ELSEVIER

International Journal of Pharmaceutics 109 (1994) 271–281

international journal of pharmaceutics

Use of sparingly soluble salts to prepare oral sustained release suspensions

Ketan P. Shah *, Lester Chafetz

The Center for Pharmaceutical Technology, School of Pharmacy, University of Missouri-Kansas City, 5005 Rockhill Road, Kansas City, MO 64110–2499, USA

(Received 10 January 1994; Modified version received 21 March 1994; Accepted 28 March 1994)

Abstract

The feasibility of preparing oral sustained release suspensions by using sparingly soluble salts of soluble ionic drugs was assessed in this study. Diltiazem was used as a model drug. A less soluble pectate salt of the drug was prepared and encapsulated by a solvent evaporation process. Cellulose acetate butyrate (CAB) was used as the coating polymer. Percent drug release from CAB microcapsules was modified by using hydrophilic polymers and varying microcapsule drug load. The release was independent of pH and ionic strength of the dissolution medium, an advantage over the existing ion-exchange resin approach. The release profiles fitted a bi-exponential equation, suggesting a biphasic release mechanism; an initial burst effect was obtained followed by slow diffusion of drug through the polymeric coat. Suspensions of diltiazem pectate-loaded microcapsules were prepared in a preserved medium containing sorbitol, syrup, and methylcellulose. Redispersibility of suspensions was satisfactory at room temperature and 4°C, but poor at 37°C. The suspended microcapsules resulted in 8–12% increase in drug release after 1 week storage at room temperature compared to dry microcapsules; however, the release did not increase any further upon extended storage. The suspensions were unstable at 37°C, but remained relatively stable at or below room temperature for up to 26 weeks.

Key words: Sparingly soluble salt; Diltiazem; Pectic acid; Solvent evaporation process; Microcapsules; Sustained release; Suspension

1. Introduction

Most of the oral sustained release products are available as tablets or capsules. A suspension would be easier for children and the elderly to swallow, and the dose could be readily adjusted. The formulation of sustained release suspensions, however, presents a significant challenge to pharmaceutical scientists due to the risk of drug leaching to the suspending medium during storage. In a recent review, Chang (1992) summarized various strategies that have been employed to overcome these drawbacks. Some of the strategies included the use of ion-exchange resins, saturated drug solution as a suspending medium and

* Corresponding author (present address): Global Pharmaceutical Corp., Castor and Kensington Aves, Philadelphia, PA 19124, U.S.A.

SSDI 0378-5173(94)00098-P

preparing dry suspensions for reconstitution before use.

Ion-exchange resins have been used commercially to prepare sustained release suspensions (Amsel et al., 1984; Park et al., 1984). The resin-drug adsorbates effectively prevent leaching of drug to the suspending medium during storage; however, the in vivo release profiles of suspensions fluctuate depending on the concentration of counterions present in the gastrointestinal tract. Inherently less soluble drugs, such as ibuprofen, have been encapsulated directly and dispersed in an acidic medium (pH 3.5) to prepare stable suspensions (Dalal and Narurkar, 1991; Kawashima et al., 1991). Cavallito and Jewell (1958) prepared the less soluble tannate salt of therapeutic amines to modify drug release, but an aqueous suspension of the salt showed gradual discoloration due to oxidation of gallotannins present in tannic acid.

The purpose of this study was to prepare a suitable sparingly soluble salt of a soluble ionic drug to formulate stable sustained release suspensions. Diltiazem was used as a model compound. The drug is available as a freely soluble hydrochloride salt and is quite stable to chemical degradation (Davis et al., 1986; Chafetz and Shah, 1991; Won and Iula, 1992). It is marketed in 12 to 24 h sustained release capsules for twice to once a day administration, respectively. A suspension dosage form of diltiazem would be desirable, since the drug is mainly used in the elderly population for treatment of heart disease.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride (lot no. 2269–049–001, lot no. 1429–77) was a gift from Marion Merrell Dow Inc. (Kansas City, MO). Pectic acid, ε-poly(caprolactone) (PC), poly(vinyl alcohol), and sorbitol were purchased from Aldrich Chemical Co. (Milwaukee, WI). Cellulose acetate butyrate (CAB-171–15S type) (CAB) and propyl paraben were obtained from Eastman Kodak Co. (Rochester, NY), whereas poly(ethylene glycol) 4000 (PEG), methyl cellulose 1500 cps and methyl paraben were purchased from Rugar Chemical Co. (Irvington, NY). Methylene chloride and ethyl acetate were supplied by MC&B Manufacturing Chemist (Norwood, OH) and Fisher Scientific Co. (Fair Lawn, NJ), respectively. Water obtained from the Milli Q Plus (Molsheim, France) water purification system was used for all the experiments. Sodium hydroxide, hydrochloric acid, citric acid, sodium chloride, potassium chloride, monobasic potassium phosphate, methanol and 95% ethanol used were all of reagent grade.

2.2. Equipment

An IKA Laboratories stirrer (Staufen, Germany) Model RW 20 DZM was used for preparing microcapsules by a solvent evaporation process. A Hanson Research (Northridge, CA) Model 72 dissolution apparatus was used for in vitro drug release determinations. Drug load and dissolution samples were analyzed using a Hewlett Packard (Palo Alto, CA) Model 8451A diode array spectrophotometer. The salt was dried in a Precision Scientific (Chicago, IL) Model 524 vacuum oven, and infrared spectra were recorded on a Perkin-Elmer (Norwalk, CT) Model 457 IR spectrophotometer. A Philips (Eindhoven, The Netherlands) Model 515 scanning electron microscope was used to study the surface morphology of microcapsules.

2.3. Preparation of sparingly soluble diltiazem pectate

A stoichiometric amount of diltiazem free base was dissolved in ethanol and added to a 5% aqueous dispersion of pectic acid at room temperature (equivalent weight of 0.8 g pectic acid was 3.74). The resulting mixture was stirred until no further change in pH was observed (final pH approx. 5.5). Diltiazem pectate was filtered off, washed with methanol to remove the unreacted drug and dried at 40°C under vacuum for 30 min. Drug content of the salt was determined spectrophotometrically by dissolving a known amount in sodium chloride solution.

Table 1
Encapsulation of diltiazem pectate with varying ratios of CAB/PEG and CAB/PC polymers [a] using the solvent evaporation process

Formulation	PEG [b] (%)	PC [c] (%)	Actual drug load [d] (%) (SD)	Incorporation efficiency [e] (%)
1	0	–	13.4 (0.4)	74.0
2	5	–	13.6 (0.3)	75.1
3	20	–	14.9 (0.2)	82.3
4	35	–	17.9 (0.3)	98.9
5	50	–	20.2	111.6
6	–	5	13.7 (1.1)	75.7
7	–	20	13.3 (0.8)	73.5
8	–	35	14.3 (0.7)	79.0
9	–	50	12.0 (0.4)	66.3
10	–	75	10.5 (0.3)	58.0
11	–	100	8.8	48.3

[a] Total amount of polymers used: 0.8 g.
[b] Polyethylene glycol 4000 (as a percent of total polymer).
[c] ε-Poly(caprolactone) (as a percent of total polymer).
[d] Theoretical drug load: 18.1%.
[e] Percent incorporation efficiency = (actual drug load/theoretical drug load) × 100.

2.4. Microencapsulation of diltiazem pectate

An o/w solvent evaporation process, similar to that used by Babay et al. (1988) to encapsulate indomethacin, was used to encapsulate diltiazem pectate. Cellulose acetate butyrate was used as the coating polymer, and hydrophilic polymers such as PEG or PC were used to modify drug release. Table 1 lists the different formulations prepared using combination of these polymers. The solvent evaporation process employed was as follows: The polymers were dissolved in 15 ml of methylene chloride, and diltiazem pectate was dispersed in the polymer solution. The resulting dispersion was added to 200 ml of 0.2% w/v poly(vinyl alcohol) to form a stable emulsion. The emulsion was stirred at 550 rpm for about 1.5 h to evaporate the organic solvent. The microcapsules were filtered, washed with water and air dried at the end of the process.

2.5. Drug load determination of microcapsules

About 20 mg of accurately weighed microcapsules were added to 25 ml ethyl acetate to dissolve the polymer coat. The organic layer was extracted with 50 ml of 0.1 N hydrochloric acid and the aqueous layer containing the drug was assayed spectrophotometrically at 236 nm. Drug load determinations were performed in triplicate.

2.6. Preparation of suspensions

Diltiazem pectate-loaded microcapsules (less than 200 μm in diameter), prepared using formulation 3, were dispersed in a medium containing water (1 part), sorbitol (1 part), simple syrup NF (1 part) and 1% methylcellulose solution (2 parts) to prepare 1% w/v suspensions. Suspensions were preserved by adding 1% methyl and 0.1% propyl parabens to the suspending medium. The suspensions were stored at 37°C, room temperature and 4°C for up to 26 weeks and evaluated for in vitro dissolution at the end of each stability period.

2.7. In vitro dissolution of microcapsules and suspensions

A USP dissolution apparatus 2 (paddle method) was used to determine in vitro release profiles of dry and suspended microcapsules in duplicate. About 50 mg of accurately weighed microcapsules (smaller than 200 μm) or 5 ml of the suspension were dispersed in 500 ml of pH 7.4 phosphate buffer at 37°C and 100 rpm. Samples were removed periodically and analyzed spectrophotometrically at 236 nm. The effect of dissolution medium pH on drug release was studied at pH 1.2 (potassium chloride/hydrochloric acid buffer), pH 6.0 and 7.4 (phosphate buffers) and pH 4.8 (citrate buffer), whereas the effect of ionic strength was studied in 0.1, 0.25, and 0.5 M potassium chloride solutions.

2.8. Microscopy studies

Scanning electron microscopy was used to examine the surface morphology of microcapsules. The dried microcapsules were fastened to a holder using double-sided tape and were sputter coated with gold-palladium for 3 min at 40 mA (250 Å/coat per min). The suspended microcapsules were filtered and dried after the stability period

and processed in a manner similar to that of the dry microcapsules. All photographs were taken at 15 kV and the scale and magnification for each photograph are indicated at the bottom of the figures.

3. Results and discussion

It is difficult to formulate a soluble drug in a sustained release suspension due to leaching of drug to the surrounding medium during encapsulation and storage. The fact that an oral suspension requires the use of particles less than 200 μm in diameter to avoid a gritty sensation during administration provides an additional challenge to the formulator. This paper describes the approach of sparingly soluble salt used to prepare stable sustained release suspensions of soluble drugs. A less soluble pectate salt of the model drug, diltiazem hydrochloride, was prepared and encapsulated for this purpose.

Initial encapsulation experiments were conducted in an Aeromatic® STREA1 air suspension coater. The coating material used was a 90:10 mixture of Eudragit RL and RS 30 D aqueous polymeric dispersions, containing triethylamine as plasticizer. A significant amount of particles agglomerated after applying about half of the total coating solution. Encapsulation of fine particles in an air suspension coater is difficult, as a greater amount of coating solution is required to cover the increased surface area of fine particles. The droplet size of the atomized coating solution should also be smaller than the particles being coated in order to prevent agglomeration. Since it was not feasible to modify the STREA1 coater to overcome the above limitations, a laboratory-scale solvent evaporation process was alternatively used to encapsulate diltiazem pectate. Although the microcapsules prepared by the solvent evaporation process gave a high burst effect and incomplete drug release, the process was used mainly to demonstrate the principle behind the sparingly soluble salt approach. Complete evaporation of the organic solvent (methylene chloride) used during processing was difficult to achieve, thus rendering the process commercially impractical. Better encapsulation techniques are recommended for any commercial application of this approach.

3.1. Preparation of sparingly soluble salt

Several acids were investigated in an attempt to prepare a sparingly soluble salt of diltiazem. Acids were chosen empirically, since there is no way to predict the influence of a particular species on drug properties. Some of the acids used included alginic, tannic, pectic, stearic and sulfonic acids. Diltiazem formed sparingly soluble salts with tannic and pectic acids. Diltiazem tannate was not used to prepare suspensions because an aqueous dispersion of the salt showed progressive discoloration due to oxidation of gallotannins present in tannic acid.

Diltiazem pectate was obtained as a creamy white amorphous powder by reacting the free base and pectic acid in a hydroalcoholic medium at room temperature (yield: 99%). The drug content of the salt was $62.5 \pm 1.7\%$ (theoretical drug content: 65.5%). The aqueous solubility of diltiazem pectate was about 300 μg/ml at 25°C, compared to the freely soluble hydrochloride salt. Pectic acid did not interfere with the UV analysis of diltiazem, whereas the IR spectrum of diltiazem pectate showed two strong characteristic bands at 1600 and 1400 cm^{-1} for the carboxylate anion, confirming the formation of a true salt. Complete dissolution of 50 mg diltiazem pectate in 500 ml of deionized water (sink conditions) at 37°C and 50 rpm was achieved within 3.5 h; however, the salt dissolved immediately in ionic solutions such as normal saline. The rapid dissolution was due to weak association between diltiazem and pectic acid that fell apart in the presence of other ions. The instability of diltiazem pectate in ionic media suggested that there would be no oral bioavailability problems with this salt; however, it also suggested the necessity to encapsulate the salt particles with diffusion-controlled coatings to control drug release.

3.2. Microencapsulation studies

The solvent evaporation process was used to encapsulate diltiazem pectate salt particles. The

process involved forming a stable o/w emulsion between the organic phase containing the polymer(s) and diltiazem pectate, and an aqueous phase containing the emulsifier. The organic phase was evaporated by constant stirring, leaving behind round, solid microcapsules. Since diltiazem pectate was dispersed in the polymer solution during encapsulation process, the polymer congealed around the salt to form 'microcapsules' with the majority of drug present in the core. This process works best for compounds that have limited aqueous solubility.

Several polymers such as ethylcellulose (45 cps), cellulose acetate butyrate (CAB) and Eudragit® RS 100 were screened for the encapsulation process. A certain amount of drug partitioned into the aqueous phase during processing. The drug loss depended on the rate of precipitation of polymers during processing, which in turn depended on the solubility of polymers in the organic solvent. Cellulose acetate butyrate was the least soluble in methylene chloride (the organic solvent used in microcapsule preparation) compared to the other polymers and gave minimum drug loss (approx. 20%) during processing. More than 90% of the microcapsules prepared by the above process were less than 250 μm in diameter. The amount of organic solvent used to dissolve the polymers was optimized to 20 ml. Concentrated polymeric solutions resulted in larger microcapsules, whereas dilute solutions required longer processing times. Microcapsules less than 200 μm were used in the preparation of sustained release suspensions.

3.3. Drug release studies

Encapsulation of diltiazem pectate with CAB gave incomplete drug release, as shown in Fig. 1, due to formation of microcapsules in which the drug was partially embedded. Hydrophilic polymers such as polyethylene glycol 4000 (PEG) or ε-poly(caprolactone) (PC) were used to provide channels in the microcapsule surface to enhance drug release. Different formulations were prepared by varying the CAB to hydrophilic polymer (PEG or PC) ratio, as shown in Table 1. The drug load and incorporation efficiency for each formulation are also listed in Table 1. The percent incorporation efficiency increased with PEG and decreased with PC, as the concentration of hydrophilic polymers increased. This was attributed to the precipitation behavior of polymers from the processing medium. In the case of CAB/PEG

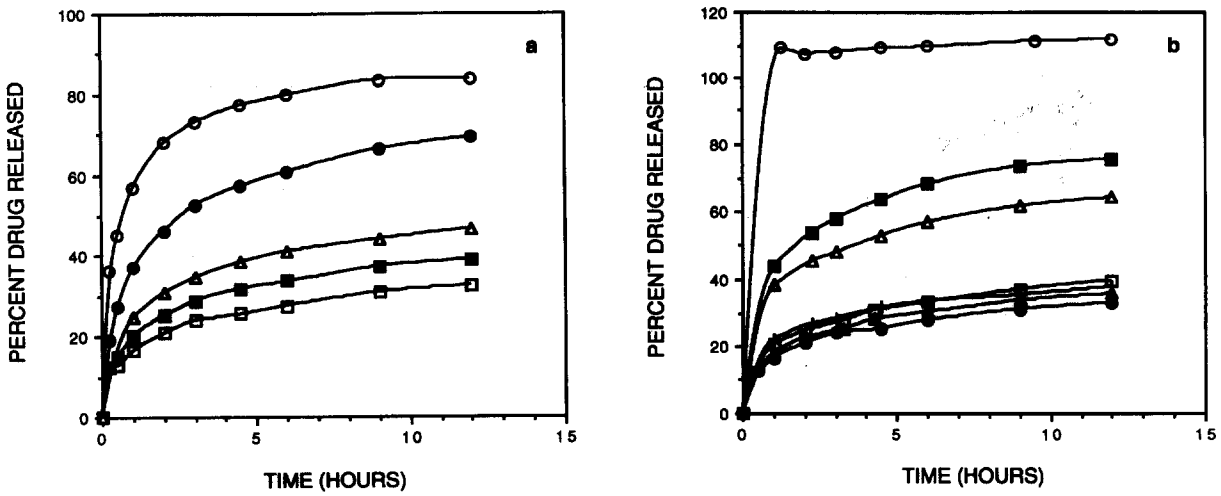

Fig. 1. Effect of hydrophilic polymers on drug release from CAB microcapsules. Study conditions: 37°C and 100 rpm in pH 7.4 phosphate buffer. (a) Polyethylene glycol 4000 (PEG): (□) 0%, (■) 5%, (△) 20%, (●) 35%, (○) 50%. (b) ε-Poly(caprolactone) (PC): (●) 0%, (□) 5%, (▲) 20%, (+) 35%, (△) 50%, (■) 75%, (○) 100%.

microcapsules, both the polymers precipitated within 5 min after addition of the organic phase to the aqueous phase, encapsulating the drug with minimal loss. An apparent incorporation efficiency of more than 100% was achieved due to partial dissolution of PEG in the processing medium. However, with CAB/PC microcapsules, PC precipitated slowly over 15 min. Therefore, as the amount of PC in the microcapsule increased, more drug partitioned into the aqueous phase before depositing in microcapsules.

Drug release profiles for various CAB/PEG and CAB/PC microcapsules in pH 7.4 phosphate buffer at 37°C and 100 rpm are shown in Fig. 1a and b. The release was proportional to the concentration of hydrophilic polymers used except for PC concentrations below 50%. However, closer inspection of the release profiles revealed a significant difference in burst effect followed by similar dissolution rates for various formulations. The higher burst effect was correlated to increased porosity of the microcapsule surface, as seen from the scanning electron micrographs in Fig. 2. Pores were formed during processing due to the partial dissolution of PEG, evaporation of the organic solvent and partitioning of diltiazem pectate into the aqueous phase. At PC concentration below 50%, there was no noticeable difference in surface morphology, suggesting that the rate of polymer precipitation was not very different among these formulations. It is believed that a critical 50% PC concentration is needed to impart irregularity in the microcapsule surface.

Since microcapsules prepared by CAB/PEG polymer combination gave better quality microcapsules with higher drug loads, they were further characterized and used to prepare oral sustained release suspensions. Drug release from CAB/PEG microcapsules was independent of dissolution medium pH and ionic strength as

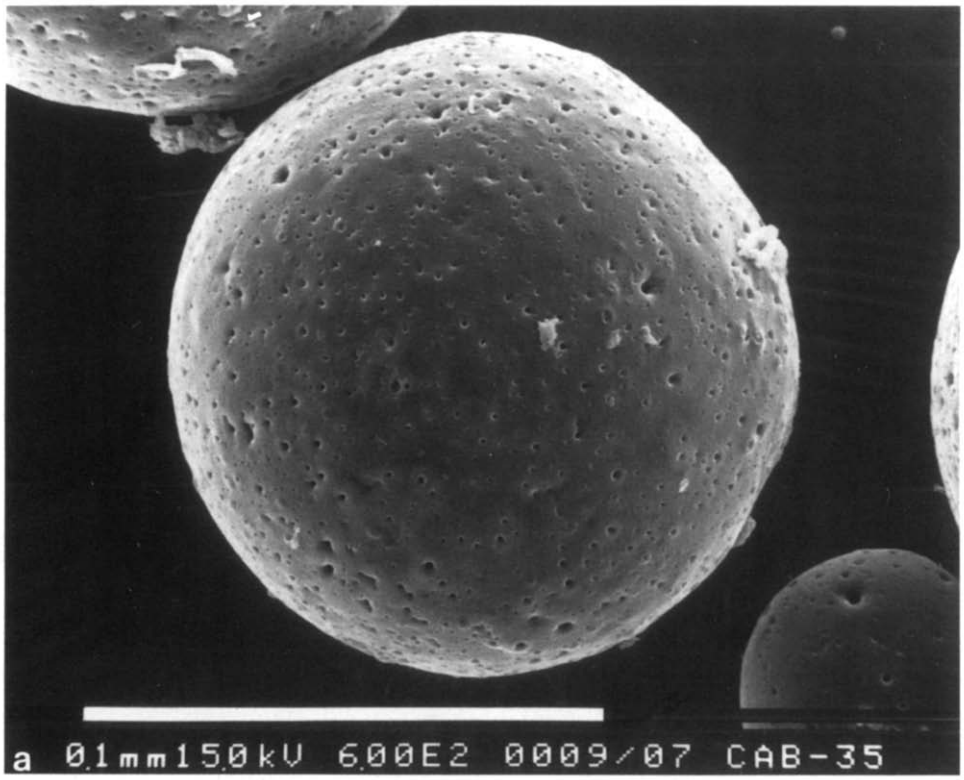

Fig. 2. Scanning electron micrographs of various CAB microcapsules loaded with diltiazem pectate. (a) CAB/PEG = 80:20; (b) CAB/PEG = 50:50; (c) CAB/PC = 65:35.

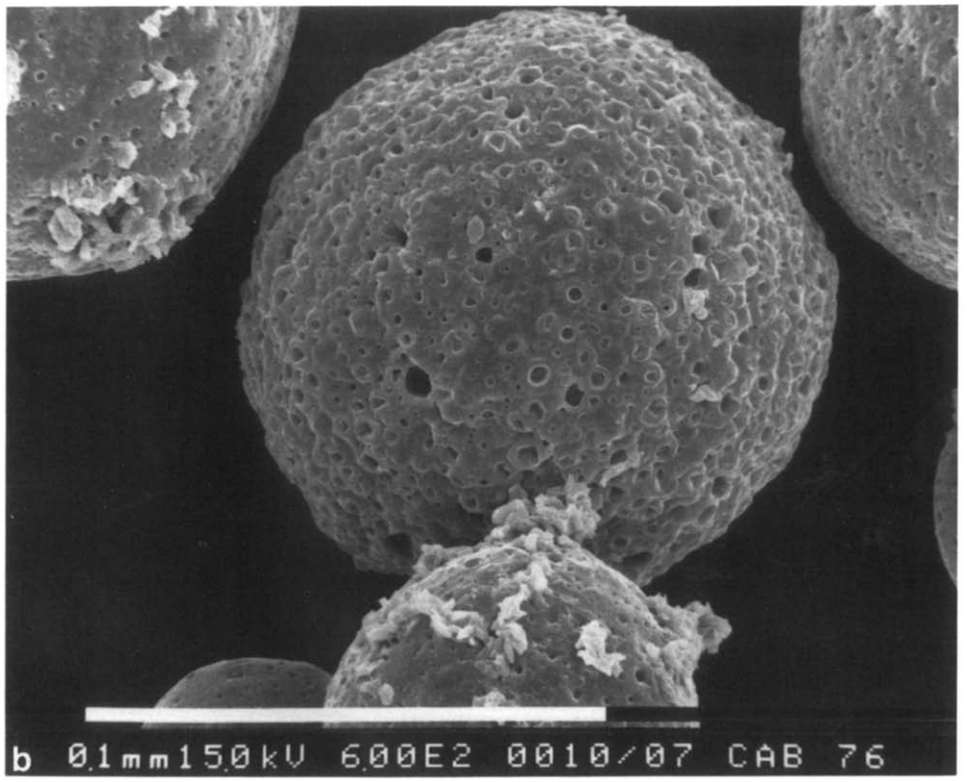

Fig. 2 (continued).

demonstrated in Fig. 3a and b, respectively. Diltiazem pectate dissolved in the presence of a minimum amount of ions by metathesis – a process of exchange of ions, giving ionic strength independent drug release. This is an advantage over the resin approach, where the drug release varies with ionic concentration of the surrounding medium.

Drug release from CAB/PEG microcapsules increased with drug load, as shown in Fig. 4, due to a decreased polymer to drug ratio. The dissolution data shown in Fig. 4 fitted a bi-exponential equation of the type;

$$D = Ae^{-k_1 t} + Be^{-k_2 t} \quad (1)$$

where, D denotes the percent drug undissolved after time t, A and B are constants and k_1 and k_2 represent the rate constants for the rapid and slow release mechanisms, respectively. A similar equation was used previously to describe drug release kinetics from tablets and microspheres (Laakso et al., 1984; Malamataris and Avgerinos, 1990). Fitting of data to the above empirical equation suggested a biphasic release mechanism for the diltiazem pectate-loaded microcapsules. The easily accessible drug entrapped in the pores or present on the surface released immediately to give the initial burst effect. The rate-limiting diffusion of the embedded drug through the pores and polymer coat resulted in the later slow release. The rate constants (k_1 and k_2) for both the release mechanisms increased with drug load of microcapsules. The rate constants k_1 increased from 1.12 to 1.52 h^{-1} and k_2 increased from 0.0057 to 0.0637 h^{-1}; however, a larger burst effect (k_1) dominated the release profiles.

3.4. Stability evaluation of sustained release suspensions

Microcapsules prepared using formulation 3 were used to formulate sustained release suspen-

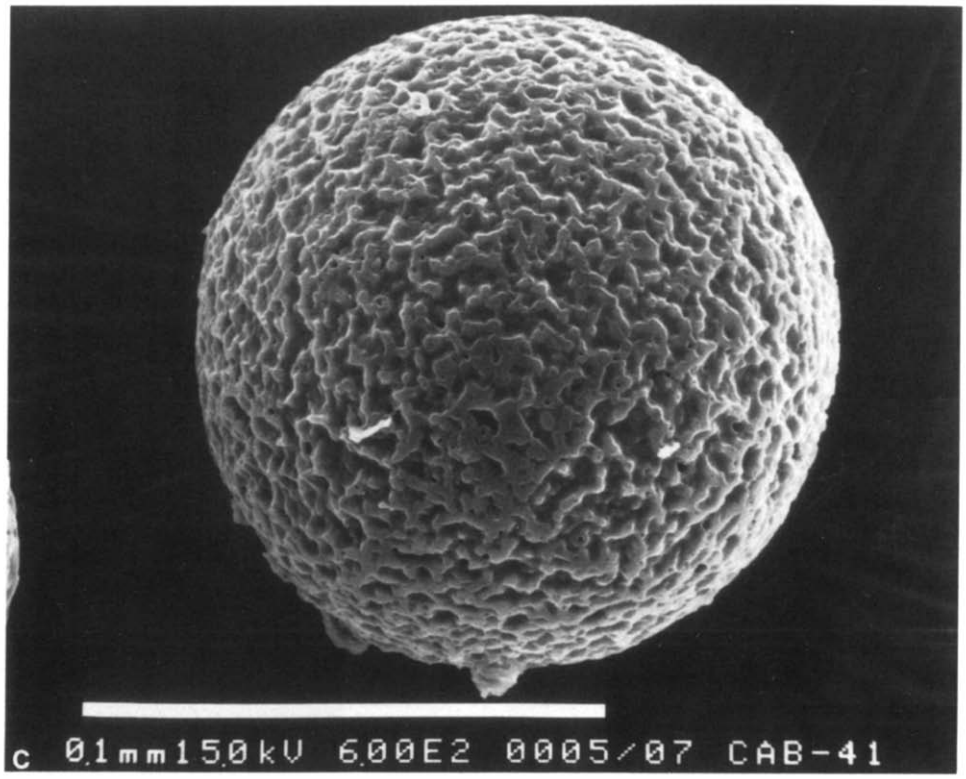

Fig. 2 (continued).

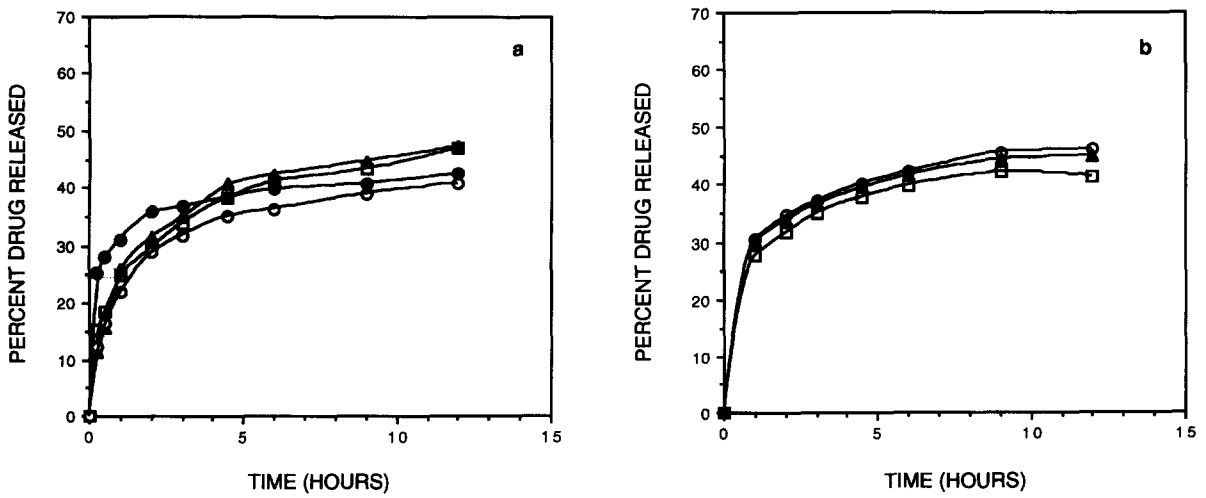

Fig. 3. Percent drug release from CAB/PEG microcapsules in different dissolution media at 37°C and 100 rpm. (a) Effect of pH: (●) pH 1.2, (▲) pH 4.8, (○) pH 6.0, (□) pH 7.4. (b) Effect of ionic strength: (○) 0.5 M KCl, (□) 0.25 M KCl, (▲) 0.1 M KCl.

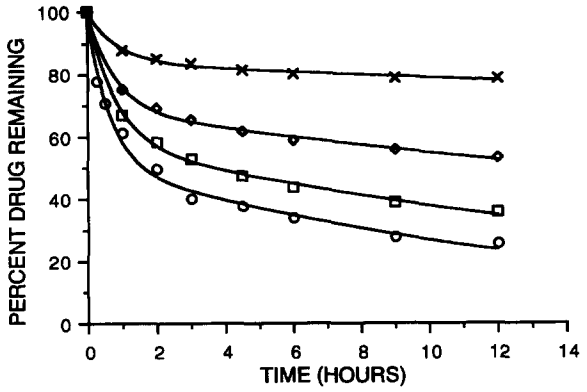

Fig. 4. Effect of drug load on release from CAB/PEG microcapsules. Study conditions as in Fig. 1. (○) 24.0%, (□) 20.8%, (◇) 18.1%, (×) 12.5%.

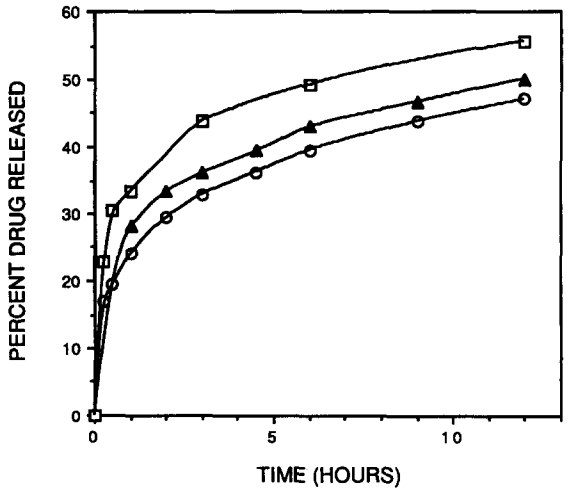

Fig. 5. Drug release from microcapsules suspended in aqueous media for 1 week at room temperature. Study conditions as in Fig. 1. (○) Dry microcapsules; (▲) microcapsules suspended in a medium containing water, sorbitol, syrup and methylcellulose (1:1:1:2); (□) microcapsules suspended in a medium containing water, propylene glycol, syrup and methylcellulose (1:1:1:2).

sions, since they gave intermediate drug release (about 50% over 12 h). This permitted study of the effect of different formulation variables on percent drug release and storage stability of suspensions. Preliminary studies showed that an aqueous medium containing sorbitol, syrup and 1% methylcellulose solution was most suitable for preparing stable suspensions. The suspended microcapsules resulted in slightly greater drug release compared to dry microcapsules after 1 week storage at room temperature, as shown in Fig. 5. The release was much greater when propylene glycol was used in the suspending medium instead of sorbitol. The increase in drug release was within 8–12% for different drug loads of microcapsules, suspended and stored at room temperature for 1 week, as shown in Table 2. However, none of the suspensions even at higher drug load exhibited drug dumping. Leaching of the easily accessible drug, present on the microcapsule surface, to the suspending medium was responsible for the greater drug release. The use of a suspending medium saturated with diltiazem pectate suppressed partitioning of the drug during storage.

Since diltiazem pectate dissociated and dissolved in the presence of a minimum amount of ions, ionic materials were excluded from the suspension formulation. Sorbitol and syrup, used to impart palatability, gave a well-structured vehicle in which the microcapsules remained suspended for an extended period. Suspensions were successfully redispersed after prolonged storage at room temperature and 4°C. The redispersibility

Table 2
Stability of suspended microcapsules containing different drug loads after 1 week storage at room temperature

Drug load (%)	Percent drug released from microcapsules after a 12 h dissolution study		Percent increase in drug release
	Unsuspended	Suspended	Suspended/Unsuspended
12.5	22.2	24.9	12.2
18.1	46.3	50.1	8.2
20.8	59.8	66.4	11.0
24.0	80.5	87.4	8.6

Table 3
Extended stability study of a suspension [a] stored at various temperatures for up to 26 weeks

Temperature	Percent drug released in 12 h [b]				
	1 week	2 weeks	4 weeks	12 weeks	26 weeks
37°C	51.7	51.0	49.9	61.9	59.9
Room temperature	50.1	50.3	47.0	53.2	53.1
4°C	48.8	52.5	46.1	49.6	46.9

[a] Microcapsules suspended in a preserved medium containing water, sorbitol, syrup and methylcellulose (1:1:1:2); drug load: 18.1%.
[b] Drug release from dry microcapsules after a 12 h dissolution study = 46.3%.

was poor at 37°C after 12 weeks storage, due to partial gelling of the suspending medium.

Sprockel and Price (1989) achieved slightly greater release from suspended microcapsules containing chlorpheniramine-resin adsorbate at room temperature, however, the release did not increase any further with prolonged storage. In another study (Pongpaibul et al., 1990), microcapsules of dextromethorphen-resin adsorbates were dispersed in an ion-free medium to prepare stable suspensions; however, the stability of suspensions was followed for only 40 days. The suspensions prepared in this study were stored at 37°C, room temperature, and 4°C for up to 26 weeks. Table 3 summarizes the data on the extended stability of suspensions. Suspensions stored at room temperature and 4°C were relatively stable for at least 26 weeks with only a slight increase in

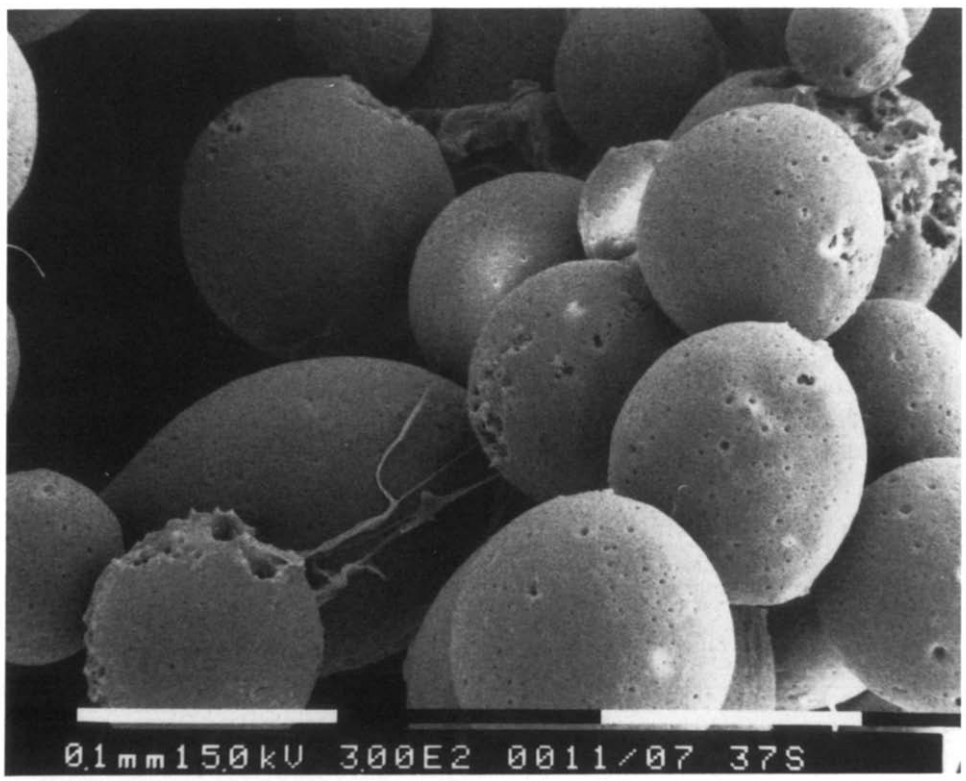

Fig. 6. Scanning electron micrograph of suspended microcapsules after storage at 37°C for 26 weeks.

dissolution. However, the suspensions stored at 37°C gave a significantly higher release ($p < 0.05$) after 12 weeks storage. Instability of suspensions at higher temperature was attributed to increased solubility of diltiazem pectate and partial dissolution of PEG from the microcapsule walls. This was reflected in the increased porosity of microcapsules stored at 37°C for 26 weeks, as observed under a scanning electron microscope (Fig. 6). The discrepancy in percent drug release with 4 week stability samples (refer to Table 3) was related to improper transfer of the suspended microcapsules to the dissolution medium during testing.

The stability study described here was not designed to follow degradation of diltiazem in the suspending medium. The maximum half-life for hydrolysis of diltiazem hydrochloride is about 6 months at pH 3.0 and 25°C (Chafetz and Shah, 1991). This is obviously not enough for the shelf-life of a commercial suspension (usually 2–3 years). The use of a sparingly soluble salt should improve the stability of diltiazem in aqueous media, since only a small amount of drug will be in solution at any time. In practice, the in vitro release profiles of microcapsules are correlated with bioavailability studies and differently releasing microcapsules are mixed together to obtain a desirable in vivo release profile. However, the bioavailability studies were beyond the scope of this work.

Acknowledgments

Diltiazem hydrochloride used in the study was donated by Marion Merrell Dow Inc. (Kansas City, MO). This work was supported by funds from the Center for Pharmaceutical Technology and Marion Merrell Dow Inc.

References

Amsel, L.P., Hinsvark, O.N., Rotenberg, K. and Sheumaker, J.L., Recent advances in sustained-release technology using ion-exchange polymers. *Pharm. Technol.*, 8 (1984) 28–48.

Babay, D., Hoffman, A. and Benita, S., Design and release kinetic pattern evaluation of indomethacin microspheres intended for oral administration. *Biomaterials*, 9 (1988) 482–488.

Cavallito, C.J. and Jewell, R., Modification of rates of gastrointestinal absorption of drugs: I. Amines. *J. Pharm. Sci.*, 47 (1958) 165–168.

Chafetz, L. and Shah, K.P., Stability of diltiazem in acid solution. *J. Pharm. Sci.*, 80 (1991) 171–172.

Chang, R.-K., Formulation approaches for sustained-release oral suspensions. *Pharm. Technol.*, 16 (1992) 134–136.

Dalal, P.S. and Narurkar, M.M., In vitro and In vivo evaluation of sustained release suspensions of ibuprofen. *Int. J. Pharm.*, 73 (1991) 157–162.

Davis, S.S., Illum, L., Triccas, I.M. and Winchcomb, K.N., The simultaneous degradation and sorption of diltiazem in aqueous solution. *Int. J. Pharm.*, 30 (1986) 29–33.

Kawashima, Y., Iwamoto, T., Niwa, T., Takeuchi, H. and Itoh, Y., Preparation and characterization of a new controlled release ibuprofen suspension for improving suspendability. *Int. J. Pharm.*, 75 (1991) 25–36.

Laakso, R., Kristofferson, E. and Marvola, M., Bi-exponential first order release kinetics of indomethacin from tablets containing polysorbate 80. *Int. J. Pharm.*, 19 (1984) 35–42.

Malamataris, S. and Avgerinos, A., Controlled release indomethacin microspheres prepared using an emulsion solvent-diffusion technique. *Int. J. Pharm.*, 62 (1990) 105–111.

Park, K., Wood, R. and Robinson, J., Oral controlled release systems. In Langer, R.S. and Wise, D.L. (Eds), *Medical Applications of Controlled Release*, Vol. I, CRC Press, FL, 1984, pp. 159–201.

Pongpaibul, Y., Sayed, H. and Whitworth, C.W., Preparation and evaluation of a long acting liquid antitussive product. *Drug Dev. Ind. Pharm.*, 16 (1990) 935–943.

Sprockel, O.L. and Price, J.C., Evaluation of sustained release aqueous suspensions containing microencapsulated drug-resin complexes. *Drug Dev. Ind. Pharm.*, 15 (1989) 1275–1287.

Won, C.M. and Iula, A.K., Kinetics of hydrolysis of diltiazem. *Int. J. Pharm.*, 79 (1992) 183–190.