Preparation and Evaluation of Cellulose Acetate Butyrate and Poly(ethylene oxide) Blend Microspheres for Gastroretentive Floating Delivery of Repaglinide

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ABSTRACT: In this study, hollow microspheres of cellulose acetate butyrate (CAB) and poly(ethylene oxide) (PEO) were prepared by emulsion–solvent evaporation method. Repaglinide was successfully encapsulated into floating microspheres. Various formulations were prepared by varying the ratio of CAB and PEO, drug loading and concentration of poly(vinyl alcohol) (PVA) solution. Encapsulation of the drug up to 95% was achieved. The microspheres tend to float over the simulated gastric media for more than 10 h. The micromeritic properties of microspheres reveal the excellent flow and good packing properties. The % buoyancy of microspheres was found to be up to 87. SEM showed that microspheres have many pores on their surfaces. Particle size ranges from 159 to 601 μm. DSC and X-RD revealed the amorphous dispersion in the polymer matrix. *In vitro* release experiments were performed in simulated gastric fluid. *In vitro* release studies indicated the dependence of release rate on the extent of drug loading and the amount of PEO in the microspheres; slow release was extended up to 12 h. The release data were fitted to an empirical equation to compute the diffusional exponent (n), which indicated that the release mechanism followed the non-Fickian trend. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 105: 2764–2771, 2007

Key words: floating drug delivery; cellulose acetate butyrate; microspheres; repaglinide; controlled release

INTRODUCTION

To develop oral drug delivery systems, it is necessary to optimize both the residence time of the system within the gastrointestinal tract (GIT) and the release rate of the drug from the system. One of the novel approaches in this area is gastroretentive delivery system.[1–3] Prolonging the gastric retention of a delivery system is sometimes desirable for achieving therapeutic benefit of drugs that are absorbed from the upper part of GIT or that are less soluble in or are degraded by the alkaline pH at the lower part of GIT.[4] Gastroretentive delivery systems are thus beneficial for such drugs in improving their bioavailability, therapeutic efficacy, and possible reduction of dose.[5,6] These systems also offer various pharmacokinetic advantages like maintenance of constant therapeutic concentrations of drug over a prolonged period of time and thus, reduce the fluctuation in therapeutic concentrations by minimizing the risk of drug resistance.

An incomplete release of the drug and shorter residence time of the dosage form in the upper GIT would lead to lower bioavailability of the drug. Therefore, prolonged gastric retention[7,8] is important in achieving control over the gastric retention time (GRT) because this helps to retain the controlled release (CR) system in the stomach for a longer time.[9] Also, this improves the bioavailability of basic drugs having poor solubility in acidic pH. Several approaches are currently used to prolong the GRT. These include floating drug delivery systems, also called hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, high-density systems, and other delayed-gastric-emptying devices. Of these, the buoyant preparation is a simple and practical approach to achieve an increased gastric residence time for the dosage form that has less density than the gastric fluid and sustained drug release.[10,11]

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TABLE I
Formulation Parameters, Encapsulation Efficiency, Volume Mean Particle Size, and *n* Values

Formulation code	CAB (wt %)	PEO (wt %)	Drug-loading (wt %)	Concentration of PVA solution (wt %)	Encapsulation efficiency (%)	Volume meanparticle size (μm)	*n*	*r*
CF	100	0	10	2	84.7	265	0.86	0.999
F1	90	10	5	1	81.5	159	0.50	0.986
F2	90	10	10	1	87.4	260	0.69	0.993
F3	90	10	20	1	93.5	398	0.77	0.992
F4	90	10	5	2	85.0	345	0.84	0.990
F5	90	10	10	2	89.4	391	0.61	0.993
F6	90	10	20	2	95.2	488	0.76	0.999
F7	80	20	5	1	71.3	471	0.63	0.992
F8	80	20	10	1	79.6	478	0.64	0.980
F9	80	20	20	1	90.1	562	0.72	0.987
F10	80	20	5	2	87.6	578	0.71	0.989
F11	80	20	10	2	89.7	590	0.62	0.988
F12	80	20	20	2	92.3	601	0.58	0.997

Polyethylene oxide (PEO) is a nontoxic and water-soluble polymer, widely used in chemical, cosmetic, and pharmaceutical industries. PEO gels produced in water can be dehydrated and the material so produced is extremely hydrophilic and possesses a good bioadhesive property.[12] Cellulose acetate butyrate (CAB) was chosen as a model hydrophobic polymer, because it has been used frequently in matrices or coating membranes of CR dosage forms.[13–15] Earlier, Park and Kim[16] have studied the phase behavior and crystallization of a PEO/CAB blend using various techniques such as DSC, SAXS, etc. The objective of this study is to prepare and evaluate the CAB and PEO blend microspheres for the gastroretentive floating drug delivery of an antidiabetic drug such as repaglinide.[17] In this study, PEO acts as a hydrophilic filler, which helps to enhance the release rate of the hydrophobic drug. Repaglinide, a meglitinide analog having very short half-life of about 1 h and a low bioavailability (50%) with a poor absorption in the upper intestinal tract was chosen as the model antidiabetic drug. Repaglinide was earlier suggested for the development of dosage forms with increased GRT.[10,11]

EXPERIMENTAL

Materials

Repaglinide was received as a gift sample from Sun Pharmaceutical Industries Limited, Mumbai, India. Poly(ethylene oxide) (PEO) of molecular weight ~ 200,000 was procured from Aldrich Chemical Company, Milwaukee, WI, USA. CAB of molecular weight ~ 35,000 was purchased from Hi Media Chemicals, Mumbai, India. Analytical reagent grade dichloromethane, Tween 80® and poly(vinyl alcohol) (PVA) of molecular weight 125,000 were all purchased from S.D. Fine Chemicals, Mumbai, India.

Methods

Preparation of microspheres

Floating microspheres of CAB and PEO were prepared by emulsion-solvent evaporation method. CAB, PEO (total quantity of polymer used was 1 g) and different amounts of drug (based on dry weight of CAB–PEO mixture) were all dissolved in 10 mL of dichloromethane (DCM). The solution was then emulsified into 100 mL of PVA solution to form o/w emulsion using a mechanical stirrer (IKA Labortechnik, Germany) at 600 rpm rotation speed at the ambient temperature for 3 h. Here, the PVA solution acts as a stabilizer. The microspheres were separated using 0.2 μm membrane filter by applying vacuum. Then, microspheres were washed 2–3 times successively with distilled water to remove the surface-adhered PVA and filtered to collect the microspheres. Different formulations were prepared by varying the amount of CAB, PEO, drug loadings and PVA concentrations. Totally 12 formulations were prepared. Formulation codes and formulation parameters are given in Table I. The structures of repaglinide, PEO and CAB are presented in Figure 1.

Encapsulation efficiency

A 10 mg of microspheres weighed accurately was dissolved in 10 mL of DCM. The resulting solution was filtered through 0.2 μm membrane filter and analyzed by UV spectrophotometer (Secomam, model Anthelie, France) at the λ_{max} value of 243 nm. Calcu-

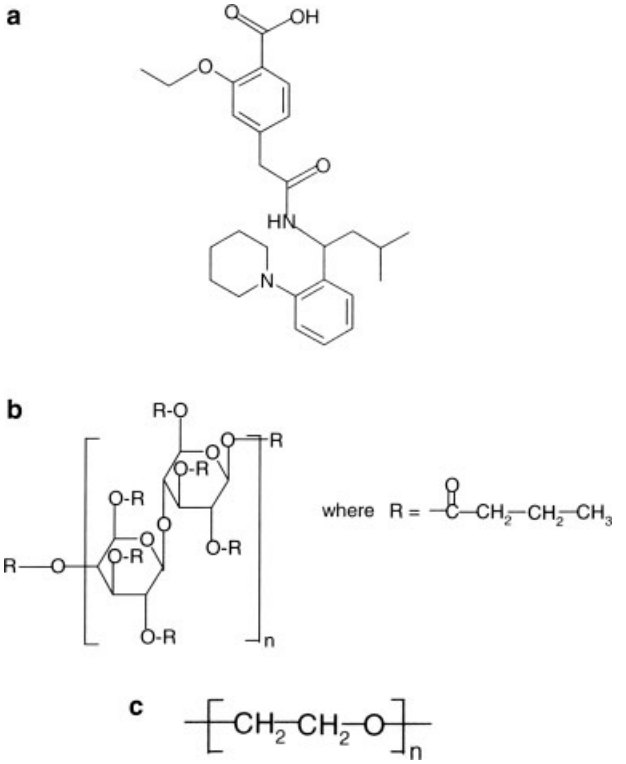

Figure 1 Chemical structures of (a) repaglinide, (b) CAB and (c) PEO.

lated drug loading and % encapsulation efficiency were calculated as:

$$\text{Calculated drug loading} = \left(\frac{\text{Amount of drug loading}}{\text{Amount of microspheres}}\right) \times 100 \quad (1)$$

$$\text{Encapsulation efficiency (\%)} = \left(\frac{\text{Calculated drug loading}}{\text{Theoretical drug loading}}\right) \times 100 \quad (2)$$

Each determination was made in triplicate. These data for various formulations are presented in Table I are the averages of triplicate measurements.

Floating behavior

About 100 mg of the floating microspheres were placed in simulated gastric fluid (SGF) (pH 1.2, 100 mL) containing 0.02% (w/v) Tween 80. The mixture was stirred at 100 rpm speed in a magnetic stirrer. After 12 h, the layer of buoyant microspheres was pipetted and separated by filtration. Microspheres in the sinking particulate layer were separated by filtration. Particles of both types were dried in an oven at 40°C for 6 h. Both the fractions of microspheres were weighed and the buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking microspheres.

$$\text{Buoyancy (\%)} = \left(\frac{W_f}{W_f + W_s}\right) \times 100 \quad (3)$$

where W_f and W_s are the weights of floating and settled microspheres, respectively. All the determinations were made in triplicate.

Micromeritic properties

Microspheres were characterized for their micromeritic properties such as true density, tapped density, compressibility index, and flow properties. The mechanical shaker was used to determine the tapped density and % compressibility index as follows:

$$\text{Tapped density } (P_p) = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}} \quad (4)$$

$$\text{Compressibility index (\%)} = \left[1 - \frac{V}{Vo}\right] \times 100 \quad (5)$$

Here, V and Vo are volumes of the sample after and before the standard tapping, respectively. True density was determined by the liquid displacement method (isopropanol was used as the displacing liquid). Porosity (ε) was calculated using the equation:

$$\varepsilon = \left(1 - \frac{P_p}{P_t}\right) \times 100 \quad (6)$$

where P_t and P_p are true density and tapped density, respectively. Angle of repose, θ of the microspheres, which measures the resistance to particle flow was determined by a fixed funnel method and calculated as:

$$\tan\,\theta = \frac{2H}{D} \quad (7)$$

where H is the free standing height of the microspheres heap and D is diameter of the heap. All experiments were performed in triplicate for each sample and the average values were considered for data interpretation. These data for micromeritic properties are given in Table II.

Particle size measurements

Particle size and size distributions were measured using laser light scattering technique (Mastersizer-2000, Malvern, UK). Particle size was measured using the dry sample adapter to record the volume

TABLE II
Micromeritic Properties of Floating Microspheres

Formulation code	CAB (wt %)	PEO (wt %)	True density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Porosity (%)	Angle of repose (θ)	Buoyancy (%)
CF	100	0	0.780 ± 0.04	0.421 ± 0.02	12.35 ± 0.19	46.05 ± 1.8	28.64 ± 1.37°	70
F1	90	10	0.783 ± 0.03	0.407 ± 0.01	15.04 ± 0.48	47.91 ± 1.3	31.15 ± 1.95°	81
F2	90	10	0.787 ± 0.02	0.513 ± 0.06	13.0 ± 0.85	34.82 ± 1.1	30.70 ± 2.3°	77
F3	90	10	0.790 ± 0.04	0.561 ± 0.04	11.43 ± 0.67	29.07 ± 1.7	27.0 ± 1.05°	72
F4	90	10	0.784 ± 0.01	0.416 ± 0.01	14.12 ± 0.35	46.94 ± 1.8	40.04 ± 1.21°	85
F5	90	10	0.786 ± 0.03	0.498 ± 0.04	13.46 ± 0.58	36.64 ± 2.4	36.25 ± 2.04°	81
F6	90	10	0.789 ± 0.03	0.553 ± 0.05	11.37 ± 0.22	29.91 ± 1.3	31.84 ± 1.73°	78
F7	80	20	0.796 ± 0.04	0.438 ± 0.03	12.50 ± 0.28	37.23 ± 2.2	33.06 ± 2.44°	85
F8	80	20	0.805 ± 0.08	0.500 ± 0.03	11.76 ± 0.36	39.11 ± 3.2	31.43 ± 1.25°	84
F9	80	20	0.821 ± 0.05	0.527 ± 0.02	5.71 ± 0.18	46.73 ± 3.4	29.1 ± 1.1°	82
F10	80	20	0.798 ± 0.04	0.404 ± 0.06	12.23 ± 0.84	49.37 ± 1.7	36.15 ± 1.84°	89
F11	80	20	0.802 ± 0.03	0.471 ± 0.03	10.87 ± 0.56	41.27 ± 2.7	34.62 ± 2.23°	86
F12	80	20	0.824 ± 0.05	0.512 ± 0.02	6.03 ± 0.31	37.86 ± 1.6	30.87 ± 1.16°	84

mean diameter (V_d). The data of particle size distribution are given in Table I.

Differential scanning calorimetric study

Differential scanning calorimetry (DSC) (Rheometric Scientific, UK) was performed on drug-loaded microspheres, placebo microspheres, and pure repaglinide. Samples were heated from 25°C to 400°C at the rate of 10°C/min in a nitrogen atmosphere (flow rate of 20 mL/min).

X-ray diffraction study

Crystallinity of repaglinide after encapsulation was evaluated by X-ray diffraction measurements recorded for placebo microspheres, drug-loaded microspheres and pure drug using X-ray diffractometer (x-Pert, Philips, UK). Scanning was done up to 2θ of 50°.

Scanning electron microscopic study

SEM photographs of the floating microspheres loaded with drug were taken. Microspheres were sputtered with gold to make them conducting and placed on a copper stub. Scanning was done using JEOL model JSM-840A, Japan instrument.

In vitro release studies

In vitro drug release from different formulations of floating microspheres was investigated in SGF containing 0.02% (w/v) Tween-80 as per the procedures reported earlier.[10] These experiments were performed using the fully automated dissolution tester, coupled with a UV system (Logan Instruments, Model D 800, NJ), equipped with six baskets at the stirring speed of 100 rpm. A weighed quantity of each sample was placed in 500 mL of dissolution medium maintained at 37°C. The instrument automatically measures the concentration of the drug released at particular time intervals by UV spectrophotometer coupled with flow-through cells attached to the instrument. It then puts the solution automatically back into the dissolution bowl. The repaglinide concentration was determined spectrophotometrically at the fixed λ_{max} of 243 nm. These studies were performed in triplicate for each sample, but average values were considered in data analysis.

RESULTS AND DISCUSSION

Preparation and characterization of microspheres

In the present study, CAB and PEO blend microspheres for gastroretentive floating drug delivery of an antidiabetic drug such as repaglinide were prepared by emulsion-solvent evaporation technique. A solution of CAB, PEO, and repaglinide in DCM was poured into an agitated aqueous solution of PVA. The subsequent slow evaporation of DCM leads to the formation of internal cavities within the microspheres. Incorporation of PEO into the formulation produced a porous structure to the microspheres. During the formation of microspheres, PEO present on the surface dissolved in aqueous phase, resulting in the formation of pores on the surface of microspheres. These pores produce a buoyancy effect for the microspheres. The PEO present inside the matrix acts as a hydrophilic filler, thus enhancing the release of the drug. The % encapsulation efficiency of all the formulations varied from 71.3 to 95.2. As the drug-loading in the matrix increases, there will be an increase in % encapsulation efficiency because of the hydrophobic nature of the drug, which got

retained during the microsphere formation. The % encapsulation efficiency was also found to be higher in case of formulations containing 10 wt % PEO as compared to 20 wt % PEO. This could be due to the more hydrophilic nature of PEO, thereby leading to the leaching out of more of drug particles during the microsphere preparation. The % encapsulation efficiency data are shown in Table I.

Floating properties of the microspheres were studied by placing in 0.1*N* HCl containing 0.02% (w/v) Tween 80 surfactant to simulate the gastric conditions. However, the use of 0.02% Tween 80 was to account for the wetting effect of natural surface-active agents, such as phospholipids in GIT. Despite the solution being stirred for more than 10 h, hollow microspheres still floated, indicating that microspheres have excellent buoyancy effect. Density values of the microspheres (< 1.000 g/cm^3) were less than that of the gastric fluid (~ 1.004 g/cm^3), further supporting their floating behavior. The *in vitro* floating test was conducted on drug-loaded microspheres. In all the formulations, more than 70% of microspheres were floated. The control formulation (CF) showed 70% floatability. Formulations containing 10 wt % PEO showed less floatability than those containing 20 wt % PEO. For instance, formulations F1, F2, and F3 showed less buoyancy effects compared to formulations F7, F8, and F9 and similar trends were observed for formulations F4, F5, and F6 as compared to F10, F11, and F12. This could be due to the fact that as the content of PEO in the matrix increases, there is an increase in the hydrophilicity of the matrix, leading to the dissolution of more PEO from the microspheres. The dissolution of PEO would produce more pores on the surface of the microspheres. Also, buoyancy effect decreased as the drug-loading of the matrix was increased from 5 to 20 wt %. Again, this may be due to an increase in the density of microspheres at higher drug-loadings. These results are shown in Table II.

Micromeritic properties

Usually, the microparticulate drug delivery systems are formulated as single-unit dosage forms in the form of tablets or capsules. Such microparticulate systems should possess the required micromeritic properties. The flow property of hollow microspheres was studied by calculating the angle of repose, θ and compressibility index, *I*. These data along with the related parameters are also presented in Table II. The values of θ ranged between 27° and 40°, indicating a reasonable flow potential for the microspheres. These results are further substantiated by the values of *I*, which ranged between 5.7 and 15%, suggesting good flow characteristics of the microspheres.[4,10] The better flow property indicates that hollow microspheres produced are nonaggregated. The tapped density values ranged from 0.404 to 0.561 g/cm^3, while their true densities ranged between 0.780 and 0.824 g/cm^3. The true density values vary depending upon the amount of PEO in the matrix. The formulations F7, F8 and F9 (20 wt % PEO) showed higher densities as compared to formulations F1, F2, and F3 (10 wt % PEO) and also similar trends were observed for formulations F10, F11, and F12 (20 wt % PEO) as compared to formulations F4, F5, and F6 (10 wt % PEO). Also, formulations with higher drug-loadings exhibited increased true densities. Formulation F3 (20 wt % drug-loading) has a higher density than F2 (10 wt % drug-loading), but F2 has greater density than F1 (5 wt %) and similar results were obtained for other formulations.

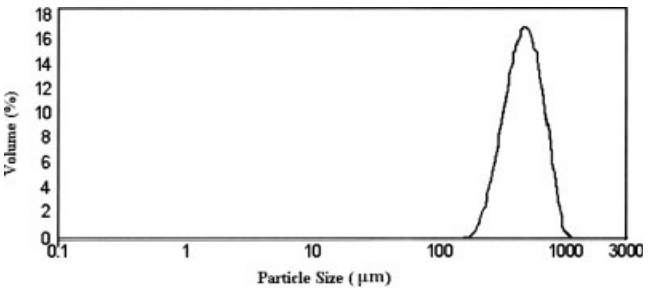

Figure 2 Representative particle size distribution of Formulation F12.

Particle size analysis

It is observed that particle size increased as the PEO content increased. For instance, formulation F7 (20 wt % PEO) has a bigger particle size than F1 (10 wt % PEO). Similarly, formulations F2 and F3 have higher particle sizes as compared to formulations F8 and F9. This could be due to the accumulation of more of PEO in the matrix at higher PEO content, leading to the formation of larger particles. Particle size also varies depending upon the drug loading. As the drug loading increased from 5 to 20 wt %, particle size also increased accordingly. Formulation F2 has larger particle size than F1, whereas F3 exhibits higher particle size than F2. This is due to the retention of more of drug particles at higher drug loadings during the microsphere preparation. Viscosity of the medium also plays an important role in the microsphere preparation. As the viscosity of the medium increases, there will be a formation of bigger droplets of the polymer solution in the aqueous medium. Thus, formulations prepared with 2 wt % PVA solution have higher particle size than formulations prepared with 1 wt % PVA. Hence, formulation F4 has a higher particle size than F1. Similarly, formulations F5 and F6 have

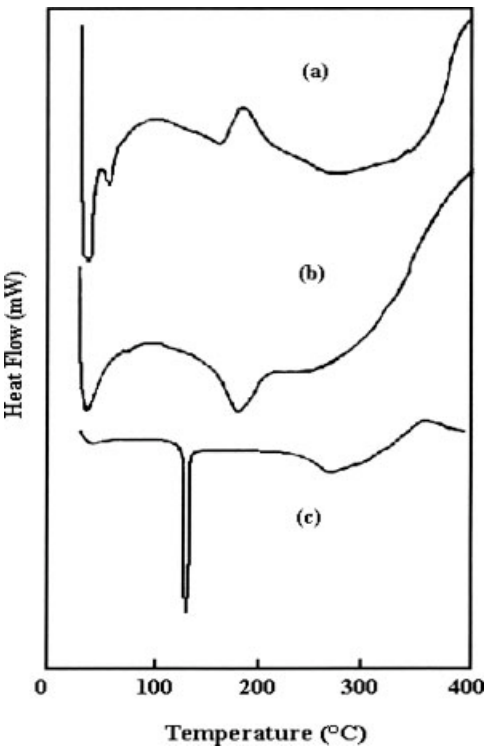

Figure 3 DSC thermograms of (a) placebo microspheres, (b) drug-loaded microspheres and (c) pure drug.

larger particle sizes than F2 and F3. The representative particle size diagram for formulation F12 is shown in Figure 2.

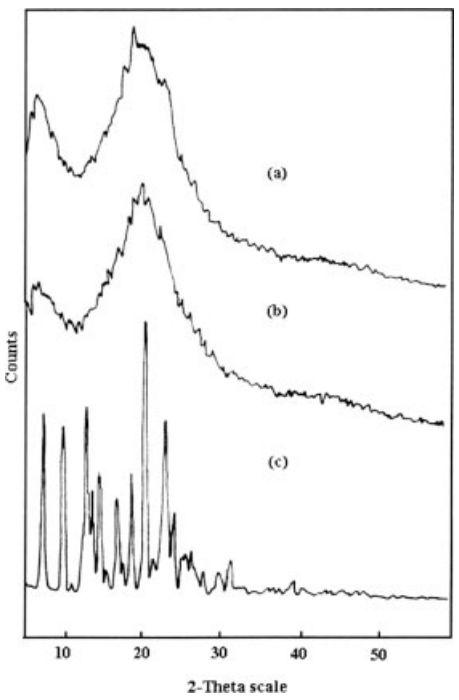

Figure 4 X-RD tracings of (a) placebo microspheres, (b) drug-loaded microspheres and (c) pure drug.

Differential scanning calorimetric studies

DSC thermograms of (a) placebo microspheres, (b) drug-loaded microspheres, and (c) pure repaglinide are presented in Figure 3. The placebo microspheres showed two sharp peaks at 32° and 60° and one broad peak at 175°C due to endothermic transition of the polymer. In case of drug-loaded microspheres, two peaks were observed at 38°C and 190°C, respectively, due to endothermic transitions. Thermogram of the repaglinide showed a sharp peak at 134°C and one small and a broad peak at 280°C, indicating the melting of the drug. Hence, no peak corresponding to repaglinide was observed in the drug-loaded microspheres, indicating the amorphous dispersion of drug molecules into the polymer matrix.

X-ray diffraction studies

X-ray diffractograms of (a) placebo microspheres, (b) drug-loaded microspheres and (c) pure repaglinide are presented in Figure 4. Repaglinide has shown

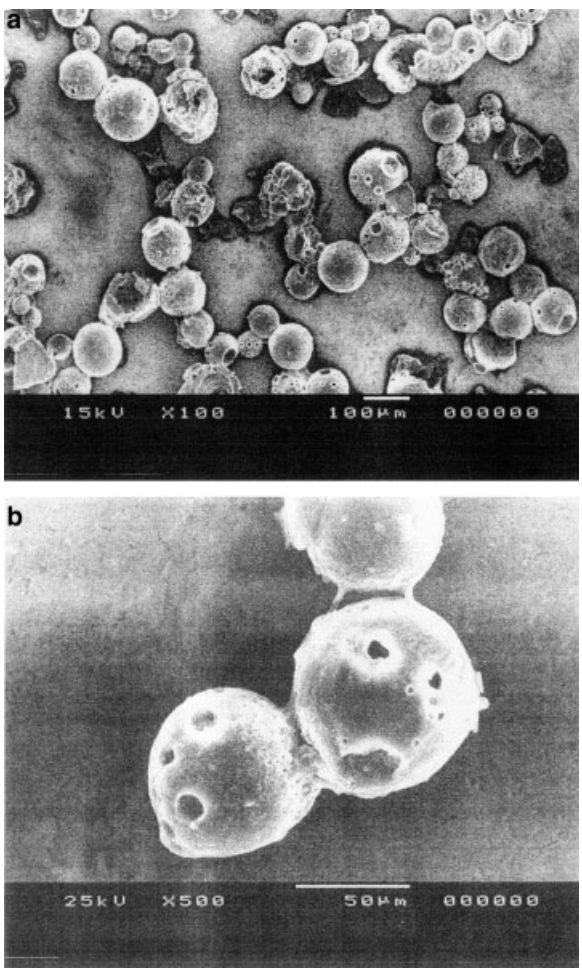

Figure 5 SEM images of (a) group of microspheres and (b) a single microsphere.

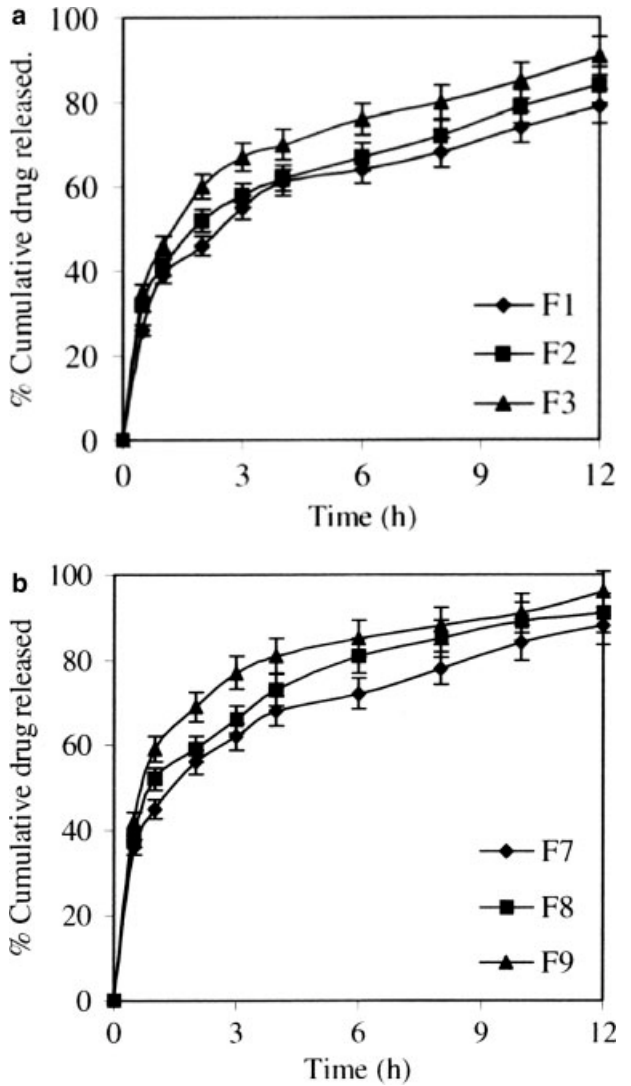

Figure 6 Effect of drug loading of formulations (a) F1, F2, and F3 and (b) F7, F8, and F9 on *in vitro* release profiles.

the characteristic intense peaks at 2θ of 5.4°, 7.4°, 10°, 13°, 17.4°, 21°, and 23° because of its crystallinity. However, this peak has disappeared in repaglinide-loaded microspheres, but only peaks observed in placebo polymer matrix were seen. X-RD peak depends upon the crystal size; but in the present study, for all the drug-loaded formulations, the characteristic peak of repaglinide could overlap with the noise of the coated polymer itself. Further, the encapsulated drug is amorphous, which is very difficult to measure at the detection limit of the crystal size. This indicates that drug is dispersed at a molecular level in the polymer matrix and hence, no crystals were found in the drug-loaded matrices.

Scanning electron microscopic studies

The porous and spherical nature of the microspheres is evident from SEM micrographs [Fig. 5(a,b)]. As can be seen, there are many pores on the surface of microspheres, because of the dissolution of PEO from the blend microspheres as well as evaporation of the DCM from the matrix, leading to the formation of pores and cavities on the surface of microspheres.

In vitro release studies

To understand the drug release from the repaglinide-loaded blend floating microspheres of CAB and PEO, the *in vitro* release experiments were carried out in SGF media containing 0.02% (w/v) Tween 80. The effect of drug loading on *in vitro* release profiles for formulations F1, F2, and F3 are compared in Figure 6(a). Formulation F3 shows a higher release rate than F2 and similarly, F2 showed a higher release rate than F1. Also, similar trends were observed for formulations F7, F8, and F9 [Fig. 6(b)]. As the drug loading is increased, there will be accumulation of more of water insoluble drug particles in the polymer matrix, but burst effect was observed in all the formulations. This indicates that release rates vary depending upon the amount of drug present in the matrices, that is release is higher in case of formulations containing higher amounts of drug and similarly, release is slower for formulations containing lower amount of drug.

Results of the effect of PEO content in formulations F1, F7, F2, F8, F3, F9, and CF on their release rates are presented in Figure 7. The % cumulative release is higher for F7 as compared to F1. Formulation F2 shows the higher release rate as compared to F8 and similarly, F3 exhibits higher release rate than F9. Therefore, as the PEO content of the polymer

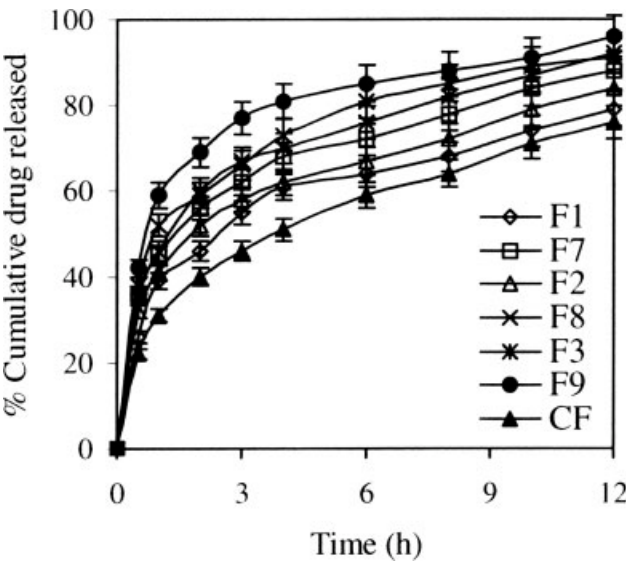

Figure 7 Effect of PEO content on *in vitro* release profile of formulations F1, F7, F2, F8, F3, F9, and CF.

matrix increases, the release rate also increases because of the hydrophilic nature of PEO. This might have created a tortuous path for the water molecules to permeate, but the degree of tortuosity depends upon the volume fraction of the filler. It is also noticed that all formulations exhibited higher release rates than the CF due to the presence of PEO, which acts as a hydrophilic filler in the formulations developed.

The mechanism of drug release from the blend microspheres of CAB and PEO was studied by fitting the release data to an empirical equation[18]:

$$\frac{M_t}{M_\infty} = kt^n \tag{8}$$

where k is a rate constant characteristic of the drug-polymer system and n is diffusional exponent. A value of $n = 0.5$ indicates Fickian mechanism and if $n = 1.0$, Case-II (zero order) transport is present. The values of n ranging between 0.5 and 0.86 suggest the anomalous transport mechanism.[4,18] The results of n calculated by using eq. (8) are also included in Table I, which indicate the anomalous transport trends.

CONCLUSIONS

The present study reports on the development of blend microspheres of CAB and PEO to study the gastroretentive slow release of repaglinide using the solvent evaporation method. The drug-loaded microspheres showed encapsulation efficiencies up to 95%. The microspheres also showed good micromeritic properties for their suitability as oral dosage forms. The microspheres having lower densities exhibited good buoyancy effect and hence, these could be retained in the gastric environment for more than 10 h. Thus, the present formulations are helpful in improving the bioavailability of antidiabetic drug such as repaglinide. The n values ranged between 0.5 to 0.86, indicating the anomalous release trend.

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