several stages of development and evaluation in order to determine suitable excipient usage levels and processing parameters. Although formulation strategies such as the use of a hydrophobic matrix and/or film coating can be employed to attain a certain level of drug release, each technique would require optimization and need to be examined separately to determine its level of effectiveness in the dosage form.

Beads produced by extrusion–spheronization offer potential therapeutic advantages of reproducibility of drug blood levels, improved bioavailability, and a lowered risk of side effects by preventing dose dumping (Bechgaard & Nielsen, 1978). Moreover, beads can be manufactured with higher drug loads, a narrow particle size distribution, spherical shape, good flow properties, and low friability (Vervaet, Baert, & Remon, 1995). Beads with similar densities and particle sizes will show a lesser tendency toward segregation during tableting and this can decrease problems, such as weight variation and content uniformity (Aulton, Dyer, & Khan, 1994).

Theophylline and cimetidine are highly water-soluble drugs and were chosen for this study as they are less soluble than acetaminophen and therefore, their release profiles can be better controlled within the constraints of this multiparticulate system (Cantor, Hoag, & Augsburger, 2008). Drugs that are good candidates for modified release would be those with high aqueous solubility, relatively short half-lives, and narrow therapeutic indices (Buckton, Ganderton, & Shah, 1988). By using a combination of a hydrophobic matrix, acrylic-based granulating agent, and polymeric barrier film coatings, formulations containing highly water-soluble drugs can be made dissolution rate limited for extended release (>8 h); and this can ultimately benefit patients by reducing dosing frequency.

Although much has been published on the topic of hydrophilic matrices in tablets, to our knowledge, no work to date

has examined the potential role of micronized ethylcellulose (EC) powder as a hydrophobic matrix in extruded drug-loaded beads, except for the acetaminophen research that was previously discussed by Cantor et al. (2008). Additionally, little work has also been published examining what effect multiple release retardant techniques in combination with an EC matrix may have on drug-release profiles (Tiwari, Murthy, Pai, Mehta, & Chowdary, 2003). EC can yield a variety of release profiles dependent on many factors, such as total polymer level, viscosity, particle size, and so forth. A relatively new product, the low viscosity (7 cP) micronized grade of EC (mean particle size: 9 μm) was selected for this work because of its proven success in granulation whereas coarse grades were unsuccessful (Agrawal, Manek, Kolling, & Neau, 2003). The large surface area of the micronized EC powder should enable it to uniquely participate in the bead matrix to delay drug release. Hydrophobic polymers such as EC can also provide several advantages, ranging from good stability to varying moisture and pH levels, the latter because of its non-ionic nature. EC is also cost effective and has broad regulatory acceptance in the pharmaceutical industry.

Acrylic polymers can also be used alone or in conjunction with EC to delay release of water-soluble drugs. Eudragit® RS 30D is a low permeability aqueous dispersion of a pH-independent methacrylate copolymer that has been used successfully in film coating for beads (Heng, Hao, Chan, & Chew, 2004; Zhu, Mehta, & McGinity, 2006), tablets (Alkhatib & Sakr, 2003; Lee, Ryu, & Cui, 1999), as a tablet matrix during direct compression when used in its powdered form (Rey, Wagner, Wehrle, & Schmidt, 2000), and infrequently as a wet granulation binder (Wang et al., 1997). Another alternative in film coating of drug beads is to use an aqueous pseudolatex dispersion of plasticized EC known as Surelease®. This polymer has been previously used to coat phenylpropanolamine HCl beads and the authors found that increasing the coating level from 10 to 15% wt/wt lowered the mean pore diameter and porosity of the coating layer to delay drug release of this highly water-soluble drug salt (Vuppala, Parikh, & Bhagat, 1997).

The drawback for preparing tablets from drug beads which have received a modified release coating is that the compressive stress can cause the coating to develop cracks and rupture, thus destroying the extended release effect. This is manifested as an increase in the drug dissolution rate. Different placebo cushioning agents with varying particle sizes, material properties (plastic or brittle) or bulk densities have been previously used in trying to overcome this obstacle such as Avicel® PH-200 powder (Dashevsky, Kolter, & Bodmeier, 2004), freeze-dried beads (Habib, Augsburger, & Shangraw, 2002), wax beads (Debunne, Vervaet, Mangelings, & Remon, 2004; Vergote, Kiekens, Vervaet, & Remon, 2002; Zhou, Vervaet, & Remon, 1996; Zhou, Vervaet, Schelkens, Lefebvre, & Remon, 1998), and beads composed of microcrystalline cellulose alone (Celik & Maganti, 1994), in combination with a soft waxy material such as polyethylene glycol (Nicklasson & Alderborn, 1999a; Torrado & Augsburger, 1994), or with other excipients such as lactose (Aulton et al., 1994); or dibasic calcium phosphate dihydrate (Nicklasson & Alderborn, 1999b). Moreover, Debunne et al. (2004) and Vergote et al. (2002) compacted mixtures of paraffin wax beads with coated drug beads and demonstrated through cross-sectional scanning electron micrographs of tablets that this was a viable dosage form by showing intact drug beads embedded in the wax matrix.

However, with all the variables mentioned earlier, the drug-release data is largely dependent not only on the polymeric coating and levels used on the drug beads, but also on the physical and mechanical properties of both the drug and placebo beads themselves. Furthermore, segregation during mixing and tableting remains a potential problem when blending coated drug beads with Avicel® powders (Aulton et al., 1994; Dashevsky et al., 2004) or with low bulk density beads prepared by freeze drying (Habib et al., 2002).

For example, previous work has shown that compression of beads coated with EC pseudolatexes from either Aquacoat® (Dashevsky et al., 2004) or Surelease® (Chang & Rudnic, 1991; Palmieri & Wehrle, 1997) resulted in the rupture of the coating as evidenced by a high dissolution rate. Celik and Maganti (1994) used propranolol HCl beads coated with Surelease® at 10% wt/wt, 15% wt/wt, and 20% wt/wt and found that regardless of the amount of coating applied, the beads lost their sustained release properties upon application of relatively low compression pressures. Additionally, more recent work also indicated that EC films were more brittle than the acrylic films (i.e., Eudragit® RS/RL 30D or Eudragit® NE 30D) and that EC films also showed large cracks under strain (Bussemer, Peppas, & Bodmeier, 2003). On the other hand, while compacted propanolol HCl beads coated with an acrylic dispersion of Kollicoat® SR 30D also showed coating rupture during dissolution, adding 10% wt/wt triethyl citrate (TEC) as a plasticizer successfully prevented coating damage from occurring because of the increased flexibility of the film (Dashevsky et al., 2004).

The composition of the cushioning placebo beads also plays a major role in preventing coating damage to the drug beads. Although placebos composed of Avicel® and lactose were ineffective cushioning agents because of their strength and lack of plasticity (Aulton et al., 1994), Salako, Podczeck, and Newton (1998) found that beads containing glyceryl monostearate (GMS) were more deformable during compaction than beads prepared from harder materials. Blending GMS beads with coated drug beads prior to compaction can assist in maintaining the sustained drug-release effect; this is because the GMS beads function as lubricants to reduce interparticle and die wall friction as well as facilitate interparticle packing during tableting (Lundqvist, Podczeck, & Newton, 1998; Pinto, Podczeck, & Newton, 1997). However, it is important to keep in mind that during dissolution, high levels of such hydrophobic materials can cause liquid penetration into the tablet matrix to be the rate-limiting step. Moreover, some authors believe that the

plastic materials present in placebo beads, such as GMS, can actually increase tablet compactability. This effect from compacted GMS beads is believed to be because of their more deformable nature, which can allow for a high degree of interparticle bonding and thus, an increase in tablet tensile strength (Iloanusi & Schwartz, 1998; Lundqvist, Podczeck, & Newton, 1997; Mount & Schwartz, 1996).

The overall objective of this research is to develop modified release tablet formulations of different water-soluble drugs with in vitro release profiles greater than 8 h. Moreover, it was also desired to study (a) the effectiveness that each different formulation variable (i.e., EC level in matrix, RS/RL ratio, type of bead coating polymer used, and so forth) had on the suppression of drug release, (b) the protective cushioning effect of the different placebo beads, and (c) how release was affected by the differences in drug solubility.

MATERIALS AND METHODS

Materials

Fine particle EC 7 cP viscosity grade (Ethocel 7-FP Premium) with an ethoxyl content of 48.0–49.5% was a gift from Dow Chemical Company (Midland, MI, USA). Microcrystalline cellulose NF was supplied by FMC Corp., Princeton, NJ, USA. Talc (Imperial 500 USP) was used in bead coating formulations and supplied by Luzenac (Greenwood Village, CO, USA).

Cimetidine USP, theophylline anhydrous USP, and glycerol monostearate flakes were purchased from Spectrum Chemicals (New Brunswick, NJ, USA). Milled calcium phosphate dibasic anhydrous was obtained from Innophos (Cranbury, NJ, USA). Sodium Starch Glycolate NF was supplied by JRS Pharma, Patterson, NY, USA; Starch 1500 NF and Surelease® (EC pseudolatex dispersion) were supplied by Colorcon (West Point, PA, USA); Eudragit® RS 30D (Ammonio methacrylate copolymer "type B") and Eudragit® NE 30D (Methacrylic ester copolymer) were supplied by Degussa Pharma Polymers (Piscataway, NJ, USA). TEC, used as a plasticizer, was supplied by Morflex, Inc. (Greensboro, NC, USA).

Bead Manufacture: Theophylline or Cimetidine Beads and Lipid-Based Placebos

All powders for drug bead formulations were mixed in a 16-quart twin-shell blender (Patterson-Kelley Co., East Stroudsburg, PA, USA) for 10 min. Batches of 1,500 g were granulated in a planetary mixer (Model KU-1, Erweka, Heusenstamm, Germany) using Eudragit® RS 30D polymer solution. Distilled water (q.s.) was also added in order to obtain the correct consistency for extrusion; and mixing continued until individual moist drug granules appeared (Table 1). Control formulations were prepared with calcium phosphate dibasic anhydrous in place of EC. However, the control batches did not readily absorb moisture and granulate well even after mixing, therefore, these batches were dried on stainless steel trays for approximately 3 h at 50°C. This mass was then returned to the planetary mixer to obtain granules before proceeding. After the wet mass was prepared, it was extruded at 37 rpm using a single-screw extruder (Model # EXKS-7, Fuji Paudal Co., Osaka, Japan) fitted with a screen of 1-mm aperture size. The extrudates were then immediately spheronized for 1 min at 500 rpm using a spheronizer (Model 15, GB Caleva Ltd., Ascot, UK) equipped with a 375 mm diameter cross-hatched plate. The drug beads were dried for 24 h at 50°C to a final moisture content of <1.0% using a tray drier (Model 1018E, Colton, Detroit, MI, USA).

TABLE 1
Drug Bead Formulations for Theophylline or Cimetidine

Component[a]	Ethylcellulose (EC)	Control
Theophylline or Cimetidine (15 mg)	8.6	8.6
Avicel® PH-101	15.4	15.4
Ca_2HPO_4, anhydrous	0.0	58.0
Eudragit® RS 30D	18.0	18.0
Ethylcellulose, 7cP	58.0	0.0
Distilled water[b]	20.0	32.0

[a]All quantities are in % wt/wt.
[b]Calculated on a dry weight basis.

The lipid-based placebo beads used excipients listed in Table 2. All powders were initially dry blended together. Batches of 1,300 g were prepared by first heating the GMS to 80°C in a stainless steel beaker on a double boiler. All powders were then slowly added into the GMS while the mixture was being continuously stirred with a metal spatula. Once the powder blend was added, the mixture was subsequently homogenized using a high shear homogenizer (Model PT 10/35, Polytron® Kinematica AG, Brinkmann Instruments, Westbury, NY, USA) at 22,000 rpm for an additional 10 min. An ice bath was used to cool the mixture to 50°C, and then the material was hand sieved through a #12 screen and the beads were immediately spheronized at 550 rpm for 25 s. The material was again sieved on a #30 screen and the fines discarded.

TABLE 2
Placebo Wax Bead Formulation

Component[a]	%
Glycerol monostearate	50.0
Starch 1500	42.0
Sodium Starch Glycolate	8.0

[a]All quantities are in wt/wt.

Particle Size and Shape Analysis

Bead particle size was determined in duplicate by sieve analysis and was performed with a 6–9 g sample using an Allen Bradley ATM Model L3P Sonic Sifter® (Milwaukee, WI, USA). The screen sizes used were #18, #20, #25, #30, #35, and #40. All tests were run for 5 min with amplitude and pulse settings of five.

Graphical analysis showed the particle size distributions to be log-normal since the logarithmic transformation decreased the skewness of the distribution. The percentage by weight retained on each sieve was determined and the geometric mean diameter, labeled as GMD or d_g, and geometric *SD*, σ_g, of the particle size distributions were calculated using the following equations (Fan et al., 2005):

$$\log d_g = \frac{\sum (n_i * \log d_i)}{\sum n_i}, \quad (1)$$

where n_i is the weight percentage of particles in the *i*th interval, for all n_i; and d_i is equal to the midpoint of the diameter of the size interval in the *i*th interval, for all d_i.

$$\log \sigma_g = \left[\frac{\sum n_i (\log d_i)^2}{\sum n_i} \right]^{1/2}, \quad (2)$$

A two-dimensional shape factor was measured using a Nikon Eclipse ME600 optical microscope (Nikon, Inc., Melville, NY, USA) coupled with SPOT v. 3.5.6 image analysis software (Diagnostic Instruments, Inc., Sterling Heights, MI, USA). Illumination was achieved via transmission; the total magnification was 50×. The calculation used the following equation with a value of 1 indicating a perfect sphere, and any value less than that reflecting a deviation from sphericity (Debunne et al., 2004):

$$\text{Sphericity} = \frac{(4\pi \cdot \text{projected area})}{(\text{perimeter})^2}. \quad (3)$$

True Density

True density was measured using a helium displacement pycnometer (Accupyc 1330, Micromeritics, Norcross, GA, USA) according to the USP 29 general chapter <699> on density of solids. The densities reported are the average of five determinations.

Moisture and Bulk Density

All batches were dried to a loss on drying (LOD) <1.0% with an endpoint rate set at <0.01%/min. LOD was determined on dried batches using a Computrac Max 2000XL Moisture Analyzer (Arizona Instruments, Tempe, AZ, USA). Bulk densities of beads were determined in duplicate using a powder funnel to gently fill beads up to the 60-mL mark on a 100-mL graduated cylinder.

Coating of Theophylline and Cimetidine Beads

Coating trials were performed at UPM Pharmaceuticals, Inc. (Baltimore, MD, USA). Batches of 400 g of beads containing either theophylline or cimetidine were coated to a 15% wt/wt theoretical weight gain with either Surelease® or Eudragit® NE 30D using a Glatt GPCG-2 fluid bed processor (Binzen, Germany) equipped with an 0.8-mm nozzle. Surelease® was diluted from a 25% wt/wt dispersion to 15% solids with water before beginning the coating operation. Bottom spraying was performed using a 10 in. Wurster insert (3.625 in. diameter), a Master Flex LS peristaltic pump, and an atomizing air pressure of 1 bar. For Surelease® coating, the inlet air temperature was approximately 60–65°C, product temperature 40°C, and exhaust air temperature was 39°C. The beads were then dried in the same apparatus for 5 min at the same temperatures.

Coating of beads using Eudragit® NE 30D was performed according to the following formulation:

Ingredient	%
Eudragit® NE 30D	74.90
Talc 500 USP	9.98
Water	15.12

The Eudragit® NE 30D dispersion was first passed through a #20 screen and accurately weighed into a stainless steel beaker; then the appropriate amount of water was added. This solution was subsequently homogenized on low speed (setting 1) using an IKA Ultra Turrax T-25 homogenizer (IKA Works, Inc., Wilmington, NC, USA). Talc was then slowly added and mixing continued for an additional 1 min. The coating conditions for Eudragit® NE 30D are as follows: the inlet air temperature was approximately 35°C, product temperature 26°C, and exhaust air temperature was 25°C. The beads were then dried in the same apparatus for 5 min at the same temperatures.

Tableting and Tablet Evaluation

For manual tableting studies, 10 g of a combination of drug and placebo beads in various ratios were added to a plastic bag and mixed for 3 min. For automatic tableting studies, 400 g of a combination of drug beads and placebo beads in various ratios were added to a plastic bag and mixed for 3 min. A single-station instrumented Stokes B2 rotary tablet press (operating at 30 rpm) equipped with an instrumented eye bolt for compression force and an ejection cam for ejection force was used with 8.7 mm round, concave punches. Beads were accurately weighed and manually filled into the die to achieve target tablet weights of 350 ± 5 mg. Tablet crushing strength

(hardness) was determined by diametric compression using a hardness tester (Model HT-300, Key International, Inc., Englishtown, NJ, USA). All tablets were allowed to stay at ambient temperature for 24 h before hardness testing to allow for elastic recovery. Eighteen tablets were subjected to 100 rotations in a friabilator (Model TA, Erweka, GmbH, Germany) rotating at 25 rpm following USP 24 Method <1216>. To improve tablet crushing strength, tablets were heated for 24 h at 50°C using an oven.

Dissolution Testing

Dissolution testing of tablets or beads was performed in 900 mL distilled water at 37 ± 0.5°C using USP apparatus II at 50 rpm (Vankel VK 7000, VanKel Industries, Inc., Cary, NC, USA). The temperature was maintained using a bath heater (Model VK 750D, VanKel, Edison, NJ, USA). Samples (1.5 mL) were manually withdrawn at specified time intervals and replaced by new media. The samples were placed in Eppendorf® centrifuge tubes and spun using a Eppendorf® 5415C centrifuge (Brinkmann Instruments, Inc., Westbury, NY, USA) at 13,000 rpm for 2 min. This was found to be more effective than filtration and led to more stable spectrophotometric readings. The cimetidine and theophlline samples were spectrophotometrically analyzed according to USP 24, at 219 and 270 nm, respectively, using a Spectronic Genesys 2 UV/VIS spectrophotometer (Thermo Electron Corp., Waltham, MA, USA). The weight of tablets used was 350 mg, and when beads were studied, an amount corresponding to the equivalent drug amount from tablets was used. All dissolution testing was performed under sink conditions and profiles are the mean of six replicates. Standard curves ($R^2 \geq .999$) were generated for each drug and the amount of dissolved drug was normalized based on the amount present in the tablet or bead.

The similarity factor, f_2, was used to determine if dissolution profiles were different; generally an f_2 value between 50 and 100 is taken as the criterion for equivalence. The f_2 metric equation is a logarithmic transformation of the sum of the squared error (Guidance for Industry, 2000) and is expressed as

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}, \qquad (4)$$

where n is the number of time points, R_t and T_t are the percent drug dissolved for the reference and test products, respectively, at each time point t. Dissolution data time points below 85% drug release and only one sampling time point above 85% were used in the calculations of the f_2 metric, since the use of additional data points above 85% release (i.e., after the dissolution plateau has been reached) has been previously shown to bias the similarity factor and introduce error (Shah, Tsong, Sathe, & Liu, 1998). This pair-wise method of comparing dissolution profiles has been suggested by SUPAC for immediate release solid oral dosage forms to determine bioequivalence (Guidance for Industry, 1995), but is also suitable when making comparisons among modified release dosages as well.

Statistical Analysis

Statistical analysis of the data was performed using analysis of variance (ANOVA) with least significant difference (LSD) as the post hoc test. A p-value of less than .05 was considered significant (SPSS v.12, Chicago, IL).

RESULTS AND DISCUSSION

Characterization of Uncoated and Coated Drug Beads and Lipid-Based Placebo Beads

The characterization of some physical properties of uncoated and coated theophylline–EC and cimetidine–EC beads and their controls along with the lipid-based placebo beads is shown in Tables 3 and 4. Although the uncoated control beads were similar in particle size they were significantly

TABLE 3
Bulk and True Densities, Particle Size and Sphericity for Uncoated Theophylline and Cimetidine Beads

Sample	Bulk Density[a] (g/cm^3)	True Density[b] (g/cm^3)	Particle Size $d_g \pm \sigma_g$[c] (μm)	Sphericity[d]
Cimetidine–EC	0.63 ± 0.03[e]	1.21 ± 0.00[e]	812.1 ± 1.2	0.93 ± 0.03[e]
Cimetidine control	1.00 ± 0.04[e]	1.93 ± 0.00[e]	798.2 ± 1.2	0.92 ± 0.05
Theophylline–EC	0.59 ± 0.01[e]	1.22 ± 0.00[e]	793.9 ± 1.5	0.89 ± 0.05[v]
Theophylline control	1.00 ± 0.04[e]	1.96 ± 0.00[e]	809.4 ± 1.2	0.87 ± 0.05[e]

[a]$M \pm SD$; $n = 2$.
[b]$M \pm SD$; $n = 5$.
[c]Geometric mean diameter ± geometric SD, $n = 2$.
[d]$M \pm SD$; $n = 30$.
[e]Means are significantly different within each column by one-way ANOVA with LSD as the post hoc test ($p < .05$).

TABLE 4
Bulk and True Densities, Particle Size and Sphericity for Coated Theophylline and Cimetidine Beads and Placebo Beads

Sample	Bulk Density[a] (g/cm^3)	True Density[b] (g/cm^3)	Particle Size $d_g \pm \sigma_g$[c] (μm)	Sphericity[d]
Cimetidine–EC (Surelease®)	0.63 ± 0.02	1.20 ± 0.00[e]	854.0 ± 1.1	0.91 ± 0.04[e]
Theophylline–EC (Surelease®)	0.65 ± 0.00[e]	1.22 ± 0.00[e]	855.1 ± 1.3	0.89 ± 0.03[e]
Cimetidine–EC (NE 30D)	0.69 ± 0.01[e]	1.24 ± 0.00[e]	881.7 ± 1.2	0.91 ± 0.04[e]
Theophylline–EC (NE 30D)	0.69 ± 0.01[e]	1.27 ± 0.00[e]	862.7 ± 1.2	0.91 ± 0.04[e]
Placebo	0.58 ± 0.00[e]	1.21 ± 0.00[e]	858.0 ± 1.3	0.73 ± 0.08[e]

[a]$M \pm SD$; $n = 2$.
[b]$M \pm SD$; $n = 5$.
[c]Geometric mean diameter ± geometric SD, $n = 2$.
[d]$M \pm SD$; $n = 30$.
[e]Means are significantly different within each column by one-way ANOVA with LSD as the post hoc test ($p < .05$).

denser ($p < .05$) than their EC counterparts. This is because the less dense EC has been replaced entirely in their formulation by dicalcium phosphate dihydrate. Both uncoated and coated drug beads were observed to have similar sphericity values (sphericity ≈ 0.90). The placebo beads, being composed of 50% GMS, generally had lower densities compared with coated drug beads and because they were hand-screened, had significantly lower ($p < .05$) sphericity values with the highest *SD*.

Although the bulk and true densities of placebo beads appeared similar to Surelease®-coated theophylline beads, they were still considered statistically significantly different ($p < .05$). Likewise, the particle size of the placebo beads was also similar to the Surelease®-coated drug beads. However, the densities of Eudragit® NE 30D-coated drug beads were approximately 20% higher when compared with placebo beads. When comparing the bead size increase between uncoated and coated drug beads, it was noticed that the use of Eudragit® NE 30D consistently yielded larger bead sizes over Surelease®, perhaps owing to the higher tackiness of the Eudragit® NE 30D dispersion. Although these density and size differences will have a definite impact on the segregation tendency of blends of drug beads and placebo beads during tableting, different screen sizes can be selected for both the extruder and placebo beads to meet any desired size and to bring the differences in either particle size or density to a minimum.

Tablet Properties

It was found that heating the 350 mg theophylline or cimetidine tablets for 24 h at 50°C significantly improved their crushing strength and friability. Without the heat treatment, average tablet crushing strength was 3.0–4.5 kP but after curing, the crushing strength ranged from 4.7 to 8.0 kP. In examining 12.75 mg theophylline tablets containing 50% Surelease®-coated beads, the crushing strength difference between uncured and cured tablets was 3.7 ± 0.7 kP and 5.7 ± 1.0 kP, respectively. Likewise, the friability difference between uncured and cured tablets was 1.59 ± 0.05% and 0.26 ± 0.07%, respectively. Friability values were well within USP limits of less than 1.0% for cured tablets.

It appears that a possible reason for this increase in tablet crushing strength is because of the partial melting and recrystallization of the GMS (m.p. 53°C) around the drug beads. Crushing strength values ≥8 kP are considered practical and indicate that tablets would have the appropriate mechanical strength to undergo further processing, as in a coating operation or during packaging and handling (Alvarez-Fuentes, Fernandez-Arevalo, Gonzalez-Rodriguez, Cirri, & Mura, 2004).

Theophylline and cimetidine are both considered to be highly water soluble and have fairly short half lives, making them ideal candidates for controlled release dosage forms. Both drugs are weak bases; however, theophylline has one pK_a at 8.6–8.8 and therefore, it will be almost completely ionized and soluble at a pH of 6.5, which corresponds to the pH of distilled water used for dissolution. Cimetidine has two pK_a values of 7.0 and 11.0 and will be somewhat less soluble than theophylline at the pH of the dissolution media (Bavin, Post, & Zarembo, 1984; Cohen, 1975).

Theophylline Release from Tablets

The effect of EC level, effect of TEC plasticizer, and Eudragit® RS/RL ratio on theophylline release from tablets ($n = 6$) were studied during dissolution. Although the 58% EC formulation released drug slower than the 0% EC control (without TEC), based on the f_2 metric, where dissolution profiles with f_2 values less than 50 are considered dissimilar, the two profiles were similar ($f_2 = 58.6$) (Figure 1). During preliminary research, other EC levels of 29 and 40% were examined. However, it was found that the drug release was essentially the same as the control, necessitating an increase in

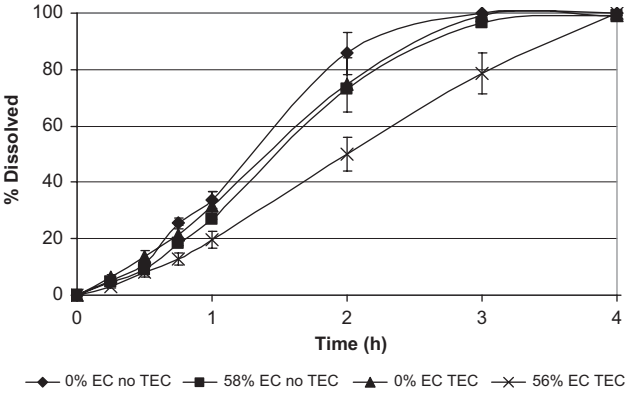

FIGURE 1. Effect of EC and TEC (20% wt/wt) on theophylline release ($n = 6$); $M \pm SD$.

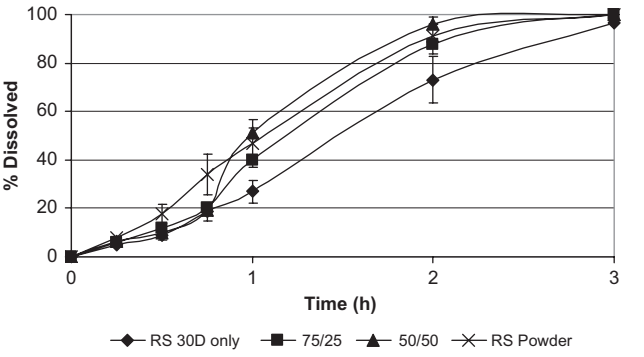

FIGURE 2. Effect of RS/RL ratio and form (18%) on theophylline release from tablets ($n = 6$); $M \pm$ SD.

the EC level. Although it would appear that a sufficient quantity of EC is needed in the matrix before a release retardant effect is observed, even with an EC level of 58%, drug release was still only between 3 and 4 h, not sufficient for controlled release.

Based on this data, TEC was added as a plasticizer at a level of 20% wt/wt based on the level of Eudragit® RS polymer solids content. Although the slowest release profile was of 56% EC with TEC, the total theophylline release was still only about 4 h. However, when comparing the effect of TEC on the release profiles of control and EC tablets, the f_2 metric was 42.3, indicating that TEC was impacting the drug release to some degree. It is not surprising that EC alone was not able to sufficiently delay drug release longer than 8 h.

EC is insoluble in water and will therefore behave as discrete insoluble particles in the dissolution media, thus, allowing the drug to diffuse through the interparticle voids. Without the formation of a cohesive gel network, as the case with HPMC, or without the formation of solid bridges linking the polymer chains together, retarding release of water-soluble drugs for a sufficient prolonged length of time will be difficult solely by increasing the EC level in the bead matrix.

Optimizing the Eudragit® RS/RL ratio is important since this formulation parameter can have a significant impact on drug release. The fastest release profiles were from either the 50/50 ratio (50% RS/50% RL blend) or using Eudragit® RS powder, while the slowest drug release was because of the formulation using 18% Eudragit® RS 30D alone (Figure 2). The RS 30D polymer dispersion should have a slower release profile compared with the RS powder because the dispersion undergoes a milling process whereby the particle size is reduced to less than 1 μm (Lehmann, 2001), and this increased surface area can act to retard drug release by forming a more homogeneous and coalesced polymer film surrounding the drug particles. Because the RS 30D grade has a 50% lower concentration of hydrophilic quaternary ammonium ions, it is less permeable to water than the RL 30D grade and therefore, has a greater ability to delay drug release from the beads. However, even with all the different formulation techniques examined, the theophylline release from compacted beads was still rather rapid at less than 4 h, thus necessitating the use of film coating for the drug beads in the future.

Theophylline Release: Effect of Different Bead Coating Polymers

When preparing tablets from coated drug beads, the drug bead:placebo bead ratio plays an important role in determining the rate of drug release. This is because at a high drug bead:placebo bead ratio, there will be a lower quantity of placebo beads present to act as cushioning agents and there will be a greater likelihood that the coating integrity of the drug beads will be compromised. A good way to assess this damage would be to compare dissolution profiles of coated beads alone with the same coated, compacted beads from a tablet. If profiles are quite different, then it can be assumed that the compression force used caused some degree of damage to the coated beads during tableting.

It was surprising to find that the coated control beads had the slowest release profile, even slower than the coated EC beads (Figure 3). At a pH of 6.5, corresponding to distilled water, the dibasic calcium phosphate in the bead matrix acts as an effective barrier against drug release (Railkar & Schwartz, 2001). This is because dibasic calcium phosphate requires an acidic pH in order to solubilize during dissolution. However, while coated, control beads alone released at the slowest rate, tablets prepared from these beads began releasing drug much more rapidly, especially after 4 h. This phenomena may be caused because the control beads are denser, and are composed of a high level of a brittle material which does not withstand the compaction process very well. A comparison of the release profiles of both coated EC beads versus coated EC beads in tablets showed they were similar; and differed by about 7% after 8 h, with the tablet releasing drug slightly faster than the coated beads alone. Incidentally, all of these tablets were prepared at very low compression forces of 200 kg or pressures of 10 MPa.

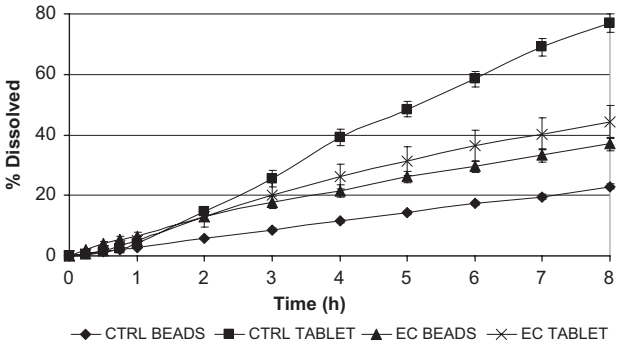

FIGURE 3. Effect of compression on theophylline beads coated with 15% Surelease®. EC versus control formulation (n = 6); $M \pm SD$.

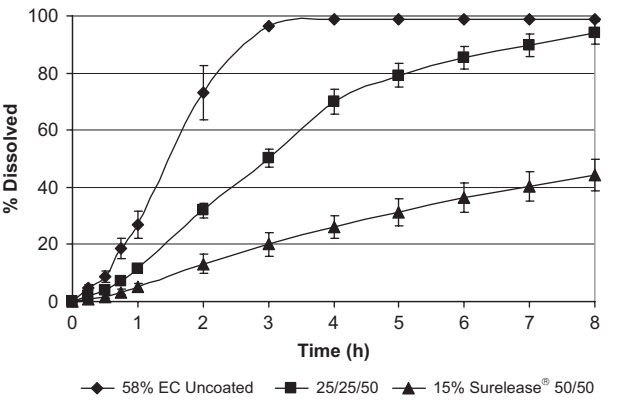

FIGURE 4. Comparison of theophylline tablets: uncoated beads versus coated beads (15% Surelease®) versus combination (25% uncoated beads, 25% of 15% wt/wt Surelease®-coated beads and 50% placebo beads; 25/25/50) (n = 6); $M \pm SD$.

Furthermore, the theophylline–EC beads coated with Surelease® and used at 50% wt/wt with placebo beads in tablets gave a final drug release of 44.2% after 8 h. Thus, this formulation was able to satisfy the specific aim of providing greater than 8 h of drug release for this highly water-soluble drug. This useful information provides a starting point to make water-soluble drug formulations dissolution rate limited. For instance, if modified release tablets were desired for metoprolol tartrate, a drug with a solubility roughly 125 times as high as theophylline, higher coating levels would have to be used and different film forming polymers would need to be evaluated.

It is important to note that although 50% wt/wt lipid-based placebos were added to the tablet formulations, which corresponds to 87.5 mg or 25% by weight, a hydrophobic effect from the wax was not observed during dissolution. Addition of these placebo beads did not appear to have a significant effect on delaying the release of water-soluble drugs. Chatchawalsaisin, Podczeck, and Newton (2005) prepared beads containing either diclofenac sodium, paracetamol, or ibuprofen by incorporating the drug into molten GMS, and found that the addition of GMS did not retard drug dissolution but only caused a slight decrease in the mean dissolution time (MDT) even as the level of GMS was increased. Diclofenac sodium formulations containing 80% GMS had slightly lower values for MDT than the formulations without GMS and formulations containing either 90% GMS or microcrystalline cellulose were approximately the same. They concluded that the drug release from the beads was controlled by the solubility of the drug and not by the presence of GMS.

A thorough understanding of the physical and chemical properties of the drug beads and placebo beads can lead to a custom-designed dosage form where the ratio of the coated drug beads to placebo beads is adjusted in order to obtain certain dissolution release profiles (zero order, pulsatile, and so forth) suitable for certain disease states. Moreover, uncoated drug beads can also be added at certain levels to give some immediate drug release from the tablets. Such a concept was attempted and is shown in Figure 4. Although no immediate release spike of theophylline was observed from the 25/25/50 combination tablets, this profile shows a much faster release when compared with the tablets containing 50% (wt/wt) drug beads coated with 15% (wt/wt) Surelease®. This is because the latter has a higher percentage of coated beads in the tablet.

By comparing the dissolution profiles of coated beads alone with coated, compacted beads in tablets, we can assess the extent of coating damage when a significantly faster drug-release rate is observed. Although tablets containing Surelease®-coated beads release drug faster than coated beads alone the profiles are still equivalent (f_2 = 63.5). Therefore, there is some coating damage occurring but it is not extensive (Figure 5). The release profiles are much closer in the Eudragit® NE 30D samples, indicating that less coating damage has occurred. The profiles of tablets containing either Surelease® or Eudragit®

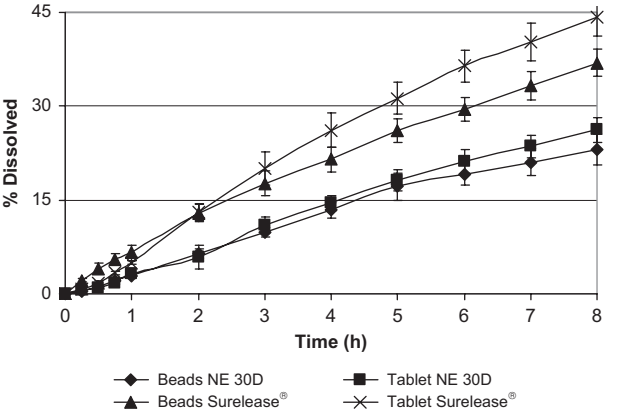

FIGURE 5. Theophylline: Effect of different coating polymers, beads versus tablets (n = 6); $M \pm SD$.

NE 30D coated beads are also determined to be different (f_2 = 44.8). In addition, it was observed on dissolution testing that the Eudragit® NE 30D beads tended to form a cohesive heap in the bottom of the dissolution vessel. The acrylic Eudragit® NE 30D polymer does tend to be tackier than the EC-based Surelease® and this may be an additional reason for the slower release rate of tablets using Eudragit® NE 30D.

Cimetidine Release from Tablets

The effect of TEC and EC was similar on drug release for both theophylline and cimetidine. Tablets prepared using control drug beads without TEC showed the fastest drug release, while EC beads with TEC showed the slowest release profile for cimetidine. It also appears that with cimetidine, TEC had a much less pronounced effect on drug release compared with theophylline, as the compacted EC beads prepared with or without TEC showed a similar release (Figure 6). The EC level was lowered slightly by 2% to account for the addition of TEC to the formulation. The f_2 metric result comparing EC versus control tablets showed that the profiles were dissimilar, but only slightly (f_2 = 47.8).

In the study of the effect of the RS/RL ratio and form on cimetidine release, dissolution profiles are quite different from theophylline. For instance, there is a greater spread between each treatment with the drug beads prepared using Eudragit® RS powder (RSPO) showing the fastest release profile while Eudragit® RS 30D shows the slowest drug release. This is likely because the Eudragit® RS 30D dispersion undergoes a milling step, causing the polymer particles to be smaller in size than the dry powder form; these smaller polymer particles will collectively have a greater surface area and can thus better retard drug release. The intermediate release profiles were from the 75/25 and 50/50 samples with the latter showing faster drug release because the 50/50 ratio has a lower percentage of the less permeable Eudragit® RS polymer. Therefore, this data serves as the justification for the selection of Eudragit® RS 30D in further formulation work (Figure 7).

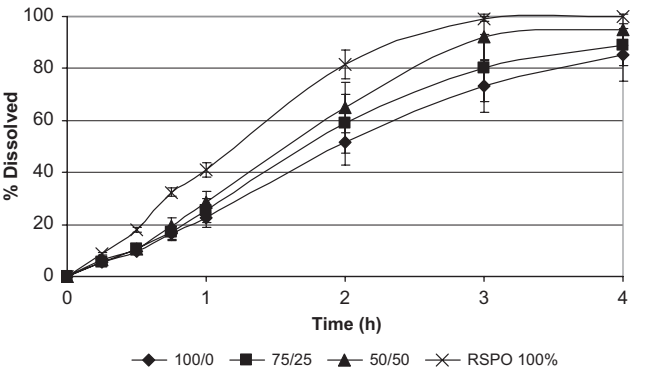

FIGURE 7. Effect of RS/RL ratio and form on cimetidine release from tablets (n = 6); $M \pm SD$.

Cimetidine Release: Effect of Drug Bead:Placebo Bead Ratio

Although the drug bead:placebo bead ratio had more of an effect on cimetidine release when Surelease®-coated beads were used, the similarity factor indicated that the 60:40 and 50:50 profiles were essentially equivalent (f_2 = 59.7). However, the 60:40 ratio tablets still displayed a faster drug release, particularly with Surelease®-coated beads. A low compression force of 200 kg was used to prepare tablets (Figure 8). The ratio may have had less of an effect on the tablet profiles from Eudragit® NE 30D-coated beads because this polymer is known to be more flexible and able to withstand more strain when compared with Surelease®.

Cimetidine Release: Effect of Different Bead Coating Polymers

In comparing the 50:50 tablets, while compacted Surelease®-coated beads showed a slightly faster release profile than coated beads alone, and faster than the Eudragit® NE 30D tablets, the differences between these two polymers were relatively minor using low compression forces of approximately 200 kg (Figure 9). However, these results do indicate

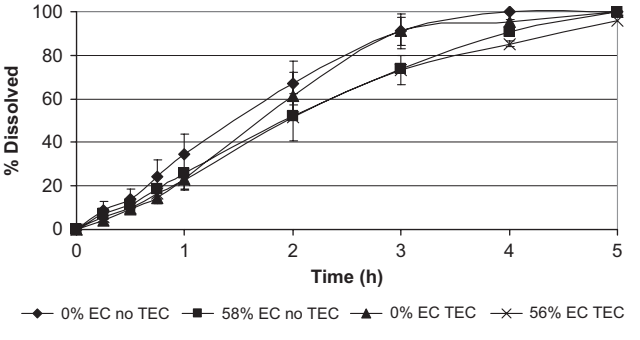

FIGURE 6. Effect of EC and TEC on cimetidine release (n = 6); $M \pm SD$.

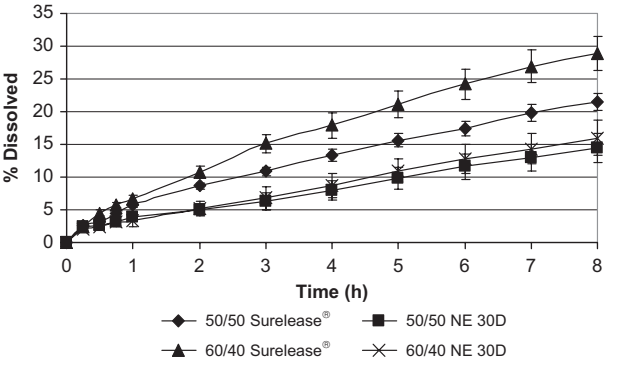

FIGURE 8. Effect of drug bead:placebo bead ratio on cimetidine release from tablets, Surelease® versus Eudragit® NE 30D at 15% wt/wt (n = 6); $M \pm SD$.

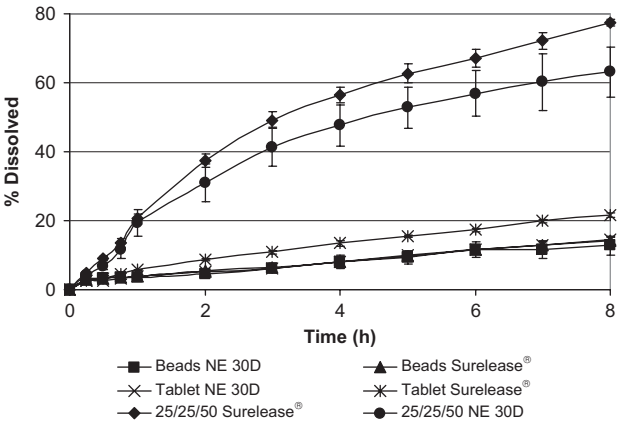

FIGURE 9. Effect of coating polymer on cimetidine release: beads versus tablet (50:50 drug:placebo ratio) 25/25/50 combination tablets contain 25% uncoated beads/25% (15% Surelease®)-coated drug beads/50% lipid-based placebos ($n = 6$); $M \pm SD$.

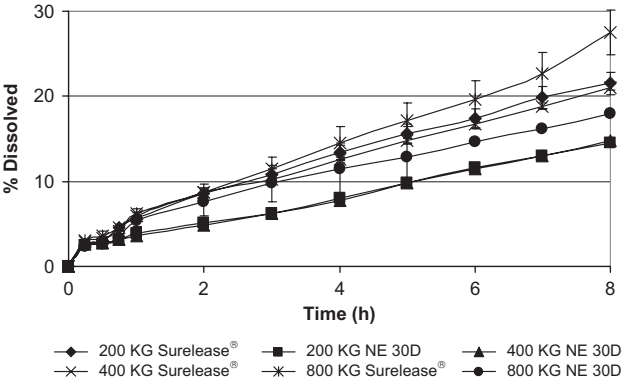

FIGURE 10. Effect of compression force (50:50 ratio) on dissolution profile. Surelease® versus Eudragit® NE 30D coated beads in tablets ($n = 6$); $M \pm SD$.

that some level of damage to the coating has occured following tableting. This graph shows that although some damage to the Surelease®-coated beads has occurred, it appears minor.

In preparing the combination tablets (25/25/50), it was hoped that a unique release profile would be obtained. For instance, differences in the lag time because of the inclusion of 25% uncoated beads. However, this was not the case as the curve shape is relatively the same. However, with the 25/25/50 combination tablets, the release difference between using Surelease® and Eudragit® NE 30D beads was somewhat more pronounced; although the similarity factor indicated that the profiles were still similar, albeit, just barely ($f_2 = 51.2$).

Cimetidine Release: Effect of Compression Force on Coating Polymers

The compression force was successively increased from 200 to 800 kg and both polymers were evaluated for their effect on drug release (Figure 10). The slowest release profiles were consistently seen with the compacted Eudragit® NE 30D beads at all compression forces when compared with the Surelease® compacted beads. However, the 800-kg treatment at 8 h only showed a 10% release difference between tablets of Eudragit® NE 30D and Surelease®. Based on this observation, it appears that the Eudragit® polymeric coating may be able to withstand the compressive forces involved with tableting better than the Surelease® polymeric coating; however, further studies would be warranted to confirm this.

Drug Release from Surelease® or Eudragit® NE 30D Coated Beads Compared (Tablets and Beads)

The f_2 metric showed that there were differences between release profiles of the different coating polymers for both theophylline and cimetidine beads compacted into tablets as well as for the coated beads alone. For example, in comparing tablets containing beads coated with either Surelease® or Eudragit® NE 30D, theophylline and cimetidine tablets gave f_2 values of 44.8 and 27.8, respectively. Likewise, in comparing beads alone coated with either polymer, theophylline and cimetidine beads alone gave f_2 values of 47.7 and 94.0, respectively. Although the two coating polymers for theophylline yielded profiles that were only slightly different from each other, cimetidine profiles were almost identical as evidenced by the f_2 value being close to 100.

There has been some recent discussion in the literature over the usefulness of the model-independent methods, such as the similarity factor, in the comparison of dissolution profiles.

This is because the f_2 metric does not take into account the shape of the curve and the unequal spacing between sampling time points. In addition, the f_2 metric cannot be used to determine statistical significance between profiles. Costa and Lobo (2001) also mentioned that simulation research indicated that this metric was too liberal in concluding similarity between dissolution profiles. Furthermore, Huang, Khanvilkar, Moore, and Hilliard-Lott (2003) cautions that just obtaining an f_2 value above 50 does not necessarily indicate that the two profiles are similar unless there is additional statistical evidence such as a *t*-test. However, even with these limitations, this metric still has its place in the pharmaceutical industry particularly as a way to compare innovator products with their generic counterparts to determine bioequivalence. In this study, the f_2 metric proved useful as a straightforward method to compare dissolution profiles during an extended 8-h period, and this information was used to decide whether a treatment was beneficially lowering the drug-release rate.

Tablets containing theophylline beads coated with Surelease® released drug most rapidly overall (Figure 11). Furthermore, this release was faster than from tablets containing Eudragit® NE 30D coated beads as well as faster than compacted cimetidine beads similarly coated with Surelease®. This

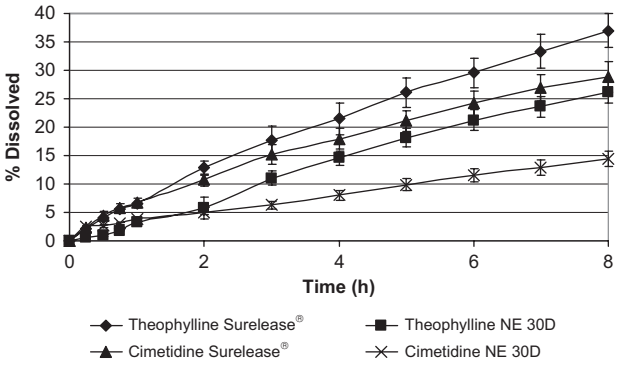

FIGURE 11. Theophylline–EC and cimetidine–EC tablets: Effect of different bead coating on drug release ($n = 6$); $M \pm SD$.

is likely because of the significantly higher aqueous solubility of theophylline when compared with cimetidine as well as perhaps the film strength and integrity. Acrylic films may be superior in this area over EC-based films since acrylic films are known to be more flexible and can withstand more strain (Bodmeier & Paeratakul, 1994). The slowest release was from tablets containing cimetidine beads coated with Eudragit® NE 30D.

Mechanism of Drug Release

The mechanism of drug release from a dosage form can be elucidated by using the Korsmeyer–Peppas equation which will indicate whether the drug transport is occurring via diffusion, erosion, or an anomalous combination of the two processes. This model is generally used to analyze the release data when the mechanism is not well known or when more than one type of release phenomena are involved. Values of the release exponent, n, will be different depending on the tablet geometry; since the tablets disintegrate into primary particles or beads rapidly within the first hour, sphere geometry values will be used for comparison purposes with this model (Ritger & Peppas, 1987).

However, there is currently no data on n values for multiparticulate systems using this model. Typically, n values are less than 1.0, but there has been some data reporting values in excess of 1.0. Sanghavi, Kamath, and Amin (1990) reported values of n between 0.48 and 1.0 for sustained release tablets of theophylline prepared using various hydrophilic and hydrophobic polymers, with HPMC K15M having the largest values. In addition, Sumathi and Ray (2002) reported values of n as high as 1.25 for tablets prepared with acetaminophen and tamarind seed polysaccharide cross-linked with epichlorohydrin. These authors also found out that the value of n varied from anomalous to near zero order as the solubility of drugs decreases; for example, while $n = 0.60$ for caffeine, indomethacin, an insoluble drug, yielded an n value of 0.98.

The Korsmeyer–Peppas model is only valid for data fitting on the initial portion of the curve where the fractional release (M_t/M_∞) is less than 60% (Peppas & Sahlin, 1989; Ritger & Peppas, 1987;). Moreover, the Higuchi model is also valid up to 60% of drug release. However, when Ebube et al. (1997) used this model to calculate release, values of M_t/M_∞ between 75 and 80% were used. Including drug-release data in excess of 60% of total release in a mathematical model is more of a problem with high-dose (>25 mg) systems as release after 60% can impact sink conditions; doses used in this research varied from 10 to 20 mg.

The criteria for selection of the best model(s) included good correlations (e.g., high R^2 and F-statistic and low SE of the y estimation, low sum of squared residuals, SSR, and low Akaike's Information Criterion, AIC, values). High values of the coefficient of determination, R^2, indicate that most of the observed variability is explained by the data. Adjusted R^2 values are an estimate of how well the current model would fit another data set from the same population. All F-statistic values were significant indicating that a linear relationship exists between percentage release and time.

The Hixson–Crowell model treats the drug particles on a volume basis and indicates that the drug dissolves out at a cube root rate. The model is only valid for data once tablet disintegration is complete, which occurs within the first 60 min for this study, and also assumes that the shape or volume of the particles decreases with time during dissolution (Brooke, 1975; Cartensen, Wright, Blessel, & Sheridan, 1978). Previous work of Merchant, Shoaib, Tazeen, and Yousuf (2006) using HPMC matrix tablets of cefpodoxime showed that the Hixson–Crowell model provided the best fit for dissolution data over the first-order or Korsmeyer–Peppas models. These authors noted that the applicability of the dissolution data to the Hixson–Crowell model indicated that the surface area and diameter of the tablets were changing with the progressive dissolution of the HPMC gel matrix.

In order to ascertain whether the coated beads were changing shape during dissolution, they were examined using optical microscopy; and it appeared that the coated beads remained intact with similar size during dissolution. The drug appeared to elute from pores developed in the coating membrane. The fact that the dissolution data mathematically fit best overall using the Hixson–Crowell model (Tables 5–7) was an unexpected finding. This delivery system is complex with competing mass transfer phenomena of diffusion and erosion occurring simultaneously; and although the results show a good mathematical fit, this model is not entirely applicable because the beads used in this study also showed little change in size as dissolution progresses. The first-order model, with similar statistical values as the Hixson–Crowell model and without the mechanistic limitations, may provide a better explanation of the drug-release kinetics.

Although some previous research has shown the drug release data from uncoated and coated beads to fit the Higuchi model well (Zhang, Schwartz, & Schnaare, 1991a, b), this current data showed consistently high numbers for the SSR and

TABLE 5
Kinetic and Statistical Parameters of Various Mathematical Models Obtained on Fitting Drug-Release Data of Cimetidine Beads (58% ethylcellulose and 18% of Eudragit® RS 30D) coated with 15% wt/wt Eudragit® NE 30D

Parameter	Zero-order	First-order	Hixson–Crowell	Korsmeyer–Peppas	Higuchi
Parameters for assessing model fit					
R^2	.986	.986	.985	.925	.957
Adjusted R^2	.984	.984	.983	.917	.952
F	626.2	631.8	577.6	111.1	198.0
SSR	2.02	2.4×10^{-4}	9.8×10^{-5}	0.24	6.2
AIC	−0.37	−4.31	−4.69	−1.31	0.11
Parameters for kinetic equation					
k	1.35	0.02	0.01	$n = 0.46$	4.5
SE (slope)	0.05	6×10^{-4}	4×10^{-4}	0.04	0.32
SE (*y*-est)	0.23	0.003	0.002	0.06	0.59

k is the release rate constant with units of % per hour, h^{-1}, $(\%)^{1/3}$ per hour, and $\%/(t^{1/2})$ for zero-order, first-order, Hixson–Crowell, and Higuchi models, respectively. For the Korsmeyer–Peppas model, the release exponent, *n*, has units of h^{-n}. R^2 is the coefficient of determination; *F* is the observed *F*-statistic value; SSR is the sum of squared residuals; AIC is the Akaike Information Criterion; *SE* (slope) is the standard error of slope; *SE* (*y*-est) is the standard error of the *y* estimation.

TABLE 6
Kinetic and Statistical Parameters of Various Mathematical Models Obtained on Fitting Drug-Release Data of Tablets (200 kg Force) Prepared from Cimetidine Beads (58% Ethylcellulose and 18% of Eudragit® RS 30D) and Placebo Beads in a 1:1 ratio. Beads are Coated with 15% wt/wt Eudragit® NE 30D

Parameter	Zero-order	First-order	Hixson–Crowell	Korsmeyer–Peppas	Higuchi
Parameters for assessing model fit					
R^2	.998	.997	.998	.961	.963
Adjusted R^2	.998	.997	.998	.956	.959
F	4,645	3,277	4,116	220	233
SSR	0.51	8.9×10^{-5}	2.9×10^{-5}	0.17	9.8
AIC	−0.97	−4.73	−5.22	−1.45	0.31
Parameters for kinetic equation					
k	1.85	0.02	0.01	$n = 0.55$	6.1
SE (slope)	0.03	3.6×10^{-4}	2.0×10^{-4}	0.04	0.40
SE (*y*-est)	0.12	0.002	8.9×10^{-4}	0.05	0.74

k is the release rate constant with units of % per hour, h^{-1}, $(\%)^{1/3}$ per hour, and $\%/(t^{1/2})$ for zero-order, first-order, Hixson–Crowell, and Higuchi models, respectively. For the Korsmeyer–Peppas model, the release exponent, *n*, has units of h^{-n}. R^2 is the coefficient of determination; *F* is the observed *F*-statistic value, SSR is the sum of squared residuals; AIC is the Akaike Information Criterion; *SE* (slope) is the standard error of slope; *SE* (*y*-est) is the standard error of the *y* estimation.

AIC values, low correlations, and poor linearity. Although correlations were good for the zero-order model in this project, the AIC values were high, disqualifying it from selection as the model to best explain the data. The AIC is defined by $\log(\mathrm{SSR}/n) + 2(K)/n$, where *n* is the number of observations in the sample, SSR the sum of the squared residuals, and *K* the number of coefficients in the model. The AIC can be used as an objective measure to select the dissolution model with the best fit to the data. The more negative the value of AIC, the better the model fits the data. Because the AIC is based on both the fit to the data and the number of estimated parameters, if two models each fit the data well, the AIC will be lower for the model with fewer estimated parameters or independent variables (Sood & Panchagnula, 1998; Zhang et al., 1991a, b).

While the Hixson–Crowell model did not provide the optimum explanation overall, it did display high linearity ($R^2 \geq .95$) and consistently showed the lowest SSR and AIC values,

TABLE 7
Kinetic and Statistical Parameters of Various Mathematical Models Obtained on Fitting Drug-Release Data of Tablets (200 kg Force) Prepared from Cimetidine Beads (58% Ethylcellulose and 18% of Eudragit® RS 30D) and Placebo Beads in a 1:1 ratio. Beads are Coated with 15% wt/wt Surelease®

Parameter	Zero-order	First-order	Hixson–Crowell	Korsmeyer–Peppas	Higuchi
Parameters for assessing model fit					
R^2	.924	.973	.949	.969	.986
Adjusted R^2	.915	.969	.943	.966	.985
F	108.9	319.1	167.9	256.1	640.5
SSR	379.6	0.04	0.02	0.25	68.9
AIC	1.90	−2.14	−2.34	−1.20	1.20
Parameters for kinetic equation					
k	7.72	0.13	0.07	$n = 0.82$	26.9
SE (slope)	0.74	0.007	0.06	0.05	1.06
SE (*y*-est)	3.2	0.03	0.02	0.06	2.0

k is the release rate constant with units of % per hour, h^{-1}, $(\%)^{1/3}$ per hour, and $\%/(t^{1/2})$ for zero-order, first-order, Hixson–Crowell, and Higuchi models, respectively. For the Korsmeyer–Peppas model, the release exponent, *n*, has units of h^{-n}. R^2 is the coefficient of determination; *F* is the observed *F*-statistic value, SSR is the sum of squared residuals; AIC is the Akaike Information Criterion; *SE* (slope) is the standard error of slope; *SE* (*y*-est) is the standard error of the *y* estimation.

and generally had the highest *F* values. Theophylline tablets prepared either with control beads (0% EC) or uncoated beads (58% EC) had low *F* values and low AIC values of around −2.0 and the highest values for *n* ($n = 1.6$), indicating super case-II transport or erosion was occurring.

This probably reflects the fact that both EC and calcium phosphate dibasic are behaving as discrete insoluble particles and this contributes to an erosive, disintegrating effect. Furthermore, the case-II transport release mechanism also involves the dissolution of the polymer chain matrix; which includes EC and the acrylic polymer Eudragit® RS 30D for the EC beads, and Eudragit® RS 30D for the control beads (Sood & Panchagnula, 1998). The theophylline data for tablets containing Surelease®-coated beads and uncoated theophylline–EC beads alone showed that the AIC values doubled to −4.0, the *F* values increased significantly, and very low SSR values were obtained. Overall, Korsmeyer–Peppas results from theophylline and cimetidine data for the release exponent, *n*, indicated that drug release was either anomalous, being a combination of diffusion and erosion, or super case-II transport, with values of $n > 1.0$.

All cimetidine-coated beads gave *n* values between 0.43 and 0.85, qualifying the release mechanism as anomalous. Data from Eudragit® NE 30D-coated beads alone are shown in Table 5, and data from tablets prepared from either Eudragit® NE 30D-coated beads or Surelease®-coated beads are shown in Tables 6 and 7, respectively. The data from tablets containing cimetidine beads coated with Eudragit® NE 30D had the lowest AIC value overall at −5.22.

Chatchawalsaisin et al. (2005) noted that when beads were formed by incorporating either diclofenac sodium, paracetamol, or ibuprofen into 30% molten GMS, release followed square root of time kinetics for all drugs except for ibuprofen, which followed first-order kinetics. However, at 60% GMS levels, the release of diclofenac sodium followed a cube root relationship. They concluded that the mechanism of drug release varies with the type and chemical properties of drug used, as well as the presence, quantity, and method of incorporation of GMS. The fact that ibuprofen consistently followed first-order kinetics and differed in the release mechanism from the other two drugs could be explained by the fact that it is waxy and more hydrophobic than either paracetamol or diclofenac sodium, which are water soluble. Hayshi et al. (2005) studied sustained-release preparations of theophylline matrix tablets by combining hydrophobic wax granules with hydrophilic polymer granules (drug + HPMC) at ratios from 10:90 to 90:10. They found the release mechanism to be anomalous ($n \approx 0.6$) with the release profiles best fit to a first-order kinetic model.

Overall, the Korsmeyer–Peppas model indicated that these multiparticulate systems are complex and that they display anomalous drug release during dissolution ($0.45 < n < 0.89$). More specifically, although the data may fit the Hixson–Crowell model well mathematically, this model is not ideal to explain the release from non-disintegrating beads where there is minimal change in shape and/or volume. In vitro release of multiparticulate tablet formulations containing between 20 and 25% GMS by weight and the highly water-soluble drugs theophylline or cimetidine, is best explained by first-order kinetics rather than by either the Higuchi or Hixson–Crowell models.

CONCLUSIONS

Although dissolution studies revealed that EC was ineffective by itself as a hydrophobic matrix at providing modified release

profiles for water-soluble drugs greater than 8 h, coating the beads with either Surelase® or Eudragit® NE 30D for use in tablets can provide the added extension of release. Although tablets containing Surelease®-coated theophylline beads released drug fastest overall ($t_{44.2\%}$ = 8 h), profiles showed that coating damage was still minimal (<10%). This is likely because of the increased solubility of theophylline compared with cimetidine as well as the intrinsic properties of the Surelease® films, known to be more sensitive to the effects of strain.

The first-order model consistently explained the dissolution data best for both drugs as judged by high R^2 values (>.95), and low values for the AIC and residuals. Using a combination of criteria for selection of the most appropriate mathematical model provides greater accuracy as well as improved understanding of the drug-release processes occurring during dissolution.

Based on the results showing a similarity in bead density and particle size, it appears that blends of Surelease®-coated drug beads and GMS placebo beads may have a minimal segregation propensity during mixing and tableting. Additionally, the lipid-based placebos demonstrated their robust formulation in serving as effective cushioning agents to protect the coating on the drug beads from significant damage under a number of different conditions while tableting. Therefore, this compacted multiparticulate system can enable a once-a-day dosing regimen with the potential for reduced side effects as therapeutic benefits for a patient.

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