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Release profile comparison and stability of diltiazem–resin microcapsules in sustained release suspensions

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Abstract

A sustained release suspension of diltiazem, a short half-life calcium channel blocker, was developed to reduce frequency of drug administration, ease of dose adjustment and improve patient compliance. In this study, the sustained release of diltiazem was obtained by complexing the drug with Dowex® 50W×4 and Dowex® 50W×8, strong cationic exchange resins with 4% and 8% degree of cross-linking, respectively. The diltiazem–Dowex® 50W×4 complexes provided the highest drug release and were subsequently used to prepare the microcapsules by emulsion–solvent evaporation method, using 0.75–5.00% cellulose acetate butyrate (CAB) in methylene chloride as a coating solution. As the concentration of CAB increased, the size of microcapsule increased and the drug release from the microcapsule was retarded. From release profile comparison using f_1 and f_2 factors, it was found that the microcapsules coated with 1.75% CAB provided a release profile equivalent to the commercial product of diltiazem sustained release capsule, Herbesser® 90SR. Furthermore, sustained release suspensions of the diltiazem microcapsules were formulated with the use of 0.8% sodium carboxymethylcellulose or 0.4% xanthan gum as a suspending agent. The suspension of 0.4% xanthan gum showed superior in physical appearance after 120-day storage at 30 and 45 °C. In addition, all sustained release suspensions possessed good stability with low drug leaching and their release profiles were unchanged when compared with the dried microcapsules for 120 days at 30 and 45 °C.

Keywords: Diltiazem; Ion-exchange resin; Emulsion–solvent evaporation; Sustained release suspension

1. Introduction

Diltiazem hydrochloride is a benzothiazepine calcium channel blocker. It is widely used in the treatment of angina pectoris and hypertension (Buckley et al., 1990), especially in children and elderly patients (Montamat and Abernety, 1989; Flynn and Pasko, 2000). The drug has a relatively short half-life (3–5 h) and is usually administered 3–4 times daily in the form of an immediate release formulation (Buckley et al., 1990). A sustained release formulation may be necessary to reduce the frequency of the drug administration and thus improve patient compliance. At present, commercially available sustained release products of diltiazem are 12- and 24-h sustained release capsules for twice and once daily administration, respectively. However, sustained release diltiazem suspensions may be more desirable for pediatric and geriatric patients or patients who are unable to tolerate a solid dosage form due to the difficulty in swallowing. Moreover, liquid suspensions are more flexible in the dose adjustment (Frishman, 1993).

Ion-exchange resin as a drug carrier is one of the methods used in preparing the sustained release suspension (Pongpaibul et al., 1990; Cuna et al., 2000; Elder, 2005). The ion-exchange resin can be bound with ionizable water-soluble drug molecule to form reversible complex. The drug release from the drug–resin complex occurs by replacement of drug molecule by another ion with same charge such as sodium, potassium and chloride ions in GI tract and diffusion of drug molecule from the resin (Borodkin, 1993). Selection of suitable degree of cross-linking of resin leads to the desirable drug release profile (Burke et al., 1986; Gracia-Encina et al., 1993; Elder, 2005). In addition, coating the drug–resin beads with rate controlling membrane can modify the release rate from the drug resinates (Sprockel and Price, 1989; Pongpaibul et al., 1990; Cuna et al., 2000).

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The advantages of using ion-exchange resins as drug carriers include enable formulation of either liquid or solid sustained released dosage form, providing uniform drug absorption and reducing local irritation when compared to non-disintegration single unit dosage form, increasing stability by protecting the drug from hydrolysis and improving palatability (Raghunathan et al., 1981). More importantly, the ionic complex offers an ability to prevent the diffusion of drug when suspended in a non-ionic medium because the drug release will be promoted by the presence of completing ions (Schacht, 1983; Deasy, 1984).

The purpose of this study was to study the release of diltiazem–resin complexes to develop a sustained release suspension of diltiazem. The diltiazem–resin complexes were obtained by the reaction between diltiazem hydrochloride and strong cationic exchange resin (Dowex® 50W). After encapsulating with cellulose acetate butyrate (CAB), the microcapsules of the complexes were investigated their physicochemical properties and the drug release compared with a diltiazem sustained release capsule, Herbesser® 90SR. Additionally, a sustained release diltiazem suspension was formulated and evaluated its physical, chemical and release-rate stabilities at 30 °C, which is an average room temperature of the local studied area, and at accelerated temperature of 45 °C.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride was purchased from Enwark Exin, India. The cationic resins used were Dowex® 50W×4 and Dowex® 50W×8 (Dow Chemical, Midland, USA) and the coating polymer was cellulose acetate butyrate (Aldrich Chemical, Milwaukee, USA). Polyvinyl alcohol (Sigma Chemical, St. Louis, USA) was used as a stabilizer. The solvents were methylene chloride (Lab Scan, Ireland), acetone (J.T. Baker, Phillipsburg, USA) and acetonitrile (J.T. Baker, Phillipsburg, USA). The ingredients used in suspensions were sodium carboxymethylcellulose, SCMC (Nichirin Chemical, Japan), xanthan gum, sucrose, glycerin, 70% sorbitol, sunset yellow, methyl paraben and propyl paraben. All chemicals were pharmaceutical grade and used without further modification.

2.2. Preparation of diltiazem–resin complexes

The cationic exchange resins (Dowex® 50W×4 and Dowex® 50W×8) were purified by modifying the method described by Irwin et al. (1987). Ten grams of resins was placed in a flask and washed triplicately with 50 ml of deionized water, followed by successively washing with 95% ethanol (50 ml), 50% ethanol (50 ml) and deionized water (50 ml) to remove organic and color impurities. Consequently, the resins were activated with 60 ml of 2 M NaOH and 60 ml of 2 M HCl, respectively, and washed several times with deionized water. The activated resins were dried at 50 °C in a hot air oven for 12 h.

The preparation of diltiazem–resin complexes was performed by a batch method (Sprockel and Price, 1989). Five grams of activated resins was added with 100 ml of 15% (w/v) diltiazem HCl solution. The mixture was continuously shaken for 24 h at room temperature. The diltiazem–resin complexes were filtered through a filter paper (Whatman® No. 1, England), washed several times with deionized water and dried at 50 °C for 12 h.

2.3. Microencapsulation of diltiazem–resin complexes

Microcapsules were prepared by an emulsion–solvent evaporation method (Torres et al., 1998) with some modification. One gram of diltiazem–resin complexes was suspended in 20 ml solution of CAB in methylene chloride at different concentrations, i.e. 0.75%, 1.25%, 1.75%, 2.50% and 5.00% (w/v). Then, the mixture was emulsified in 1000 ml of 0.25% polyvinyl alcohol solution. The system was continuously stirred by a propeller stirrer at 1000 rpm for 1 h. The microcapsules were then collected by vacuum filtration, washed with 200 ml of deionized water and dried at 50 °C for 12 h.

2.4. Characterization of the microcapsules

2.4.1. Microscopic study

The microscopic appearance of the drug–resin complexes and its microcapsules was observed under scanning electron microscope (Jeol, JSM-5410 LV, Tokyo, Japan). The drug–resin complexes and their microcapsules were coated uniformly with gold after fixing the samples in individual stubs. The scanning electron microscope photomicrographs were taken at 15 kV at various magnifications appropriate to each formulation.

2.4.2. Determination of particle size and distribution

The particle size and size distribution of the microcapsules were determined by a laser diffraction particle size analyzer (Mastersizer, Marvern, UK). The particle size distribution was obtained when a laser light passed through the particles, and then diffracted the intensity in an angular distribution. The data obtained were evaluated using volume distribution diameter (d) values of 10%, 50% and 90% and Span values. The Span value which is a statistical parameter useful to evaluate the particle size distribution was calculated applying the following equation:

$$\text{Span} = \frac{d90\% - d10\%}{d50\%}$$

2.4.3. Determination of coating polymer on microcapsules

One hundred milligrams of the microcapsules was accurately weighed and washed 3 times with 10 ml of acetone in order to remove polymer coating. The remaining diltiazem–resin cores were dried at 50 °C for 12 h and weighed. The percentage of coating polymer was calculated by the following:

$$\%\text{coating polymer} = \frac{\text{microcapsule weight} - \text{dried complexes weight}}{\text{microcapsule weight}} \times 100$$

2.4.4. Quantitative analysis of diltiazem content in microcapsules

One hundred milligrams of the microcapsules was washed 3 times with 10 ml acetone and dried at 50 °C for 12 h. Then, the dried complex cores were added with 500 ml of 0.1 M HCl to elute diltiazem from the complexes while stirring with a magnetic stirrer. The eluate was decanted and replaced with the same volume of the fresh acid solution. The eluate was assayed for diltiazem concentration by UV spectrophotometry at 237 nm. The elution process was repeated until the last eluate had absorbance lower than 0.01. The sum of diltiazem content in each eluate was the total content of diltiazem in the microcapsules.

2.4.5. Determination of in vitro drug release

The release of diltiazem from microcapsule was carried out using USP 24 dissolution apparatus II, paddle (USP 24, 2000). Dissolution media were 900 ml simulated gastric fluid (SGF) and 900 ml simulated intestinal fluid (SIF), and controlled at 37 ± 1 °C. Rotation speed was 50 ± 1 rpm. An accurate weight of the microcapsules, equivalent to 90 mg of diltiazem was added in dissolution medium while the solution was agitated using the paddle. A 5 ml of sample was collected and replaced with fresh medium at appropriate interval. An absorbance of collected sample was measured by UV spectrophotometry at 237 nm.

2.5. Formulation of sustained release suspension of diltiazem microcapsules

To formulate a stable suspension, 0.8% (w/v) SCMC or 0.4% (w/v) xanthan gum was evaluated to use as a suspending agent. Diltiazem–resin complex microcapsules (equivalent to diltiazem HCl 5.90 mg/5 ml) were dispersed in 10 ml glycerin as a wetting agent. The mucilage of suspending agent was poured and mixed with the wetted microcapsules. Syrup USP 30 ml, 70% sorbitol 10 ml and paraben concentrate 1 ml were added consecutively. Finally, the suspension volume was adjusted to 100 ml with deionized water and kept in the tight-light resistant container. The prepared suspension was kept at 30 and 45 °C and evaluated for physical properties after 30 days. The formulation with optimum physical properties was selected to prepare a favored suspension with the addition of sunset yellow and orange essence.

2.6. Stability studies of sustained release suspension

All prepared suspensions were kept at 30 and 45 °C and evaluated for their physical and chemical properties including pH, sedimentation volume, redispersibility, viscosity, drug leaching, drug content and *in vitro* drug release every 30 days for 120 days.

2.6.1. pH

The pH of prepared suspension was measured by using a pH meter (Acumet AB15, Fisher Scientific).

2.6.2. Sedimentation volume

Sedimentation volume of suspension was determined by placing 15 ml of suspension into a 20-ml test tube. The sedimentation volume was the ratio of the final volume of sediment to original volume of the suspension before settling (Mathews and Rhodes, 1968).

2.6.3. Redispersibility

Redispersibility of the settled suspension was evaluated after testing for sedimentation volume by rotating in screw-capped test tube 360° at 20 rpm. The number of revolution was recorded when the suspension restored to homogeneity (Mathews and Rhodes, 1968).

2.6.4. Viscosity

Viscosity of suspension was determined by a cone and plate viscometer (Haake VT500, Germany). The temperature was controlled at 30 ± 1 °C and the viscosity was determined at 50 rpm.

2.6.5. Drug leaching and drug content

Five milliliters of the homogeneous suspension was centrifuged at 3000 rpm for 10 min until the microcapsules were separated. A clear supernatant was transferred to a 25 ml volumetric flask. The microcapsules in test tube were washed 3 times with a 5 ml portion of deionized water. All solutions and the supernatant were mixed in a 25 ml volumetric flask and adjusted to volume with deionized water. The content of diltiazem was assayed by HPLC spectroscopy.

The remaining microcapsules were washed 3 times with a 5-ml portion of acetone to remove the coating polymer. The drug–resin cores were transferred into a 500 ml volumetric flask. Five hundred milliliters of 0.1 M HCl was added to elute diltiazem from the resinates while stirring with magnetic stirrer. The elute was decanted and replaced with the same volume of fresh solution. The pool of each eluate was appropriately diluted and assayed by HPLC spectroscopy.

2.6.6. Determination of in vitro drug release

The release of diltiazem from prepared suspension was determined using the same procedure as described previously. Five milliliters of uniformly dispersed suspension was taken and placed directly into a dissolution vessel. Then, the solution was agitated and withdrawn at predetermined interval to analyze for drug release by HPLC spectroscopy.

2.6.7. Analysis of diltiazem by HPLC method

An analysis method of diltiazem by HPLC was followed diltiazem hydrochloride extended release USP 24 monograph (USP 24, 2000) with slight modification. The mobile phase was 50:50 v/v acetonitrile and pH 7.4 phosphate buffer solution. The HPLC chromatography was equipped with Column ODR, 5 μm, 4.6 mm × 250 mm (Chrompack® C_{18}, The Netherlands) and connected with a 237 nm ultraviolet detector. The flow rate of mobile phase was monitored at 1.0 ml/min and an injection volume was 20 μl. The experiment was performed at an ambient temperature. Quantitative was achieved by measuring the peak area of diltiazem. Prior to the analysis, the HPLC system was validated for precision and accuracy of the procedure.

3. Results and discussion

3.1. Preparation of diltiazem–resin microcapsules

The ion-exchange resins used in this study were Dowex® 50W×4 and Dowex® 50W×8 which are strong cationic ion-exchange resins consisting of sulfonic acids attached to an insoluble polystyrene divinylbenzene copolymer. The degree of cross-linking is controlled by the percent of divinylbenzene in the copolymer. Dowex® 50W×4 and Dowex® 50W×8 have 4% and 8% degree of divinylbenzene in copolymer, respectively. Two methods have been reported for preparation of drug–resin complexes, known as a column method and a batch method (Deasy, 1984; Borodkin, 1993). In the first method, highly concentrated drug solution is passed through a column of resin particles. This procedure provides maximum potency and efficiency and is suitable for large particle resins. The second method is performed by agitating the drug solution with quantity of resin particles until equilibrium is established. The later procedure was used to prepare diltiazem–resin complexes in this study because of simpler, quicker and more suitable for very fine particles.

Diltiazem HCl is highly soluble in water having solubility of 56.6 g/100 ml (Pool, 1996). The dissolved diltiazem HCl exists in the protonated drug ions which can displace the hydrogen counter-ion (H^+) at the sulfonic acid functional groups on the ion-exchange resin particle. The ion-exchange process in the preparation can be illustrated as follows:

$$\text{Re–SO}_3^-\text{H}^+ + \text{diltiazem}^+ \rightarrow \text{Re–SO}_3^-\text{diltiazem}^+ + \text{H}^+$$

where Re is an insoluble portion of resin and diltiazem$^+$ is diltiazem ion.

In the preliminary study, the equilibrium times of diltiazem–resin complex formation for Dowex® 50W×4 and Dowex® 50W×8 were found to be 10 and 12 h, respectively (data not shown). From the result, it can be concluded that the diltiazem–resin exchange process depended upon the degree of cross-linking of resin. The lower degree of cross-linking resin (Dowex® 50W×4) reached an equilibrium faster than the higher one (Dowex® 50W×8).

The content of diltiazem in the complexes was analyzed to be 67.26% and 61.21% for Dowex® 50W×4 and Dowex® 50W×8, respectively. The result shows that the lower degree of cross-linking resulted in the higher content of diltiazem loaded ($p < 0.05$). This may be due to the fact that higher degree of cross-linking resins have a tighter pore structure and smaller in pore size which prevent access of the protonated drug molecule to the ionic site with in the resin particle (Irwin et al., 1987). The results correspond with the report by Burke et al. (1986) which showed that the content of propanolol hydrochloride decreased with increasing degree of cross-linking of resin.

The release profiles of diltiazem–resin complexes in SGF and SIF are shown in Fig. 1. Dowex® 50W×4 provided faster release of diltiazem than Dowex® 50W×8 in both dissolution media. The drug release from Dowex® 50W×4 in SGF and SIF reached equilibrium at approximately 180 and 300 min, respectively. In contrast, the diltiazem release from Dowex® 50W×8 did not reach equilibrium at the experimental period (Fig. 1). The higher degree of cross-linking resins showed slower release of diltiazem. This may involve the swelling properties of the resin because the higher degree of cross-linking resins swell less than the lower one and hence are more resistant to diffusion of drug molecule throughout the resin particle (Irwin et al., 1987). However, the release of diltiazem from the same degree of cross-linking resins in SGF and SIF was not significantly different ($p > 0.05$), indicating that there was no influence of the dissolution medium over the release of diltiazem–resin complexes.

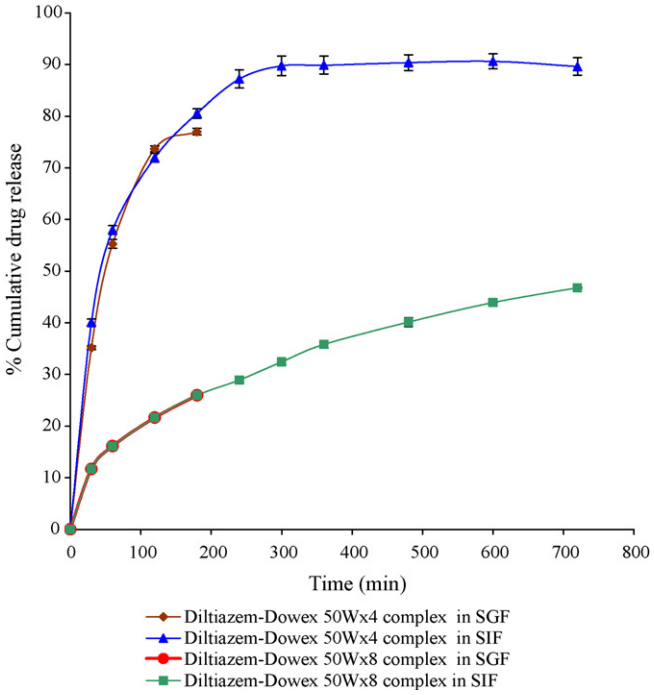

Fig. 1. Release profiles of diltiazem from the diltiazem–resin complexes prepared by using different degrees of cross-linking resins in simulated gastric fluid (SGF) pH 1.2 and simulated intestinal fluid (SIF) pH 7.5.

Moreover, it was observed that the release of diltiazem from the drug–resin complexes in both dissolution media was incomplete. The maximum releases of diltiazem from Dowex® 50W×4 and Dowex® 50W×8 were 77–91% and 27–47%, respectively. This may be due to an entrapment of some drug in deep pores of the resin matrix, resulted in difficulty of drug release into the dissolution medium (Irwin et al., 1987). Several previous studies reported similar results. For instance, Raghunathan et al. (1981) reported that only 80% phenylpropanolamine released in 0.1N HCl when the drug was complexed with Amberlite® IRP-69. Burke et al. (1986) found that only 50% of propanolol hydrochloride released from Dowex® 50W and Torres et al. (1990) showed that about 40–60% fluorescein could release which depended upon degree of cross-linking of resin. From the above results, the diltiazem–resin complex with Dowex® 50W×4 was selected for encapsulation because of the higher drug release.

Table 1
Particle size analysis of the diltiazem–Dowex® 50W×4 complex and its microcapsules coated with different concentrations of cellulose acetate butyrate

Particles	Diameters at different percentiles ± S.D. (μm)			Mean diameter (μm)	Span
	10	50	90		
Uncoated diltiazem–Dowex® 50W×4 complex	73.55 ± 1.25	121.65 ± 1.38	234.20 ± 1.85	135.95 ± 7.32	1.32
Diltiazem–Dowex® 50W×4 coated with 0.75% CAB[a]	72.33 ± 1.65	126.88 ± 0.98	236.79 ± 1.98	145.24 ± 13.26	1.30
Diltiazem–Dowex® 50W×4 coated with 1.25% CAB[a]	66.36 ± 1.95	135.31 ± 1.75	257.88 ± 2.58	157.59 ± 18.05	1.42
Diltiazem–Dowex® 50W×4 coated with 1.75% CAB[a]	98.93 ± 1.58	187.03 ± 3.32	321.25 ± 2.22	199.09 ± 22.19	1.19
Diltiazem–Dowex® 50W×4 coated with 2.50% CAB[a]	119.27 ± 2.17	237.32 ± 1.64	352.92 ± 1.86	225.46 ± 29.43	0.98
Diltiazem–Dowex® 50W×4 coated with 5.00% CAB[a]	170.93 ± 2.08	301.46 ± 2.38	478.02 ± 3.72	312.27 ± 45.61	1.02

[a] Cellulose acetate butyrate.

3.2. Characterization of diltiazem–resin microcapsules

3.2.1. Size and size distribution

The particle size and particle size distribution of the diltiazem–Dowex® 50W×4 complex and its microcapsules prepared by using different concentrations of CAB were determined by a laser diffraction particle size analyzer. The mean diameter and the Span values are presented in Table 1. The particle sizes of the microcapsules were in the range of 145–300 μm. The Span values of all microcapsules were relatively low, indicating narrow size distribution. In addition, the percentage of the coating material was analyzed to be 4.92%, 8.64%, 12.83%, 22.87% and 31.19% for the microcapsules coated with 0.75%, 1.25%, 1.75%, 2.50% and 5.00% (w/v) CAB, respectively. Therefore, the percentage of coating polymer on microcapsule increased with increasing the concentration of CAB in the coating solution, leading to an increase of the particle size of the microcapsules. This result is in agreement with the study by Torres et al. (1998) who reported that the particle size of terbutaline–resin complex microcapsules increased with increasing concentration of the coating polymer.

3.2.2. Morphology of the microcapsules

The scanning electron micrographs of the microcapsules are shown in Fig. 2. The lower concentrations of CAB (0.75–1.75%, w/v) tended to give the separated microcapsules with smooth and non-porous surface whereas the higher concentrations (2.50–5.00%, w/v) resulted in rough surface microcapsules with aggregation caused by the deposition of excessive coating which formed a bridge between the microcapsules. When the coating polymer concentration increased, the viscosity also increased and dispersion of drug–resin complex particles before the coating polymer deposition became more difficult, thus producing more aggregated microcapsules and less homogeneous in size distribution (Torres et al., 1998). However, the aggregation was observed only under the scanning electron microscope but not by visual observation.

3.2.3. Drug content and in vitro drug release from the microcapsules

The diltiazem contents in all microcapsules were quantified to be in the range of 45.33–63.02%, depending on the concentration of the coating polymer. As the concentration of CAB increased, the drug contents in the microcapsules decreased. Nevertheless, the diltiazem microcapsules with high drug contents could be achieved in this study.

The release profiles of the diltiazem–Dowex® 50W×4 microcapsules prepared with different concentrations of coating polymer in SGF and SIF are presented in Fig. 3. Form the results, the rate of diltiazem released from uncoated diltiazem–Dowex® 50W×4 complexes was relatively rapid. After encapsulation, the release rate of diltiazem from microcapsule was decreased. The release of diltiazem from the microcapsule prepared using 0.75%, 1.25%, 1.75%, 2.50% and 5.00% (w/v) CAB solutions reached 53.87%, 42.68%, 30.56%, 15.75% and 2.23%, respectively, at 3 h in SGF, and 87.94%, 85.48%, 73.15%, 34.00% and 4.84%, respectively, at 12 h in SIF. The results show that the high concentration of the coating solution resulted in more sustained release pattern.

It had been postulated that the drug release of the drug–resin complex and its microcapsule is controlled by three possible mechanisms (Gyselinck et al., 1982), which are (1) the exchange reaction between the counter-ion and drug molecules (mass or chemical reaction control), (2) the release of drug through the porous within its particles (particle diffusion control) and (3) the release of drug across the thin layer around the particle (membrane diffusion control). However, particle diffusion control plays a major role in the release of drug from drug–resin complex and its microcapsule (Motycka and Nairn, 1979; Torres et al., 1990; Ichikawa et al., 2001). The two expressions often used for testing of particle diffusion control are Reichenberg's and Bhaskar's particle diffusion controlled models (Reichenberg, 1953; Bhaskar et al., 1986). In the first model, the expressions presented by Reichenberg (1953) are shown below:

$$Bt = -\ln(1 - F) - 0.04977 \quad \text{when} \quad F > 0.85 \tag{1}$$

$$Bt = 2\pi - \frac{\pi^2 F}{3} - 2\pi\left(1 - \frac{\pi F}{3}\right)^{1/2} \quad \text{when} \quad F \leq 0.85 \tag{2}$$

$$B = \frac{4\pi^2 D}{d_p^2} \tag{3}$$

where F is the fraction of dissolution value, d_p is the mean diameter of resin (mm), D is the diffusion coefficient or diffusivity (mm^2/min), B is the exchange rate constant (min^{-1}) and t is time (min). The value of Bt may be plotted against the experimental value of t and a straight line passing through the origin is obtained. The diffusivity can be computed by Eq. (3).

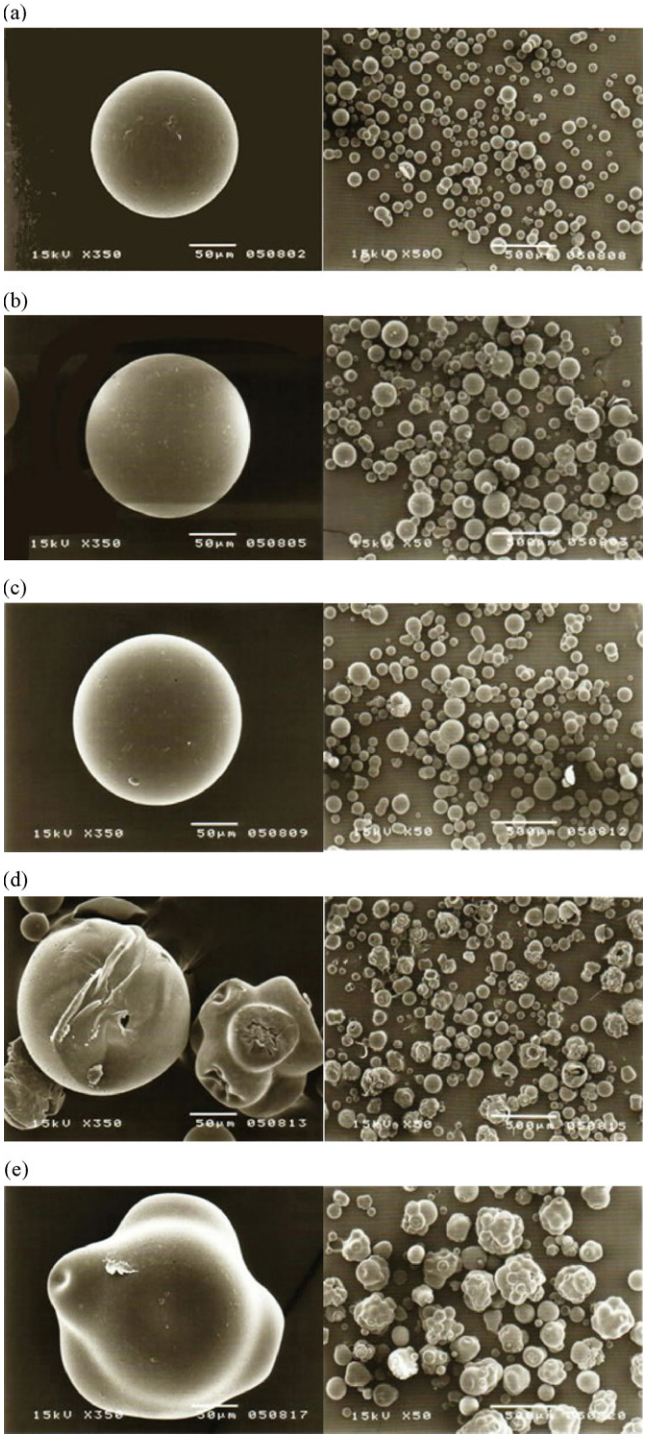

Fig. 2. Scanning electron micrographs of the diltiazem–Dowex® 50W×4 microcapsules coated with different concentrations of cellulose acetate butyrate (CAB): (a) 0.75% CAB, (b) 1.25% CAB, (c) 1.75% CAB, (d) 2.50% CAB and (e) 5.00% CAB.

The alternative method is Bhaskar expression (Bhaskar et al., 1986) which is used to evaluate particle diffusion control as shown by the following equations:

$$-\ln(1-F) = \ln\left(\frac{Q_0}{Q_t}\right) = 1.59\left(\frac{6}{d_p}\right)^{1.3} D^{0.65} t^{0.65} \quad (4)$$

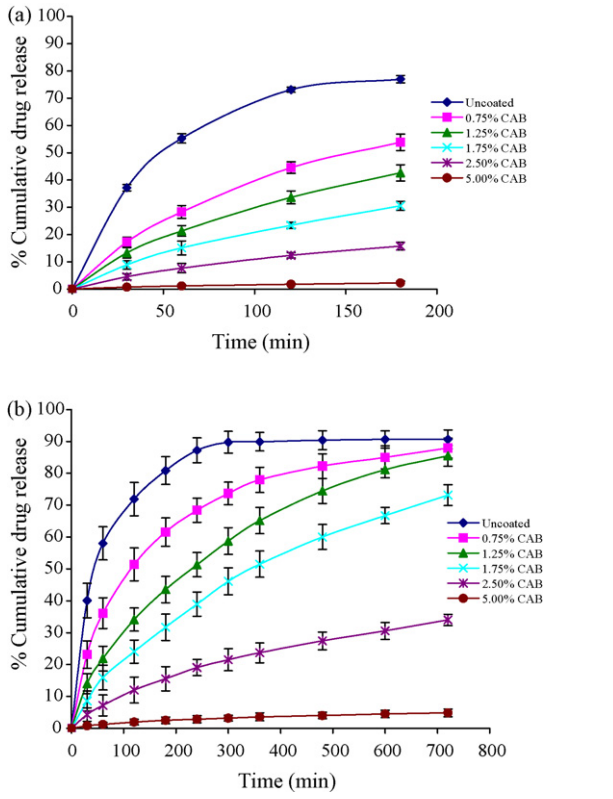

Fig. 3. Drug release profiles of the diltiazem–Dowex® 50W×4 microcapsules coated with different concentrations of cellulose acetate butyrate solution in (a) SGF pH 1.2 and (b) SIF pH 7.5 ($n = 6$).

$$D = \frac{d_p^2}{36}\left(\frac{\text{slope}}{1.59}\right)^{1/0.65} \quad (5)$$

where F is the fraction of dissolution value, d_p is the mean diameter of resin (mm), D is the diffusion coefficient or diffusivity (mm^2/min) and t is time (min). Particle diffusion control can be extrapolated by calculating from a linear relationship between $-\ln(1-F)$ and $t^{0.65}$. The slope of the straight line is used to calculate the diffusivity by Eq. (5).

Table 2 shows the release parameters of the microcapsules calculated by Reichenberg's and Bhaskar's diffusion controlled models. The release of the drug was fitted with both Reichenberg's model (the plot of Bt and t) and Bhaskar's model (a plot of $-\ln(1-F)$ and $t^{0.65}$) as indicated by a correlation coefficient >0.95. Additionally, the diffusivity values determined by both models were almost equal. Therefore, the results from Table 2 indicate that the kinetics of diltiazem release from the ion-exchange resin microcapsules was controlled by particle diffusion control or by the release of drug through the porous particles as generally found in the drug–ion-exchange resin systems (Adeyeye et al., 2005; Pongjanyakul et al., 2005a,b).

3.2.4. Release profile comparison

The release profiles of the diltiazem–resin complex microcapsules in SIF pH 7.5 were compared to a commercial diltiazem sustained release capsule, Herbesser® 90SR, as shown in Fig. 4. Moore and Flanner (1996) described two equations for dissolution profile comparison which were a difference factor, f_1

Table 2
Release parameters of the diltiazem–Dowex® 50W×4 complex and its microcapsules prepared using different concentrations of cellulose acetate butyrate in the coating solution

Concentration of CAB in the coating solution (%, w/v)	Reichenberg's model			Bhaskar's model	
	Exchange rate constant (min^{-1})	Diffusivity (cm^2/s)	r^2	Diffusivity (cm^2/s)	r^2
Uncoated diltiazem–Dowex® 50W×4	6.30×10^{-3}	2.07×10^{-8}	0.9928	2.15×10^{-8}	0.9982
0.75	2.46×10^{-3}	8.08×10^{-9}	0.9743	8.39×10^{-9}	0.9915
1.25	1.84×10^{-3}	6.04×10^{-9}	0.9698	5.80×10^{-9}	0.9686
1.75	1.03×10^{-3}	3.38×10^{-9}	0.9557	3.16×10^{-9}	0.9986
2.50	1.60×10^{-4}	2.56×10^{-10}	0.9887	6.38×10^{-10}	0.9985
5.00	2.90×10^{-6}	9.53×10^{-12}	0.9960	2.75×10^{-11}	0.9776

(Eq. (6)) and a similarity factor, f_2 (Eq. (7)). The US-FDA endorses both equations as acceptable methods for dissolution profile comparison, although the similarity factor, f_2 is preferred (O'Hara et al., 1998; Peh and Wong, 2000). The equations for calculating the two factors are as follows:

$$f_1\,(\%) = \left\{ \frac{\sum_{t=1}^{n} |R_t - T|}{\sum_{t=1}^{n} R_t} \right\} \times 100 \qquad (6)$$

$$f_2 = 50 \log_{10} \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \qquad (7)$$

where n is the number of dissolution time points; R_t and T_t are the reference and test release values at time t, respectively; w_t is an optional weight factor. Values of f_1 between 0 and 15 or f_2 between 50 and 100 ensure sameness or equivalent of the two dissolution profiles.

The release profile comparison factors, f_1 and f_2, between Herbesser® 90SR and diltiazem–resin complex microcapsules calculated from Eqs. (6) and (7) are shown in Table 3. The result shows that only the microcapsules coated with 1.75% CAB showed f_1 value between 0 and 15, and f_2 between 50 and 100, indicating the drug release profile equivalent to the commercial product. Therefore, these microcapsules were selected for formulation studies of sustained release suspension.

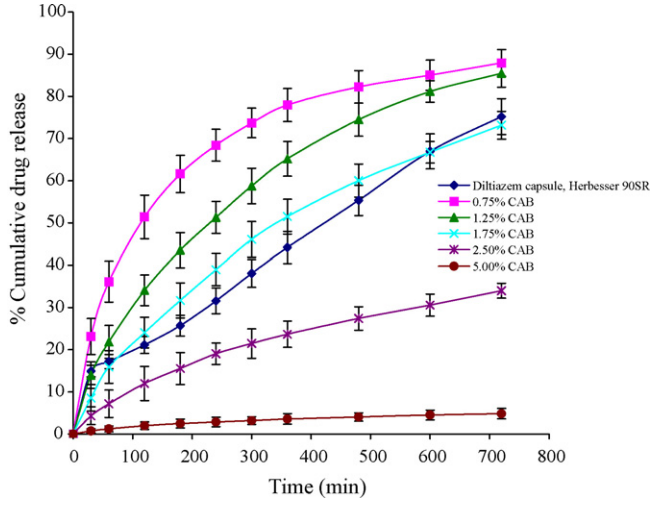

Fig. 4. Release profiles of diltiazem sustained release capsules and diltiazem–resin complex microcapsules prepared by using different concentrations of coating solution in SIF pH 7.5 ($n = 6$).

According to the diltiazem extended release capsules monograph in USP 24 (2000), the percentage of the labeled amount of diltiazem dissolved is between 10% and 25% at 3 h, between 45% and 85% at 9 h and not less than 70% at 12 h. The release data show that the microcapsules coated with 1.75% CAB conformed to the diltiazem HCl extended release capsules monograph.

3.3. Formulation of diltiazem–resin microcapsule suspension

The microcapsule suspension was formulated according to two major considerations in which the system should contain low ionic strength vehicle consisted of low ionized additive so as to avoid the premature drug release (Irwin et al., 1987; Sprockel et al., 1989; Pongpaibul et al., 1990; Plaizier-Vercammen, 1992; Borodkin, 1993), and the particle size of microcapsule should be less than 200 μm in diameter to protect a gritty sensation during administration (Amsel et al., 1984; Irwin et al., 1987; Pongpaibul et al., 1990; Elder, 2005). Besides, the compositions used in the formulation should have the same charge as the resins so that they would not bind onto the resins. In the preliminary study, it was found that 0.8% (w/v) SCMC or 0.4% (w/v) xanthan gum was a suitable suspending agent used to prepare a stable suspension.

3.3.1. Physical properties of diltiazem–resin microcapsule suspensions

Physical properties of the microcapsule suspensions of 0.8% (w/v) SCMC and 0.4% (w/v) xanthan gum at different storage times are presented in Tables 4 and 5, respectively. The pH of both microcapsule suspensions slightly increased from initial time to 30-day storage, and then remained constant after 30 days. This may be due to the diltiazem leaching from diltiazem–resin complexes by replacing with trace amount of cationic ion from the ingredients in the suspension, i.e. sunset yellow at the beginning of storage.

The sedimentation volume of suspensions using 0.8% SCMC gradually decreased to about 0.2 at 90 days. After 90 days, the sedimentation volume was relatively constant, the microcapsules were settled and formed caking suspension.

Table 3
Release profile comparison data and comparison factors, f_1 and f_2, between the commercial product (Herbesser® 90SR) and the diltiazem–Dowex® 50W×4 complex microcapsules

Time (min)	Commercial product, R_t	Microcapsules prepared using different concentration of cellulose acetate butyrate in coating solution (%, w/v)														
		0.75%			1.25%			1.75%			2.50%			5.00%		
		T_t	$R_t - T_t$	$(R_t - T_t)^2$	T_t	$R_t - T_t$	$(R_t - T_t)^2$	T_t	$R_t - T_t$	$(R_t - T_t)^2$	T_t	$R_t - T_t$	$(R_t - T_t)^2$	T_t	$R_t - T_t$	$(R_t - T_t)^2$
30	14.93	23.13	8.20	67.24	14.00	0.93	0.86	8.58	6.35	40.32	4.32	10.61	112.57	0.76	14.17	200.79
60	17.19	36.13	18.94	358.72	21.88	4.69	22.00	15.90	1.29	1.66	7.18	10.01	100.20	1.21	15.98	255.36
120	21.15	51.42	30.27	916.27	34.09	12.94	167.44	24.06	2.91	8.47	11.99	9.16	83.91	1.97	19.18	367.87
180	25.71	61.57	35.86	1285.94	43.54	17.83	317.91	31.69	5.98	35.76	15.55	10.16	103.23	2.48	23.23	539.63
240	31.59	68.41	36.82	1355.71	51.31	19.72	388.88	38.97	7.38	54.46	19.06	12.53	157.00	2.85	28.74	825.99
300	38.08	73.69	35.61	1268.07	58.75	20.67	427.25	46.09	8.01	64.16	21.49	16.59	275.23	3.18	34.90	1218.01
360	44.19	77.94	33.75	1139.06	65.17	20.98	440.16	51.49	7.30	53.29	23.69	20.50	420.25	3.58	40.61	1649.17
480	55.33	82.26	26.93	725.22	74.49	19.16	367.11	60.04	4.71	22.18	27.42	27.91	778.97	4.03	51.30	2631.69
600	66.95	85.03	18.08	326.89	81.15	14.20	201.64	66.75	0.20	0.04	30.58	36.37	1322.7	4.52	62.43	3897.50
720	75.21	87.94	12.73	162.05	85.48	10.27	105.47	73.15	2.06	4.24	34.00	41.21	1698.2	4.84	70.37	4951.94
Sum	390.33	647.52	257.1	7605.19	529.86	141.3	2438.7	416.72	46.19	284.60	195.28	195.05	5052.3	29.42	360.9	16537.9
f_1			65.89			36.22			11.83			49.97			92.46	
f_2			27.96			40.28			63.27			32.29			19.53	

Table 4
Physical properties of the formulated microcapsule suspensions using 0.8% sodium carboxymethylcellulose as a suspending agent ($n = 3$)

Time (day)	Physical properties													
	Appearance		pH (S.D.)		Sedimentation volume (S.D.)		Redispersibility value (S.D.)		Viscosity (Pa s) (S.D.)		%Drug content (S.D.)		%Drug leaching (S.D.)	
	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C
Initial	Orange and transparent medium	Orange and transparent medium	4.97 (0.32)	4.97 (0.32)	1.00 (0.00)	1.00 (0.00)	ND[a]	ND[a]	22.93 (1.02)	22.93 (1.02)	98.64 (0.37)	98.64 (0.37)	0.37 (0.09)	0.37 (0.09)
30	Unchanged	Unchanged	5.15 (0.22)	5.18 (0.41)	0.52 (0.02)	0.54 (0.01)	36.00 (2.65)	32.67 (3.21)	26.28 (1.34)	26.84 (1.27)	98.21 (0.58)	98.07 (0.57)	0.54 (0.05)	0.57 (0.06)
60	Unchanged	Unchanged	5.12 (0.57)	5.19 (0.68)	0.34 (0.03)	0.36 (0.01)	48.67 (1.53)	50.67 (1.53)	25.96 (0.98)	26.92 (1.15)	98.84 (0.35)	97.36 (0.40)	1.12 (0.10)	1.37 (0.17)
90	Unchanged	Unchanged	5.14 (0.40)	5.24 (0.34)	0.23 (0.01)	0.21 (0.01)	60.35 (1.15)	61.67 (2.31)	25.17 (0.88)	25.42 (0.97)	97.39 (0.87)	96.16 (0.41)	1.82 (0.14)	1.93 (0.17)
120	Unchanged	Unchanged	5.09 (0.39)	5.22 (0.48)	0.24 (0.02)	0.22 (0.02)	59.33 (0.58)	61.07 (1.73)	26.35 (1.19)	25.14 (1.33)	97.27 (0.88)	95.89 (0.47)	1.96 (0.10)	2.01 (0.12)

30 and 45 °C denote the storage temperature.
[a] Not determined.

Table 5
Physical properties of the formulated microcapsule suspensions using 0.4% xanthan gum as a suspending agent ($n = 3$)

Time (day)	Physical properties												
	Appearance		pH (S.D.)		Sedimentation volume (S.D.)		Redispersibility value (S.D.)		Viscosity (Pa s) (S.D.)		%Drug content (S.D.)		%Drug leaching (S.D.)	
	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C	30 °C	45 °C
Initial	Orange and opaque medium	Orange and opaque medium	4.09 (0.22)	4.09 (0.22)	1.00 (0.00)	1.00 (0.00)	ND[a]	ND[a]	23.65 (1.87)	23.65 (1.87)	98.29 (0.32)	98.29 (0.32)	0.38 (0.04)	0.38 (0.04)
30	Unchanged	Unchanged	4.20 (0.54)	4.27 (0.63)	0.83 (0.01)	0.88 (0.03)	14.33 (2.08)	16.33 (2.31)	24.25 (1.30)	25.86 (1.21)	98.02 (0.42)	97.86 (0.45)	0.58 (0.06)	0.60 (0.03)
60	Unchanged	Unchanged	4.21 (0.23)	4.33 (0.37)	0.51 (0.02)	0.55 (0.02)	17.00 (1.73)	19.33 (1.53)	27.56 (0.84)	27.97 (1.42)	97.72 (0.27)	97.27 (0.31)	1.01 (0.10)	1.25 (0.13)
90	Unchanged	Unchanged	4.20 (0.31)	4.37 (0.21)	0.53 (0.01)	0.56 (0.02)	23.67 (1.15)	20.67 (0.58)	28.11 (0.99)	28.84 (0.77)	97.49 (0.34)	97.17 (0.27)	1.76 (0.19)	1.74 (0.43)
120	Unchanged	Unchanged	4.28 (0.11)	4.30 (0.36)	0.52 (0.01)	0.55 (0.01)	24.33 (1.53)	21.33 (2.08)	27.40 (1.36)	28.08 (1.22)	97.11 (0.36)	96.07 (0.32)	1.83 (0.06)	1.95 (0.07)

30 and 45 °C denote the storage temperature.
[a] Not determined.

This result confirmed by high values of redispersibility (~60 or more). On the other hand, the suspension using 0.4% xanthan gum possessed better sedimentation volume and redispersibility value. The sedimentation volume decreased to about 0.5 within 60 days and then remained constant throughout the study period. The redispersibility value was less than 25 for entire study period while the viscosity of both suspensions was unchanged. This may be concluded that the suspension of 0.4% xanthan gum provided better physical properties than that of 0.8% SCMC.

3.3.2. Drug content and drug leaching

The percent drug content in microcapsules and drug leaching in suspending medium are also presented in Tables 4 and 5. The results indicate that the percent diltiazem content in the microcapsules of both suspensions after storage for 120 days declined 2–3% from initial value. This may be due to the leaching of the drug from the microcapsules by replacement of trace cationic ion in the suspending medium, as previously discussed. This result is in agreement with the percent of drug leaching in suspending medium which slowly increased at the initial time of the study and became relatively constant after 90 days. From the results, it can be concluded that both formulations provided a good chemical stability at least 120-day storage at 30 and 45 °C.

3.3.3. In vitro release studies of microcapsule suspension

The release profiles of drug–ion-exchange resin microcapsules in suspensions may be affected by storage temperatures. Adeyeye et al. (2005) reported that the release of diclofenac–resin microcapsules in methylcellulose suspensions decreased with increased temperature due to polymer relaxation which sealed the drug within the matrix. In this study, the release profiles of diltiazem–resin microcapsule suspensions of 0.8% SCMC and 0.4% xanthan gum at different storage temperatures and times were observed and compared with the dried microcapsules as seen in Fig. 5. The result shows that the release profiles from the microcapsule suspensions at different storage times were almost superimposed with that from the dried microcapsules coated with 1.75% CAB. Using f_1 and f_2 from Eqs. (6) and (7) to compare the release of the suspensions and the microcapsules, it was found that f_1 values were between 0 and 15, and f_2 values were between 50 and 100 when using the dried microcapsules as a reference (Table 6). Therefore, the release profiles of microcapsule suspensions at different storage temperatures and times were equivalent to that of the dried microcapsules, leading to the conclusion that there was no influence of the storage time and temperature over the release profile of the diltiazem–resin microcapsule suspensions.

According to the US-FDA's requirements, the controlled released preparation must be absence of dose dumping (Skelly and Barr, 1987). Dose dumping can be defined as the products release drug at a grater rate than the customary amount of drug per dosing interval (Welling and Dobrinska, 1987). The *in vitro* release indicates that the diltiazem–resin microcapsule suspensions prepared in this study did not possess the dose dumping effect.

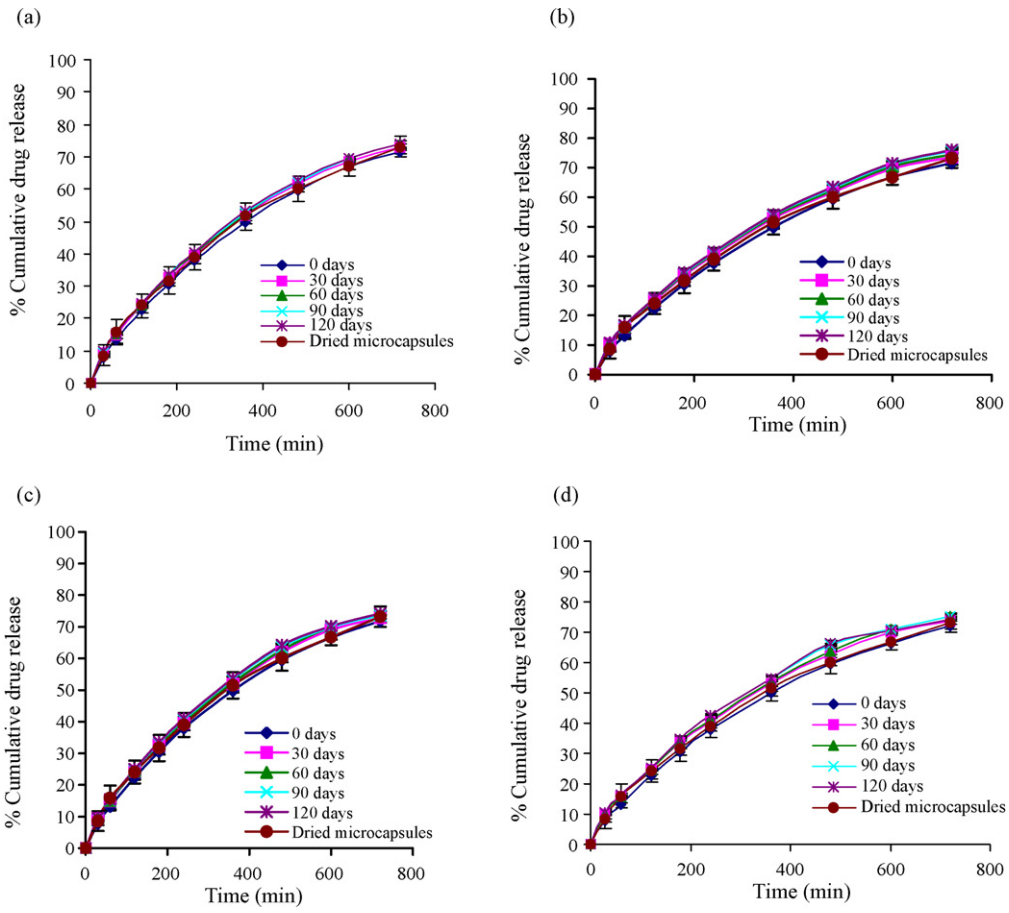

Fig. 5. Release profiles in SIF pH 7.5 of the 1.75% CAB diltiazem–Dowex® 50W×4 microcapsule suspensions of (a) 0.8% SCMC at 30 °C, (b) 0.8% SCMC at 45 °C, (c) 0.4% xanthan gum at 30 °C and (d) 0.4% xanthan gum at 45 °C compared with the dried microcapsules coated with 1.75% CAB ($n = 6$).

Table 6
Release profile comparison between the diltiazem–Dowex® 50W×4 microcapsules coated with 1.75% CAB and the developed suspensions

Formulation	Storage temperature (°C)	Factor	Storage time (day)				
			0	30	60	90	120
0.8% sodium carboxymethylcellulose suspension	30	f_1	2.95	1.93	2.76	3.15	3.56
		f_2	88.66	93.21	89.84	88.49	86.46
	45	f_1	2.95	3.30	4.60	5.88	6.38
		f_2	88.66	87.31	82.79	78.68	77.19
0.4% xanthan gum suspension	30	f_1	2.97	2.26	3.02	3.97	4.62
		f_2	88.74	91.56	87.79	83.93	81.56
	45	f_1	2.97	3.79	4.95	6.67	6.78
		f_2	88.74	84.80	80.57	74.88	74.14

4. Conclusions

The sustained release suspension of diltiazem was successfully achieved by the use of drug–resin complex core as well as the CAB coating to control the drug release. The release kinetics from the microcapsules of diltiazem-complex was founded to be particle diffusion controlled, and the release was depended mainly on the degree of cross-linking of the resin and the concentration of the coating solution. The microcapsules of low degree of cross-linking resin (Dowex® 50W×4) coated with 1.75% CAB showed a drug release profile equivalent to the commercial product of diltiazem sustained release capsule, Herbesser® 90SR. For the development of the sustained release suspensions, it was found that 0.8% SCMC and 0.4% xanthan gum were the suitable suspending agents; however, the suspension of 0.4% xanthan gum provided better physical properties. Finally, the sustained release suspensions of diltiazem developed in this study showed chemical stability and unchanged release profiles for 120 days at 30 and 45 °C.

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