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Encapsulation and characterization of controlled release flurbiprofen loaded microspheres using beeswax as an encapsulating agent

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Abstract The aim of the present study was to extend the use of flurbiprofen in clinical settings by avoiding its harmful gastric effects. For this purpose, we designed the controlled release solid lipid flurbiprofen microspheres (SLFM) by emulsion congealing technique. Drug was entrapped into gastro resistant biodegradable beeswax microspheres which were prepared at different drug/beeswax ratios 1:1, 1:2 and 1:3 using gelatin and tween 20 as emulsifying agents. The effect of emulsifiers and the effect drug/beeswax ratios were studied on hydration rate, encapsulating efficiency, micromeritic properties, scanning electron microscopy (SEM), fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffraction (X-RD) analysis and in vitro drug release at pH 1.2 for 2 h and at pH 6.8 for 10 h. SEM revealed that microspheres made with tween 20 were smooth while microspheres made with gelatin showed porous morphology, however, they were all spherical in nature. The practical yield (recovery) showed a dependence on drug-beeswax ratio and it was variable from 53 to 84%. High loading encapsulating efficiency of flurbiprofen from 8 to 94% was achieved. FTIR and DSC analysis confirmed the absence of any drug polymer interaction indicating drug stability during microencapsulation. X-RD of pure flurbiprofen shows sharp peaks, which decreases on encapsulation, indicating decrease in the crystallinity of drug in microspheres. The micromeritic studies confirmed the presence of excellent and good flow properties of microspheres. Entrapment efficiency, morphology, practical yield, hydration rate, flow properties demonstrated their dependence on the HLB value of emulsifiers and emulsifiers with higher HLB were found more appropriate for effective microencapsulation of flurbiprofen. The release kinetics followed zero order mechanism of drug release at pH 6.8. Release pattern depends on the morphology of flurbiprofen microspheres and amount of beeswax used in the microspheres preparation. The microspheres prepared with high HLB values i.e., tween 20 showed effective control of drug release from microspheres. The absence of drug release at pH 1.2 proved the suitability of beeswax for its use as a gastro resistant material.

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1 Introduction

The problems associated with conventional drug delivery include an uneven biodistribution throughout the body, a lack of drug targeting specificity, the necessity of a large dose to achieve high local concentration and adverse side effects due to such high doses. It is realized that innovative delivery of drugs not only increase safety and efficacy levels but also improves the overall performance of the drug [1]. Microspheres are small solid particulate carriers containing dispersed drug particles either in solution or crystalline form [2]. The microspheres formulation provides an optimum control of kinetics of drug release from the administered dosage form [3]. Moreover, controlled release preparations are preferred to achieve maximum therapeutic effects with a low risk of adverse effects [4].

Microspheres can be prepared by a number of techniques but pharmaceutical processing techniques which offer freedom from organic solvents are preferred due to stringent global environmental concerns. Therefore,

attempts are continuously made to reduce the use of organic solvents in the processing of pharmaceuticals [5]. Hence, many reports are published on techniques such as emulsion congealing [6], melt granulation [7] and melt dispersion [8]. Lipids, waxes and polyethylene glycols are the most favorable materials for these techniques. Drug is incorporated in these carriers to achieve controlled release, taste masking and stability improvement [9].

Wax, a common carrier in various melt techniques, contains a wide group of chemicals such as glycerides, fatty acids, fatty alcohols and their esters. These are widely used as release retardants in the design of sustained release beads, tablets, suspensions, implants and microspheres. The advantages of waxes include good stability at varying pH and moisture levels, well-established safe application (biocompatible and nonimmunogenic) in humans due to their nonswellable and water insoluble nature, minimal effect on food in the gastrointestinal tract and no dose dumping [10]. Beeswax, carnauba wax and microcrystalline wax were evaluated as waxy carriers for melt processing techniques [8, 11].

Microspheres prepared by the use of wax are usually called as solid lipid microspheres. Solid lipid microspheres appear as very attractive carrier systems when protection of drug against chemical degradation or prolonged release is required. They offer some advantages as lower cytoxicity due to absence of organic solvents in the production process and the relatively low costs of the excipients. In addition, preparation method of solid lipid microspheres has good reproducibility and does not need complex equipment due to one step production procedure [12, 13]. Beeswax is a natural product used in pharmaceutical, cosmetics, food and other industries. It is highly crystalline and is frequently used in the preparation of controlled release drug preparations [3].

Flurbiprofen, 2-(2-flurobiphenyl-4y1) propionic acid is a nonsteroidal antiinflammatory drug used to treat rheumatoid arthritis, osteoarthritis and mild to moderate pain. The gastrointestinal irritation and ulcerogenic effect along with the short half-life (3-4 h) has led to the design of sustained release formulation of flurbiprofen [14].

In this study, beeswax was used as solid lipid, emulsion congealing technique was used for preparing flurbiprofen loaded microspheres. The prepared flurbiprofen loaded microspheres were evaluated by measuring entrapment efficiency, rheological properties, scanning electron microscopy (SEM), fourier transform infrared spectroscopy (FTIR), XRD, differential scanning calorimetry (DSC) and drug release.

2 Materials and methods

Flurbiprofen was generously donated by Shrooq Pharmaceuticals (Pvt) Ltd. Lahore, Pakistan. Gelatin, tween 20 and potassium dihydrogen phosphate were purchased from Merck, Germany. Beeswax and dialysis tubing cellulose (Mw cutt off 6491 Sigma-Aldrich, USA), potassium bromide of IR grade (Fischer Scientific, UK) were purchased. All the reagents were of analytical grade.

2.1 Preparation of microspheres

Flurbiprofen microspheres using beeswax were prepared by emulsion congealing technique and flurbiprofen was incorporated into microspheres at different drug/wax ratios (1:1), (1:2) and (1:3). For this purpose beeswax was melted in water bath at 90°C and appropriate amount of flurbiprofen was added. The mixture was poured into 200 ml hot aqueous solution containing 1% w/v tween 20 or gelatin using propeller stirrer at 1000 rpm. Stirring process was maintained for 30 min until coarse emulsion cooled down to room temperature. After filteration, the obtained microspheres were washed three times with distilled water, dried at room temperature and then passed through a sieve number 25.

Three formulations FB1, FB2 and FB3 were prepared with gelatin as an emulsifying agent (Table 1) and other three formulations FB4, FB5 and FB6 were prepared with tween 20 as an emulsifying agent (Table 2). Two blank formulations were also prepared; one was made with gelatin and second was made with tween 20. Each formulation was prepared at least thrice and the resulting batches were combined for characterization.

Table 1 Formulations prepared with gelatin

Gelatin 1% w/v						
Formulation code	FB 1		FB 2		FB 3	
	Drug	Beeswax	Drug	Beeswax	Drug	Beeswax
Ratio	1	1	1	2	1	3
Weight (g)	1.5	1.5	1.5	3	2	6

Table 2 Formulations prepared with tween 20

1% w/v Tween 20						
Formulation code	FB 4		FB 5		FB 6	
	Drug	Beeswax	Drug	Beeswax	Drug	Beeswax
Ratio	1	1	1	2	1	3
Weight (g)	1.5	1.5	1.5	3	2	6

3 Characterization

3.1 Recovery of formed microspheres

After preparation the microspheres were dried overnight at room temperature. Recovery is the ratio of the weight of microspheres obtained to that total weight of solid contents charged at the beginning of the microencapsulation process.

$$\text{Percent yield} = \frac{\text{weight of microspheres (g)}}{\text{weight of all species charged (g)}} \times 100$$

3.2 Determination of percentage encapsulation efficiency

Percentage encapsulation efficiency is percentage of drug encapsulated in the microspheres relating to initial quantity used. Appropriate amount of microspheres in 100 ml of phosphate buffer pH 6.8 were placed in an ultrasonic bath at 70°C for complete removal of flurbiprofen from beeswax. After cooling to room temperature, it was filtered through 0.45 μm filter paper. 0.4 ml supernatant was taken into a syringe and diluted to 4 ml with phosphate buffer solution of pH 6.8. After filtration the absorbance of flurbiprofen at 247 nm was measured using a UV–VIS spectrophotometer (UV–VIS spectrophotometer IRMECO U2020). The measured absorbance was then converted to the amount of flurbiprofen by using standard calibration curve. Percentage encapsulation efficiency was calculated as follows [15]:

$$\text{Encapsulation efficiency } \% = \frac{\text{entrapped amount of drug per g microsphere}}{\text{theoratical amount of drug per g microsphere}} \times 100$$

3.3 Measurement of microsphere hydration

At the end of each microencapsulation process microspheres were weighed immediately (M_1) and again weighed after drying to a constant weight (M_2). The percentage of microshere hydration was calculated as [16]:

$$\text{Microsphere hydration } \% = \frac{M_1}{M_2} \times 100$$

3.4 Rheological studies of microspheres

3.4.1 Bulk density

It is determined by following formula:

$$\text{Bulk density} = \frac{\text{sample weight}}{\text{sample volume}}$$

3.4.2 Tapped density

Tapped density is used to investigate packing properties of microspheres into capsules but may affect a number of pharmaceutical processes like flow, mixing and tableting. The taped density was measured by employing the conventional tapping method using 10 ml measuring cylinder and the number of tapings was 100 as it was sufficient to bring about a plateau condition. Tapped density was calculated by the following formula:

$$\text{Tapped density} = \frac{\text{weight of microspheres}}{\text{volume of microspheres after 100 tapings}}$$

3.4.3 Compressibility index

It is indirect measurement of bulk density, size and shape, surface area, moisture content and cohesiveness of materials since all of them can influence the compressibility index. It is also called Carr's Index. It is calculated as follows [17]:

$$\text{Ci} = \frac{\text{initial volume} - \text{final volume}}{\text{initial volume}} \times 100$$

Ci less than 15% gives good flow characteristics and above 25% indicates poor flow characteristics.

3.4.4 Hausner's ratio

It is another index of flowability of the microspheres. It is calculated using following formula:

$$\text{Hausner's ratio} = \frac{\text{volume before tapping}}{\text{volume after tapping}}$$

A value <1.2 is preferable for free flow. However a Hausner's ratio close to 1 indicates good flow properties [17].

3.4.5 Angle of repose

Angle of repose was measured by passing beads through a funnel on the horizontal surface. The height (h) of the heap formed was measured and radius (r) of cone base was also determined. The angle of repose (θ) was calculated as:

$$Tan\theta = \frac{h}{r}$$

3.4.6 Scanning electron microscopy

Surface morphology of the microspheres was observed on the scanning electron microscope (Model S3400N).

3.4.7 Fourier transform infrared spectroscopy

Drug polymer interactions were studied by FTIR spectroscopy (FTIR Shimadzu 8400 S). The spectra were recorded for pure drug and drug loaded microspheres using FTIR. Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400–4000 cm^{-1} and the resolution was 2 cm^{-1}.

3.4.8 X-ray powder diffractometry

X-ray powder diffractometry was carried out to investigate the effect of microencapsulation process on crystallinity of drug. Powdered samples were irradiated with monochromatized X-rays (Cu-kα). The scanning rate employed was 2° min^{-1}, over the 4 to 40°-diffraction angle (2θ) range. The X-ray powder diffractometry (X-RD) patterns of drug and drug-loaded microspheres were recorded.

3.4.9 Differential Scanning Calorimetry

The DSC analysis of pure drug, bees wax and drug-loaded microspheres were carried out using Mettler toledo DSC-823e to evaluate any possible drug-polymer interaction. Polymer, flurbiprofen and drug-loaded microspheres were triturated separately to get a finely divided powder and heated in sealed aluminium pans at a rate of 10°C/min from 0 to 120°C temperature range under a nitrogen flow of 40 ml/min. Reproducibility was checked by running the sample in triplicate [18].

3.4.10 In vitro drug release

In vitro release of flurbiprofen from microspheres was studied using a USP dissolution apparatus (Pharmatest). Phosphate buffer solutions of pH 1.2 and 6.8 were used as dissolution medium, their pH was adjusted by adding HCl or NaOH solutions. 100 mg of micropspheres were added in cellulose dialysis tube containing 4 ml of dissolution medium and tied to the paddle. The paddle was rotated at 100 rpm in 500 ml of phosphate buffer solution of pH 1.2 or pH 6.8 at 37°C. A 5 ml sample was withdrawn at predetermined time intervals i.e. 0.5, 1, 2, 3, 4, 5, 6, 8 and 10 h and an equal volume of fresh dissolution medium, which was prewarmed at 37°C, was replaced. Collected samples were suitably diluted and then analyzed for flurbiprofen contents by measuring the absorbance at 247 nm using an ultraviolet spectrophotometer (UV–VIS spectrophotometer IRMECO U2020). The concentration of flurbiprofen in test samples was calculated using calibration curve. Three samples were run of each formulation in solutions of pH 1.2 and 6.8.

3.4.11 Drug release kinetics

Drug release kinetics was assumed to reflect different release mechanisms of controlled release drug delivery systems. Therefore, five kinetics models were applied to analyze the in vitro data to find the best fitting equation.

Zero-order release equation [19];

$$F_t = K_0 t \tag{1}$$

where F_t represents the fraction of drug released in time t and K_0 is the apparent rate constant of zero-order release constant.

First-order equation [20];

$$\ln(1 - F) = -K_1 t \tag{2}$$

where F represents the fraction of drug released in time t and K_1 is the first-order release constant.

Higuchi equation [21];

$$F = K_2 t^{1/2} \tag{3}$$

where F represents the fraction of drug released in time t and K_2 is the Higuchi constant.

Hixson–Crowell equation [22];

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC}\, t \tag{4}$$

Peppas equation [23];

$$\frac{M_t}{M_\infty} = K_3\, t^n \tag{5}$$

In Korsmeyer-Peppas equation M_t and M_∞ are the amount of drug released at time t and ∞, respectively and n is the diffusional coefficient. In spherical matrices, if $n < 0.43$, a Fickian (case-I), $0.43 < n < 0.85$, a non-Fickian, and $n > 0.85$, a case-II (zero order) drug release mechanism dominates.

4 Results and discussion

Flurbiprofen microspheres using beeswax were prepared by emulsion congealing technique, the microspheres were white, free flowing and spherical in shape. Beeswax seems suitable to prepare gastro-resistant microspheres [3]. The preparation method used in this study was advantageous for the entrapment of water-insoluble drugs. Surfactants (gelatin or tween 20) at a concentration of 1% w/v, made the hydrophobic material wet able and formed individual microspheres. An attempt was made to prepare flurbiprofen loaded microspheres without the addition of a surfactant but failed and resulted an aggregated cake during the congealing of wax. This caking was originating from high interfacial tension between the hydrophobic material and the aqueous phase. The aggregation tendency is reduced by

Table 3 Encapsulation efficiency, % recovery and hydration rate of various formulations of microspheres

Formulations	Encapsulation efficiency %	% Recovery	Hydration rate
FB 1	87.06	72.39	177.27
FB 2	92.32	72.72	171.88
FB 3	89.54	52.78	148.80
FB 4	89.13	84.06	243.48
FB 5	94.25	69.61	213.33
FB 6	92.39	63.94	210.00

using surface active agents in the aqueous phase [24]. A 1% w/v concentration of surfactant was found to produce discrete microspheres with good flow properties.

Stirring rate also influenced the size and yield of microspheres. In this study, a stirring speed of 1000 rpm produced microspheres of reproducible particle size and yield of the microspheres remained constant at this stirring speed. It was observed that increasing the stirring speed (1200 rpm) there is low recovery. This low recovery was due to smaller microspheres which were lost during successive washings. Decreasing stirring speed lower than

Table 4 Micromeritic properties of various formulations of microspheres

Micromeritic properties of microspheres					
Formulations	Bulk density	Tapped density	Compressibility index (ci)	Hausner's ratio	Angle of repose
FB 1	0.36	0.42	14.00	1.16	27.61
FB 2	0.35	0.40	13.00	1.15	24.12
FB 3	0.40	0.44	10.00	1.11	23.09
FB 4	0.50	0.55	9.00	1.10	19.98
FB 5	0.55	0.60	8.00	1.09	18.43
FB 6	0.55	0.62	11.00	1.12	15.95

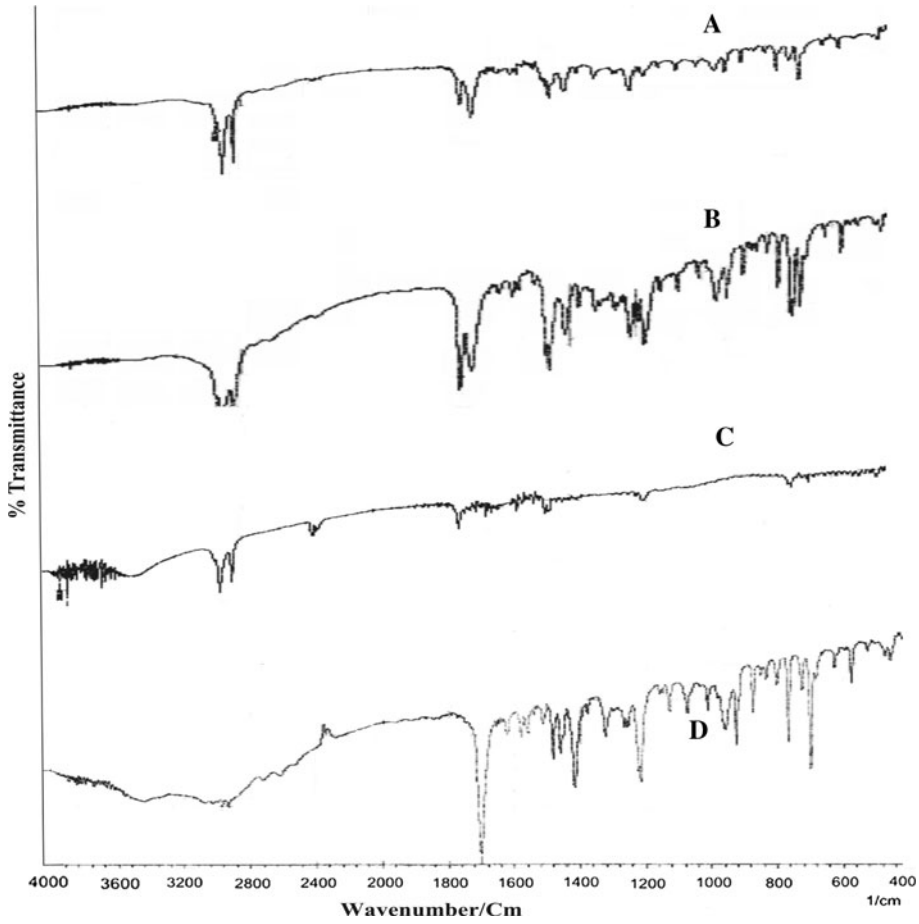

Fig. 1 FTIR Spectra; *A*, microspheres made in the presence of gelatin: *B*, microspheres made in the presence of tween 20: *C*, bees wax: *D*, flurbiprofen

900 rpm, larger microspheres were formed and melted material also adhered to the walls of beaker which causes lowering the recovery. Similar findings were reported by Giannola et al. and Varshosaz and Keihanfar [3, 24].

The percentage recovery of microspheres increased, as beeswax added to each formulation decreased, similar findings were published by Dandagi et al. [2], who prepared biodegradable microparticulate system of captopril using beeswax. In our study sample FB4 showed maximum yield and it was found 84%. Minimum yield 53% was observed and it was for sample FB3 (Table 3). It was found that tween 20 increases the stability of emulsion droplets formed during the homogenization process and prevents coalescence of emulsion droplets resulting in relatively greater yield.

The entrapment efficiency of microspheres was variable from 87 to 94% (Table 3). The entrapment efficiency for microspheres made in the presence of gelatin was less than

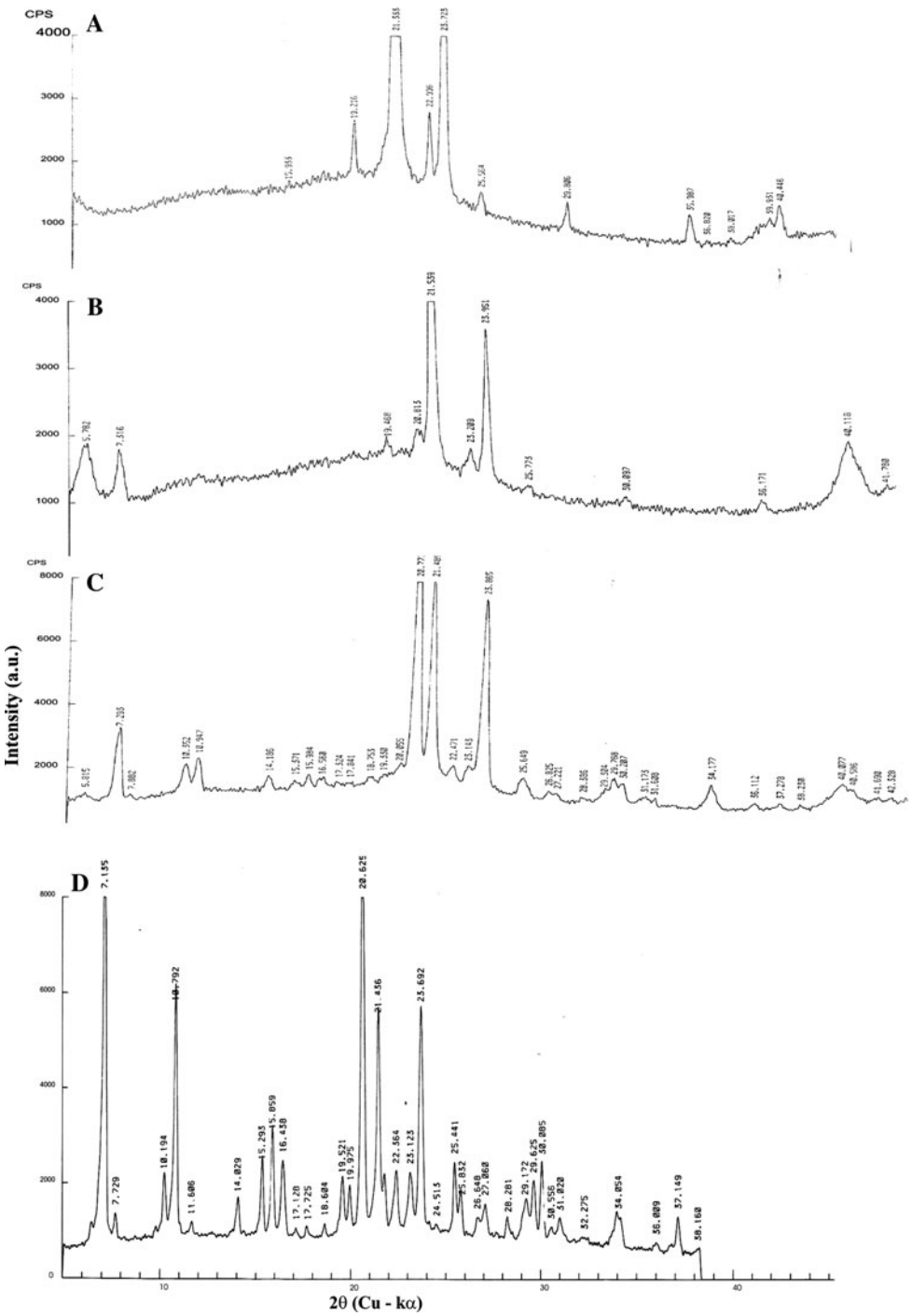

Fig. 2 XRD patterns; *A*, bees wax: *B*, microspheres made in the presence of gelatin: *C*, microspheres made in the presence of tween 20: *D*, flurbiprofen

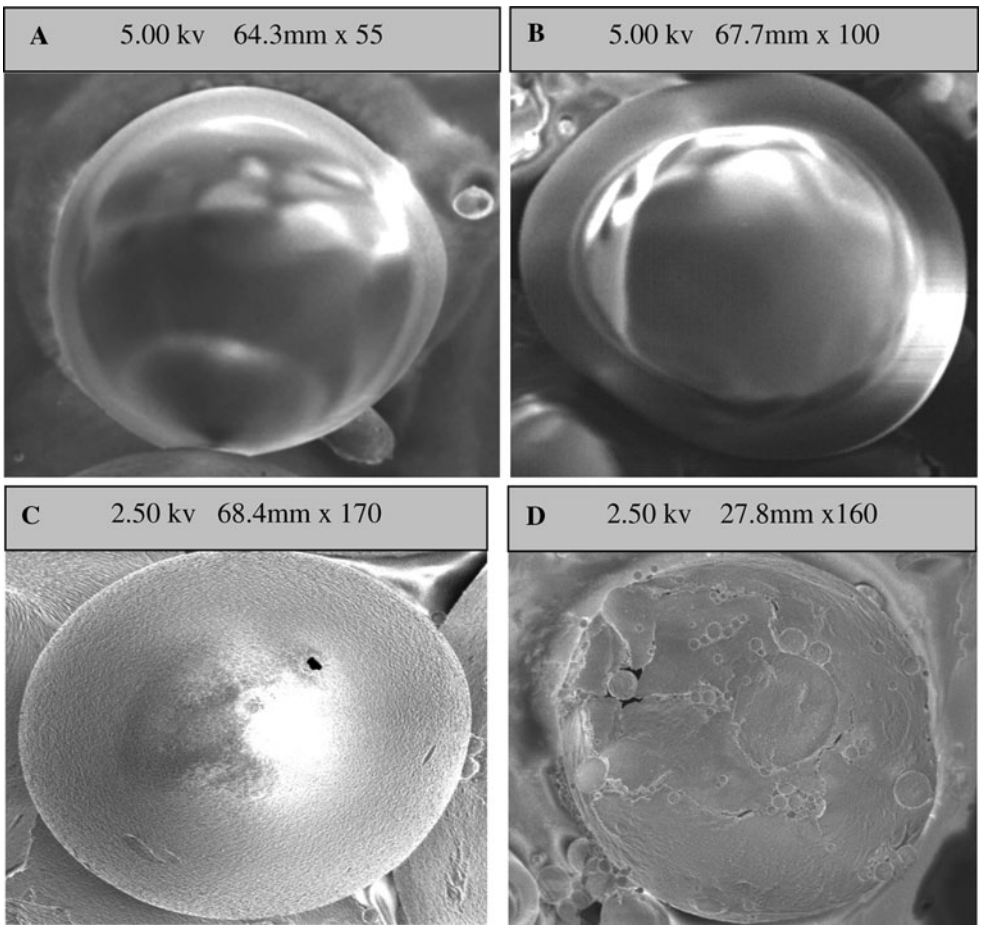

Fig. 3 SEM photographs; **a** blank microspheres made in the presence of tween 20: **b** flurbiprofen loaded microspheres (1:2) made in the presence of tween 20: **c** blank microspheres made in the presence of gelatin: **d** flurbiprofen loaded microspheres (1:2) made in the presence of gelatin

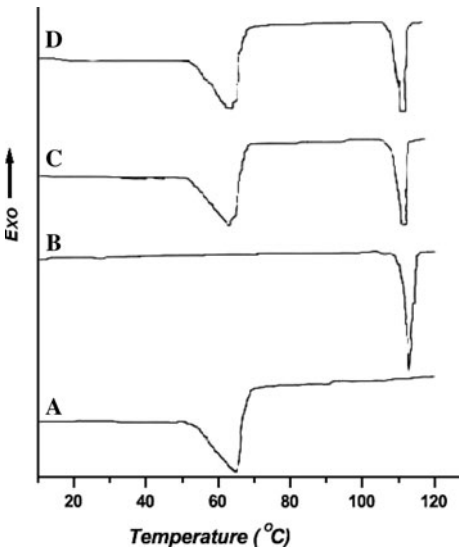

Fig. 4 DSC Thermograms of A = Bees wax, B = Flurbiprofen, C = Microspheres made with Tween 20 (1:2) and D = Microspheres made with Gelatin (1:2)

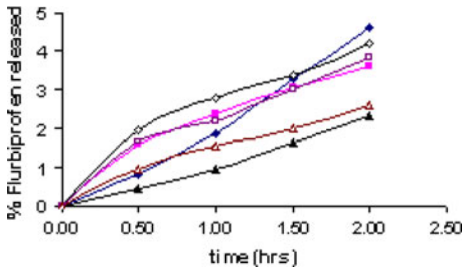

Fig. 5 Flurbiprofen released from various formulations of microspheres at pH 1.2. FB1 (*filled diamond*), FB2 (*filled square*), FB3 (*filled triangle*), FB4 (*open diamond*), FB5: (*open square*), FB6 (*open triangle*)

that for microspheres made in the presence of tween 20 as surfactant. The great encapsulation efficiency of microsphere prepared in the presence of tween 20 was due to the ability of tween 20 to prevent the drug loss to the external aqueous phase.

The results of hydration of beeswax microspheres showed the lipophilic behaviour of beeswax (Table 3). The

beeswax is not wetted by water due to high interfacial tension between water and beeswax, but the presence of surfactant causes lowering of this interfacial tension. The value of hydration of microspheres made in the presence of gelatin was less than that the value of hydration of microspheres made in the presence of tween 20 as surfactant. It was found that surfactant having a hydrophilic-lipophilic balance (HLB) value 17 was more appropriate to increase wet ability of lipophilic (beeswax) material with aqueous phase and promote drug incorporation in the microspheres. That may be due to the fact that surfactants with higher HLB values increase the dispersion of beeswax in aqueous phase as suggested by Gowda et al. [25].

The results of the micromeritic properties of all formulations of the microspheres are shown in Table 4**.** The results of compressibility index of all formulations of microspheres are ranging from 8 to 14, showing good flow characteristics of microspheres. The Hausner's ratio of all formulations was less than 1.25 indicating free flowing property [17]. This free flow behaviour of the microspheres is further confirmed by the results of angle of repose. The results of angle of repose of the microsphere formulations made by the use of gelatin are above 20 indicating the good flow properties of microspheres. The values of angle of repose of microspheres made in the presence of tween 20 are below 20 showing excellent flow behaviour of microspheres. The excellent flow properties of the microspheres made with tween 20 may be due to its high HLB value. The HLB value of tween 20 is seventeen while that of gelatin is 9.8. In addition to flow properties, the microspheres prepared in the presence of tween 20 were more smooth and spherical causing decrease in cohesive and adhesive forces between individual microspheres. Microspheres prepared with decreased drug to polymer ratio (FB 1 > FB 2 > FB 3 and FB 4 > FB 5 > FB 6) showed higher angle of repose because of large microspheres formed.

The FTIR spectra of flurbipren loaded microspheres (Fig**.** 1) showed characteristic broad peeks of flurbiprofen in the range of 2500–3500 cm^{-1} due to hydrogen bonding. The characteristic peaks of flurbiprofen at 1698 and 2920 cm^{-1} were due to carbonyl and hydrogen stretching respectively. From the FTIR studies, the characteristic bands for important functional group of pure drug, blank microspheres and drug-loaded microspheres showed that the characteristic bands of flurbiprofen were not altered after successful encapsulation. No chemical intractions between the drug and beeswax were observed [18].

The X-ray powder diffraction patterns of microspheres along with those of raw crystals of drug and beeswax are shown in Fig. 2. Significant reduction in the peak intensities was observed in the XRD patterns of both types of microspheres which indicate reduced crystallinity of drug.

SEM photographs (Fig. 3) showed the typical morphological appearance of beeswax microspheres in scanning electron microscope. The microspheres were spherical and possessed a continuous smooth surface. SEM of flurbiprofen loaded microspheres revealed that the surface texture of the microspheres becomes smooth as the percent of beeswax is increased. SEM also revealed that the surface of blank microspheres were more smooth than the surface of drug loaded microspheres. SEM photographs revealed the absence of crystals of drug on the surface of the microspheres made with tween 20 indicating uniform distribution of drug within these microspheres [25]. Microspheres prepared in the presence of gelatin are porous and have less smooth surface as compared to those which were prepared in the presence of tween 20. This evidence indicates that the surfactants of high HLB values produce more spherical and smooth surfaced microspheres and seem suitable for the production of solid lipid microspheres.

The drug can be either dispersed in crystalline or amorphous form in the polymeric matrix during the process of microencapsulation [26]. Any abrupt or drastic change in the thermal behavior of either the drug or polymer may indicate a possible drug-polymer interaction. The thermal curves of pure components and of the drug-polymer microspheres are presented in Fig. 4. A sharp exotherm ($T_{peak} = 116°C$) was observed for flurbiprofen at the temperature corresponding to its melting point. In the case of beeswax, exothermic peak was observed in the temperature range of 60–64°C. The characteristic, well recognizable thermal profile of the drug at the temperature corresponding to its melting point was also observed in flurbiprofen-beeswax micropspheres indicating absence of any possible drug-beeswax interaction. It appeared that

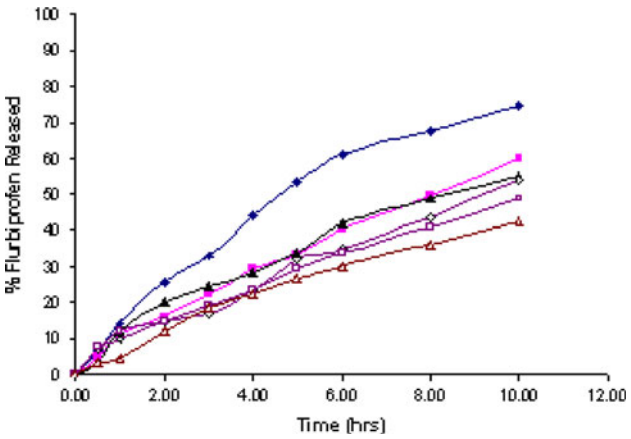

Fig. 6 Flurbiprofen released from various formulations of microspheres at pH 6.8. FB1 (*filled diamond*), FB2 (*filled square*), FB3 (*filled triangle*), FB4 (*open diamond*), FB5: (*open square*), FB6 (*open triangle*)

Table 5 Release kinetics of flurbiprofen from microspheres at pH 6.8

Formulations	Zero order kinetics		First order kinetics		Higuchi kinetics		Hixson–Crowell kinetics		Korsemeyer–Peppas kinetics	
	R^2	k_0	R^2	k_1	R^2	k_H	R^2	k_{HC}	R^2	n
FB 1	0.944	7.6708	0.624	0.3207	0.9746	26.216	0.6738	0.319	0.6692	1.1038
FB 2	0.9902	5.8472	0.6902	0.3125	0.9591	19.355	0.715	0.2928	0.7145	1.0573
FB 3	0.963	5.4633	0.6518	0.3121	0.974	18.479	0.6781	0.2863	0.7271	1.096
FB 4	0.9902	5.1639	0.6929	0.2931	0.9412	16.933	0.7063	0.2736	0.6576	0.9496
FB 5	0.9803	4.5598	0.6392	0.2734	0.9688	15.247	0.6524	0.2541	0.6109	0.888
FB 6	0.9739	4.3075	0.7372	0.3181	0.9649	14.421	0.7255	0.2733	0.8137	1.1114

there was a significant reduction of drug crystallinity in the microspheres because thermal peak of drug loss its sharp appearance in microspheres [27].

From the release studies, it was observed that there was less release of drug in the solution of gastric pH. In the first 2 h, at gastric pH, less than 5% of the drug release was observed (Fig. 5). This fact suggests that beeswax is gastro-resistant material and retard the release of drug in stomach and seems effective in lowering the side effects associated with flurbiprofen [25]. The microspheres showed a sustained release pattern at pH 6.8 (Fig. 6). Gelatin based microspheres showed greater release than tween 20 based microspheres. This might be due to the gelatin based microspheres were porous in nature and possessed drug crystals on surface as shown in SEM photographs of the microspheres.

The drug release from microspheres prepared at low drug-beeswax ratios was faster than that of microspheres prepared at high drug polymer ratios because of the small size of the microspheres provide a large surface area which causes fast drug release [18].

Five equations were used to study the drug release kinetics from the microspheres and the results are presented in Table 5. The methodology of drug release in waxy material is controlled by erosion/diffusion of drugs. In this study, drug release from the various waxy formulations exhibited zero order kinetics [28]. Our waxy microspheres showed a very good diffusion profile which best fitted to zero order (Table 5). Due to erosion of waxy material and diffusion of drug through the bees wax, a constant release rate was observed. It was further confirmed by n values. The results indicated that increasing the proportion of beeswax decreased the release rate of drug, which may be due to the slow rate of penetration of dissolution medium into the microspheres.

5 Conclusion

In this study, controlled release microspheres of flurbiprofen were prepared successfully utilizing beeswax as a retardant material by a simple emulsion congealing microencapsulation technique. The physical properties of microspheres and their drug release rates varied according to the drug entrapped in the microspheres. As the ratio of drug beeswax varied from 1:1 to 1:3, the release rate of flurbiprofen decreased. This study revealed that flurbiprofen loaded microspheres of beeswax can be used for the drug delivery at a constant rate. A significant effect of surfactant was found on production, physical properties and drug release. The surfactants of high HLB values seemed suitable for the preparation of microspheres of beeswax. Concerning the emulsion congealing technique, it is easy to apply, rapid, and inexpensive and does not require the use of organic solvents, which could be poisonous to the human body. This study also demonstrated the potential of waxes in the formulation of microspheres for water insoluble drugs.

References

1. Catherine CB, Srtephen W, Charles S, Curtis AG. Potential drug-cell delivery routes using maganetic nanoparticles. Eur Cells Mater. 2003;6:29–34.
2. Dandagi PM, Mastiholimath VS, Patil MB, Gupta MK. Biodegradable micro particulate system of captopril. Int J Pharm. 2006;307:83–8.
3. Giannola LI, De Caro V, Rizzo MC. Preparation of White Beeswax Microspheres loaded with Valproic Acid and Kinetic Study of Drug Release. Drug Dev Ind Pharm. 1995;21:797–807.
4. Wall BP, Perkin JE, Sunderland VB, Zorbas A. Dissolution and saliva concentrations of some lithium dosage forms. J Pharm Pharmacol. 1982;34:601–3.
5. Kamble R, Maheshwari M, Paradkar A, Kadam S. Melt solidification technique: incorporation of higher wax contents in ibuprofen beads. AAPS PharmSciTech. 2004;5:1–8.
6. Uner M, Gonulllu U, Yener G, Altinkurt T. A new appraoch for preparing controlled release ketoprofen tablets by using beeswax. Il farmaco. 2005;60:27–31.
7. Schaefer T, Holm P, Kristensen HG. Melt granulation in a laboratory scale high shear mixer. Drug Dev Ind Pharm. 1990;16:1249–77.
8. Bodmeier R, Wang J, Bhagwatwar H. Process and formulation variables in the preparation of wax microparticles by melt

dispersion technique for water insoluble drugs. J Microencapsul. 1992;9:89–98.
9. Paradkar AR, Ambike AA, Jadhav BK, Mahadik KR. Characterization of curcummin-PVP solid dispersion obtained by spray drying. Int J Pharm. 2004;271:281–6.
10. Obaidet AA, Obaidet RM. Controlled release of tramadol hydrochloride from matrices repared using glyceryl behenate. Eur J Pharm Biopharm. 2001;52:231–5.
11. Adeyeye CM, Price JC. Development and evaluation of sustained release ibuprofen-wax microspheres. I. Effect of formulation variables on physical characteristics. Pharm Res. 1991;8:1377–83.
12. Vergote GJ, Vervact C, Van Driessche I, Hoste S, De Smedt S, Demeester J, et al. In vivo evaluation of matrix pellets containing nanocrystalline ketoprofen. Int J Pharm. 2001;240:79–84.
13. Muhlen AZ, Schwartz C, Mehnert W. Solid lipid nanopsiticles (SLN) for controlled drug delivery—drug release and release mechanism. Eur J Pharm Biopharm. 1998;45:149–55.
14. Dollery C. Therapeutic drugs. New York: Churchill Livingstone; 1991. pp. F91–94.
15. Samati Y, Yuksel N, Tarimci N. Preparation and characterization of poly(D, L-lactic-co-glycolic Acid) microspheres containing flurbiprofen sodium. Drug Deliv. 2006;13:105–11.
16. Sah H. Microencapsulation techniques using ethyl acetate as dispersed solvent: effects of its extraction rate on the characteristics of PLGA microspheres. J Control release. 1997;47:233–45.
17. Shariff A, Manna PK, Paranjothy KLK, Manjula M. Entrapment of andrographolide in cross linked alginate pellets: h. physicochemical characterization to study the pelletization of andrographolide. Pak J Pharm Sci. 2007;20:1–9.
18. Tayade TP, Kale DR. Encapsulation of water insoluble drug by a cross linking technique: effect of process and formulation variables on encapsulation efficiency, particle size and in vitro dissolution rate. AAPS PharmSci. 2004;6(1):article12.
19. Najib N, Suleiman M. The kinetics of drug release from ethyl cellulose solid dispersion. Drug Dev Ind pharm. 1985;11:2169–89.
20. Desai SJ, Singh P, Simonelli AP, Higuchi WI. Investigation of factors influencing release of solid drug dispersed in inert matrices. II. Quantitative studies involving polyethylene plastic matrix. J Pharm Sci. 1966;55:1230–4.
21. Higuchi T. Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrix. J Pharm Sci. 1963;50:1145–9.
22. Hixon AW, Crowel JH. Dependence of reaction velocity upon surface and agitation: I- Theoretical considerations. Ind Eng Chem. 1931;23:923–31.
23. Peppas NA. Analysis of fickian and non-fickian drug release from polymer. Pharm Acta Helv. 1985;60:110–1.
24. Varshosaz J, Keihanfar M. Development and evaluation of sustained-release propranolol wax microspheres. J Microencapsul. 2001;18:277–84.
25. Gowda DV, Shivakumar HG. Preparation and evaluation of waxes/fat microspheres loaded with lithium carbonate for controlled release. Indian J Pharm Sci. 2007;69:251–6.
26. Bodmeier R, Chen H. Preparation and characterization of microspheres containing the anti-inflammatory agents, indomethacin, ibuprofen, and ketoprofen. J Control Release. 1989;10:167–75.
27. Jones DS, Pearce KJ. Investigation of the effects of some process variables on, microencapsulation of propranolol HCl by solvent evaporation method. Int J Pharm. 1995;118:99–205.
28. Ishino R, Sunada H. Studies on application of wax matrix system for controlled drug release. Chem Pharm Bull. 1993;41:586–9.