Carbohydrate Polymers 85 (2011) 592–598

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Development and evaluation of ethylcellulose floating microspheres loaded with ranitidine hydrochloride by novel solvent evaporation-matrix erosion method

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ARTICLE INFO

Article history:
Received 17 January 2011
Received in revised form 17 February 2011
Accepted 11 March 2011
Available online 21 March 2011

Keywords:
Floating microspheres
Ethylcellulose
Ranitidine hydrochloride
Polyethylene glycol

ABSTRACT

Ranitidine hydrochloride loaded floating microspheres were prepared by novel solvent evaporation-matrix erosion method using ethylcellulose and polyethylene glycol (PEG) blend. PEG employed as pore forming agent to induce buoyancy. Formulated microspheres were evaluated for various physicochemical properties. Drug loading, entrapment and encapsulation of microspheres were 23–32, 86–96 and 75–86% (w/w), respectively. The average particle sizes were between 45 and 106 μm and reduced as % of PEG increases in the microspheres. Ethylcellulose microspheres prepared with 20–33.3% of PEG showed floating properties. Scanning electron microscopy revealed the presence of pores on the surface of floating microspheres due to matrix erosion, which are responsible for floating ability. Fourier-transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction studies indicated intact and amorphous nature of entrapped drug in the microspheres. The drug loaded microspheres could float 10 h and sustain the drug release over 4–6 h.

1. Introduction

Conventional oral drug delivery systems such as tablets and capsules guarantee a prompt release of the drug; but they fail to maintain the drug concentration within the therapeutically effective range for a required period. To maintain effective plasma drug concentration, these dosage forms must be administered frequently (Bruck, 1983). Presently, oral controlled drug delivery systems have emerged largely to overcome the problems experienced with the conventional dosage forms. Basically, oral controlled drug delivery systems consist of a drug reservoir from which the drug is released slowly during its transits in GIT, in a predetermined rate to maintain constant absorption of the drug. Drugs used in oral controlled drug delivery must have uniform absorption in the entire gastrointestinal tract.

The development of oral controlled drug delivery possesses a problem for drugs whose absorption changes due to various factors such as dissolution, solubility, pH, enzymes and microbial flora (Saravanan, Balaji, Kavitha, & Kingsley, 2009). Floating drug delivery system is one of the approaches (Lee, Park, & Cho, 1999; Singh & Kim, 2000) to increase gastric residence time and localize the drug at the stomach. This approach will enhance bioavailability of those drugs, which are poorly absorbed from the intestine. Drugs such as piroxicam (Joseph, Lakshmi, & Jayakrishnan, 2002), furosemide (Menon, Ritschel, & Sakr, 1994), theophylline (Stithit, Chen, & Price, 1998), acetohydroxamic acid (Umamaheswari, Jain, Bhadra, & Jain, 2003), 5-fluorouracil (Vaghani, Vasanti, Chaturvedi, Satish, & Jivani, 2010) and ranitidine hydrochloride (Mastiholimath, Dandagi, Gadad, Rashmi, & Kulkarni, 2008) were formulated as floating microspheres in order to retain them in the stomach.

Ranitidine hydrochloride (RH) is a H_2 receptor antagonist (Grant, 1989) used in the treatment of peptic ulcer. Since the biological half life of the drug is between 2 and 3 h, it is necessary to administer the drug frequently which may produce saw tooth kinetics and results in ineffective therapy. The drug can be preferably administered in controlled release dosage forms to obtain a better effect. RH has variable absorption in the gastrointestinal tract and particularly the absorption in the intestine is less due to microbial degradation (Basit & Lacey, 2001; Williams et al., 1992). Hence an oral controlled release preparation of ranitidine should be preferably placed in the stomach to achieve uniform drug absorption.

Ethylcellulose is one of the most utilized polymers in the development of microspheres for controlled drug delivery due to its biocompatibility, versatility and lower cost. Floating microspheres using ethylcellulose have received much attention recently (Mastiholimath et al., 2008; Vaghani et al., 2010) for controlled drug delivery in the stomach. These microspheres were prepared by evaporation of organic solvents to get porous microsphere

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doi:10.1016/j.carbpol.2011.03.020

structure to float. In the present investigation, we are reporting an alternative, novel matrix erosion technique to formulate ethylcellulose floating microspheres for controlled and local delivery of drugs in the stomach. A blend of ethylcellulose and polyethylene glycol (PEG) 4000 was used to make floating microspheres. Matrix erosion due to dissolution of PEG from microsphere was exploited to produce floating microspheres.

In our previous work, we have reported (Saravanan et al., 2009) localization of RH loaded gelatin microspheres in the stomach using a magnetic field for stomach specific delivery. Application of a suitable magnet near the target area is the practical limitation of these formulations. Hence in the present work RH loaded ethylcellulose floating microspheres were developed for stomach specific drug delivery. Ethylcellulose microspheres were formulated with various proportion of PEG and characterized by drug loading, entrapment and encapsulation efficiency, buoyancy, particle size, scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), X-ray diffraction (XRD) and *in vitro* release studies.

2. Materials and methods

2.1. Materials

Ethylcellulose (viscosity range 18–22 cp and ethoxy content of 48–49.5%) was purchased from Rainbow-2000, Chennai, India. Polyethylene glycol (4000) was purchased from Sisco Research Laboratories Pvt. Ltd. Mumbai, India. Ranitidine hydrochloride I.P., obtained from Cassel Research Laboratory Pvt. Ltd., Chennai, India. All other reagents used were of analytical grade. Simulated gastric fluid (pH 1.2) without enzymes was prepared with a composition of 0.2% (w/v) of sodium chloride and 0.7% (v/v) of HCl in distilled water.

2.2. Preparation of microspheres

20% ethylcellulose solution was prepared by dissolving required quantity of ethylcellulose in a mixture of acetone and methanol (1:1). 5 ml of this solution was used in the preparation of each batch of microspheres as specified in Table 1. Required quantity of PEG and/or RH, as per the formula given in Table 1 was dissolved separately in 5 ml of methanol. The above two solutions were mixed and stirred thoroughly to form a homogeneous solution. This mixture was dispersed in 50 ml of liquid paraffin, and stirred with the help of a mechanical stirrer (Remi, India, approx. 500 rpm) for about 6 h at room temperature to form rigid spherical spheres. Microspheres were filtered using Whatman filter paper, washed with 15 ml of petroleum ether thrice and dried at 40 °C overnight.

2.3. Determination of drug loading and encapsulation efficiency

100 mg of microspheres were weighed and kept overnight in 1 N HCl to extract RH. Suitable dilutions of the filtrate were prepared and the quantity of RH was estimated at 315 nm using UV–vis spectrophotometer (Shimadzu 1601). The percentage of drug loading can be estimated by using the following formula:

$$L = \frac{Q_m}{W_m} \times 100$$

where L is the percentage loading of microspheres, Q_m is the quantity of drug in g present in W_m of microspheres and W_m is the weight of microspheres in g. The percentage of encapsulation was determined by using the following formula:

$$E = \frac{Q_p}{Q_t} \times 100$$

Table 1
Physicochemical parameters and buoyancy of microspheres.

Batch no.	Ethyl cellulose (g)	PEG (g)	Ranitidine HCl (g)	Yield (g) $n = 3 \pm$ sd	% of drug loading		Drug entrapment %	Drug encapsulation %	Particle size μm ($n = 300 \pm$ sd)	Theoretical % of PEG	% buoyancy at different time interval ($n = 3 \pm$ sd)					Floatation time (min)
					Theoretical	Actual $n = 3 \pm$ sd					2 h	4 h	8 h	10 h	12 h	
1	1	–	0.5	1.350 ± 0.12	33.33	31.91 ± 0. 6	95.73	86.14	106.1 ± 18.1	–	0	0	0	0	0	–
2	1	0.125	0.5	1.420 ± 0.25	30.76	26.25 ± 0.45	85.33	74.55	94.2 ± 15.6	7.7	0	0	0	0	0	–
3	1	0.250	0.5	1.525 ± 0.15	28.57	24.56 ± 0.78	85.96	74.90	83.7 ± 16.2	14.3	11 ± 2.3	0	0	0	0	–
4	1	0.375	0.5	1.650 ± 0.23	26.66	24.16 ± 0.67	90.62	79.72	71.7 ± 10.9	20	52 ± 4.5	42 ± 3.2	0	0	0	5–10 min
5	1	0.500	0.5	1.730 ± 0.21	25.00	22.9 ± 0.81	91.64	79.26	59.4 ± 9.2	25	65 ± 6.2	59 ± 4.1	54 ± 3.5	41 ± 4.3	0	<5 min
6	1	0.125	0	–	–	–	–	–	87.1 ± 12.2	11.1	0	0	0	0	0	–
7	1	0.250	0	–	–	–	–	–	74.3 ± 10.8	20	59 ± 2.3	55 ± 1.2	51 ± 2.3	48 ± 2.9	45 ± 3.1	5–10 min
8	1	0.375	0	–	–	–	–	–	63.5 ± 9.5	27.3	68 ± 1.6	65 ± 1.7	63 ± 1.9	59 ± 3.4	55 ± 2.5	<5 min
9	1	0.500	0	–	–	–	–	–	48.9 ± 8.9	33.3	73 ± 3.1	70 ± 2.5	68 ± 2.2	64 ± 1.9	61 ± 1.7	<5 min

where E is the % of encapsulation of microspheres, Q_p is the quantity of drug encapsulated in microspheres (g), Q_t is the total quantity of drug utilized for encapsulation process (g). Q_p is the product of drug content per g of microspheres and yield of microspheres (g).

2.4. Test for buoyancy

The microspheres (200 mg) were transferred to a series of six 500 ml beakers containing 400 ml of simulated gastric fluid without enzymes maintained at 37 °C. The content of the beakers was stirred at 100 rpm by magnetic pellet. At different time intervals (2, 4, 6, 8, 10, 12 h) floating and non-floating microspheres were separated, dried at 45 °C until a constant weight is obtained. Then the microspheres were weighed and percentage of buoyancy is calculated by using following equation (Umamaheswari et al., 2003).

$$\text{Buoyancy}\,(\%) = \frac{Q_f}{Q_f + Q_s}$$

where Q_f is the weight of floating microspheres and Q_s is the weight of settled microspheres collected at different time intervals.

Floatation time: The time required for 50% (w/w) of the microsphere to float was noted as floatation time. It was determined by the method described under buoyancy but sampling was done at 5, 10, 15 and 20 min to determine flotation time.

2.5. Scanning electron microscopy

The sample for the scanning electron microscopy (SEM) analysis was prepared by sprinkling the microspheres one side of double adhesive stub. The stub was then coated with gold using Jeol JFC 1100 sputter coater. The SEM analysis of the microspheres was carried out by using Jeol JSM 5300, Japan. The microspheres were viewed at an accelerating voltage of 15 kV.

2.6. Particle size analysis

The size of 300 particles of each batch was measured by using a calibrated micrometer attached (Saravanan, Anbu, Maharajan, & Sadasivan Pillai, 2008) with a microscope and the average diameter was calculated.

2.7. Fourier transform infrared spectroscopy

Infrared spectrums of RH, PEG 4000, ethylcellulose/PEG loaded and unloaded microspheres were taken using KBr pellet technique and were recorded on a Nicolet 20 DXB FT-IR spectrophotometer.

2.8. Differential scanning calorimetry

Differential scanning calorimetry (DSC) of RH, PEG and microspheres was performed using Perkin-Elmer DSC–7 model. The instrument was calibrated with indium. All the samples (≈5 mg) were heated in aluminum pans using dry nitrogen as the effluent gas. The analysis was performed with a heating range of 50–300 °C and at a rate of 20 °C min^{-1}.

2.9. X-ray diffraction

RH, RH loaded ethylcellulose/PEG microspheres, physical mixture of RH and unloaded ethylcellulose/PEG microspheres were subjected to X-ray diffraction study in an X-ray diffractometer (XD-D_1, Shimadzu, Japan), within the range 5–80° of 2θ. The working conditions were CuKα radiation, 30 kV, 20 mA and with a slit of 1–1–0.3 mm.

2.10. In vitro release

The *in vitro* release studies were done by a modified method suggested by Zhou et al. (2006). As the formulation is for stomach specific delivery, simulated gastric fluid without enzymes is used as the release medium. Each batch of microspheres containing 25 mg of drug was individually added to 250 ml of simulated gastric fluid in flasks. The flasks were shaken (60 oscillations/min) in an incubator (Remi, India) at 37 °C. One milliliter of sample was withdrawn at regular time intervals and same volume of gastric fluid was replaced. After suitable dilution, RH content was estimated at 315 nm using UV–vis spectrophotometer.

3. Results and discussion

3.1. Preparation, drug loading, entrapment and encapsulation efficiency of ethylcellulose microspheres

Formulation of ethylcellulose floating microspheres by a novel solvent evaporation/matrix-erosion method was reported in the present investigation. Solvents such as methanol, ethanol, acetone, dichloromethane and chloroform in single/combination were tried to dissolve RH, ethyl cellulose and PEG. No such single solvent could dissolve polymer and drug. RH is soluble in methanol and sparingly soluble in ethanol. Mixture of acetone:methanol (1:1) was found to be suitable solvent for ethylcellulose, PEG and RH. We have tried fixed oil such as arachis oil, sesame oil and olive oil as the dispersion medium. Usage of these oils resulted in poor yield and produced irregular shaped particles due to partial miscibility of solvent system and polymer employed. Dispersion of drug/polymer solution in liquid paraffin yielded discrete and spherical particles. A calibration curve of RH in 1 N HCl was made at 315 nm in the presence of PEG/ethylcellulose and no spectral interference was observed during drug content analysis. All batches of formulated microspheres showed above 85% entrapment and revealed successful microencapsulation of ranitidine hydrochloride by the present method. Drug loading, entrapment and encapsulation of formulated microspheres were 23–32, 86–96 and 75–86% (w/w), respectively (Table 1). The formulated microspheres were tested for residual solvent (methanol, acetone and petroleum ether) by gas chromatography as explained in our previous publication (Saravanan et al., 2008). All microspheres showed no residual solvent and indicated efficient drying time and temperature used in the process.

3.2. Buoyancy

When the microspheres are dispersed in simulated gastric fluid without enzymes, due to high water solubility, PEG goes into solution forming pores on microspheres due to matrix erosion. This phenomenon makes the microspheres to float. Ethylcellulose microspheres prepared with 20–33.3% of polyethylene glycol showed good floating properties as shown in Table 1. Unloaded ethylcellulose/PEG microspheres could float up to 12 h. Drug loading reduced floating efficiency as indicated in Table 1. Ethylcellulose microspheres prepared with 25% (w/w) of PEG and 23% (w/w) of drug float up to 10 h. Ethylcellulose microspheres prepared with 20% (w/w) PEG and 24% (w/w) drug floats only for 4 h. All other drug loaded microspheres were unable to float (Table 1). Fig. 1 shows the floating microspheres against sank microspheres during the buoyancy test. The formulated microspheres could float within 5–10 min depending upon the % of PEG present in the microspheres. As the % of PEG increases, floatation time reduces as shown in Table 1.

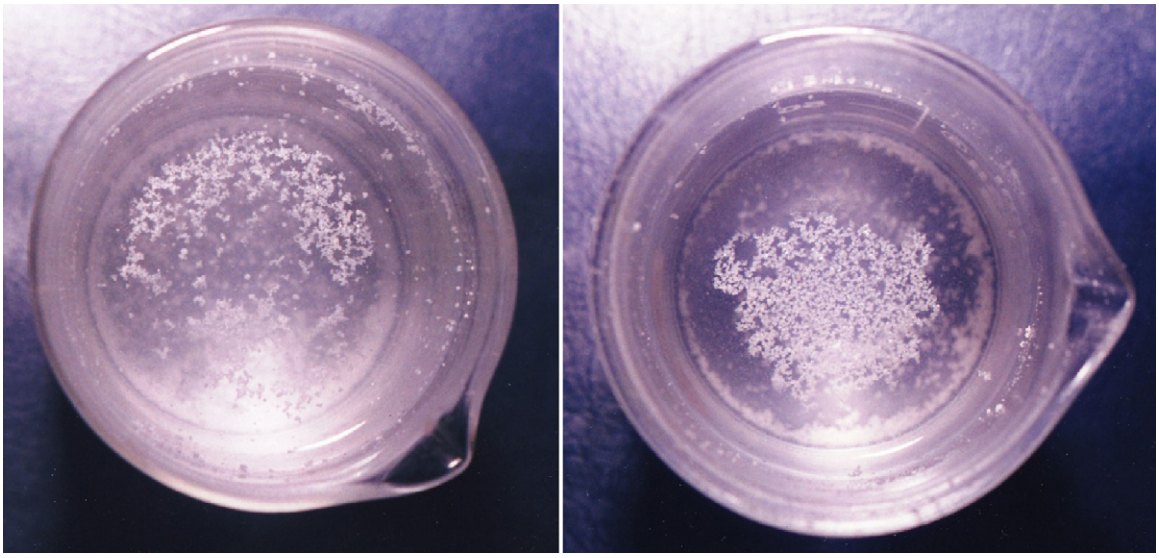

Fig. 1. Picture of floating microspheres against sank microspheres. Batch 4 and 5 formulations are shown in the left and right side, respectively.

3.3. SEM

The microspheres were spherical, discrete and having a rough surface as evidenced by Fig. 2. The surface of ethylcellulose/PEG microspheres did not show any pores on the surface. SEM of floating microspheres collected after dispersion in simulated gastric fluid revealed the presence of pores on the surface which is responsible for floating behavior. The pores found in batch 4 & 5 microspheres

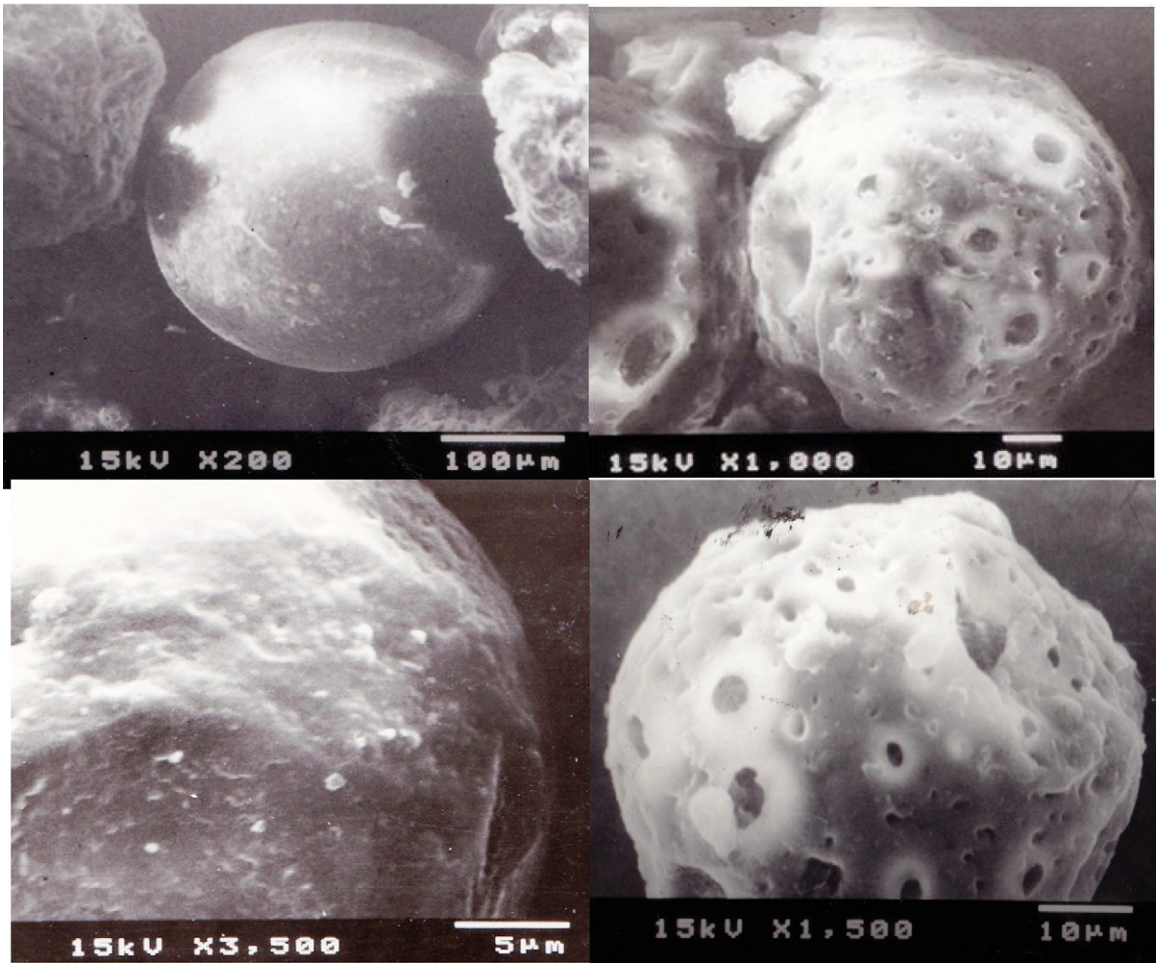

Fig. 2. Photographs showing surface morphology of ranitidine hydrochloride loaded ethylcellulose microspheres before (left) and after (right) dispersion in simulated gastric fluid without enzymes. Surface of microspheres did not show any pores before dispersion (left) but produced pores after dispersion (right) due to dissolution of crytalline PEG, indicating matrix erosion. Top and bottom of the picture show batches 4 and 5, respectively.

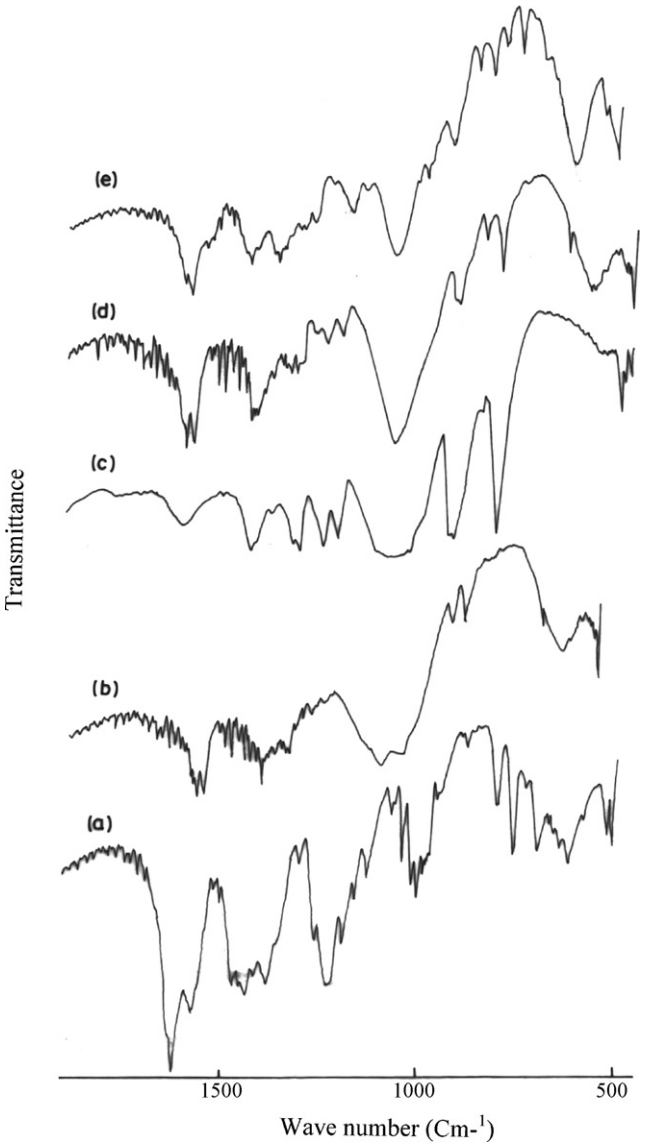

Fig. 3. FT-IR spectrum of ranitidine hydrochloride (a), ethyl cellulose (b), polyethylene glycol (c), ethylcellulose/PEG microspheres without(d) and with ranitidine hydrochloride (e).

are shown in the right side of Fig. 2. The SEM of microspheres before dispersion (Fig. 2, photographs in the left) showed no pores on the surface. This clearly indicated that the floating nature of microspheres is due to matrix erosion resulted by solubilization of PEG from ethylcellulose microspheres when they were dispersed in gastric fluid without enzymes.

3.4. Particle size analysis-influence of PEG in the size of ethylcellulose microspheres

The average particle sizes of microspheres were between 45 and 106 μm. The size of microspheres was reduced as % of PEG increased in the ethyl cellulose microspheres (Table 1), could be due to surface active property of PEG. Sizes of unloaded microspheres are less than the drug loaded microspheres. The exact reason for reduction of particle size in the presence of PEG is an unclear phenomenon but similar observation is reported by Kharkov, Shlyakhov, Krutkov, Kabanova, and Chegolya (1976) where the presence of PEG in non-ionic surfactant improved the stability of emulsion with reduced globule size.

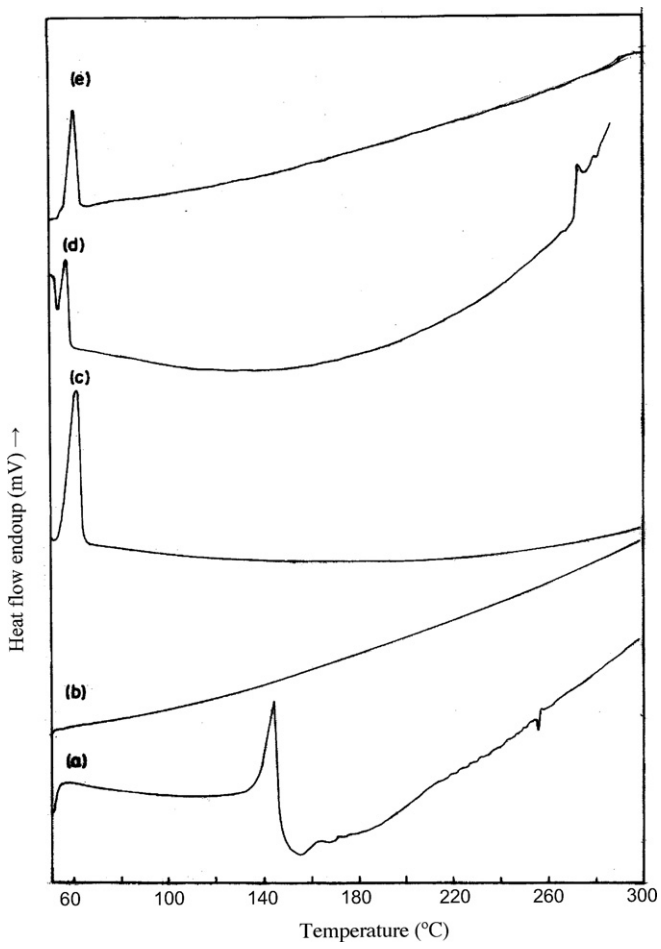

Fig. 4. DSC of ranitidine hydrochloride (a), ethylcellulose (b), PEG (c) ethylcellulose/PEG microspheres without drug (d) and ethylcellulose/PEG microspheres loaded with ranitidine hydrochloride (e).

3.5. FT-IR spectroscopy

FT-IR spectrum of RH shown in Fig. 3a was identical to the reference spectrum given in British Pharmacopoeia. The peaks at 1028 and 1495 cm^{-1} are recommended as identification markers for RH as per Indian Pharmacopoeia. The spectral analysis of RH in our study (Fig. 3a) showed a peak at 1618 C m^{-1} for C–N stretching and at 1507, 1021, 879, 806, 760 C m^{-1} for other functional groups. IR spectrum of ethylcellulose and PEG are shown in Fig. 3b and c, respectively. The peaks appeared at 1200–1250 and 750–950 C m^{-1} in the spectra of PEG (Fig. 3c) also appeared in ethylcellulose/PEG microspheres prepared without (Fig. 3d) and with (Fig. 3e) RH. This revealed the presence of PEG in the formulated microspheres. RH peaks were less intensive but intact in drug loaded microspheres (Fig. 3e). This indicates the absence of drug polymer interactions.

3.6. DSC

Thermogram of RH (Fig. 4a) showed a sharp peak at 145 °C, indicating crystalline nature of drug. Thermogram of ethylcellulose microspheres (Fig. 4b) showed no peak and indicated amorphous nature of polymer in the microspheres. Thermogram of PEG showed (Fig. 4c) a peak at its melting point of 63 °C, indicating crystalline nature of the PEG 4000. The peak of PEG also appeared in the ethylcellulose/PEG microspheres without (Fig. 4d) and with (Fig. 4e) drug and revealed the crystalline nature of PEG in the microspheres. This crystalline nature of PEG in the microspheres plays a vital

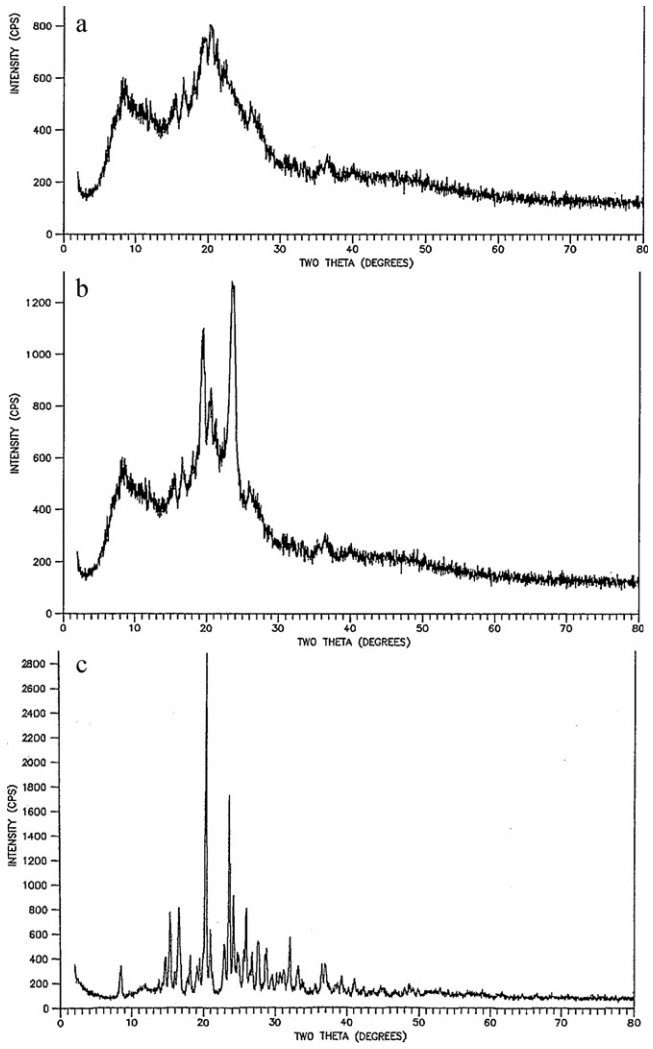

Fig. 5. X-ray diffraction pattern of ranitidine hydrochloride (a), physical mixture of ranitidine hydrochloride/ethylcellulose–PEG unloaded microspheres (1:1) (b) and ethylcellulose–PEG microspheres loaded with ranitidine hydrochloride (c).

role in the formation of pores in the microspheres. When in contact with water, PEG undergoes dissolution and leaves the space which was occupied by the crystals to produce pores. This is further supported by an increase in floating time in the microspheres prepared with the higher percentage of PEG. The peak observed at the melting point of RH (Fig. 4a) was absent in ethylcellulose/PEG microspheres loaded with RH (Fig. 4e). This observation indicates amorphous nature of entrapped drug in the microspheres.

3.7. X-ray diffraction

XRD of RH showed (Fig. 5a) intense peaks at 21° and 24°. These peaks were present in the physical mixture (Fig. 5b) of microspheres and RH but absent in drug loaded microspheres (Fig. 5c). These observations along with DSC studies confirm the amorphous nature of RH in the formulated microspheres.

3.8. In vitro release

The microspheres sustained the drug release over 4–6 h as shown in Fig. 6. The release of RH from microspheres prepared with ethylcellulose alone was slow and sustained than the release from ethylcellulose/PEG microspheres. Increase in PEG content in the microspheres produced faster drug release and microspheres prepared with highest % of PEG released the entire drug within 4 h. The presence of pores in floating microspheres is responsible for faster dissolution rate. 50% of loaded drugs were released within 30 min and remaining 50% was released during next 4–5 h.

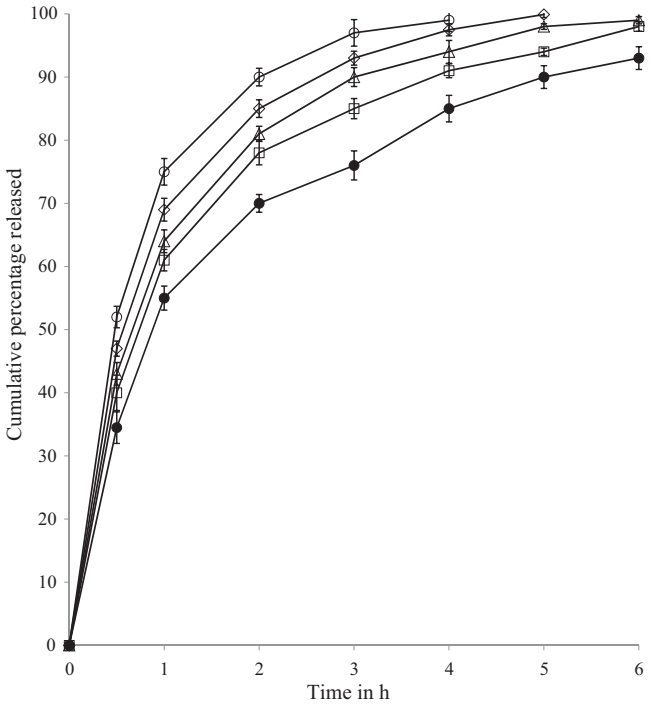

Fig. 6. *In vitro* release of ranitidine hydrochloride from ethylcellulose microspheres (●) prepared without polyethylene glycol and from ethylcellulose microspheres prepared with 7.7 (□), 14.3 (△), 20 (◇) and 25 (○) % (w/w) polyethylene glycol 4000 ($n = 3 \pm$ sd).

4. Conclusions

Microspheres formulated with ethylcellulose/PEG blend by novel solvent evaporation and matrix erosion method were able to float 12 h without and 10 h with RH. SEM revealed the presence of pores on floating microspheres due to matrix erosion, which are responsible for the floating ability. FT-IR, DSC and XRD indicated intact and amorphous nature of entrapped drug. The microspheres sustained the drug release over a period of 4–6 h. The above results revealed the possibility of development of floating drug delivery system using ethylcellulose/PEG polymer blend for sustained and local delivery in the stomach.

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