Drug Development and Industrial Pharmacy, 25(10), 1093–1098 (1999)

RESEARCH PAPER

Drug Release from Spray Layered and Coated Drug-Containing Beads: Effects of pH and Comparison of Different Dissolution Methods

Waranush Sorasuchart,* Jacqueline Wardrop,† and James W. Ayres

College of Pharmacy, Oregon State University, Corvallis, OR 97331

ABSTRACT

Based on dissolution profiles of three model drugs on spray layered beads with the same percentage of Aquacoat® coating, it was concluded that in vitro dissolution of oral controlled-release formulations should be performed in both gastric and intestinal media for ionizable drugs. Ketoprofen (weak acid, pK_a 4.8), nicardipine HCl (salt of weak organic base, pK_a 8.6), and acetaminophen (very weak organic acid, pK_a 9.7, not ionized at physiologic pH) provided different dissolution characteristics in enzyme-free simulated gastric fluid (pH 1.4) and enzyme-free simulated intestinal fluid (pH 7.4), indicating that the rate of drug release was pH dependent and related to drug ionization even though the solubility of the coating (ethylcellulose) is pH independent. In acidic media, ketoprofen release from the beads containing low-level coating (3%) was slower than that of nicardipine HCl, with the opposite holding true in basic media. Acetaminophen was released at approximately the same rate in both acidic and basic media. A comparison of drug release profiles for nicardipine HCl nude beads was also investigated among three different dissolution methods: USP dissolution apparatus I (basket method, 50 rpm), USP dissolution apparatus II (paddle method, 50 rpm), and USP dissolution apparatus III (Bio-Dis®, Van-Kel Industries, 5 and 10 dpm). Release profiles obtained from all methods were similar, indicating that the three dissolution methods were comparable.

* Current address: Sugen, Inc., 230 East Grand Avenue, South San Francisco, CA 94080-4811
† Current address: Analytical Development Center, Abbott Laboratories, North Chicago, IL 60064

INTRODUCTION

Controlled-release drug products containing coated beads stay longer in dissolution media or biological systems than immediate-release dosage forms, thus scattering the beads along the gastrointestinal tract and exposing the drug beads to varying pH [pH 1 in fasting stomach (1) to pH 7.8 in the distal region of the intestine]. Therefore, pH has a major effect on drug release from these controlled-release formulations.

Dissolution testing is essential in designing and evaluating controlled-release dosage forms. Appropriate dissolution media should be selected carefully for particular drug and dosage form combinations.

Effects of pH of dissolution media on release rates of three model drugs with different solubilities and pK_a's from Aquacoat® (FMC Corporation, Newark, DE) coated beads were investigated. Aquacoat dispersion contains a solid content of 27% ethylcellulose and 3% sodium lauryl sulfate in water. Solubility of ethylcellulose is pH independent; however, it was previously reported that the release rates of theophylline (2), phenylpropanolamine HCl (2), and propranolol HCl (3) from Aquacoat coated beads were pH dependent.

In dissolution testing of controlled-release dosage forms, gastric and intestinal media may be used to simulate the pH throughout the gastrointestinal tract. Nevertheless, the basket (USP apparatus I) and paddle (USP apparatus II) are not convenient when a change of dissolution media is needed. Recently included in the U.S. Pharmacopeia (USP) (4), USP apparatus III (reciprocating cylinders, Bio-Dis®, Van-Kel Industries, Cary, NC) eliminates manual and tedious work in changing dissolution media, providing an advantage when dissolution testing is performed in a pH step gradient. Drug release profiles obtained with the Bio-Dis in pH step gradient dissolution media were comparable to those of the NF XIII (5) official bottle rotation method (6). Using an empirical equation to fit parameters for a specific formulation, Rohrs et. al. reported that dipping rates of 5–8 dpm of Bio-Dis would be equivalent to 50 rpm for the paddle method or 100 rpm for the basket method (7). In this study, comparative dissolution testing of dips per minute (Bio-Dis) equivalent to standard rounds per minute (basket and paddle) was performed.

MATERIALS AND METHODS

Materials

Nicardipine HCl (lot 4628) was supplied by Teva Pharmaceuticals (Sellersville, PA). Ketoprofen was supplied by Biocraft (Fairfield, NJ). Acetaminophen was purchased from Sigma Chemical Company (St. Louis, MO). Other chemicals used included triethyl citrate 99% (TEC; Aldrich Chemical Company, Inc., Milwaukee, WI), dibutyl sebacate (DBS; Sigma Chemical Co.), hydroxypropylcellulose (Klucel, Hercules, Inc., Wilmington, DE), polyvinylpyrrolidinone K-30 (PVP; EM Science, Gibbstown, NJ), Aquacoat (FMC Corporation). Nonpareil sugar beads were purchased from Crompton and Knowles Corporation (Pennsauken, NJ). Other chemicals were reagent grade.

Methods

Nude and Coated Bead Preparation

Each drug was spray layered with binder onto 100 g of nonpareil sugar beads (25–30 mesh) in a coating chamber of a fluid-bed spray coater (Strea-1, Aeromatic, Inc., Columbia, MD) containing a 7-inch Wurster column. The Wurster column was approximately 1 inch away from the bottom of the screen of the coater, which was connected to a Lab-line/PRL high-speed fluid-bed dryer (Lab-line, Melrose Park, IL).

Spray layering was performed at 40°C. Air pressure was maintained at 10 psi, and the blower speed was set at 80–90% of full capacity to allow beads to move freely. Drug solution/suspension was constantly delivered by a peristaltic pump (Rabbit® peristaltic pump, Gilson Medical Elecronics, Middleton, WI). During spray layering, the drug solution/suspension was stirred by a magnetic stirrer to ensure homogeneity. Drug-layered beads were dried in the coating chamber for another 30 min at the same temperature and air flow before removing. Beads were then sieved to remove agglomerated and fine particles.

Drug spray-layered beads (nude beads) were then overcoated with 3% weight gain Aquacoat that was previously diluted 1:1 with distilled deionized water and stirred with plasticizers (15% w/w TEC and 15% w/w DBS). Spray coating was performed using the fluid-bed spray coater. Other conditions were as previously described.

Dissolution Testing of Aquacoat Coated Beads

Dissolution profiles of Aquacoat coated drug-layered beads were determined using the USP XXIII apparatus II, paddle stirring method (VK 7000®, VanKel Industries). Dissolution media (filtered, degassed, and maintained at 37.0°C) included 900 ml of enzyme-free simulated gastric fluid (pH 1.4 ± 0.1) for the first 2 hr and 900 ml of enzyme-free simulated intestinal fluid (pH 7.4 ± 0.1)

subsequently. In the case of nicardipine HCl, the dissolution tank was protected from light with cardboard.

Dissolution tests of Aquacoat coated drug-containing beads were performed in triplicate. The beads were weighed and dropped in the dissolution vessels at time zero. Dissolution was studied at a paddle rotation speed of 50 rpm. Samples of 3 ml dissolution media were withdrawn without medium replacement at 0.25, 0.5, 0.75, 1, 1.5, and 2 hours (in gastric fluid) and at 2.25, 2.5, 2.75, 3, 4, 5, 6, 8, 12, and 18 hr (in intestinal fluid) using an autosampler (Peristaltic Pump VK 810® connected to System Monitor VK 8000®, VanKel Industries). All samples were filtered through 5-μm Acrodisc® (Gelman Sciences, Ann Arbor, MI). At 2 hr, the gastric fluid containing beads was filtered. Beads were gently collected and transferred to intestinal fluid previously maintained at 37.0°C. Paddle rotation was continued at a rate of 50 rpm.

The amounts of ketoprofen, nicardipine HCl, or acetaminophen released were detected directly by an ultraviolet (UV) spectrophotometer (Hewlett Packard 8452 A diode array spectrophotomer, Hewlett Packard GmbH, Waldbronn 2, Federal Republic of Germany) at wavelengths of 258, 358, and 244 nm, respectively. Standard solutions were prepared by serial dilutions from 1 mg/ml stock solutions.

Dissolution profiles of ketoprofen and nicardipine HCl from coated beads were also obtained in intestinal fluid only (no gastric pretreatment) using the paddle method at the rate of 50 rpm. Samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hr without replacement. Determination of amounts of drug released was as previously described.

Comparison of Dissolution Testing of Nicardipine HCl Nude Beads by Three USP Dissolution Methods

Dissolution profiles of nicardipine HCl nude beads were compared for three USP dissolution methods. In each method, dissolution testing was performed in triplicate in citrate buffer (pH 4.5) or in enzyme-free simulated gastric-intestinal fluids as previously described. When the citrate buffer was used, samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18, and 24 hr without replacement. When the gastric-intestinal fluids were used, samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2 hr (in gastric fluid) and at 2.17, 2.33, 2.5, 2.75, 3, 3.5, and 4 hr (in intestinal fluid) without replacement. Samples were filtered through 5-μm Acrodisc. Amounts of drug released were detected as previously described.

USP Apparatus I (Basket Method)

Beads were weighed and put in the baskets, which were then placed in the dissolution medium at the same time. Baskets were rotated at 50 rpm. For dissolution testing in gastric-intestinal fluids, the baskets were drained and patted to remove excess solution before transferring to intestinal fluid.

USP Apparatus II (Paddle Method)

Beads were weighed and dropped in the dissolution medium at time zero. Dissolution testing was performed at a paddle rotation rate of 50 rpm. Dissolution testing in the gastric-intestinal fluids was as previously described.

USP Apparatus III (Bio-Dis)

Each of the dissolution vessels in the first row of the Bio-Dis contained 250 ml of enzyme-free simulated gastric fluid for the first 2 hr, and each of those in the second row contained 250 ml of enzyme-free simulated intestinal fluid. The beads were weighed and placed in the dipping tubes, which contained a bottom screen. Dipping was performed at the rate of 5 or 10 dips per minute. The first dip was held for 3 sec. The dipping tubes were drained for 1 min before moving to intestinal fluid.

Statistical Analysis

Linear regression analysis for correlations of percentages of drug release for each dissolution method was performed using Microsoft Excel® 5.0.

RESULTS AND DISCUSSION

Table 1 summarizes the chemical characteristics of the three model drugs. Ratios of ionized to nonionized forms of drugs are described in Henderson and Hasselbalch's equations (Eqs. 1 and 2). Table 2 describes the ratios of ionized to nonionized forms of each drug at pH 1.4 and pH 7.4.

For weak acids (9),

$$\frac{\text{Ionized}}{\text{Nonionized}} = 10^{(\text{pH}-\text{p}K_a)} \quad (1)$$

For weak bases (9),

$$\frac{\text{Nonionized}}{\text{Ionized}} = 10^{(\text{pH}-\text{p}K_a)} \quad (2)$$

Effects of pH on the rate of drug release are illustrated in Figs. 1 and 2. Even though the polymer in Aquacoat (ethylcellulose) is pH independent, release rates of keto-

Table 1

Chemical Characteristics of Ketoprofen, Nicardipine HCl, and Acetaminophen

Drug	Acid-Base Property	pK_a	Drug Solubility in Water
Ketoprofen	Weak organic acid	4.8	1:18,000[a]
Nicardipine HCl	Salt of weak organic base	8.6	1:850[a]
Acetaminophen	Very weak organic acid	9.7	1:70[b]

[a]Solubilities were obtained experimentally.
[b]Solubility was obtained from Ref. 8.

Table 2

Ratios of Ionized to Nonionized Forms

pH of Dissolution Media	Ratio of Ionized to Nonionized Forms		
	Ketoprofen	Nicardipine HCl	Acetaminophen
1.4	$3.98 \times 10^{-4}/1$	$1.58 \times 10^{7}/1$	$5.01 \times 10^{-9}/1$
7.4	398/1	15.85/1	0.005/1

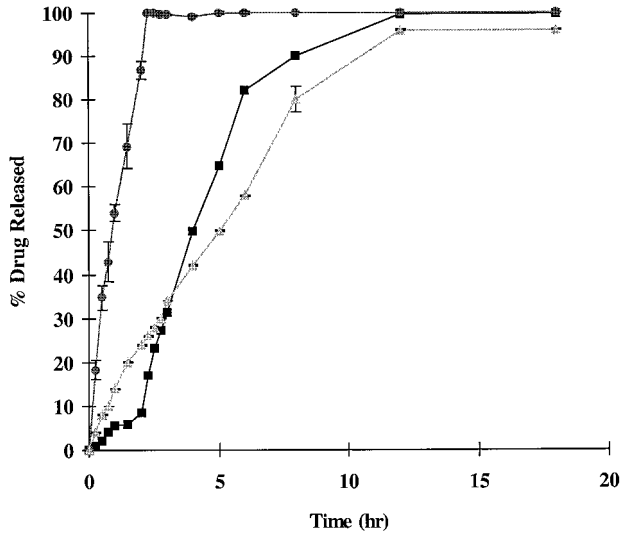

Figure 1. Dissolution profiles of model drugs in enzyme-free simulated gastric fluid (pH 1.4) for 2 hr and then in enzyme-free simulated intestinal fluid (pH 7.4) (paddle method). Error bar represents standard deviation. ■, ketoprofen; ●, nicardipine HCl; and ▲, acetaminophen.

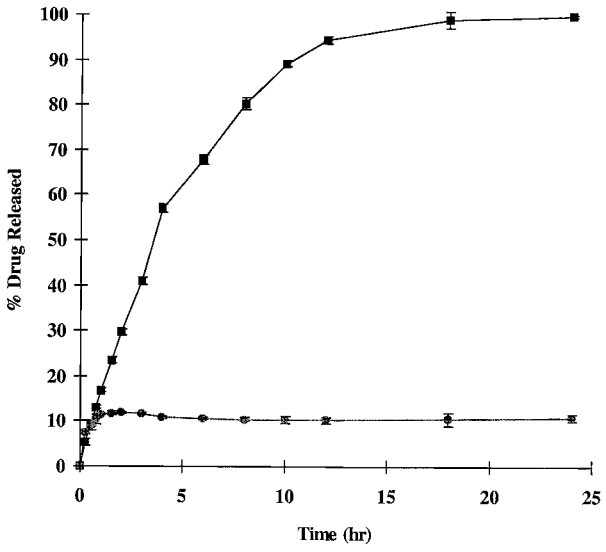

Figure 2. Dissolution profiles of ketoprofen and nicardipine HCl in enzyme-free simulated intestinal fluid (pH 7.4) (paddle method). Error bar represents standard deviation. ■, ketoprofen; and ●, nicardipine HCl.

profen and nicardipine HCl were pH dependent. Ketoprofen (weak acid) and nicardipine HCl (salt of weak base) are slightly soluble in water (Table 1). Drug solubilities of both compounds depend on degrees of drug ionization (Table 2). Ketoprofen was more ionized in basic medium and thus was released faster than in acidic medium. Nicardipine HCl was more ionized in acidic medium and thus was released faster than in basic medium. Figure 2 demonstrates that, in basic medium, the release of ketoprofen was very fast, while that of nicardipine HCl was very slow. On the other hand, acetaminophen (very weak acid) is relatively more soluble in water; therefore, the release rates were similar in both dissolution media and were not affected by degree of ionization. In acidic media, acetaminophen release was much slower than release of nicardipine HCl, but faster than ketoprofen release. In basic media, acetaminophen release was much slower than ketoprofen release, but faster than nicardipine HCl release.

The release patterns were opposite the results obtained in Ref. 2 from the beads containing a higher level of overcoating (16% w/w), for which the complete film was formed. Overcoating of 3% was not enough to form a complete coating film; thus, the release rates were more likely matrix controlled, which depended on dissolution rates of drugs (ionized form of drugs), while the release rates from the beads containing 16% overcoating were

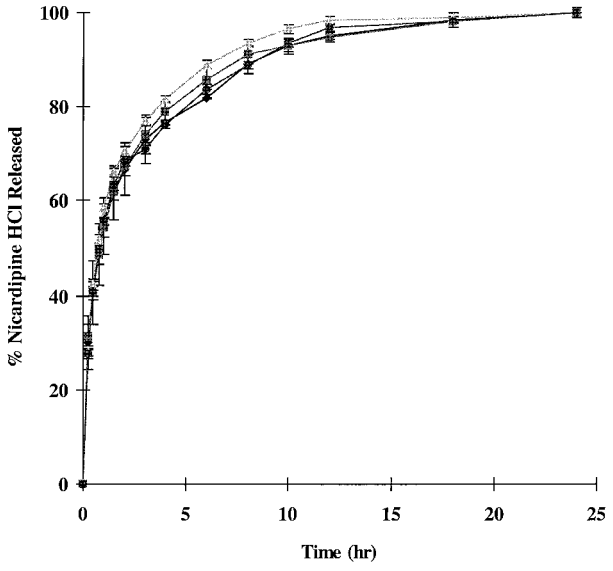

Figure 3. Dissolution profiles of nicardipine HCl nude beads in citrate buffer (pH 4.5). Error bar represents standard deviation. ◆, basket 50 rpm; ■, paddle 50 rpm; ▲, Bio-Dis 5 dpm; and ●, Bio-Dis 10 dpm.

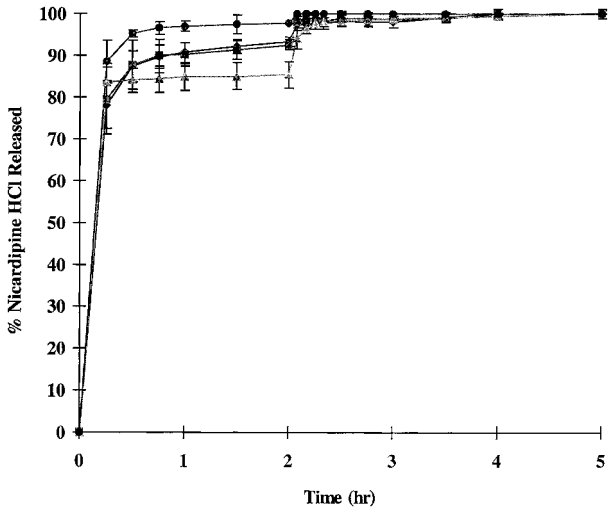

Figure 4. Dissolution profiles of nicardipine HCl nude beads in gastric fluid (pH 1.4) for 2 hr and then in intestinal fluid (pH 7.4). Error bar represents standard deviation. ◆, basket 50 rpm; ■, paddle 50 rpm; ▲, Bio-Dis 5 dpm; and ●, Bio-Dis 10 dpm.

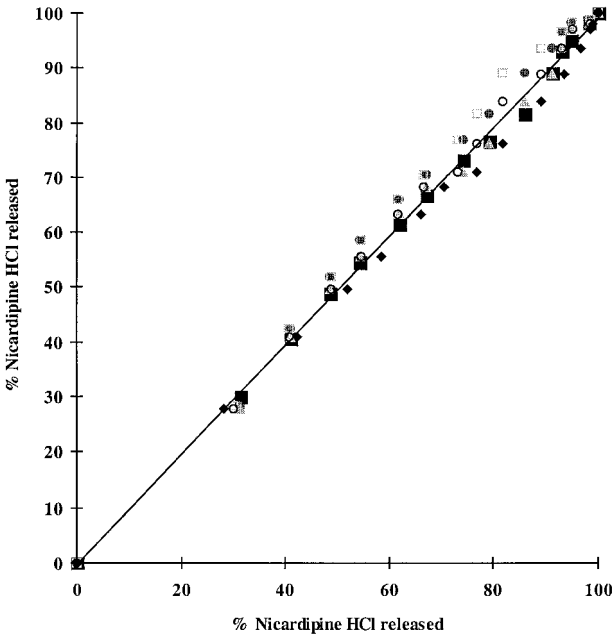

Figure 5. Correlations of percentage nicardipine HCl released in citrate buffer (pH 4.8) between each pair of dissolution methods. ■, paddle 50 rpm–basket 50 rpm (R^2 = .9982); ●, paddle 50 rpm–Bio-Dis 5 dpm (R^2 = .9962); ▲, paddle 50 rpm–Bio-Dis 10 dpm (R^2 = .9958); □, basket 50 rpm–Bio-Dis 5 dpm (R^2 = .9980); ○, basket 50 rpm–Bio-Dis 10 dpm (R^2 = .9979); ◆, Bio-Dis 5 dpm–Bio-Dis 10 dpm (R^2 = .9959).

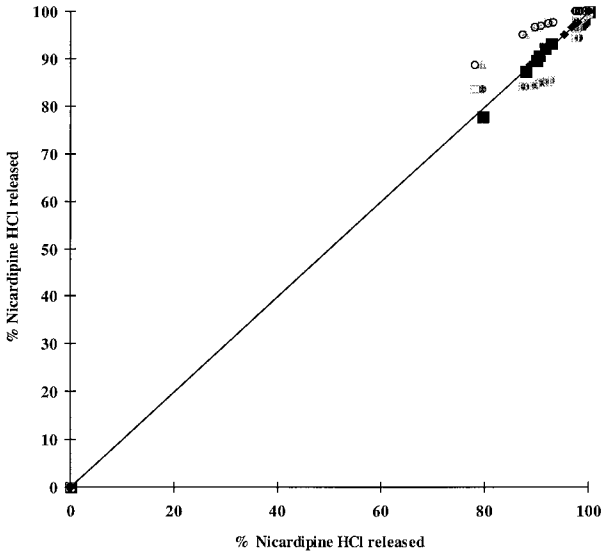

Figure 6. Correlations of percentage nicardipine HCl released in enzyme-free simulated gastric and intestinal fluids between each pair of dissolution methods. ■, paddle 50 rpm–basket 50 rpm (R^2 = .9994); ●, paddle 50 rpm–Bio-Dis 5 dpm (R^2 = .9840); ▲, paddle 50 rpm–Bio-Dis 10 dpm (R^2 = .9843); □, basket 50 rpm–Bio-Dis 5 dpm (R^2 = .9793); ○, basket 50 rpm–Bio-Dis 10 dpm (R^2 = .9836); ◆, Bio-Dis 5 dpm–Bio-Dis 10 dpm (R^2 = .9569).

controlled by rates of diffusion through the coating film and therefore based on concentration of nonionized form of drugs.

Comparisons of three USP dissolution methods are illustrated in Fig. 3 (citrate buffer as dissolution medium) and Fig. 4 (gastric and intestinal fluids as dissolution media). In both citrate buffer and gastric-intestinal fluids, the release profiles of nicardipine HCl obtained from the basket method (50 rpm), paddle method (50 rpm), and Bio-Dis (5 and 10 dpm) were similar. A linear correlation between each pair of dissolution methods in both dissolution media was found, as shown in Figs. 5 and 6 (R^2 .96–.99). Figure 6 data points are ''clumped'' because release is so rapid in all methods.

CONCLUSIONS

Rate of drug release from Aquacoat coated beads was pH dependent even though the coating polymer solubility (ethylcellulose) is pH independent. Drug release from the beads containing a low level of overcoating (3%) was faster when the drug was more ionized. Thus, to formulate gastrointestinal controlled-release drug products, drug solubility or ionization should be considered along with level of polymer overcoating. Furthermore, in vitro dissolution of controlled-release formulations should be performed in both gastric and intestinal media for molecules that ionize anywhere in the gastrointestinal tract.

Drug release profiles obtained from three USP dissolution methods were similar, indicating that the three methods were comparable. Therefore, the Bio-Dis method at a dipping rate of 5 or 10 dpm was equivalent to the paddle or basket method at the rate of 50 rpm. The Bio-Dis method is preferred when more than one dissolution medium is utilized.

ACKNOWLEDGMENTS

Thanks are due to Dr. Kris Holt for the ketoprofen beads and their dissolution results in gastric-intestinal fluids. Acetaminophen release rates were obtained from Mohammad Hossain's Ph.D. thesis (9). Thanks also go to Marcus Cox, Matthew Brazer, and Shi-Gyong Jeong for their technical assistance.

REFERENCES

1. L. Shagel and A. B. C. Yu, *Applied Biopharmaceutics and Pharmacokinetics*, Appleton and Lange, 1991.
2. FMC Corporation, *Aquacoat® Application Book*, Author, Philadelphia, PA.
3. D. E. Hutchings and A. Sakr, *J. Pharm. Sci*., 83(10), 1386–1390 (October 1994).
4. U.S. Pharmacopeial Convention, *United States Pharmacopeia XXIII/National Formulary XVIII*, Author, Rockville, MD, 1995, pp. 1791–1799.
5. American Pharmaceutical Association, *The National Formulary XIII*, Author, Washington, DC, 1970, pp. 882–883.
6. B. Esbelin, E. Beyssac, J.-M. Aiache, G. K. Shiu, and J. P. Skelly, *J. Pharm. Sci*., 80(10), 991–994 (October 1991).
7. B. R. Rohrs, D. L. Burch-Clark, M. J. Witt, and D. J. Stelzer, *J. Pharm. Sci*., 84(8), 922–926 (August 1995).
8. J. E. F. Reynold (Ed.), *Martindale, The Extra Pharmacopoeia*, 30th ed., Pharmaceutical Press, London, 1993, p. 27.
9. M. Hossain, Ph.D. thesis, Oregon State University, Corvallis, 1991.