MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 1, pp. 9–18, 2003

RESEARCH PAPER

Blinding Controlled-Release Tablets for Clinical Trials

Linda A. Felton* and Cody J. Wiley

College of Pharmacy, University of New Mexico, Albuquerque, New Mexico, USA

ABSTRACT

The objective of the current study was to develop a method to blind commercially available Wellbutrin® SR 150 mg sustained-release tablets for a clinical study. Overcoating was selected as the most appropriate blinding method. Hydroxypropyl methylcellulose (Opadry® II) containing red iron oxide and titanium dioxide was applied to the Wellbutrin tablets at coating levels ranging from 0.5% to 4% weight gain. When compared against the uncoated product, no significant differences in drug release were noted over an 8-hr period. Matching placebo tablets, prepared using specially designed tablet tooling, were coated with the same cellulosic polymer that was used for the active. The coated active and placebo tablets were virtually indistinguishable. To test the applicability of this overcoating technique for blinding other controlled release products, the same procedure was used to coat Glucotrol® XL 5 mg tablets and Theo-Dur 200 mg tablets. The debossing on the Theo-Dur tablets and the laser-drilled hole on the surface of the Glucotrol tablets prevented blinding. The Theo-Dur tablets were mechanically weak and not able to withstand the coating process. Dissolution testing revealed significantly higher amounts of drug were released from the blinded Glucotrol tablets compared to the unblinded product at the 12 hr time point. The findings from this study suggest that overcoating with pigmented hydroxypropyl methylcellulose may not be useful for blinding all controlled-release tablets.

Key Words: Blinding; Overcoating; Film coating; Hydroxypropyl methylcellulose; Buproprion; Clinical trials.

INTRODUCTION

Clinical trials are an important part of the drug product-development process. These studies are used to evaluate the safety and efficacy of new chemical entities and to test currently approved medications for new therapeutic indications. The efficacy and side-effect profiles of the active drug may be compared to placebos or to existing standard therapies. While the physical attributes of commercially available

*Correspondence: Linda A. Felton, Ph.D., University of New Mexico, Health Sciences Center, College of Pharmacy, 2502 Marble NE, Albuquerque, NM 87131, USA; Fax: (505) 272-6749; E-mail: lfelton@unm.edu.

DOI: 10.1081/DDC-120016679
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

tablets and capsules may be useful for identification of drug products, the unique appearance of these dosage forms can be problematic in clinical trials, especially when the clinical studies collect subjective data.

To minimize the introduction of bias into clinical trials, drug products are generally blinded in such a way as to conceal or hide the drug treatment from both study participants and clinical investigators. Blinding often involves some type of manipulation of the dosage form and the most common blinding methods reported include removal of logo markings, overencapsulation, milling and filling, overcoating, and manufacturing a generic product.[1] Irrespective of the technique used, blinding must not significantly alter the drug release characteristics, the physical stability of the dosage form, or the chemical stability of the active component.

The blinding of controlled-release solid-dosage forms presents some unique challenges to the pharmaceutical scientist. Conventional blinding techniques, such as milling and filling, may alter the mechanism of drug release and, thus, may not be appropriate. The objectives of the current study were to develop a method to blind commercially available Wellbutrin SR 150 mg sustained-release tablets and to evaluate the applicability of this blinding method for other sustained-release drug products.

MATERIALS AND METHODS

Commercially available Wellbutrin SR 150 mg tablets (Glaxo Wellcome, Inc., Research Triangle Park, NC) were donated from the Department of Veteran's Affairs Medical Center in Albuquerque, New Mexico. The sustained-release Wellbutrin product is a shallow biconvex round tablet with a purple film coating covering the sustained-release matrix core. The name and strength of the product are imprinted in black edible ink on one side of the tablet. The Glucotrol XL 5 mg tablets (Pfizer, Inc., New York, NY) and the Theo-Dur 200 mg tablets (Key Pharmaceuticals, Inc., Kenilworth, NJ) were purchased from the Medicine Chest Pharmacy (McLean, VA). Glucotrol XL tablets are standard biconvex round tablets coated with a white cellulose-acetate polymeric film. One side of the tablet surface is imprinted with the product name and strength, while a laser-drilled hole is found on the other side of the tablet. The Theo-Dur extended release tablets are uncoated standard biconvex oval tablets, debossed with the name and strength of the product on one side and a score mark on the other side of the tablet.

Colorcon (West Point, PA) supplied the Opadry II polymeric material used for the project. Opadry II is a complete film coating system that consisted of hydroxypropyl methylcellulose (HPMC), polydextrose, triacetin, polyethylene glycol, synthetic red iron oxide, and titanium dioxide. Both red iron oxide and titanium dioxide have opacifying properties that were expected to facilitate concealing the surface of the commercial tablets.[2]

Coating of Tablets

A 10% (w/w) suspension of the polymeric coating material was prepared by dispersing the Opadry II powder in deioinized water. The coating suspension was mixed with a magnetic stirrer for 45 min prior to the initiation of the spraying process. Approximately 500 g of tablets were placed in a LDCS-3 perforated coating pan apparatus (Vector Corp., Marion, IA). The processing parameters used in during coating are shown in Table 1. Twenty tablets were withdrawn from the rotating drum at specific times corresponding to weight gains of 0.5%, 1.0%, 2.0%, 3.0%, and 4.0%. The same procedures were used to overcoat the Theo-Dur and Glucotrol XL tablets.

Visual Assessment of Blinding

Twenty tablets of each product at each coating level were visually inspected. Tablets were placed under a light on a white background and examined for signs of chipping, picking, and other coating defects, as well as visible signs of the printing on the tablet surface. Blinding was considered sufficient

Table 1. Processing parameters used during the coating process.

Processing parameter	Setting
Batch size	500 g
Bed temperature	30°C
Spray rate	2.8–3.2 g/min
Rotational pan speed	15 rpm

when no defects or distinguishing marks were found on the surface of all tablets inspected.

Dissolution of Tablets

No USP monograph currently exists for sustained-release buproprion HCl and, thus, a method was developed to determine the drug release from the commercial Wellbutrin SR product. Water was selected as the dissolution test media to be used, since buproprion HCl is highly water soluble (321 mg/mL).[3] A USP dissolution test apparatus (Method II) was used and the paddles were rotated at 100 rpm. Six tablets from each percent weight gain were tested. Samples were withdrawn at 15-min intervals for the first hour of the dissolution experiment. Subsequent sampling times included 2, 4, and 8 hr. Samples were analyzed using high-performance liquid chromatography (HPLC). The analytical column was a C_{18}, 4.6 μm × 15 cm column (Alltech Associates Inc., Deerfield, IL). The mobile phase consisted of 70:30 10 mM potassium phosphate buffer (pH 2.6):acetonitrile with 0.13% triethylamine and the flow rate was 1 mL/min. The detection wavelength was 255 nm and the retention time was approximately 8 min. The concentrations of buproprion HCl that were evaluated as standards ranged from 10 to 200 μg/mL and the absorbance was linear ($r^2 > 0.999$).

The USP Method II apparatus was also used for dissolution testing of the Glucotrol XL tablets. The rotational speed of the paddles was set at 50 rpm. The dissolution media consisted of simulated intestinal fluid without enzymes at a pH of 7.5. Although no official USP dissolution method exists for extended-release glipizide, this method was previously reported for testing drug release from controlled-release capsules[4] and is similar to the method described in the USP monograph for the immediate-release tablets. In addition to the sampling times used for the Wellbutrin product, 12 and 24 hr samples were withdrawn. Samples were analyzed using an HPLC method. The analytical column was a C_{18}, 4.6 μm × 15 cm column (Alltech Associates Inc., Deerfield, IL). The mobile phase consisted of 60:40 methanol:10 mM potassium phosphate buffer (pH 3.5). The flow rate was 1 mL/min and the detection wavelength was 225 nm. The retention time was approximately 6 min. The concentrations of glipizide that were evaluated as standards ranged from 0.5 to 10 μg/mL and the absorbance was linear ($r^2 > 0.998$).

Manufacturing of Placebo Tablets

Placebo tablet cores matching the size, shape, and weight of the Wellbutrin product were prepared using a B2, 16-station rotary tablet press (Stokes, Bristol, PA). Natoli Engineering (St. Charles, MO) fabricated the tooling based on a Wellbutrin SR 150 mg tablet sample. The tablet formulation consisted of 49% Avicel PH 302 (FMC Corporation, Philadelphia, PA), 49% Emcocel 50 (Penwest, Patterson, NY), 1% fumed silica (Cab-O-Sil M-5P, Cabot Corp., Tuscola, IL), and 1% magnesium stearate (Spectrum Laboratory Products, Inc., Gardena, CA). The two grades of microcrystalline cellulose were sieved and blended with the fumed silica in a V-shell blender (Patterson–Kelley, Stroudsburg, PA) for 15 min. Magnesium stearate was added to the V-shell and the materials mixed for an additional 7.5 min. After setting the machinery to achieve the specified weight of 418 mg (based on the original Wellbutrin SR 150 mg tablet, as shown in Table 2), the compressional force was adjusted to obtain the desired tablet thickness of 4.81 mm. These placebo cores were then coated using the same procedures previously described.

Scanning Electron Microscopy

Tablets were evaluated visually using a Hitachi S-800 scanning electron microscope (Tokyo, Japan). Individual tablets were mounted onto carbon tape. No sputtering or other sample preparation methods were employed.

RESULTS AND DISCUSSION

Development of a Method to Blind Wellbutrin SR 150 mg Tablets

Commercially available Wellbutrin SR 150 mg tablets are sustained-release matrix tablets with a purple film coating covering the core. In developing a method to blind this drug product, the mechanism of drug release had to be considered and the more conventional blind methods were deemed unsuitable. For example, the grinding of the tablet followed by filling the powder into hard gelatin capsules (milling and filling method) would significantly alter the controlled release properties of the drug product and result in dose dumping. Manufacturing a generic

Table 2. Physical characteristics of the Wellbutrin and the matching placebo tablets. Values reported are the mean (standard deviation) of 10 tablets.

	Uncoated Wellbutrin	Coated Wellbutrin[a]	Coated placebo[b]
Appearance	Dark purple, black ink	Reddish–brown	Reddish–brown
Weight	418.0 mg (4.0)	432.8 mg (3.9)	430.1 mg (2.1)
Diameter	11.19 mm (0.01)	11.21 mm (0.01)	11.21 mm (0.01)
Thickness	4.81 mm (0.03)	4.89 mm (0.03)	4.89 mm (0.03)

[a]Coated at a 2% weight gain level.
[b]Coated at a 4% weight gain level.

product similar to Wellbutrin would require an extensive amount of resources, including both developmental time and laboratory personnel, and was also not an acceptable blinding method for this study.

Overencapsulation is a process where the drug product is placed inside a hard gelatin capsule and fill material is added to prevent the tablet from rattling. This method of blinding requires that the dosage form fit within the capsule body. The largest conventional capsule size, 000, has a body diameter of approximately 9.50 mm. In the current study, the approximate 11.2-mm diameter Wellbutrin tablet (see Table 2) is too large to fit into hard gelatin capsules. Recently, manufacturers of hard gelatin capsules developed a large-diameter capsule specifically designed for overencapsulation of drug products for clinical trials. The largest of these "DB" capsules (size AA, internal diameter of 9.08 mm, manufactured by Capsugel, Greenwood, SC) is still not capable of accommodating the Wellbutrin tablets.

Another common blinding method is to simply remove the ink from the tablet or capsule surface. In the present study, the ink on the Wellbutrin product was easily removed using ethanol and no visual damage to the film coating was noted. However, the purple color of the Wellbutrin product would be very difficult to duplicate for the matching placebo and thus was not considered a viable blinding option for this study.

Overcoating is a blinding method that involves the application of a thin film of a water-soluble polymer containing opacifying agents and/or colorants to the substrate. This overcoating technique was selected as the best option for blinding the Wellbutrin tablets. The coating process is physically demanding and friable tablets may chip or break during rotation in the pan. Although the hardness and friability of the Wellbutrin SR tablets were not measured in the present study, these already-film-coated tablets were expected to withstand processing. Previous researchers have shown that polymeric film coatings increase the overall strength of tablets and resistance to attrition.[5]

The selection of the polymeric material used in the overcoating process is critical. The majority of polymeric film coatings are used to modify drug release.[6–10] In blinding drug products for clinical trials, however, manipulation of the dosage form must not significantly alter the dissolution characteristics. The polymeric material selected for this study was hydroxypropyl methylcellulose (HPMC). This polymer is water soluble and has been used to mask taste and improve product appearance at levels up to 4% with no significant change in drug release.[11] Pigments must be included in the formulation to produce a coating that can hide or conceal the color of the tablet. In the current study, red iron oxide and titanium dioxide were included in the coating formulation. Both of these colorants have opacifying properties and the dark reddish–brown color was expected to readily conceal the purple tablet surface as well as the black print. It should be noted that the addition of pigments to film-coating formulations may alter the mechanical, adhesive, and drug-release properties of the polymer.[12–16] The Opadry II used in the current study is a commercially available coating system containing the plasticizers and colorants and no adhesion or mechanical strength problems were expected to arise. A free film was prepared from the polymeric material and visually inspected for the appearance of cracks. The preparation of the free film also provided an opportunity for the researchers to work with the material prior to tablet coating.

Following the completion of the coating process, Wellbutrin SR 150 mg tablets were visually inspected to assess blinding. From Fig. 1, it is apparent that a weight gain of 0.5% was not sufficient to cover the dark ink on the tablet surface. When closely inspected, the printing on the surface of the tablet

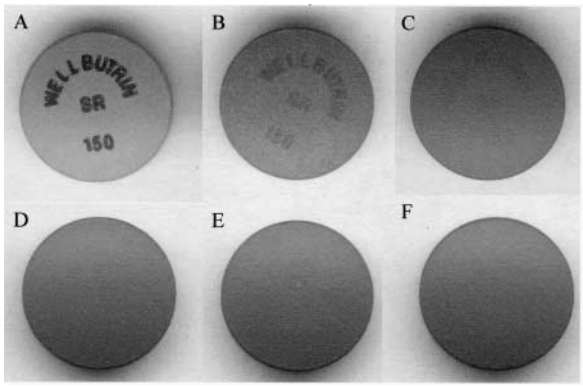

Figure 1. Influence of overcoating on the physical appearance of Wellbutrin SR 150 mg tablets. (A) 0%; (B) 0.5%; (C) 1%; (D) 2%; (E) 3%; (F) 4%.

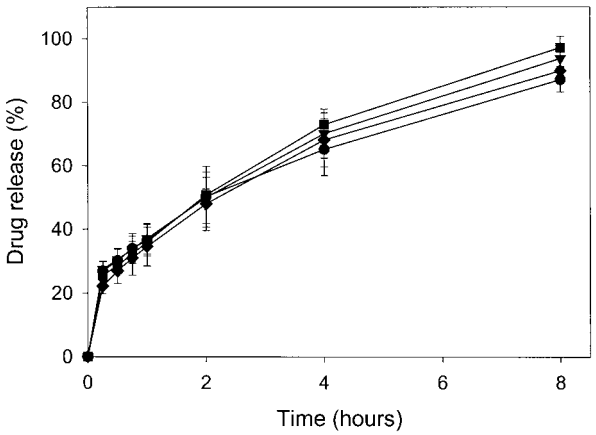

Figure 2. Influence of overcoating on drug release from Wellbutrin SR 150 mg tablets. (●) 0%; (▼) 1%; (■) 2%; (◆) 4%.

was also visible through the film coating at a 1% weight-gain level. Two percent weight gain provided sufficient opacity to conceal both the dark ink and the purple tablet surface. Higher levels of coating also blinded the Wellbutrin tablets.

Dissolution testing was conducted to determine the influence of overcoating on the drug-release properties of the Wellbutrin tablets. Since the Opadry II HPMC polymeric material is water soluble, any changes in the drug-release characteristics of the product were expected to occur early during the dissolution experiment. Thus, samples were taken at 15 min intervals during the first hour of dissolution, with subsequent sampling times of 2, 4, and 8 hr. When compared against the uncoated product, no statistically significant differences in drug concentration were noted at any of the sampling times investigated up to 8 hr, as shown in Fig. 2. Although the tablets coated with 4% HPMC showed a slightly lower percent drug release over the initial 2-hr dissolution period, a one-way analysis of variance (ANOVA) found no statistically significant differences between the unblinded and overcoated tablets. Statistical evaluation of the data using the similarity factor f_2, as described by Shah and coworkers,[17] also demonstrated no differences in dissolution profiles between the blinded and unblinded tablets.

Development of a Matching Placebo for Wellbutrin

Tablet tooling was purchased from Natoli Engineering (Saint Charles, MO) to produce the matching placebo tablet cores. The approximate dimensions of the desired placebo were similar to a microcrystalline cellulose-containing tablet that was previously produced in our laboratory, although the weight was much lower than the target value. Thus, half of the microcrystalline cellulose (MCC) was replaced with a high-density grade. Since MCC swells upon exposure to water and the coating process required application of an aqueous-based polymeric material, a slightly longer blending time of the hydrophobic lubricant magnesium stearate was employed to minimize the possibility of surface erosion of the tablet cores during the coating process.[18,19] The tableting machinery was adjusted to produce tablets with the target weight, then the compressional force was modified to obtain the desired tablet thickness. In the current study, tablet hardness was not a critical parameter required to be matched to the active. The placebo needed only to be strong enough to withstand the coating process. Tablet cores were coated using the same procedures previously described in the Materials and Methods section for overcoating the Wellbutrin product.

A 4% weight gain of Opadry II was needed to achieve a dark, opaque film similar to that of the active. This higher level of coating was presumably required due to the white tablet face of the placebo compared to the dark-purple surface of the Wellbutrin. The dimensions of the blinded active and the matching placebo are shown in Table 2. A one-way ANOVA showed no significant differences in the tablet weight ($p = 0.482$), thickness ($p = 0.997$),

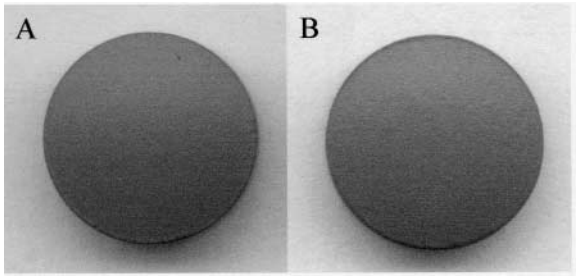

Figure 3. Overcoated Wellbutrin and placebo tablets. (A) Placebo at 4% coating; (B) Wellbutrin at 2% coating.

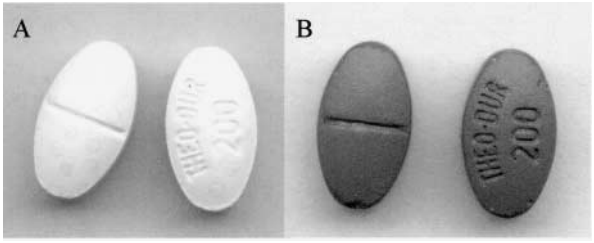

Figure 4. Influence of overcoating on the physical appearance of Theo-Dur 200 mg tablets. (A) Uncoated; (B) 2% overcoating.

and diameter ($p = 0.762$) of the two products. As shown in Fig. 3, it was nearly impossible to distinguish the active from the placebo without removing the film coating or performing some type of chemical analysis.

Applicability to Other Sustained-Release Tablets

To test the applicability of overcoating as a method to blind other controlled-release solid-dosage forms, the same procedures were repeated using Theo-Dur 200 mg and Glucotrol XL 5 mg tablets. Figure 4 shows the effect of a 2% HPMC overcoat on the appearance of the extended-release theophylline tablets. These tablets were not sufficiently robust to withstand the coating process, as evidenced by the chipping at the tablet edge. In addition, the debossing and scoring of the Theo-Dur tablets prevented adequate blinding using this overcoating method and subsequent dissolution testing was not performed.

The Glucotrol XL 5 mg tablets were visually inspected following the overcoating process to assess blinding. In comparison to the Wellbutrin tablets, higher amounts of polymer were required to cover the ink on the tablet surface, as shown in Fig. 5. At least 3% weight gain was needed to conceal the printing on the tablet surface. The higher polymer loading required for blinding was most likely due to the more pronounced contrast between the dark ink and the white tablet face, compared to the black ink/purple surface of the Wellbutrin tablets.

Glucotrol XL tablets are controlled-release, film-coated, solid-dosage forms that utilize an osmotic-pump delivery system. Water permeates through the semipermeable cellulose-acetate coating and begins to

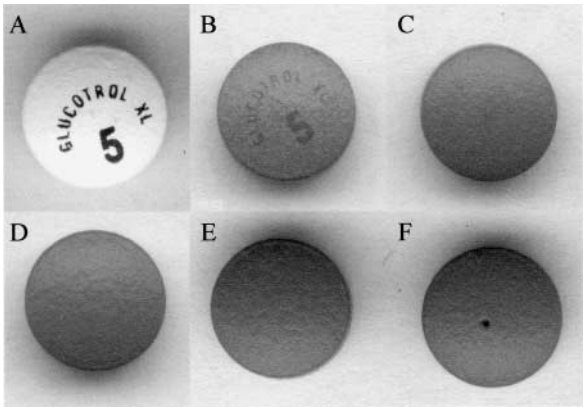

Figure 5. Influence of overcoating on the physical appearance of Glucotrol XL 5 mg tablets. (A) 0%; (B) 1%; (C) 2%; (D) 3%; (E) 4%; (F) opposite side, 4%.

dissolve the tablet core, causing an increase in the osmotic pressure.[20] It is this high-osmotic pressure that drives the drug out of the delivery device through a laser-drilled orifice in the film coating. While the ink on the tablet surface was concealed at 3% or 4% coating, the orifice on the other side of the tablet was not hidden. It may be possible, however, to purchase tooling with a small indentation that would simulate the orifice of the active.

Although the Glucotrol XL tablets were not suitably blinded, dissolution testing was still conducted to determine the effect overcoating exerted on drug release of the active and the data are presented in Fig. 6. Practically no drug was released from the tablets during the first 2 hr of the dissolution test, irrespective of the amount of polymer overcoating. These findings were expected, since drug release relies on the creation of an osmotic pressure gradient.[21] No statistically significant differences in drug release were noted through the first 8 hr of the dissolution

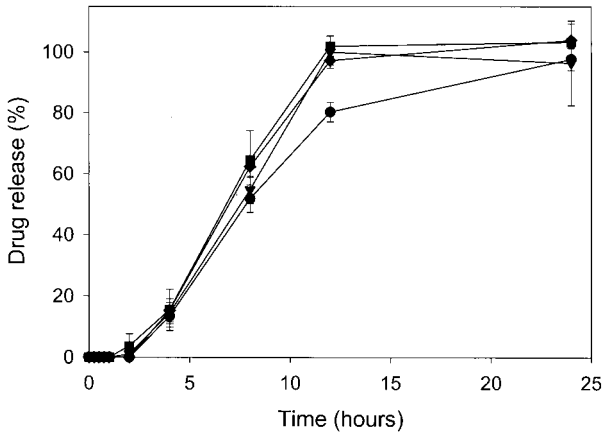

Figure 6. Influence of overcoating on drug release from Glucotrol XL 5 mg tablets. (●) 0%; (▼) 2%; (■) 3%; (◆) 4%.

experiment and at the 24-hr terminal sample. Interestingly, a one-way ANOVA demonstrated statistical differences in drug concentration at the 12-hr sampling time point ($p < 0.001$). The unblinded Glucotrol tablets released approximately 80% of the active after 12 hr of dissolution compared to nearly 100% for all overcoated products.

The authors theorized that the coating process may have damaged the integrity of the cellulose-acetate membrane in some manner. To test this hypothesis, unblinded Glucotrol XL tablets were exposed to the heat and pan rotation of the coating process for a time equivalent to 4% overcoating. In addition, a second batch of tablets was sprayed with deionized water (at the same rate as in the overcoating process) while tumbling in the coating apparatus. Both sets of tablets were examined by scanning electron microscopy and subjected to dissolution testing. No cracks or other defects in the cellulose-acetate polymeric coating were observed, as shown in Fig. 7. The size of the orifice, however, appeared to increase upon exposure to the coating conditions, as seen in Fig. 8. Previous researchers have shown that the orifice size of an osmotic-pump delivery system directly affects drug release.[22] With this possible explanation for the faster drug release seen at 12 hr in the blinded Glucotrol tablets, a dissolution test was performed on these unblinded tablets and the data are presented in Fig. 9. Surprisingly, drug release was slightly slower than the original unblinded Glucotrol tablets, although an ANOVA showed no statistical differences in drug release. Thus, the

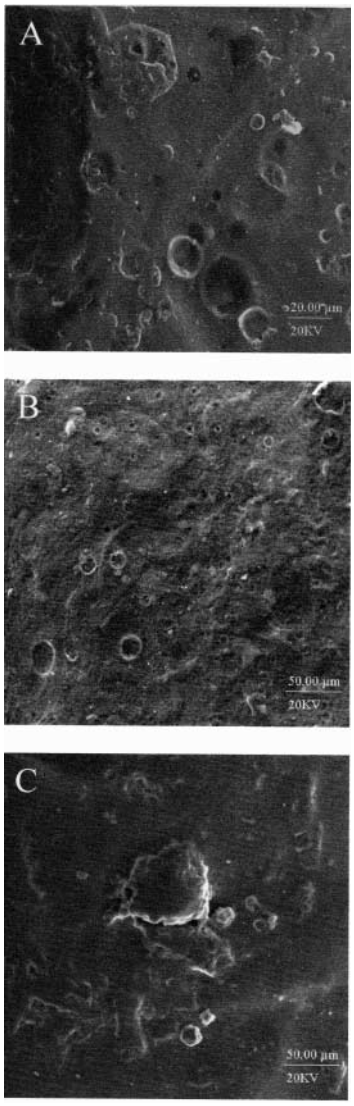

Figure 7. Scanning electron micrographs of the surface of a Glucotrol XL tablet. (A) Glucotrol tablet; (B) Glucotrol tablet following exposure to heat and pan rotation; (C) Glucotrol tablet sprayed with water and exposed to heat and pan rotation.

processing conditions did not account for the accelerated drug release observed in the overcoated products.

Previous research has shown that spraying an aqueous-based polymeric material onto a solid substrate causes dissolution of the very outer layers of the surface followed by physical mixing at the film-tablet interface.[23] The authors postulated that this interfacial interaction may have altered the surface area of the coated tablet.

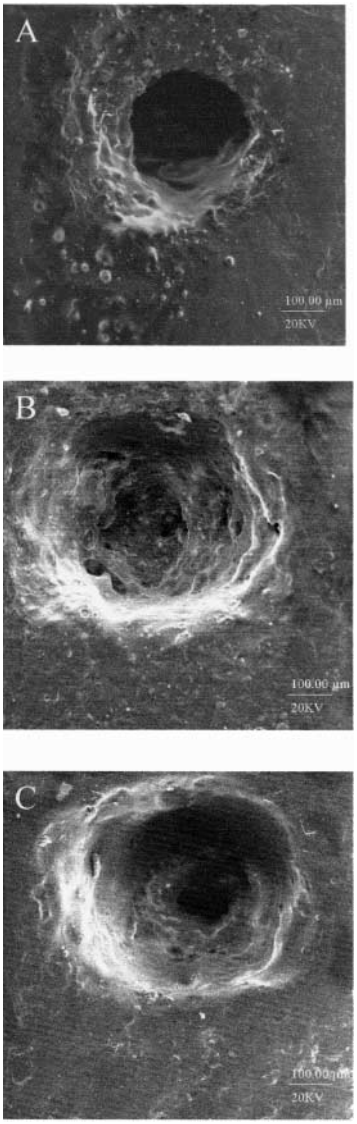

Figure 8. Scanning electron micrographs of the orifice of a Glucotrol XL tablet. (A) Glucotrol; (B) Glucotrol following exposure to heat and pan rotation; (C) Glucotrol sprayed with water and exposed to heat and pan rotation.

Dissolution testing was again conducted on the blinded and unblinded Glucotrol XL tablets. The tablets were carefully removed from the dissolution vessels after 12 hr and allowed to dry at 50°C under vacuum. The surface of these tablets was evaluated using scanning electron microscopy and the data are presented in Fig. 10. It is apparent that the surface of the overcoated tablet (Fig. 10B) was much rougher in appearance than the unblinded Glucotrol tablet (Fig. 10A). The overcoated product

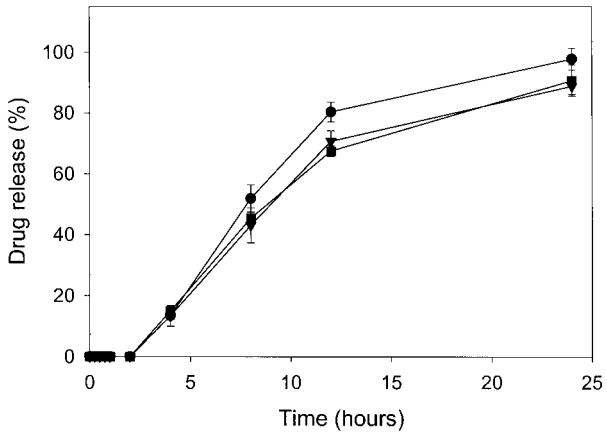

Figure 9. Influence of processing conditions on drug release from Glucotrol XL 5 mg tablets. (●) Glucotrol tablet; (▼) Glucotrol tablet following exposure to heat and pan rotation; (■) Glucotrol tablet sprayed with water and exposed to heat and pan rotation.

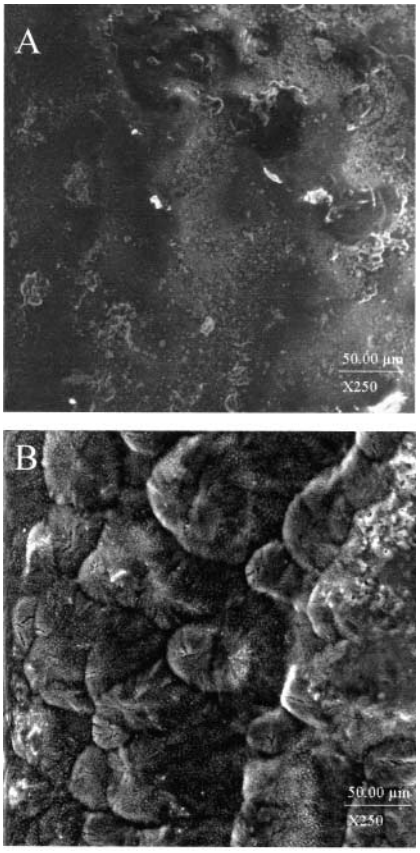

Figure 10. Scanning electron micrographs of the surface of a Glucotrol XL tablet following 12 hr of dissolution. (A) unblinded Glucotrol XL tablet; (B) overcoated Glucotrol XL tablet.

had an increased surface area that allowed more water to permeate into the tablet core, thus increasing the osmotic pressure to a greater extent and resulting in faster drug release.

CONCLUSIONS

The findings from this study demonstrate that overcoating with a red iron oxide/titanium dioxide-containing HPMC polymer may be a useful method to blind sustained-release tablets for clinical trials. Higher levels of polymer are needed to conceal dark ink on a light-colored tablet surface. Tablets must be smooth-faced and possess the physical strength to withstand the processing conditions. Dissolution testing should be conducted to ensure that the overcoating process does not alter drug release. Placebo tablets can be produced by purchasing tooling specially designed to match the active tablet.

ACKNOWLEDGMENT

These studies were supported in part by the Veteran's Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center.

REFERENCES

1. Carney, C.F.; Killeen, M.J.; Schulteis, W.M. Comparator drugs for clinical trials. Pharm. Eng. **1997**, *17*, 48–56.
2. Rowe, R.C.; Forse, S.F. The refractive indices of polymer film formers, pigments and additives used in tablet film coating: their significance and practical application. J. Pharm. Pharmacol. **1983**, *35*, 205–207.
3. Budavari, S.E. *The Merck Index*; Merck & Co. Inc.: Rahway, 1989.
4. Thrombe, A.G.; DeNoto, A.R.; Gibbes, D.C. Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients. J. Control Release **1999**, *60*, 333–341.
5. Stanley, P.; Rowe, R.C.; Newton, J.M. Theoretical considerations of the influence of polymer film coatings on the mechanical strength of tablets. J. Pharm. Pharmacol. **1981**, *33*, 557–560.
6. Lorck, C.A.; Grunenberg, P.C.; Junger, H.; Laicher, A. Influence of process parameters on sustained-release theophylline pellets coated with aqueous polymer dispersions and organic solvent-based polymer solutions. Eur. J. Pharm. Biopharm. **1997**, *43*, 149–157.
7. Tang, L.; Schwartz, J.B.; Porter, S.C.; Schnaare, R.L.; Wigent, R.J. Drug release from film-coated chlorpheniramine maleate nonpareil beads: effect of water-soluble polymer, coating level, and soluble core material. Pharm. Dev. Technol. **2000**, *5*, 383–390.
8. Chang, R.K.; Rudnic, E.M. The effect of various polymeric coating systems on the dissolution and tableting properties of potassium chloride microcapsules. Int. J. Pharm. **1991**, *70*, 261–270.
9. Felton, L.A.; Haase, M.M.; Shah, N.H.; Zhang, G.; Infeld, M.H.; Malick, A.W.; McGinity, J.W. Physical and enteric properties of soft gelatin capsules coated with Eudragit L 30 D-55. Int. J. Pharm. **1995**, *113*, 17–24.
10. Dangel, C.; Kolter, K.; Reich, H.B.; Schepky, G. Aqueous enteric coatings with methacrylic acid copolymer type C on acidic and basic drugs in tablets and pellets, Part 1: acetylsalicylic acid tablets and crystals. Pharm. Tech. **2000**, *24*, 64–70.
11. Porter, S.C. Use of Opadry, Sureteric, and Surelease for the aqueous film coating of pharmaceutical oral dosage forms. In *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd Ed.; McGinity, J.W., Ed.; Marcel Dekker Inc.: New York, 1997; 327–372.
12. Aulton, M.E.; Abdul-Razzak, M.H. The mechanical properties of hydroxypropylmethycellulose films derived from aqueous systems part 2: the influence of solid inclusions. Drug Dev. Ind. Pharm. **1984**, *10*, 541–561.
13. Gibson, S.H.M.; Rowe, R.C.; White, E.F.T. Quantitative assessment of additive-polymer interactions in pigmented hydroxypropyl methylcellulose formulations using immersion calorimetry. Int. J. Pharm. **1988**, *48*, 113–117.
14. Felton, L.A.; McGinity, J.W. Influence of pigment morphology and concentration on the adhesive properties of an aqueous-based acrylic polymer. Pharm. Res. **1997**, *14*, S-628.

15. Rowe, R.C. Modulus enhancement in pigmented tablet film coating formulations. Int. J. Pharm. **1983**, *14*, 355–359.
16. Maul, K.A.; Schmidt, P.C. Influence of different-shaped pigments and plasticizers on theophylline release from Eudragit RS30D and Aquacoat ECD30 coated pellets. STP Pharma Sci. **1997**, *7*, 498–506.
17. Shah, V.P.; Tsong, Y.; Sathe, P.; Liu, J.-P. In vitro dissolution profile comparison-statistics and analysis of the similarity factor, f2. Pharm. Res. **1998**, *15*, 889–896.
18. Felton, L.A.; McGinity, J.W. Adhesion of polymeric films to pharmaceutical solids. Eur. J. Pharm. Biopharm. **1999**, *47*, 1–14.
19. Desai, D.S.; Rubitski, B.A.; Varia, S.A.; Newman, A.W. Physical interactions of magnesium stearate with starch-derived disintegrants and their effects on capsule and tablet dissolution. Int. J. Pharm. **1993**, *91*, 217–226.
20. Lindstedt, B.; Ragnarsson, G.; Hjartstam, J. Osmotic pumping as a release mechanism for membrane-coated drug formulations. Int. J. Pharm. **1989**, *56*, 261–268.
21. Okimoto, K.; Miyake, M.; Ohnishi, N.; Rajewski, R.A.; Stella, V.J.; Irie, T.; Uekama, K. Design and evaluation of an osmotic pump tablet (OPT) for prednisolone, a poorly water soluble drug, using SBE-B-CD. Pharm. Res. **1998**, *15*, 1562–1568.
22. Theeuwes, F. Elementary osmotic pump. J. Pharm. Sci. **1975**, *64*, 1987–1991.
23. Felton, L.A.; Perry, W.L. A novel technique to quantify film-tablet interfacial thickness. Pharm. Dev. Technol. **2002**, *7*, 1–5.