*Drug Development and Industrial Pharmacy*, 34:1117–1124, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040801973982

informa
healthcare

# Application of Ion Exchange Resin in Floating Drug Delivery System

**Abhijeet A. Upadhye, Anshuman A. Ambike, Kakasaheb R. Mahadik, and Anant Paradkar**

*Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandwane, Pune, Maharashtra, India*

**The purpose of this study was to explore the application of low-density ion exchange resin (IER) Tulsion® 344, for floating drug delivery system (FDDS), and study the effect of its particle size on rate of complexation, water uptake, drug release, and in situ complex formation. Batch method was used for the preparation of complexes, which were characterized by physical methods. Tablet containing resin with high degree of crosslinking showed buoyancy lag time (BLT) of 5–8 min. Decreasing the particle size of resin showed decrease in water uptake and drug release, with no significant effect on the rate of complexation and in situ complex formation for both preformed complexes (PCs) and physical mixtures (PMs). Thus, low-density and high degree of crosslinking of resin and water uptake may be the governing factor for controlling the initial release of tablet containing PMs but not in situ complex formation. However, further sustained release may be due to in situ complex formation.**

**Keywords** ion exchange resin; floating system; in situ complexes

## INTRODUCTION

The gastrointestinal transit time is one of several physiological limitations that must be controlled in the development of peroral sustained release dosage forms (Akiyama & Nagahara, 1999; Porter & Ghebre-Sellassie, 1994). Various attempts have been made to prolong the retention time of the dosage form in the stomach, namely utilization of passage-delaying agents, use of large single-unit dosage forms, and bioadhesive drug delivery systems (Chitnis & Malshe, 1991; Hwang, Park, & Park, 1998; Krögel & Bodmeier, 1999; Lee, Park, & Choi, 1999; Singh & Kim, 2000). Compared with these former approaches, the floating drug delivery systems (FDDS), e.g., density-controlled drug delivery systems, in which low-density polypropylene foam powder was used to decrease density of tablet(Streubel & Bodmeier, 2002), bicarbonate-based drug delivery systems (Atyabi, Sharma, & Mohammad, 1996a, 1996b), and lipid-based systems (Chauhan, Shimpi, Mahadik, & Paradkar, 2004; Moes, 1993; Shimpi, Chauhan, Mahadik, & Paradkar, 2004) have provided several advantages.

Ion exchange resin (IER) is a water-insoluble, crosslinked polymer containing salt-forming groups in repeating positions on the polymer chain. Many factors affect the release of drug from IER, which include particle size of IER, degree of crosslinking of IER, pH, ionic strength of dissolution media, and nature of drug. Significant amount of work has been published concerning the use of IER for taste masking of active ingredients (Deasy, 1984; Borodkin, 1993), tablet disintegration (Desai & Bolton, 1993; Shoufeng, Senshang, Bruce, Haresh, & Yie, 2002), drug stabilization, and sustained release applications (Borokin & Sundeberg, 1971; Langer & Peppas, 1981). But application of IER in FDDS is limited. Atyabi et al. have described a novel gastric retentive system containing IER, based on bicarbonates (1996a, 1996b), which may not be applicable for drugs susceptible to alkaline pH. Sriwongjanya and Bodmier have reported the formation of in situ complexes when tablet containing physical mixture (PM) of drug and IER comes in contact with dissolution media and gives same sustained release pattern as that of preformed complexes (PCs).

Chlorpheniramine maleate (CPM), a weakly basic and highly water-soluble cationic drug, having p$K_a$ 9.2, was chosen as model drug. Free base chlorpheniramine was reported to exhibit faster release and more absorption in simulated gastric fluid (SGF) as compared with simulated intestinal fluid (Cuna & Vila, 2000; Motycka, Newth, &Nairn, 1985; Ragunathan, Amsel, Hinsvark, & Bryant, 1981; Technical Bulletin, 1981) Tulsion® 344, a strong acid cation exchange resin, is derived from a sulfonated copolymer of styrene and divinylbenzene with exchangeable counter ions of sodium. It is available in the form of spherical beads, which can be further ground to desired particle size. Its total ion exchange capacity is 4 mEq/dry gram and residual moisture content is 10% (Sriwongjanya & Bodmeier, 1998). It was selected because of its low density and applications in sustained release drug delivery system (Sprockel, Prince, & Jennings, 1989).

Address correspondence to Abhijeet A. Upadhye, "Vrindavan" Plot No 26A, Radhamohan Colony, Khokadpura, Aurangabad-431 001, Maharashtra, India. E-mail: abhiupadhye_a@rediffmail.com

The objective of this study was to design FDDS using Tulsion® 344 as well as check the effect of physical and chemical characteristics of IERs on FDDS. This was further evaluated for effect of degree of crosslinking of IER on buoyancy lag time (BLT), specific gravity, matrix integrity, and duration of floating of tablet. Also, effect of particle size of IER on the rate of complexation, in vitro drug release profile, and percentage water uptake was determined. Differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), and infrared (IR) spectroscopy studies were used for the characterization of PCs, PMs, and in situ complexes.

## MATERIALS AND METHODS

### Materials

Hydroxypropylmethyl cellulose (HPMC) (Methocel® K4M & K15M premium grade), CPM, and Tulsion® 344, a sodium polystyrene sulfonate cation exchange resin of pharmaceutical grade, were obtained as gift samples from Colorcon Asia Pvt. Ltd. (Mumbai, India), Get-Rid Pharmaceutical Pvt. Ltd. (Pune, India), and Thermax Ltd. (Chemical division, Pune, India), respectively. All other chemicals and solvents were of analytical grade.

### Methods

*Preparation of PCs and PMs*

Activation of IER was done by treatment with 5 N HCl thereafter washing with deionized water and drying in hot air oven at 50°C for 24 h. Complexes of drug and IER in the ratios 1:1, 1:2, and 1:3 parts by weight were prepared by batch method, whereby the IER particles were added to aqueous drug solution and agitated for 24 h. Drug–IER complexes were separated by centrifugation and washed with deionized water to remove unbound drug and dried in hot air oven at 50°C for 24 h. The amount of drug bound to IER was calculated as the difference between the initial and the remaining amount of drug in the supernatant analyzed at 264.4 nm by UV-spectrophotometer (V-530, JASCO, Tokyo, Japan).

PMs in the same ratios were prepared by mixing drug and IER thoroughly for 5 min in a mortar until a homogeneous mixture was obtained. The mixtures were then passed through fine mesh (250 μm).

*Characterization of PCs and PMs*

DSC, XRPD, and IR were performed as follows.

*Differential Scanning Colorimetry*. DSC studies were carried out using Mettler-Toledo DSC 821 instrument equipped with an intracooler (Mettler-Toledo, CH-8606 Greifensee Switzerland). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 20ºC/min over a temperature range of 25–175ºC. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 mL/min.

*X-Ray Powder Diffraction*. The XRPD patterns were recorded on X-ray diffractometer (PW 1729, Philips, Almeic, The Netherlands). The samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 2 and 50°2θ. The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were $5 \times 10^3$ CPS and 10 mm/°$2\theta$, respectively.

*Infrared Spectroscopy*. IR spectroscopy was performed on Fourier transformed-IR spectrophotometer (V 5300, JASCO). Pellets of drug and KBr were prepared on KBr press (Spectra Lab, Mumbai, India). The spectra were scanned over wave number range of 3,000–400 $cm^{-1}$.

*Formulation Optimization and Evaluation of FDDS*

Tablets of different formulations were prepared by dry granulation as per the composition provided in Table 1 using 8-mm punch and die set on hydraulic press. The pressure applied for compression was 100 $kg/cm^2$ for 30 s. The thickness and hardness of tablets were 2.2 ± 0.2 mm and 5 kg, respectively. The tablets were evaluated for the following parameters:

*Effect of Degree of Crosslinking of IER.* Tablets containing IER with different degree of crosslinking (Table 1, batches I to L) were evaluated for specific gravity using benzene displacement method (Agyilirah, Green, du Cret, & Banker, 1991; Sangekar, Vadino, & Chaudry, 1987). Time required to float was reported as BLT. Matrix integrity and duration of floating were inspected visually using USP 24 type II dissolution test apparatus (TDT-06P, Electrolab, Mumbai, India). Tablets were added to 900 mL of SGF maintained at 37 ± 0.5°C and stirred at 100 rpm.

*Effect of Particle Size of Resin*. The powder form of IER with different particle sizes, namely fraction below 60 mesh (250 μm), 100 mesh (150 μm), 200 mesh (80 μm) sieves was used for determination of rate of complexation by the method described as follows: The mixture of drug and IER was agitated for different time intervals from 1 to 30 min in volumetric flasks containing 25 mL deionized water. After each time interval, the supernatant was subjected to UV estimation ($\lambda$ = 264.4 nm) to determine the amount of free drug present, which would then reveal the amount of drug complexed with IER.

*Water Uptake Study*. Water uptake study of tablets (Table 1, batches M, N, and O) were performed by equilibrium weight gain method (Irwin, Belaid, & Alpar, 1987; Pongpaibul, Sayed, & Whitworth, 1989) using USP 24 type I dissolution test apparatus. The tablets were accurately weighed and placed in a dissolution basket. The baskets were immersed in a dissolution vessel containing 900 mL SGF maintained at 37 ± 0.5°C and stirred at 100 rpm. At regular intervals, the tablets were removed from the dissolution vessel, blotted with tissue paper to remove excess water, and reweighed. The percentage water uptake was calculated using Equation 1.

$$\% \text{ Water uptake} = \frac{(W_s - W_i) - W_e}{W_p - W_{pe}} \times 100 \quad (1)$$

TABLE 1
Tablet Formulations

| | | IER (mg) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Particle Size[a] | | | Degree of Crosslinking (%) | | | | Type of Mixtures | | HPMC (mg) | |
| Batch Number | Drug (mg) | 60 | 100 | 200 | 2 | 3.5 | 6.5 | 8 | PCs | PMs | K4M | K15M |
| A | 10 | – | – | – | – | – | – | | – | – | 35 | 35 |
| B | 10 | – | 10 | – | – | – | – | √ | √ | – | 15 | 15 |
| C | 10 | – | 20 | – | – | – | – | √ | √ | – | 15 | 15 |
| D | 10 | – | 30 | – | – | – | – | √ | √ | – | 15 | 15 |
| E | 10 | – | 20 | – | – | – | – | √ | √ | – | 15 | 15 |
| F | 10 | – | 20 | – | – | – | – | √ | √ | – | 20 | 20 |
| G | 10 | – | 20 | – | – | – | – | √ | √ | – | 25 | 25 |
| H | 10 | – | 20 | – | – | – | – | √ | √ | – | 30 | 30 |
| I | 10 | – | 20 | – | √ | – | – | – | – | √ | 25 | 25 |
| J | 10 | – | 20 | – | – | √ | – | – | – | √ | 25 | 25 |
| K | 10 | – | 20 | – | – | – | √ | – | – | √ | 25 | 25 |
| L | 10 | – | 20 | – | – | – | – | √ | – | √ | 25 | 25 |
| M | 10 | 20 | – | – | – | – | – | √ | √ | – | 25 | 25 |
| N | 10 | – | 20 | – | – | – | – | √ | √ | – | 25 | 25 |
| O | 10 | – | – | 20 | – | – | – | √ | √ | – | 25 | 25 |
| P | 10 | 20 | – | – | – | – | – | √ | – | √ | 25 | 25 |
| Q | 10 | – | 20 | – | – | – | – | √ | – | √ | 25 | 25 |
| R | 10 | – | – | 20 | – | – | – | √ | – | √ | 25 | 25 |

[a]Fraction below particular mesh size.
HPMC, hydroxypropylmethyl cellulose; IER, ion exchange resin; PC, preformed complex; PM, physical mixture.

where $W_i$ and $W_s$ represent initial weight of the matrix and swollen weight of matrix at time *t*, respectively. $W_p$ and $W_{pe}$ denote initial weight of the polymer added to matrix and weight of the polymer eroded upto time *t*, respectively. $W_e$ represent total weight loss due to dissolution of drug and polymer from the matrix upto time *t*. Drug loss was excluded during calculation for plain matrices.

*In Vitro Drug Release Profiles*. Drug release from tablets (Table 1, batches M to R) was studied by using USP 24 type II dissolution test apparatus. The tablets were placed in 900 mL SGF maintained at 37 ± 0.5°C and stirred at 100 rpm. Sample (5 mL) was withdrawn at predetermined time intervals and replaced with fresh dissolution medium. CPM concentration was determined spectrophotometrically at 264.4 nm.

*Characterization of In Situ Complexes.* Tablets of PMs (Table 1, batches P, Q, and R) before and after dissolution (15 min) were crushed and subjected for evaluation by DSC, XRPD, and IR to verify the possibility of in situ complex formation.

## RESULTS AND DISCUSSION

Drug and IER complexes were prepared in the ratio 1:1, 1:2, and 1:3 parts by weight by varying the amount of IER. Total drug loading was around 90% (wt/wt) in all the cases irrespective of amount of IER.

### Characterization of PCs and PMs

DSC thermogram (Figure 1) of pure drug showed sharp endothermic peak at 137.65°C, attributed to its melting. The melting endotherm of drug was observed in the thermograms of all the PMs with slight shift due to physical presence of IER. The broad endotherm around 100°C could be attributed to the loss of residual moisture. No peaks were observed in DSC curves of pure IER and PCs in the range of 25–160°C.

The XRPD spectra (Figure 2) of pure drug were characterized by prominent diffraction peaks in the range of 19.6, 20.6, 22, 25.2°2$\theta$. While in case of PMs, there was significant decrease in the intensity of some these peaks, which may be due to the dilution effect. The XRPD of pure IER and PCs showed a hallow pattern indicating presence of amorphous state. This was also supported by DSC study.

The interaction between drug and IER often leads to identifiable changes in IR profiles. IR spectra of drug, IER, PCs, and PMs are shown in Figure 3. The spectra of CPM show characteristic peaks of hydroxyl group stretching vibrations, tertiary amine stretching vibrations, and C–Cl stretching vibrations at 2,453, 1,356, and 780–650 $cm^{-1}$, respectively. The major peaks

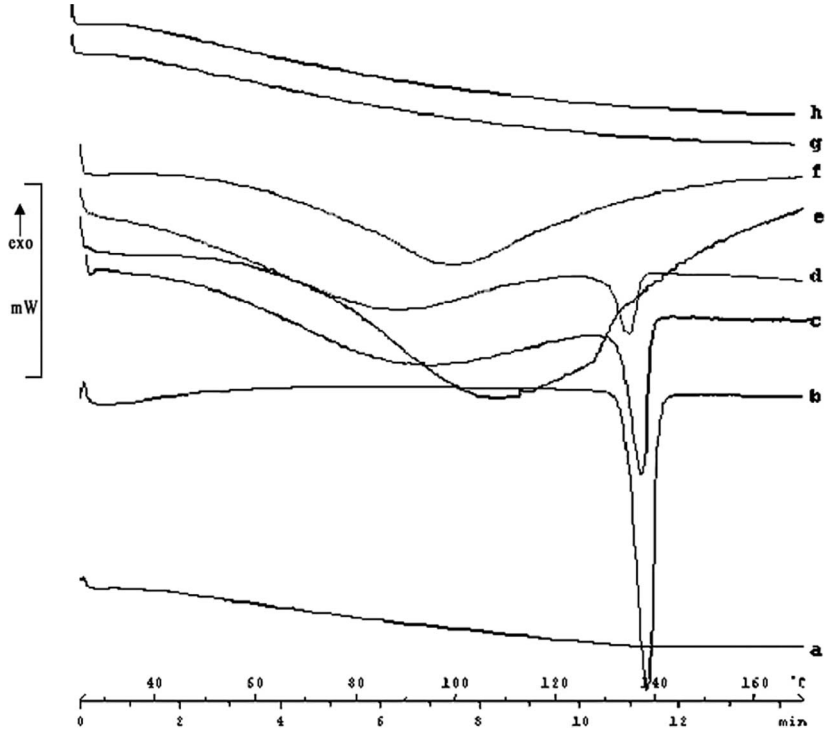


FIGURE 1. Differential scanning calorimetry (DSC) data of (a) pure resin, (b) pure drug, (c) PM (1:1), (d) PM (1:2), (e) PM (1:3), (f) PC (1:1), (g) PC (1:2), (h) PC (1:3).

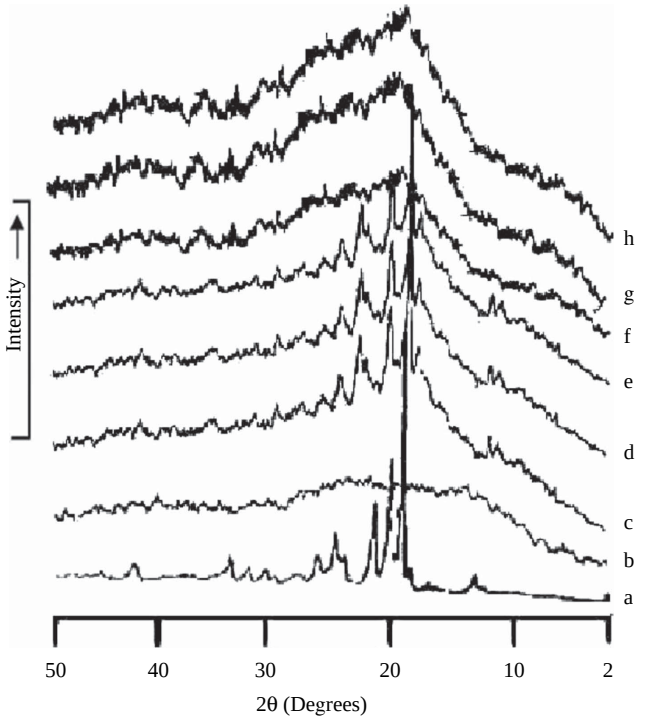


FIGURE 2. X-ray powder diffraction (XRPD) data of (a) pure drug, (b) pure resin, (c) PM (1:1), (d) PM (1:2), (e) PM (1:3), (f) PC (1:1), (g) PC (1:2), (h) PC (1:3).

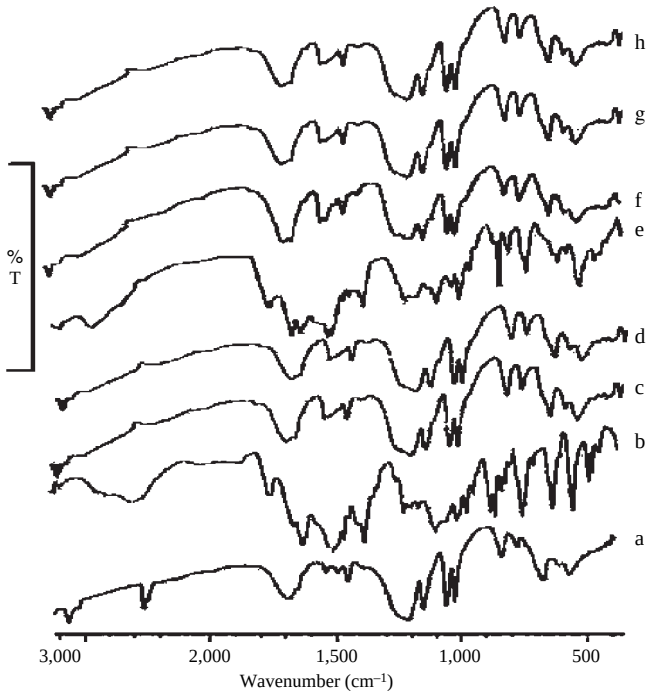


FIGURE 3. Infrared (IR) data of (a) pure resin, (b) pure drug, (c) physical mixture (PM) (1:1), (d) PM (1:2), (e) PM (1:3), (f) PC (1:1), (g) PC (1:2), (h) PC (1:3).

of CPM along with S=O stretching vibration peaks of sulfonic acid group of IER (1,039.73, 1,008.66, and 850–550 $cm^{-1}$) are observed in the spectra of PMs, whereas in PCs major peaks of tertiary amine of drug and sulfonic acid group of IER are shifted to 1,622 and 835 $cm^{-1}$, respectively. Also the peak of hydroxyl group of carboxylic acid has disappeared and peak of C–Cl has been shifted to 850–550 $cm^{-1}$. Thus, the absence of hydroxyl group of drug and shifting of peaks of sulfonate and tertiary amine group in PCs indicated the possibility of interaction of tertiary amine with sulfonate group of IER.

## Formulation Optimization and Evaluation of FDDS

BLT, total floating time of tablets, and sustained release of drug were the major criteria for optimization of FDDS. Different batches of tablet formulations were prepared as per the composition shown in Table 1. Initially, drug:IER ratio was varied from 1:1 to 1:3 parts by weight, to adjust optimum BLT and total floating time of tablet (batches B to D). It was observed that tablets of batches A, B, and D did not show floating. The presence of higher amount of non-compressible resin in batch D caused disintegration or bursting of these tablets, whereas tablets of batch C showed BLT of 5–8 min and floated up to 8 h. Hence, batch C was selected for further study. Then, drug:HPMC (K4M and K15M in 1:1 parts by weight) ratio was varied from 1:1 to 1:6 parts by weight, to get sustained release pattern upto 8 h (batches E to H). It was observed that increasing the concentration of HPMC, drug release was sustained from 100% within 5 h (batch E) to 60% in 8 h (batch H). Batch G presented optimum sustained release pattern of 80% drug release within 8 h. Finally, drug:IER:HPMC in the ratio 1:2:2.5 parts by weight was selected for further evaluation of FDDS.

It was thought that the degree of crosslinking of IER would affect the floating behavior of tablets. So, IER with different degrees of crosslinking (2, 3.5, 6.5, and 8%) was tested for changes in BLT and specific gravity (batches I to L). Decrease in BLT and specific gravity of tablets was observed with increase in degree of crosslinking of IER (Table 2).

Effect of particle size of IER (batches M to O) was studied on four factors: rate of complexation, water uptake, drug release, and formation of in situ complexes within tablet during

TABLE 2
Effect of Crosslinking of IER on BLT and Specific Gravity

| Degree of Crosslinking of IER (%) | BLT[a] (mins) | Specific Gravity[a] (Wt/mL) |
|---|---|---|
| 2 | 90 (±2.566) | 1.35 (±0.028) |
| 3.5 | 50 (±3.511) | 1.17 (±0.015) |
| 6.5 | 20 (±0.306) | 0.9863 (±0.029) |
| 8 | 6 (±1.154) | 0.7568 (±0.023) |

[a]Figures in bracket indicate mean ± *SD* (*n* = 3).
BLT, buoyancy lag time; IER, ion exchange resin.

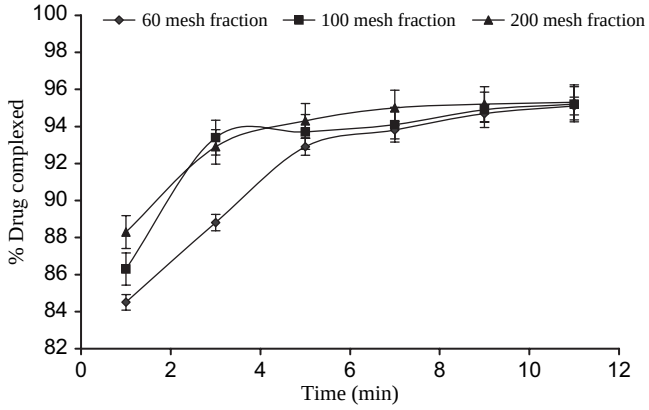


FIGURE 4. Rate of complexation of drug and ion exchange resin (IER).

dissolution. Particle size of IER had no significant effect on the total amount of drug complexed (Figure 4). However, in the initial stage (1-min time point) 200 mesh fraction showed around 88% complexation, followed by 100 mesh (˜86%) and 60 mesh (˜84%). This might be due to increased surface area of the finer particles. Water uptake of PCs (batches M to O) and PMs (batches P to R) is shown in Figures 5 and 6. The water uptake of these batches was compared with plain HPMC matrices (batch A). Batches containing coarser particle size of IER showed more water uptake than those containing finer particle size irrespective of nature of complex.

The batches containing PMs were found to be equally effective in retarding the drug release upto 8 h (Figures 7 and 8). This is may be due to in situ formation of drug and resin complex within tablet core as reported by Sriwongjanya and Bodmier.

## Characterization of In Situ Complexes

Batches P, Q, and R containing PMs of different particle size of IER were characterized before and after 15 min of

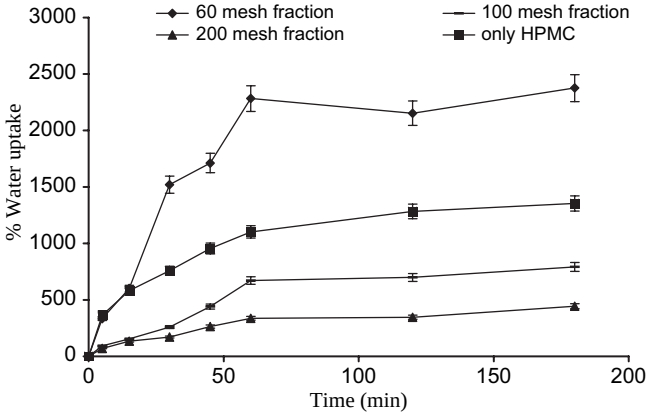


FIGURE 5. Water uptake profiles of batches M, N, and O.

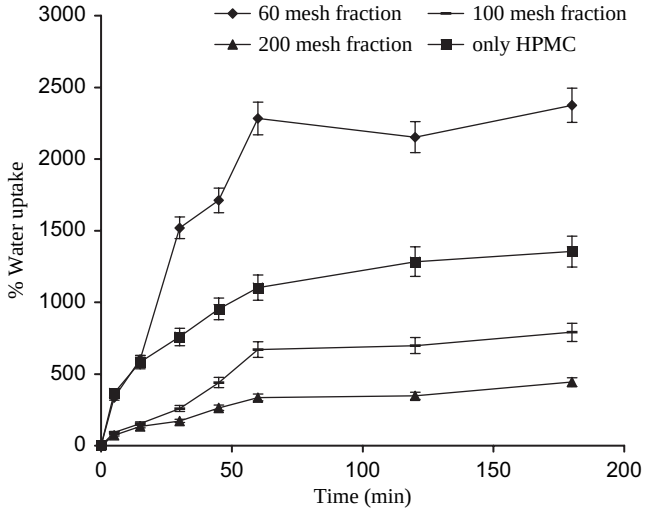


FIGURE 6. Water uptake profiles of batches P, Q, and R.

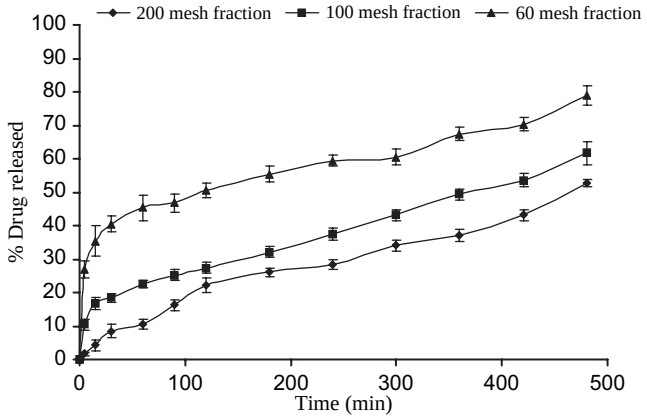


FIGURE 7. Drug release profiles of batches M, N, and O.

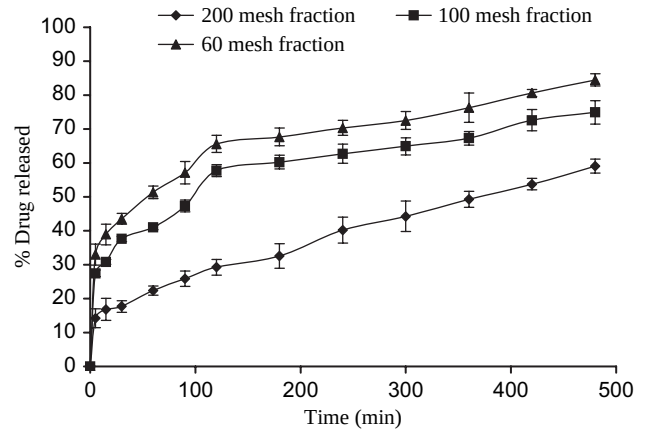


FIGURE 8. Drug release profiles of batches P, Q, and R.

dissolution to verify in situ complex formation using DSC, XRPD, and IR. IR spectra showed masking of major peaks

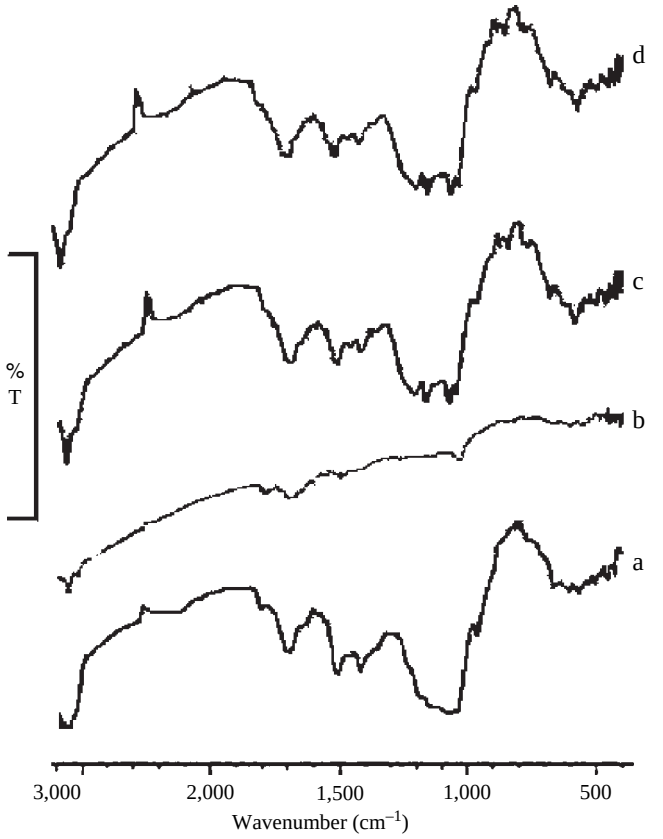


FIGURE 9. Infrared (IR) data of (A) tablet of batch P before dissolution, (B) tablet of batch P after dissolution, (C) tablet of batch Q after dissolution, (D) tablet of batch R after dissolution.

attributed to drug and resin due to physical presence of polymer (Figure 9). XRPD before dissolution showed major crystalline peak of drug at 19.6°2$\theta$, whereas other peaks were masked because of physical presence of polymer and resin. XRPD of same batches after 15 min dissolution showed a hallow, characteristic to amorphous form (Figure 10). DSC thermogram of same batches (Figure 11) before dissolution showed melting endothermic peak of drug at 137.65°C, whereas batches P and Q after 15-min dissolution showed absence of endothermic peak of drug. On the contrary, endothermic peak of drug was observed in thermogram of batch R, which could be attributed to the presence of uncomplexed drug due to lesser water uptake.

## CONCLUSION

This study shows that tablet containing high degree of crosslinking of IER (i.e., 8%) showed less than one specific gravity, less BLT, and longer duration of floating time compared with other IERs. Hence, it may be concluded that low-density IER with higher degree of crosslinking may be suitable for floating application. Moreover, no significant effect of particle size of resin was observed on floating behavior. Water

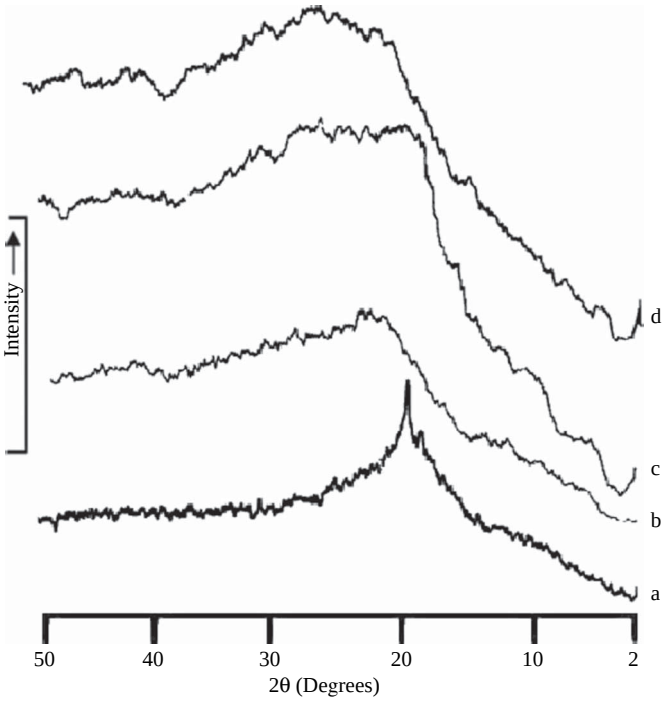


FIGURE 10. X-ray powder diffraction (XRPD) data of (A) tablet of batch P before dissolution, (B) tablet of batch P after dissolution, (C) tablet of batch Q after dissolution, (D) tablet of batch R after dissolution.

uptake was found to be the governing factor for controlling initial release of drug in the case of PMs, whereas further sustained release may be due to formation of in situ complex.

## ACKNOWLEDGMENTS

Abhijeet A. Upadhye is thankful to AICTE, New Delhi, India for financial support in the form of JRF. Anshuman A. Ambike is thankful to CSIR, New Delhi, India for the financial support in terms of CSIR-SRF. The authors are thankful to THERMAX Ltd., Chemical Division, Pune, India for financial support and gift samples of Tulsion® 344.

## REFERENCES

Agyilirah, G. A., Green, M. du Cret, R. & Banker, G. S. (1991). Evaluation of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet. *Int. J. Pharm., 75*, 241–247.

Akiyama, Y., & Nagahara, N. (1999). Novel formulation approaches to oral mucoadhesive drug delivery system. In: E. Mathiowitz, D. E. Chickering, & C. M. Lehr (Ed.), *Bioadhesive drug delivery systems-fundamentals, novel approaches and development* (pp. 477–485). New York: Marcel Dekker, Inc.

Atyabi, F., Sharma, H. L., & Mohammad, H. A. H. (1996a). Controlled drug release from coated floating ion exchange resin beads. *J. Control Release, 42*, 25–28.

Atyabi, F., Sharma, H. L., & Mohammad, H. A. H. (1996b). In vivo evaluation of a novel gastric retentive formulation based on ion exchange resin. *J. Control Release, 42*, 105–113.

Borodkin, S. S. (1993). Ion exchange resins and sustained release. In J. Swarbrick & J. C. Boylan (Ed.), *Encyclopedia of pharmaceutical technology*. New York: Marcel Dekker, *8*, pp. 203–216.

Borokin, S., & Sundeberg, P. (1971). Polycarboxylic acid ion exchange resin absorbate for taste coverage in chewable tablet. *J. Pharm. Sci., 60*, 1523–1527.

Chauhan, B., Shimpi, S., Mahadik, K. R., & Paradkar, A. (2004). Preparation and evaluation of floating risedronate sodium gelucire 39/01 matrices. *Acta. Pharm., 54*, 205–214.

Chitnis, V. S., & Malshe, V. S. (1991). Bioadhesive polymer- synthesis, evaluation and application in controlled release tablets. *Drug Dev. Ind. Pharm., 17*, 879–892.

Clarke, G. M., Newton, J. M. & Short, M. B. (1995). Comparative gastrointestinal transit of pellet systems of varying density. *Int. J. Pharm., 114*, 1–11.

Cuna, M., & Vila, J. L. (2000). Controlled-release liquid suspension based on ion exchange resin entrapped within acrylic microcapsules. *Int. J. Pharm., 199*, 151–158.

Deasy, P. B. (1984). Ion-exchange resins. In P. B. Deasy (Ed), *Microencapsulation and related drug processes*. New York: Marcel Dekker, pp. 241–252.

Desai, S., & Bolton, S. (1993). Floating controlled-release drug delivery system: In vitro-in vivo evaluation. *Pharm. Res., 10*, 1321–1325.

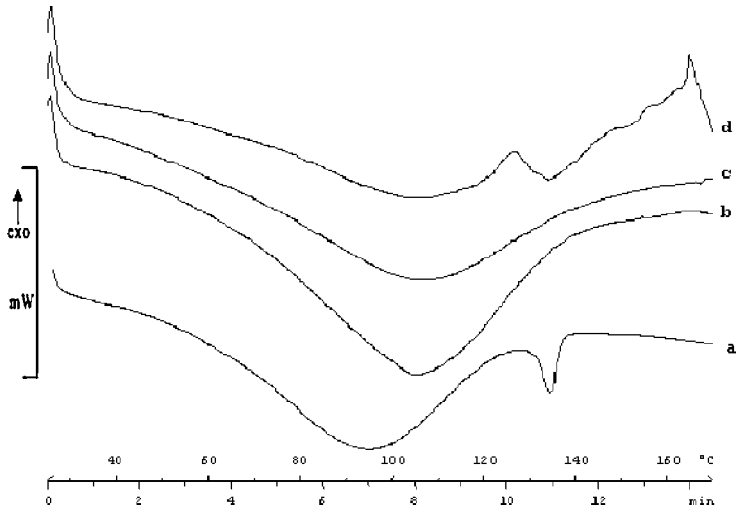


FIGURE 11. Differential scanning calorimetry (DSC) data of (A) tablet of batch P before dissolution, (B) tablet of batch P after dissolution, (C) tablet of batch Q after dissolution, (D) tablet of batch R after dissolution.

Hwang, S. J., Park, H., & Park, K. (1998). Gastric retentive drug-delivery systems. *Crit Rev. Ther. Drug. Carrier. Syst.*, *15*, 243–284.

Irwin, W. J., Belaid, K. A., & Alpar, H. O. (1987). Drug delivery by ion exchange. Part-III: Interaction of ester prodrugs of propranolol with cationic exchange ion exchange resin. *Drug Dev. Ind. Pharm.*, *13*, 2047–2066.

Krögel & Bodmeier, R. (1999). Floating or pulsatile drug delivery systems based on coated effervescent cores. *Int. J. Pharm.*, *187*, 175–184.

Langer, R. S., & Peppas, N. A. (1981). Present and future applications of biomaterials in controlled drug delivery systems. *Biomaterials*, *2*, 201–214.

Lee, J. H., Park, T. G., & Choi, H. K. (1999). Development of oral drug delivery system using floating microspheres. *J. Microencapsul.*, *16*, 715–729.

Moes, A. J. (1993). Gastroretentive dosage forms. *Crit. Rev. Ther. Drug Carrier Syst.*, *10*(2), 143–159.

Motycka, S., Newth, C. J. L., & Nairn, J. G. (1985). Preparation and evaluation of microencapsulated and coated ion-exchange resin beads containing theophylline. *J. Pharm. Sci.*, *74*, 643–646.

Pongpaibul, Y., Sayed, H. A. M., & Whitworth, C. W. (1989). Effect of process variables on drug release from microparticles containing a drug-ion exchange resin complex. *Drug Dev. Ind. Pharm.*, *15*, 2547–2558.

Porter, S. C., & Ghebre-Sellassie, I. (1994). Key factors in the development of modified-release pellets. In I. Ghebre-Sellassie (Ed.), *Multiparticulate oral drug delivery* (pp. 217–284). New York: Marcel Dekker, Inc.

Ragunathan, Y. L., Amsel, P., Hinsvark, O. N., & Bryant, W. (1981). Sustained-release drug delivery I: Coated ion resin system for phenylpropanolamine and other drugs. *J. Pharm. Sci.*, *70*, 379–384.

Sangekar, S., Vadino, W. A., & Chaudry, I. (1987). Evaluation of the effect of food and specific gravity of tablets on gastric retention time. *Int. J. Pharm.*, *35*, 187–191.

Shimpi, S., Chauhan, B., Mahadik, K. R., & Paradkar, A. (2004). Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation. *AAPS Pharm. Sci. Tech*, *5*(3), 43.

Shoufeng, L., Senshang, L., Bruce, P. D., Haresh, L. M., & Yie, W. C. (2002). Effect of formulation variables on the floating properties of gastric floating drug delivery system. *Drug Dev. Ind. Pharm.*, *28*, 783–793.

Singh, B. N., & Kim, K. H. (2000). Floating drug delivery systems: approaches to oral controlled drug delivery via gastric retention. *J. Control Release*, *63*, 235–259.

Sprockel, L. O., Prince, J. C., & Jennings, R. (1989). In-vitro/in-vivo evaluation of a liquid sustained release dosage form of chlorpheniramine. *Drug Dev. Ind. Pharm.*, *15*, 1275–1287.

Sriwongjanya, M., & Bodmeier, R. (1998). Effect of ion exchange resin on drug release from matrix tablets. *Eur. J. Pharm. Biopharm.*, *46*, 321–327.

Streubel, A., & Bodmeier, R. (2002). Floating microparticles based on low-density foam powder. *Int. J. Pharm.*, *241*, 279–292.

Technical Bulletin IE-211-5/75 – *Amberlite IRP-88*, Philadelpia, PA; Rohm and Haas.