Drug Development and Industrial Pharmacy, 23(2), 145-155 (1997)

RESEARCH PAPER

Ibuprofen Release from Beads Coated with an Experimental Latex: Effect of Certain Variables

Shailesh K. Singh and Mansoor A. Khan*

Division of Pharmaceutics, School of Pharmacy, Northeast Louisiana University, Monroe, Louisiana 71209

ABSTRACT

The objective of this study was to evaluate the effect of factors such as drug loading, particle size, plasticizer type, antiadherent type, and annealing method on the release of ibuprofen from controlled-release beads coated with an experimental latex. Further, the in vitro release kinetics and mechanism of drug transport across the polymeric membrane have been investigated. Ibuprofen-loaded beads were coated with the experimental latex using a fluidized-bed coating machine (Uniglatt). The drug release from these spherical membrane reservoir systems appeared to be diffusion controlled. Evaluation of the effect of osmotic pressure by using dissolution media of various osmolal concentrations indicated that it has no significant effect on the drug release. To further elucidate the mechanism of release from these polymeric membranes, the permeation of drug through free films was studied.

INTRODUCTION

The application of a polymer film coat is a common practice in the preparation of controlled-release dosage forms. To minimize the effect of food on bioavailability variations, the use of coated multiparticulates in development of reservoir-type modified-release products has been suggested (1). It was not until recently that the water-based coating material became available. The success of these water-based polymeric dispersions has diverted much research into development of new formulations as well as reformulation of existing products. In an earlier study, an experimental latex was employed as a controlled-release coating material on multiparticulate beads (2). A statistical optimization procedure was employed to evaluate the effect of three formulation variables—volume of the experimental latex, plasticizer concentration, and the solids content—on release of anionic drug, ibuprofen. However, it would be of interest to evaluate the effect of several other variables such as,

*To whom correspondence should be addressed.

particle size, drug loading, plasticizer type, antiadherent type, annealing method, and osmotic effect on the release of ibuprofen. These beads behave as a reservoir-type of membrane-controlled device. In vitro characterization of such membranes would be essential in optimizing the delivery from such formulations.

This study investigated the effect of several parameters such as drug loading, plasticizer type, particle size, antiadherent type, and annealing method on the drug release. Also, the effect of osmotic urea solutions on drug release and permeation through free films was evaluated.

MATERIALS

Ibuprofen USP (Albemarle Co., Baton Rouge, LA) was used as the model drug. Nu-pariel seeds (mesh No. 30/35, Ingredient Technology, NJ) were used to prepare the pellets. Opadry® (YS-I-7472, Colorcon Inc., PA) was used for seal coating. Citrate plasticizers (triethyl citrate, tributyl citrate, acetyltriethyl citrate, and acetyltributyl citrate; Morflex Chemical Co., Greensboro, NC) and dibutyl sebacate, dibutyl pthalate, Triacetin, and Myvacet 9-45 (Kodak Chemical Co., Kingsport, TN) were used as plasticizers. Titanium dioxide was used as opacifier (Warner Jenkins Co., MO). Talc and urea were purchased from Spectrum Chemical Company. Silicon dioxide (Syloid 244, W. R. Grace Co., USA) was used as antiadherent. Water used in all experiments was de-ionized and distilled. All the other chemicals were used as received.

METHODS

Preparation of Coated Beads

Several replicate batches of 500 g of Nu-pareil sugar beads (mesh No. 30/35) were used as initial cores to load 45–50% of ibuprofen on these beads. A laboratory-size Uniglatt fluidized-bed coating machine (Model 2817) was used for coating the drug suspension using a 1.2-mm insert. The flow rate was maintained such that there was no agglomeration. The air flap was kept at 75° to obtain a good drying efficiency. During the layering process the beads were dried intermittently for 10 min at 37°C. After layering, the beads were collected in a tray and dried at 45°C for 24 hr in an oven. Seal coating was applied to these loaded beads using Opadry as the polymer. This would minimize leaching of the drug and possible abrasion of layered drug. Finally, the experimental latex was applied as the controlled-release coating material. The coating equipment and conditions have been reported in an earlier study (2) and are summarized in Table 1.

Dissolution Studies

Drug release was determined using beads containing the equivalent of 400 mg of ibuprofen. In all the studies the USP Paddle Apparatus was used with 900 ml of phosphate buffer (pH 7.2) at 37°C and 100 rpm. Samples (5 ml) were withdrawn at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr, filtered using 0.45-μm filter, and assayed spectrophotometrically (Gilford) at 266.5 nm. From the absorbance values, the cumulative percent released was determined. All experiments were run in triplicate.

Content Uniformity Studies

About 100 mg of pellets were weighed separately and dissolved in 100 ml of alcohol USP. These were filtered and assayed spectrophotometrically for drug content using a calibration curve.

Effect of Particle Size

The beads were subjected to sieve analysis using a nest of U.S. standard sieves on a Retsch sieve shaker

Table 1

Coating Equipment and Process Conditions

Drug layering	
Ibuprofen, USP	45% w/w
Opadry II	6% w/w
Tween 20	2% w/w
Talc	2% w/w
Titanium dioxide	0.04% w/w
Distilled water q.s.	
Controlled-release coating	
Experimental latex	113.7 ml (11.06% w/w)
Plasticizer	26.59% w/w
Talc	3% w/w
Process conditions	
Spray process	Uniglatt (Model 2817)
Atomizing air pressure	40–45 psig
Inlet air temperature	35–40°C
Outlet air temperature	25°C
Spray nozzle size	1.2 mm
Batch size	500 g
Spray rate	10 ml/min

at a fixed setting of 20 for 5 min. All fines and agglomerates were discarded. Fractions of beads remaining in 10/12, 12/16, 16/18, 18/20, 20/25, and 25/30 mesh were collected and used for in vitro release studies.

Effect of Drug Loading

The influence of drug loading was evaluated by preparing separate batches, each containing 36%, 51%, and 60% drug dry weight per 100 mg of the core (or equivalent of 36, 51, and 60 mg, respectively, of ibuprofen). These were then coated with seal coating followed by the experimental latex, under the same conditions as shown in Table 1.

Effect of Plasticizer Type

Eight batches of seal-coated beads prepared earlier were used to evaluate the effect of plasticizer types on the drug release. The coating conditions remained as in Table 1, except for the type of plasticizer used. The plasticizers evaluated were triethyl citrate (TEC), acetyl triethyl citrate (ATEC), tributyl citrate (TBC), acetyl tributyl citrate (ATBC), dibutyl sebacate (DBS), dibutyl pthalate (DBP), Triacetin, and Myvacet 9-45 (triglycerides).

Effect of Annealing Method

Two batches of the latex-coated beads were treated by different annealing methods during the drying phase after coating. The first batch was dried in the column for 1 hr at 45°C after completion of the coating. The second batch was dried in an oven for 24 hr at 45°C. A comparative evaluation of the drug release rate was performed.

Effect of Antiadherent Type

The effect of two antiadherents, talc and colloidal silica, was evaluated on the drug release kinetics. The coating batches, prepared separately, had 3% by weight of talc or silica.

Release Kinetics

In an earlier study it was shown that the Baker–Lonsdale model appeared to provide the best fit for release of ibuprofen from optimized beads (2). Therefore, diffusion of the drug through polymeric membrane seemed to be the primary mode of drug release. Very often, diffusion in a porous membrane is accompanied by osmotic effects (3,4). To investigate such a possibility and to further elucidate the mechanism, the drug release was also determined in molal solutions of urea maintained at pH 7.2 (5).

Equilibrium Solubilities

Equilibrium solubilities were determined at 37 ± 0.5°C in urea solutions in pH 7.2 and in distilled water. For each determination, excess of drug was added to the solution at 37°C and shaken constantly. Samples were collected, diluted, filtered through a 0.45-μm filter, and assayed at appropriate time intervals until identical concentrations were obtained for two consecutive readings (5).

Permeation Through Free Films

Free films were prepared from experimental latex using the same concentration of total solids as was used to coat the beads. The experimental latex was plasticized at 26.59% w/w concentration. This plasticized latex was then sprayed uniformly on Teflon-coated glass plates. The free films were cured overnight at 40°C and kept in a tight container at room temperature.

Membrane permeability (6) was determined by quantifying the transport of ibuprofen across a circular polymeric membrane mounted in a thermostatted Valia–Chien cell (Crown Glass Co., Sommerville, NJ). Membranes of 4.91 cm^2 surface area, and 0.02 mm and 0.035 mm average thickness were used for permeation studies. The membranes were initially cut and soaked in pH 7.2 phosphate buffer for 0.5 hr prior to the start of experiment. They were then carefully placed on the receptor compartment, capped with the donor cap, and trimmed from the sides. The receptor cell contained 20 ml of phosphate buffer at pH 7.2 and the donor cell contained a saturated solution of ibuprofen (1 g in 10 ml of phosphate buffer). The media in both cells was equilibrated at 37°C and stirred with magnetic bars in order to reduce boundary layer effects. Samples (0.5 ml) were withdrawn at 0, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hr and were replaced with fresh buffer at each interval. After mixing with a fixed amount of internal standard, all the samples were analyzed by the high-performance liquid chromatographic (HPLC) method reported below.

Ibuprofen was assayed by employing a Novapack C-18, 15 cm × 3.9 mm column with a particle size of 4 μm. The equipment was an isocratic pump (Model 2350) with ISIS autosampler, an autoinjector with a

Valco valve, a UV detector (Waters, Model 484) at 257 nm, and an integrator (Shimadzu, CR-501). The mobile phase consisted of a 62:38 mixture of methanol and 4% acetic acid. A flow rate of 0.75 ml/min and an injection volume of 10 μl were used. The detector sensitivity was set at 1 AUFS. To each 0.5 ml sample in a 2 ml vial, 0.5 ml of water and 1 ml of internal standard (3 μg/ml of flurbiprofen in methanol) were added and injected by the autoinjector. The retention times of ibuprofen and flurbiprofen were 6.85 and 5.07 min, respectively. The peak height ratio against drug concentration was used to construct a standard curve which was used for the determination of cumulative amount of ibuprofen permeated.

RESULTS AND DISCUSSION

Figure 1 shows the effect of particle or the bead size on the release of ibuprofen from coated beads. The decrease in bead size results in an increase in surface area for drug diffusion and thereby results in an increase in the release of ibuprofen.

In an earlier study, optimized beads coated with the experimental latex revealed that drug release followed the Baker–Lonsdale model (2). According to this model, for a dispersed drug, the fraction of drug released decreases with an increase in the initial drug loading. Figure 2 shows the effect of three different drug loadings, 36%, 50%, and 61%, on the release of ibuprofen. A one-way analysis of variance (ANOVA) followed by Scheffe's pairwise comparisons did not reveal any significant difference in the t_{50} of 50 and 61% loading, but the t_{50} was significantly lower for the 36% loading ($p < 0.05$).

Figures 3 and 4 show the effect of eight different types of plasticizers used at the same level (26.59% w/w) on the release of ibuprofen from coated beads. Figure 3 shows the effect of citrate ester plasticizers, TEC, ATEC, TBC, and ATBC, on the release of ibuprofen. TEC showed more control than its acetyl derivative. Similarly TBC showed more control than its acetyl derivative. The molecular weight of the esters is in the order TEC < ATEC < TBC < ATBC. Thus, the release of ibuprofen from the beads coated with different plasticizers follows the same order as the molecular weights. Also as reported from literature (7) the water solubility of citrate plasticizers at 25°C for TEC, ATEC, TBC, and ATBC is 6.5, 0.72, <0.1, and <0.1

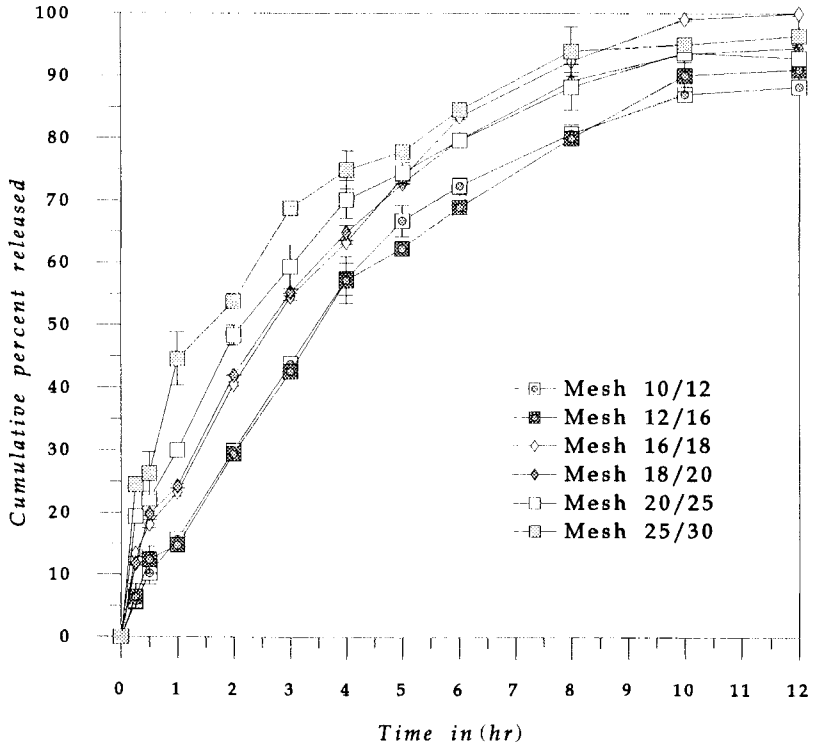

Figure 1. Effect of particle size on the release of ibuprofen from coated beads.

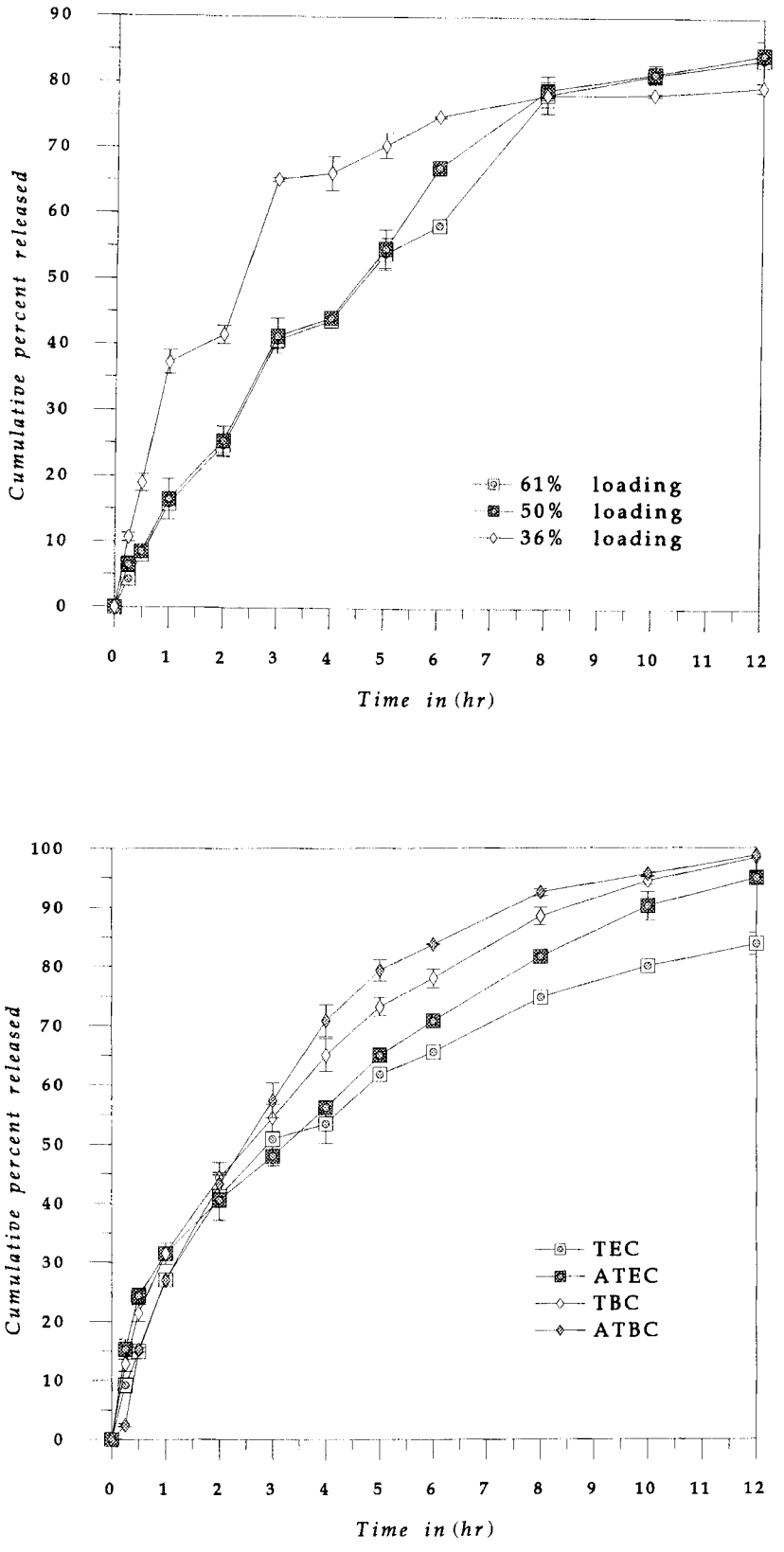

Figure 3. Effect of plasticizer type (citrate esters, 26.59% w/w) on the release of ibuprofen from coated beads.

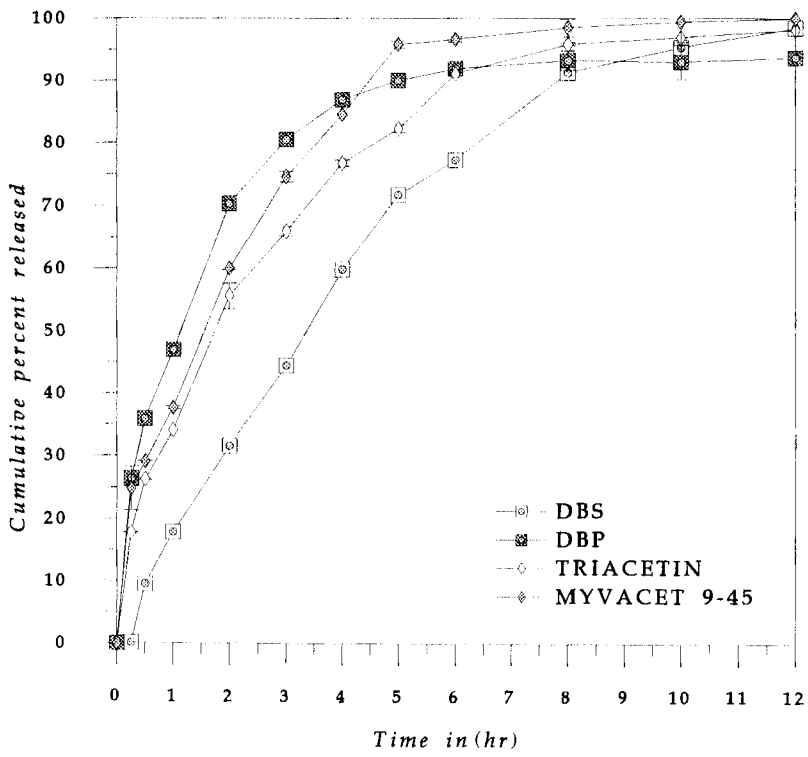

Figure 4. Effect of plasticizer type (26.59% w/w) on the release of ibuprofen from coated beads.

g/100 ml, respectively. Water solubility of the plasticizer is important because of the water-based latex, and a decrease in solubility may result in the formation of two separate phases. Because of the increase in molecular weight and a corresponding decrease in solubility of the acetyl derivative and the butyl citrate esters, two separate phases were formed. The molecules no longer dispersed in the polymer film homogeneously and probably formed a continuous phase, thereby resulting in the formation of plasticizer channels (8). These channels led to the formation of a porous membrane, increasing the release of the drug.

Figure 4 shows the effect of some other plasticizer types: DBS, DBP, Triacetin, and Myvacet 9-45. DBS showed the most control while Myvacet 9-45 (triglyceride) and DBP showed the least control. Perhaps this difference in release may also be related to the solubility of the plasticizer in the film.

Figure 5 shows the effect of annealing method on the release of ibuprofen from coated beads. The figure clearly shows more control in the release when dried in the column. The plasticizer reduces the glass transition temperature (T_g) of the latex and provides flexibility to the polymer film, which results in the phenomena called "further gradual coalescence" with the removal of moisture. However, the drying efficiency in the oven is not as good as in the column. Further, long drying times in the oven may result in the evaporation of plasticizer to some extent. Thus the possibility of formation of coherent film is reduced. Figure 6 presents the comparative SEM photographs of the film surface for beads dried in the oven and in the column. The pictures show a more uniform surface for the beads dried in the column.

Figure 7 shows the effect of antiadherent on the release of ibuprofen from coated beads. The graph shows that there is no difference in the drug release from beads coated with silica or talc. Further, a two-sample t test of the mean t_{50} for both talc and silica was computed to see if there is any significant difference in the release. The results indicated no significant difference ($p < 0.05$). However, the overall release rate due to silica appeared to be slightly higher than talc. Figure 8 presents the comparative SEM of the film surface of beads coated using talc and silica as antiadherents. The surface of the film appeared to be more uniform and smoother for beads coated with silica than with talc. Talc and

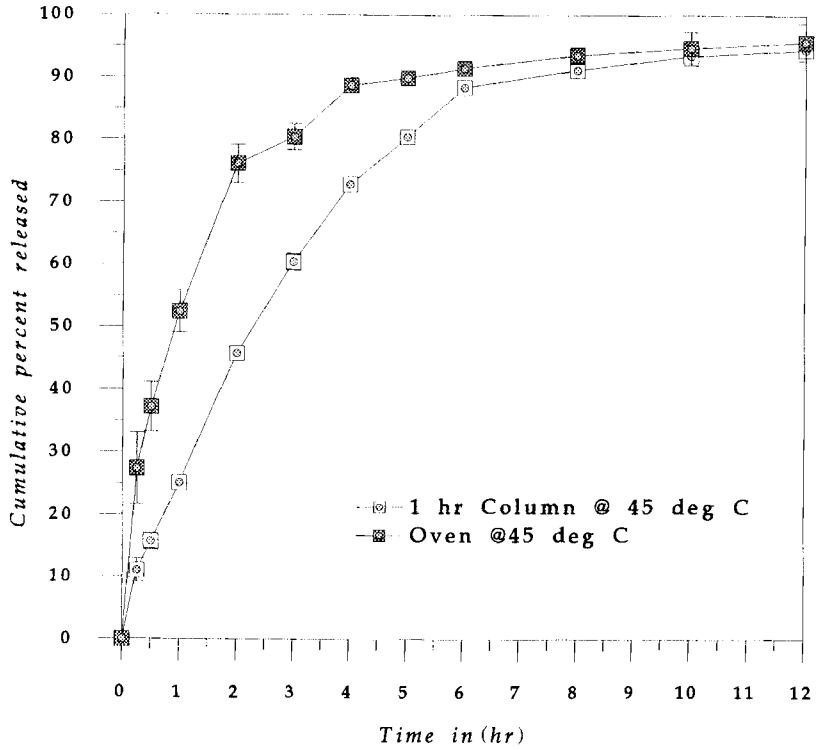

Figure 5. Effect of annealing method on the release of ibuprofen from coated beads.

silica are characterized by different physical and chemical properties (9), with the latter having more tendency to adsorb water and form a colloidal dispersion. The slight overall increase in release in case of silica could be due to this high adsorption capacity, which combines a considerable specific surface area with a strong affinity for polar compounds like water.

To investigate the effect of osmotic pressure on the release of ibuprofen from coated beads, 2, 5, and 8 molal solutions of urea were used (5). The computation

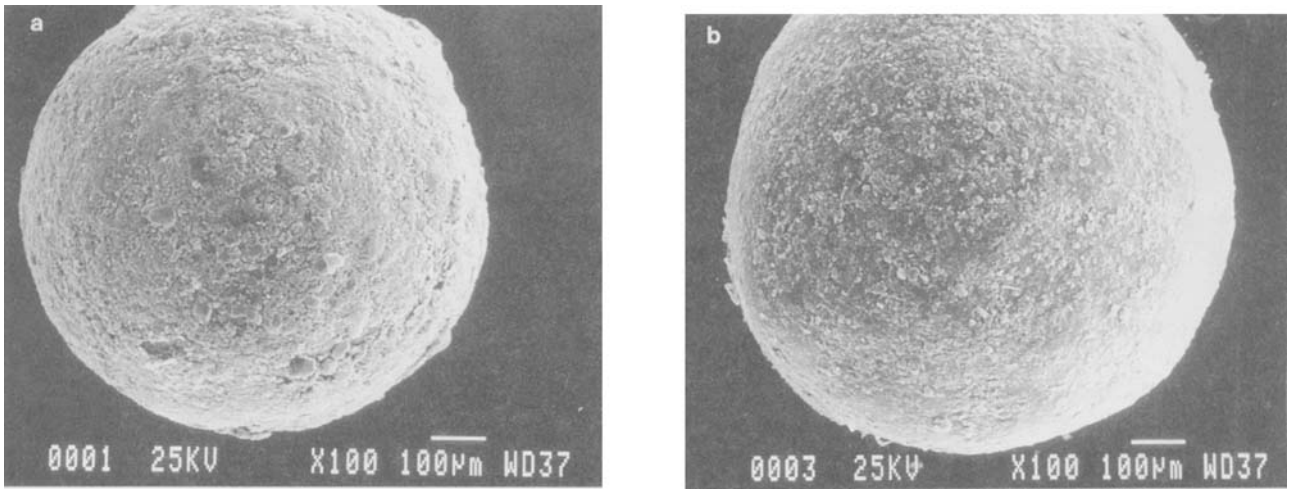

Figure 6. Comparative SEM photographs showing the surface of the film of coated beads dried in the oven (a) and dried in the column (b).

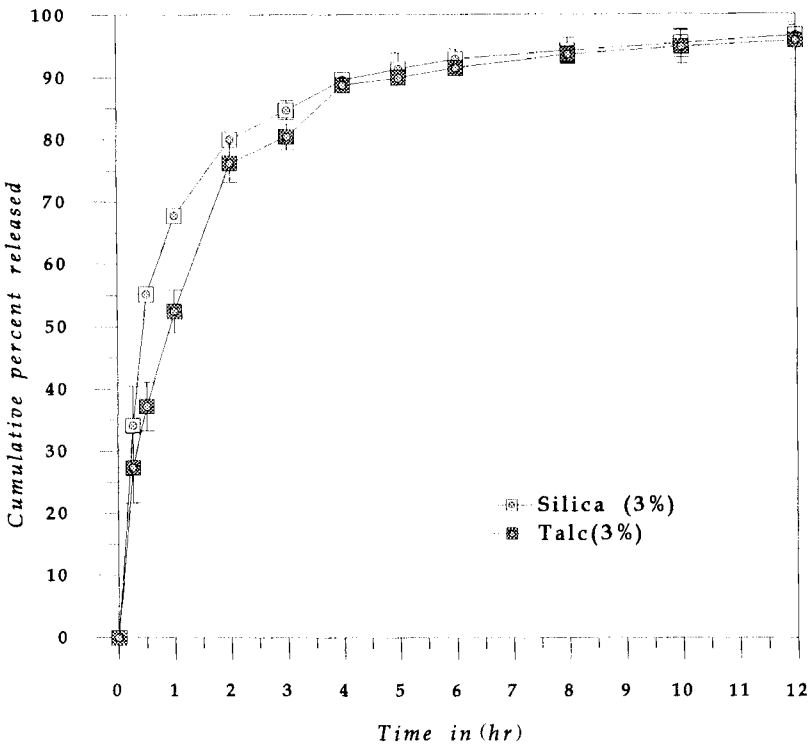

Figure 7. Effect of type of antiadherent on the release of ibuprofen from coated beads.

of osmotic pressure of the dissolution medium was performed using equations discussed by Zentner et al. (10). Figure 9 shows the cumulative percent released from ibuprofen-loaded beads in various urea solutions. Osmotic pressure in the bead may be due to the core, containing sugar spheres, and the drug. This osmotic pressure, in addition to the solubility of the drug, may be a release-regulating factor. However, solubility of ibuprofen in various solutions showed no difference with an increase in osmotic pressure, as shown in Table 2.

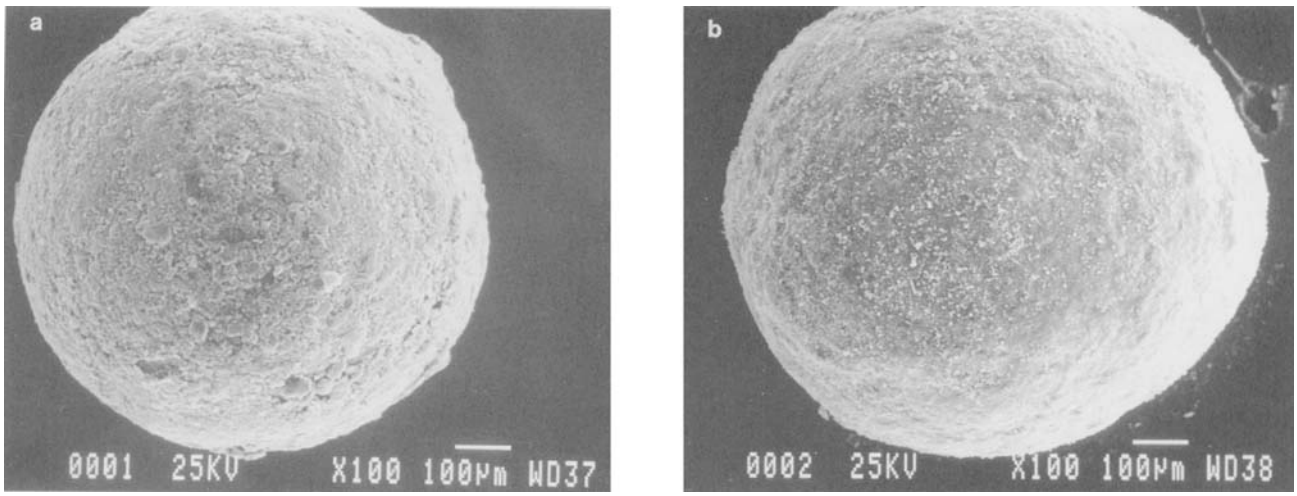

Figure 8. Comparative SEM photographs showing the surface of the film of coated beads using talc (a) and silica (b).

Table 2

Equilibrium Solubilities of Ibuprofen at 37°C in Various Urea Solutions

Dissolution Fluid	Solubility (mg/ml)	π_c (atm)[a]	π_e (atm)[b]	$\Delta\pi$ ($\pi_c - \pi_e$)
Dist. water	0.9350	148.27	0.00	148.27
2 M urea	0.9513	148.27	43.49	104.88
5 M urea	0.9410	148.27	90.50	57.87
8 M urea	0.9500	148.27	125.10	23.28

[a]π_c = 148.27 (see Appendix).
[b]Calculated using π_{ideal} = CRT · ϕ, where ϕ = molal osmotic coefficient.

The osmotic pressure in the core did not change with an increase in osmotic pressure in the external medium, because there was no change in the solubility of the drug in the different urea solution. The osmotic pressure difference ($\Delta\pi$) was due to the external medium only. Figure 9 shows no change in the release with different osmolar urea solutions, suggesting that there is no osmotic effect on the release of ibuprofen. Further, a one-way ANOVA of the mean t_{50} values of the release of ibuprofen from beads in different urea solutions indicated no significant difference ($p = 0.05$) between the mean t_{50} values.

The diffusion of ibuprofen through free film were performed in order to evaluate whether the diffusion from the film was porous or nonporous. Diffusion is defined as a process of mass transfer of individual molecules of a substance, brought about by random molecular motion and associated with a concentration gradient (11). Diffusion through a nonporous membrane is given by (12):

$$dM/dt = P \cdot S \cdot \Delta C \quad (1)$$

where P is the permeability coefficient, S is the surface area of the membrane, ΔC is the concentration differ-

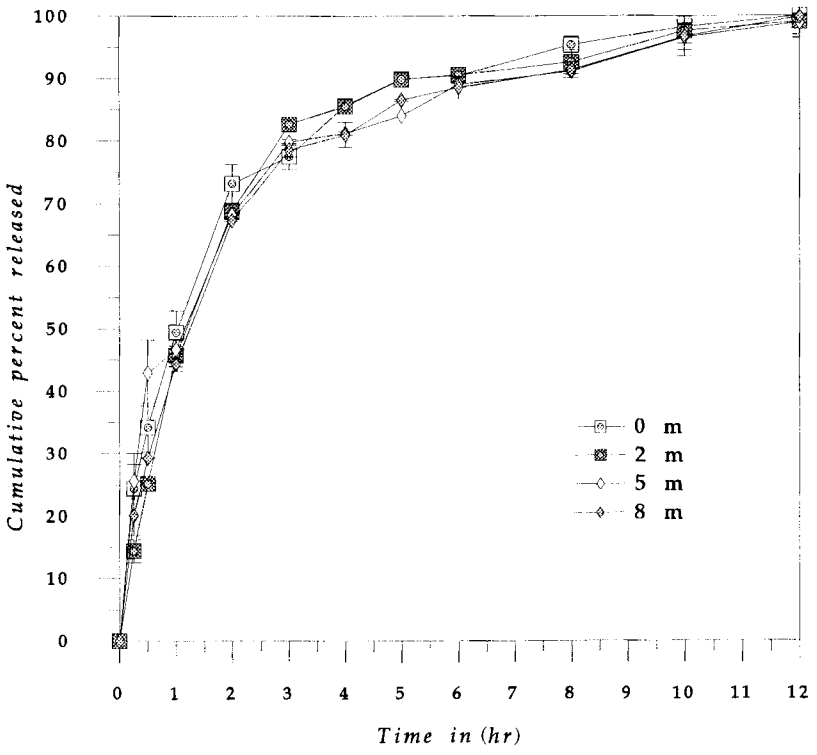

Figure 9. Effect of osmotic pressure on the release of ibuprofen from coated beads.

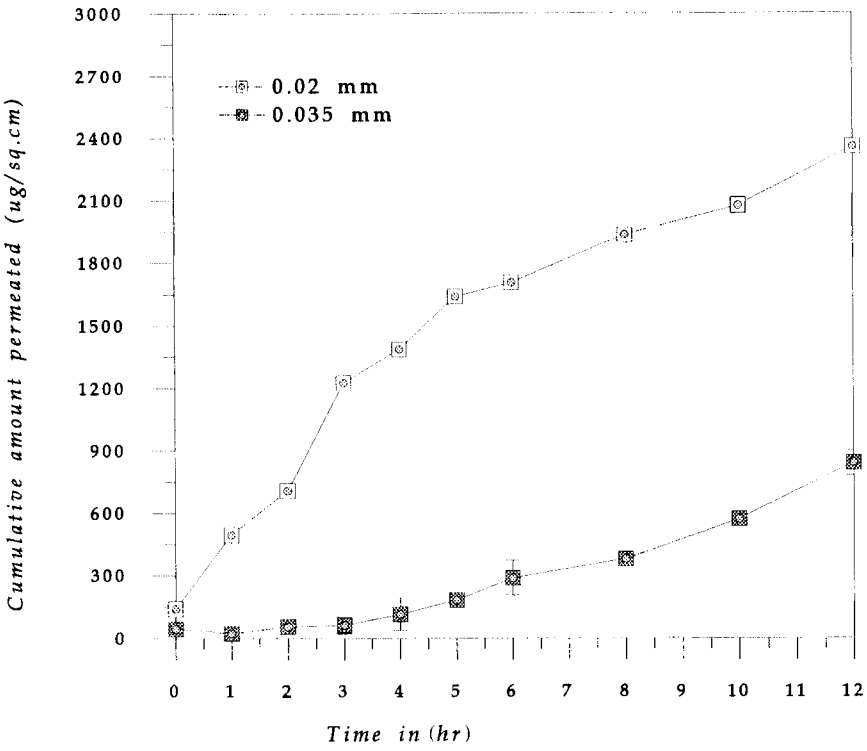

Figure 10. In vitro diffusion of ibuprofen through free films of the experimental latex.

ence between the donor and the receptor cell, and *dM/dt* is the amount of drug diffused through the membrane with respect to time. This type of diffusion is referred to as *simple molecular diffusion*.

Figure 10 shows the in vitro diffusion profiles of ibuprofen through free films of the experimental latex. The diffusion of ibuprofen across the membrane was negligible compared to the amount of drug present in the donor cell. The results indicate that the drug transport through these membranes occurs principally by simple molecular diffusion. The films with 0.02 mm thickness showed a higher flux (0.119 μg/cm^2/hr) than films with 0.035 mm thickness (flux: 0.07 μg/cm^2/hr). This shows that diffusion of the drug is dependent on the thickness of the membrane.

CONCLUSIONS

In order to design controlled-release dosage forms by the application of polymeric film coat around drug-loaded beads, it is important to evaluate the barrier properties of the film and the formulation factors which affect the release of drug through the membranes.

The effect of various factors was studied for the release of ibuprofen from beads coated with an experimental latex. The release of ibuprofen increased with decrease in particle size. There was no significant difference between the t_{50} of 50% and 61%, but it was considerably lower for 36% drug loading. The release with films using different plasticizer type showed a varied response. The choice of plasticizer is important in the formation of coherent film. Drying the coated beads in the column after coating yielded beads with more control, suggesting the formation of coherent film due to improved drying efficiency. There was no significant difference in the t_{50} of ibuprofen between silica and talc. However, the overall release rate of silica appeared to be higher than that of talc. Osmotic effects were of negligible consequence in the release of ibuprofen from coated beads. The diffusion from free films indicated that the mechanism of drug release from coated beads was primarily through simple molecular diffusion. The diffusion of ibuprofen from free films was dependent on the thickness of the film.

APPENDIX

The approximate osmotic pressure π produced by a saturated solution in an osmotic pump-like device is given by (13):

$$\pi = \frac{\nu C_s RT}{M}$$

where ν = number of particles into which a molecule ionizes; C_s = concentration of the drug at saturation; R = 0.082 l atm/mol/deg; T = 310°K; M = molecular weight of the drug.

For ibuprofen

$\nu = 1$
$C_s = 0.9350$
$M = 206.3$
$\pi = 0.1232$ atm

For sucrose (Nu-Pariels) π is 148.15 atm (8). Hence the osmotic pressure π_c is 148.27. Similarly, the π_c values for the core is calculated at different urea solutions.

ACKNOWLEDGMENT

The authors wish to acknowledge Albemarle Corp for their generous gift of ibuprofen USP. We would also like to acknowledge Crompton & Knowles, Morflex Inc., Kodak Chemical Co., Warner & Jenkins, and B. F. Goodrich Co., for their generous gift of excipient and samples. Our appreciation is extended to Dr. Indra K. Reddy and Dean William M. Bourn for their suggestions and encouragement; and to Dr. William Wilber, Dr. Manzer Durrani, and Ms. Pam Lerch of the B. F. Goodrich Co., for running the T_g samples, SEM photographs, and providing helpful suggestions.

REFERENCES

1. M. R. Harris and I. Ghebre-Sellassie, in *Aqueous Polymeric Caotings for Pharmaceutical Dosage Forms* (J. W. McGinity, ed., Marcel Dekker, New York, 1989, p. 63.
2. S. K. Singh, J. Dodge, M. J. Durrani, and M. A. Khan, Int. J. Pharm., 125, 243 (1995).
3. A. G. Ozturk, S. S. Ozturk, B. O. Palsson, T. A. Wheatly, and J. B. Dressman, J. Controlled Rel., 14, 203 (1990).
4. N. A. Peppas, *Medical Applications of Controlled Release*, Vol. II, CRS Press, Boca Raton, FL, 1984, p. 169.
5. G. S. Rekhi, S. C. Porter, and S. S. Jambekar, Drug Dev. Ind. Pharm., 21(6), 709 (1995).
6. N. Phuapradit, N. H. Shah, A. Reilkar, L. Williams, and M. H. Infeld, Drug Dev. Ind. Pharm., 21(8), 955 (1995).
7. Morflex Inc., Pharmaceutical Coatings, Bulletin 102-1.
8. J. H. Guo, Drug Dev. Ind. Pharm., 20(11), 1883 (1994).
9. C. Veechio, F. Fabian, and A. Gazzaniga, Drug Dev. Ind. Pharm., 21(15), 1781 (1995).
10. G. M. Zentner, G. S. Rork, and K. J. Himmelstein, J. Controlled Rel., 2, 217 (1985).
11. A. Martin, J. Swarbrick, and A. Cammarata (eds.), *Physical Pharmacy*, Lea & Febiger, Philadelphia, 1983, p. 399.
12. R. S. Langer and N. A. Peppas, Biomaterials, 2, 201 (1981).
13. A. Martin, J. Swarbrick, and A. Cammarata, *Physical Pharmacy: Physical Chemical Principles in the Pharmaceutical Sciences*, Lea & Febiger, Philadelphia, 1983, p. 574.