Drug Development and Industrial Pharmacy, 24(6), 509-515 (1998)

RESEARCH PAPER

Peroral Sustained-Release Film-Coated Pellets as a Means to Overcome Physicochemical and Biological Drug-Related Problems. I. In Vitro Development and Evaluation

K. Amighi,[1,*] J. Timmermans,[2] J. Puigdevall,[2] E. Baltes,[2] and A. J. Moës[1]

[1]*Laboratoire de Pharmacie Galénique et de Biopharmacie, Université Libre de Bruxelles, Campus Plaine, CP 207, Bruxelles, Belgium*
[2]*UCB S.A. Pharma Sector, Research and Development, Toxicological Research Department Chemin du Foriest, Braine-l'Alleud, Belgium*

ABSTRACT

In vitro preformulation testing has shown that the solubility and dissolution rate of the model drug compound ucb 11056 are highly pH dependent. Considering this, different sustained-release (SR) oral dosage forms of ucb 11056 were developed aiming to obtain the most constant and complete release of the drug during transit in the gastrointestinal (GI) tract. Classical approaches based on the use of SR formulations such as hydrophilic matrix tablets or pellets coated with one film-forming polymer (Eudragit® NE30D or L30D-55) did not fulfill all expectations on the basis of their in vitro evaluation, i.e., the drug release and pattern remained highly dependent on the pH of the dissolution medium. Therefore, taking advantage of the flexibility of release adjustment obtainable from coating of pellets with different kinds of pH-sensitive film layers, a quite satisfactory pH independence of the release characteristics was obtained using formulation blends of neutral and anionic acrylic polymers. For the selected SR pellets batch 15 coated with NE30D/L30D-55 (7:3), the tridimensional topographic representation of the drug release versus *time and pH showed that, notwithstanding the pH-dependent aqueous solubility of the drug, the release profiles were relatively homogeneous for any pH value ranging between 1 and 7.*

*To whom correspondence should be addressed.

INTRODUCTION

The recent progresses in the pharmaceutical manufacturing technology are most probably one of the reasons for the increasing popularity of sustained-release (SR) dosage forms. In this respect, oral SR dosage forms such as coated pellets and matrix tablets have become popular in drug therapy as attempts are being made to extend the biological half-life of certain drugs.

It is generally admitted that multiple-unit dosage forms such as pellets present some biopharmaceutical advantages, particularly regarding the duration and the individual reproducibility of the gastric emptying, in comparison with larger single-unit dosage forms. In general, it can be said that particles as large as about 2–3 mm contained in multiple-unit forms appear to be small enough to pass through the contracted pylorus and thus, empty gradually and to some extent more predictably from the stomach. On the other hand, solids larger than 7 mm are merely emptied from the stomach in the fasted state consecutive to the housekeeper wave activity during the interdigestive phase (1). Moreover, because for multiparticulates each dose consists of many subunits, there is better statistical assurance of drug release, and the risk of dose dumping is equally subdivided (2).

The development of SR oral dosage forms requires the knowledge of the physicochemical and pharmacokinetic properties of the active substance, especially the solubility at the physiological pHs and the absorption rate and extent at the different sections of the gastrointestinal (GI) tract.

In this view, the use of SR forms such as film-coated pellets permits the adjustment of specific membrane properties for each particular case. The great deal of flexibility in formulation of these forms allows, for most drugs, high-quality pharmaceutical dosage forms with optimal release characteristics to be designed. (3).

The use of pharmaceutical film coating additives, such as plasticizers (4–6), insoluble powders (7–9), or pore-forming agents (10,11), is often necessary to improve the workability and/or to obtain optimal barrier properties.

For the same reasons, the use of polymer blends might offer a wide range of applications for the formulation of film-coated controlled-release dosage forms (12,13). In particular, the anionic acrylic polymers with graded solubility in the pH range 5.5–7.0 (Eudragits® L30D-55, L100-55, L100, and S100) can be mixed in any proportions with the neutral acrylic polymer (Eudragit NE30D). The permeability of films obtained from these blends increases at intestinal pHs as a function of the content of anionic enterosoluble polymers. Such coatings could be especially useful for drugs such as theophylline (14,15) or metoprolol (16) which are well absorbed through the GI tract but have a slower absorption rate in the colon (small absorptive area) or, as in this case, for a drug showing reduced solubility and dissolution rate at intestinal pH values.

The model drug (laboratory code ucb 11056) taken to illustrate the development approach in this paper is a substance with central nervous system (CNS) properties under investigation at UCB S.A. Pharma Sector, R&D, Braine-l'Alleud, Belgium; its activity in humans is expected to be in the 100–1000 mg/day dose range. A sustained and/or controlled delivery of this drug in the GI tract is justified in order to overcome its relatively short biological half-life (0.5–1.0 hr) and to increase the extent of the safety margin by reducing the incidence of dose-dependent side-effects such as vomiting. Moreover, it is a poorly water-soluble weak organic base (pK_a 4.90, 25.0°C) expected to show irregular and incomplete absorption in the GI tract when administered by means of classical monolithic delivery systems, since its solubility and subsequent release are highly dependent on pH changes.

The aim of this work was to evaluate both the in vitro and in vivo performances of different SR oral formulations of ucb 11056. The in vitro development and evaluation are described in the present paper, and the in vivo evaluation in the beagle dog of selected dosage forms is described in a second publication.

In accordance with preformulation data obtained from solubility and intrinsic dissolution rate studies, different SR oral dosage forms of ucb 11056 were developed in order to obtain the most constant and complete release of the drug in the GI tract. For this purpose, the drug release was controlled by using a single-unit modified hydrophilic matrix tablet system and also various multiunit film-coated pellets. For the latter, the drug-loaded pellets were coated by blends of neutral (Eudragit NE30D) and anionic methacrylic acid copolymer (Eudragit L30D-55) in order to overcome a number of shortcomings related to the poor and pH-dependent aqueous solubility of the substance.

EXPERIMENTAL

Materials and Methods

Determination of the Drug Solubility and Intrinsic Dissolution Rate

The influence of the pH of the dissolution media on the solubility and the intrinsic dissolution rate of ucb

11056 was evaluated by using different phosphate–acetate buffer solutions (0.05 M) with pH values ranging from 1 to 7 and containing 0.05% w/w polysorbate 80. All determinations were performed in triplicate.

The solubility at saturation was determined after a 24-hr stirring period of suspensions of the drug in the different buffer solutions (pHs 1, 3, 5, and 7) thermostatically controlled at 37.0°C, the solute drug concentration being determined after filtration and suitable dilutions by UV spectrophotometry at 235 nm.

The intrinsic dissolution rate was determined after compacting, at high compression strength (100 kN), a mixture of 80% drug and 20% microcrystalline cellulose into a disk (1.30 cm diameter) by means of a manual hydraulic press. A constant surface area was obtained by introducing the tablet into a stainless steel die, which was previously lined with silicone grease. The intrinsic dissolution rate constant (mg/cm^2/min) was determined using the USP XXIII dissolution apparatus no. 2 (paddle) in 500 ml of medium (pHs 1.3, 3, 3.5, 5, and 7) at 37.0°C with a stirring rate of 60 rpm. The progress of dissolution was followed by continuous automated sampling of the dissolution medium and direct drug assay by UV spectrophotometry at 235 nm.

Preparation of ucb 11056 Oral Dosage Forms

Pellets of ucb 11056 having a mean diameter of 1 mm, containing approximately 60% drug, microcrystalline cellulose (Avicel® pH 101), and polyvinylpyrrolidone (Plasdone® K25), were prepared by extrusion–spheronization. SR coats were obtained by using blends of Eudragits NE30D and L30D-55 (Röhm GmbH, Pharma Polymers, Darmstadt, Germany). The ratio between the neutral (NE30D) and the anionic (L30D-55) acrylic polymer in the coating dispersion blends was, respectively, 10:0, 9:1, 8:2, 7:3, and 0:10. Hydrophilic pore-forming ingredients (Pharmacoat 606® and lactose) and talc were incorporated to the coating dispersions in order to improve the processing and/or to control the permeability of films.

The preparation of coating dispersions and the conditions adopted during the coating process are similar to those described in a previous study (17).

The mean coating level of the different batches of coated pellets was around 7.6%, and no curing stage was required to stabilize the drug release.

Two batches of film-coated pellets containing Eudragits NE30D/L30D-55 ratios of 9:1 and 7:3 (SR pellets batch 11 and 15, respectively) were finally selected for the in vivo experimentation. Quantities of coated pellets corresponding to 125 mg ucb 11056 were filled into size 1 white-opaque hard gelatin capsules.

SR hydrophilic matrix tablets (SR matrix batch 74) containing 125 mg drug, approximately 30% of a high-viscosity grade hydroxypropylmethylcellulose (Methocel K4M), about 4% of citric acid (as acidifying agent intended to locally increase the drug solubility), and presenting a mean weight and a diameter of 700 mg and 13 mm, respectively, were prepared by direct compression.

Instant-release doses of 62.5 mg ucb 11056 (half-dose content compared to the SR dosage forms), given as white-opaque hard gelatin capsules size 3 filled with the bulk powder (IR capsule batch 910306), were also prepared for the in vivo experimentation as a reference form.

In Vitro Dissolution Studies of Dosage Forms

In vitro dissolution tests were performed using the USP XXIII dissolution apparatus no. 2 (paddle) thermostatically controlled at 37.0°C with a stirring rate of 60 rpm. The dissolution medium was a phosphate–acetate buffer (0.05 M) containing 0.05% w/w polysorbate 80.

The dissolution tests were conducted according to a pH-gradient procedure intended to simulate the pH variations during transit of the form in the GI tract (17). Samples of dosage forms, equivalent to 125 mg drug load, were placed in the dissolution medium and drug release was assayed (n = 5 replicate tests for each dosage form) by UV spectrophotometry at 280 nm using an automated PU 8605/60 tablet dissolution monitoring system (Philips Analytical, Cambridge, UK).

Conversely, in vitro dissolution tests of selected dosage forms were also performed as described, except that the pH of the dissolution medium was kept constant over time at different fixed values (1–7) in order to determine the influence of pH on drug release. The drug release profiles obtained were presented using a multidimensional topographic representation (18).

RESULTS AND DISCUSSION

Drug Solubility and Intrinsic Dissolution Rate

Figure 1 shows the solubility and intrinsic dissolution rate profiles of ucb 11056 as a function of the different pH values ranging between 1 and 7. The solubility of this drug is pH dependent, consistent with the behavior expected from a weak base, being soluble in acidic media (54.2 mg/ml at pH 1.3) but only slightly soluble at more neutral pH values (3.41 mg/ml at pH 7.0).

Conversely the intrinsic dissolution rate of ucb 11056 decreases more than five times (from 2.61 to 0.49 mg/cm^2/min) when the pH of the dissolution medium is

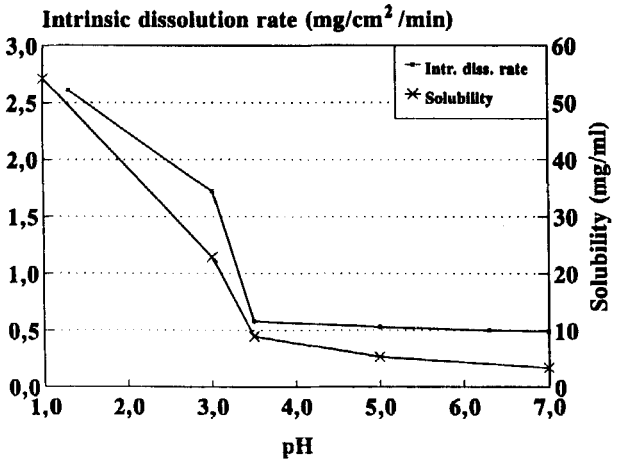

Figure 1. Influence of the pH of medium on the aqueous solubility (mg/ml) and intrinsic dissolution rate (mg/cm²/min) of ucb 11056 bulk compound.

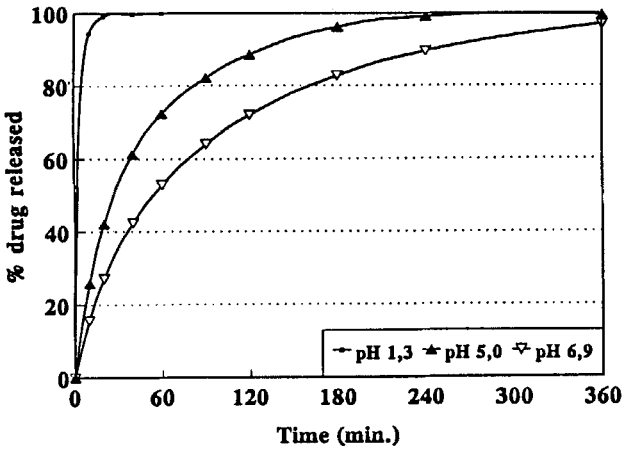

Figure 2. Release profiles of ucb 11056 from uncoated pellets in aqueous media with different pH values (1.3, 5.0, and 6.9).

increased from 1.3 to 7.0. This important decrease is already observed from pH 3.5 onward, the value of which is known to represent a usual gastric pH in humans under fed conditions. Nevertheless, even the lowest dissolution rate values observed are still superior to 0.1 mg/cm²/min, the latter being generally recognized as a limit value below which dissolution-related bioavailability problems are expected to occur.

Development and In Vitro Evaluation of Sustained-Release Oral Formulations

As a consequence to this pH-dependent solubility behavior, the drug release in solute state from any dosage form and, subsequently therefore, the apparent biological absorption rate of the active compound, might be highly dependent on the physiological pH variations encountered in the GI tract.

This is already apparent from the release kinetics of ucb 11056 from crude pellets (uncoated) as illustrated in Fig. 2. Although drug release is very fast at pH 1.3 (almost 100% available after 20 min), a substantial decrease of the release rate is noticed at pH 5.0 and further at 6.9, where more than 6 hr is necessary to achieve the release of the total dose content.

Two approaches were considered in an attempt to overcome the solubility-related shortcomings of the drug.

First, ucb 11056 was formulated as a standard SR hydrophilic matrix tablet containing additionally a small amount of citric acid. Despite the presence of this acidifying agent intended to enhance drug dissolution in an unfavorable pH environment (i.e., when the dosage form moves toward the intestine), this approach was not seen to fulfill all expectations, at least on the basis of its in vitro evaluation, which will be detailed.

A second option was therefore considered, taking advantage of the flexibility of release adjustment obtainable from pellets coated with different kinds of pH-sensitive film layers. In this new approach, which is more specifically the topic of this paper, the objective was to obtain a better control of the release characteristics all over the physiological pH range. For instance, regarding the appropriate solubility of the drug in acid media combined with the important surface area offered for dissolution by the multiunit dosage forms, the coating material must first be able to slow the release characteristics in gastric pH conditions. Conversely, as soon as the dosage form arrives in the intestine, the film permeability must increase with increasing pH values in order to offset the important decrease of drug dissolution rate observed at pHs higher than 3.

Such coatings can theoretically be obtained by mixing neutral acrylic polymer (Eudragit NE30D) and anionic methacrylic acid copolymers (Eudragits L30D-55, L100-55, L100, and S100) in different proportions. The choice of Eudragit L30D-55 is imperative in this case in order to offset the decrease of the drug dissolution rate as soon as the form enters the proximal portion of the small intestine. Furthermore, the presence in the coatings of hydrophilic pore-forming agents, such as Pharmacoat 606 and lactose, ensures that drug release

is also effective below pH 5, i.e., even before the enteric fraction of the blends has been dissolved.

The effect of blending Eudragit NE30D with L30D-55 in different proportions on the drug release rates is shown in Fig. 3 for a pH-gradient dissolution procedure. As we can see, the pellets coated with Eudragit NE30D or L30D-55 alone are not suitable as SR systems because the drug release rate and pattern remain highly dependent on the pH of the dissolution medium. Indeed, even though in the first situation drug release is strongly slowed in the simulated intestinal media with an important impact on the total amount released at the end of the test, a too-low drug release is obtained in gastric media for pellets coated with the enteric acrylic polymer alone.

Interestingly, for blends containing both of the above-mentioned acrylic polymers, the decreasing effect on drug release rate resulting from the lower solubility of ucb 11056 in the intestinal media is progressively counterbalanced when the proportion of the enteric polymer is increased in the blends. This phenomenon can more than likely be explained by the higher porosity and permeability of these films after the dissolution of the enteric fraction at intestinal pH values. As a result, more appropriate dissolution profiles are obtained for pellets coated with NE30D–L30D-55 8:2 and 7:3 blends, showing moderate drug release in gastric media as well as suitable release in intestinal media.

In view of these results, two practical SR pellet formulations could be selected, showing distinct release characteristics, in order to evaluate their adequacy of use and possible difference during the in vivo study (SR pellets batches 11 and 15, coated with NE30D–L30D-55 9:1 and 7:3, respectively).

The drug release profiles obtained under a pH-gradient dissolution procedure are compared in Fig. 4 to that of the previously developed single-unit hydrophilic matrix tablet (SR matrix batch 74).

This matrix obviously exhibits the fastest release properties in the 1.3–5 pH range but the rate is thereafter noticeably decreased for higher pH values and, as a result, drug release is not completed at the end of a 12-hr dissolution test. The acidifying agent contained in the matrix appears thus to be of little help for overcoming unfavorable drug dissolution conditions.

The pellets coated with the formulation containing the lowest enteric fraction content (SR pellets batch 11) provide a quite similar release pattern with even slower delivery rates all over the pH-gradient range examined. The deliberate choice with respect to the in vivo study of this extra-slow release dosage form will be explained in the second part of this work.

Finally, for the SR pellets batch 15 coated with NE30D/L30D-55 7:3, a marked slowing of the release rate is observed in acid media, while the dosage form nevertheless reaches almost 100% delivery at the end of the test as a result of a very prompt recovery of faster release rates as soon as the pH of dissolution medium is brought above 5.

The two-dimensional plots given in Fig. 4 unfortunately do not provide full information about the pH-dependent characteristics of these selected dosage forms, as can perhaps be more strikingly obtained from a tri-

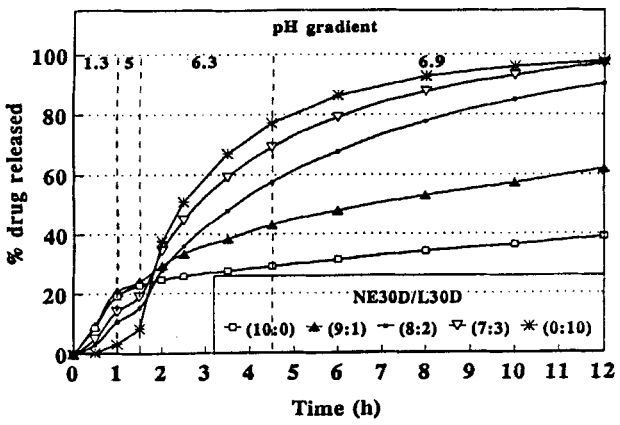

Figure 3. Release profiles of ucb 11056 from pellets coated with blends containing different proportions of Eudragit NE30D/L30D-55 (7.6% coating level), obtained in a pH-gradient dissolution procedure.

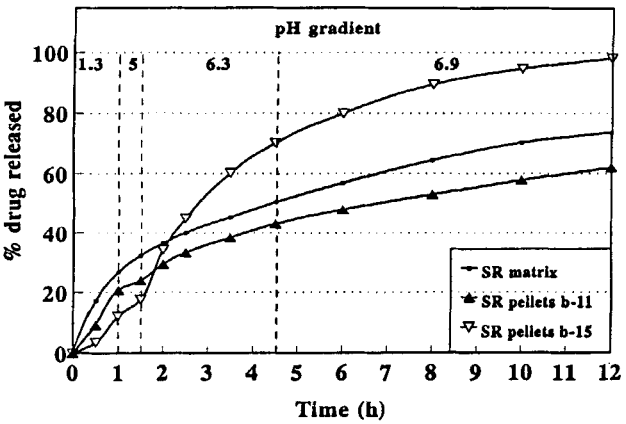

Figure 4. Release profiles of ucb 11056 from a sustained-release matrix tablet (SR matrix) and pellets coated with Eudragit NE30D/L30D-55 9:1 and 7:3 mixtures (SR pellets batches 11 and 15, respectively), obtained in a pH-gradient dissolution procedure.

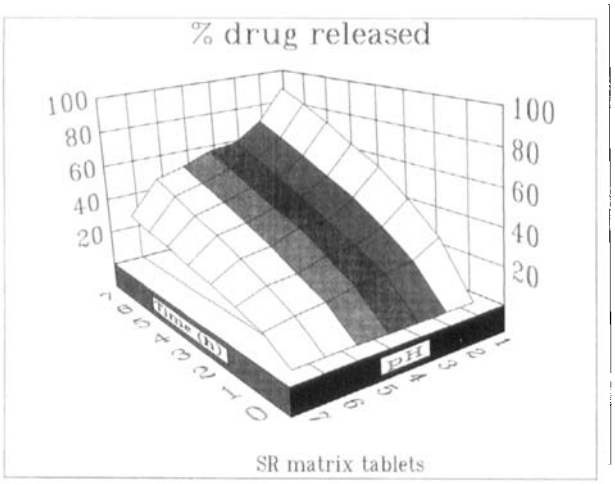

Figure 5. Tridimensional topographic representation of ucb 11056 release as a function of time and pH for a sustained-release hydrophilic matrix tablet (SR matrix batch 74).

dimensional topographical representation of the drug release versus time and pH (Figs. 5 and 6). Such a representation, coming from replicate dissolution tests carried out at different pH values kept constant in time, is also expected to be useful in helping to predict the in vivo release of drug at the different sites of the GI tract during transit.

For the SR matrix tablet, for instance (Fig. 5), the drug release is seen to remain highly dependent on the pH of the dissolution medium, still reflecting in this the intrinsic pH-dependent aqueous solubility of the compound ucb 11056. The amounts of drug released at the end of the 12-hr dissolution test are 90.6% at pH 1.0 but only 30.6% at pH 7.0. Similar results were also obtained for the pellets coated with NE30D alone and, to a lesser extent, for the pellets coated with the NE30D–L30D-55 9:1 blend (SR pellets batch 11).

Conversely, for the SR pellets batch 15, Fig. 6 clearly depicts that notwithstanding the pH-dependent aqueous solubility of the drug, the release profiles were relatively homogeneous for any pH value ranging between 1 and 7. Also, an almost 100% dose release was achieved at pH 1.0, 2.0, and 3.0 (higher solubility, pore-forming agents) and at pH 6.0 and 7.0 (higher porosity). Only a slight decrease of the drug release is noticed at pH 4 and 5, and it nevertheless reaches about 85% delivery within 12 hr. This formulation consequently appears to be optimized, at least on the basis of its in vitro evaluation and with respect to the physicochemical drawbacks outlined for the active compound.

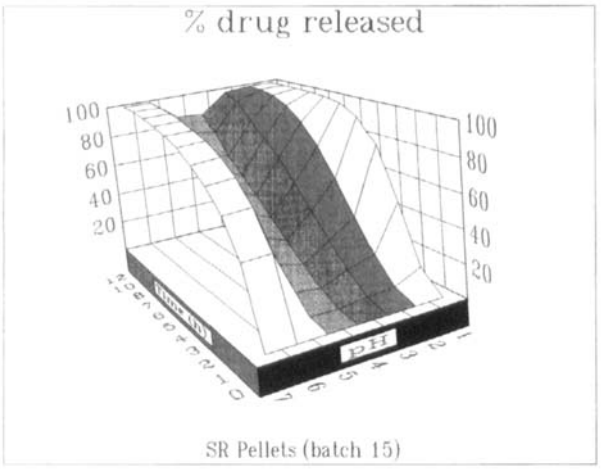

Figure 6. Tridimensional topographic representation of ucb 11056 release as a function of time and pH for pellets coated with Eudragit N30D/L30D-55 7:3 mixture (SR pellets batch 15).

CONCLUSIONS

In vitro preformulation testing has led to better understanding the solubility-related physicochemical drawbacks of the drug compound ucb 11056.

Considering this in the search for an optimized SR dosage form, a quite satisfactory pH independence of the release characteristics was nevertheless seen to be achievable by means of film-coated pellets using formulation blends of neutral and anionic acrylic polymers.

The use of multiple-unit dosage forms such as pellets must therefore be particularly recommended in the formulation of SR forms containing poorly soluble and/or slow-dissolving drugs, not only for their biopharmaceutical advantages in comparison with larger single-unit dosage forms but, also, for the higher flexibility of release adjustment obtainable because of the great deal of flexibility in formulation and the higher surface area offered for dissolution.

REFERENCES

1. K. A. Kelly, in *Physiology of the Gastrointestinal Tract* (L. R. Johnson, ed.), Raven Press, New York, 1981, pp. 393–410.
2. N. G. Lordi, in *The Theory and Practice of Industrial Pharmacy* (L. Lachman, H. A. Lieberman, and J. L. Kanig, eds.), Lea & Febiger, Philadelphia, 1986, pp. 430–456.

3. S. C. Porter, Multiparticulate oral drug delivery, in *Drugs and Pharmaceutical Science*, Vol. 65 (I. Ghebre-Sellassie, ed.), Marcel Dekker, Inc., New York, 1994, pp. 217–284.
4. J. C. Guttierrez-Rocca and J. W. McGinity, Int. J. Pharm., 103, 293–301 (1994).
5. P. C. Schmidt and F. Niemann, Drug Dev. Ind. Pharm., 19, 1603–1612 (1993).
6. B. C. Lippold, B. H. Lippold, B. K. Sutter, and W. Gunder, Drug Dev. Ind. Pharm., 16, 1725–1747 (1990).
7. L. E. Appel and G. M. Zentner, Pharm. Res., 8, 600–604 (1991).
8. I. Ghebre-Sellassie, R. H. Gordon, D. L. Middleton, R. U. Nesbitt, and M. B. Fawzi, Int. J. Pharm., 31, 43–54 (1986).
9. I. Ghebre-Sellassie, R. H. Gordon, and M. B. Fawzi, Int. J. Pharm., 37, 211–218 (1987).
10. S. C. Porter, Drug Dev. Ind. Pharm., 15, 1495–1521 (1989).
11. C. A. Gilligan and A. Li Wan Po, Int. J. Pharm., 73, 51–68 (1991).
12. K. Lehmann, Aqueous polymeric coatings for pharmaceutical dosage forms, in *Drugs and Pharmaceutical Science*, Vol. 36 (J. W. McGinty, ed.), Marcel Dekker, Inc., New York and Basel, 1989, pp. 153–245.
13. K. Lehmann and D. Dreher, Drugs Made in Germany, 31, 101–102 (1988).
14. K. H. Yuen, A. A. Deshmukh, J. M. Newton, M. D. Short, and R. Melchor, Int. J. Pharm., 97, 61–67 (1993).
15. A. H. Staib, D. Loew, S. Harder, E. H. Graul, and R. Pfab, Eur. J. Clin. Pharmacol., 30, 691–697 (1986).
16. J. Godbilon, D. Evard, N. Vidon, M. Dural, J. P. Schoeller, J. J. Beuruier, and J. Hirtz, Br. J. Clin. Pharmacol., 19, 113–118 (1985).
17. K. Amighi and A. J. Moës, Drug Dev. Ind. Pharm., 21, 2355–2369 (1995).
18. J. P. Skelly, L. A. Yamamoto, V. P. Shah, M. K. Yau, and W. H. Barr, Drug Dev. Ind. Pharm., 12, 1159–1175 (1986).