Available online at www.sciencedirect.com
SCIENCE DIRECT
International Journal of Pharmaceutics 308 (2006) 124–132
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies

M. Jelvehgari [a], M.R. Siahi-Shadbad [a], S. Azarmi [a], Gary P. Martin [b], Ali Nokhodchi [c,d,*]

[a] *School of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran*
[b] *King's College London, Pharmacy Department, 150 Stamford St., Franklin-Wilkins Building, London SE1 9NH, UK*
[c] *Medway School of Pharmacy, University of Kent and Greenwich, Central Ave., Chatham, Kent ME4 4TB, UK*
[d] *Drug Applied Research Center, Tabriz University of Medical Sciences, Iran*

Received 23 June 2005; received in revised form 10 September 2005; accepted 3 November 2005
Available online 15 December 2005

Abstract

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and athletes foot. Skin irritation is a common side effect, and it has been shown that controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, the aim of the present study was to produce ethylcellulose microparticles containing BPO which were able to control the release of BPO to the skin. In order to optimize the microparticle formulation, factors affecting the physical properties of microparticles were also investigated. Benzoyl peroxide microparticles were prepared using an emulsion solvent diffusion method by adding an organic internal phase containing benzoyl peroxide, ethyl cellulose and dichloromethane into a stirred aqueous phase containing polyvinyl alcohol. Drug content, particle size analysis and loading yield were determined in the prepared microparticles. BPO microparticles were then incorporated into standard vehicles for release studies. Scanning electron microscopy was used to study the shape and morphology of the microsponges. The micrograph of microsponges showed that they were spherical in shape and contained pores. These pores resulted from the diffusion of solvent from the surface of the microparticles and thus the particles were designated as microsponges. It was shown that the drug:polymer ratio, stirring rate, volume of dispersed phase influenced the particle size and drug release behavior of the formed microsponges and that the presence of emulsifier was essential for microsponge formation. The results showed that, generally, an increase in the ratio of drug:polymer resulted in a reduction in the release rate of BPO from microsponges which was attributed to a decreased internal porosity of the microsponges.

Keywords: Microsponge; Particle size; Porosity; Drug release

1. Introduction

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and, more recently, athlete's foot. The use of BPO has advantages in comparison to the use of antibiotics because potential bacterial resistance is avoided, and it is also preferred over keratolytic agents due to its bactericidal effect. Benzoyl peroxide is available as a lotion, cream and gel (Chellquist and Gorman, 1992) but these dosage forms are liable to produce skin irritation, particularly at the beginning of treatment (Fares et al., 1996). Skin dryness, peeling, as well as transient local edema may occur and contact sensitization has also been reported in some patients using preparations containing benzoyl peroxide. The degree of irritation is believed to be related to the amount of BPO present in the skin (Fulton and Bradley, 1974) which the encapsulation of benzoyl peroxide can reduce the side-effects to a great extent (Arabi et al., 1996; Puranik et al., 1992). For example, it has been shown that the controlled release of BPO reduced skin irritation due to the reduction in release rate of the drug from formulation (Wester et al., 1991).

The controlled release of drug from the formulation into the epidermis such that the drug remains primarily localized with only a restricted amount entering the systemic circulation, is a means of controlling side-effects. There is a need to maximize the time for the active ingredient to remain on the skin while minimizing transdermal penetration. Another potential problem in topical delivery of drugs relates to the use of unaesthetic vehi-

* Corresponding author. Tel.: +44 1634883846; fax: +44 1634883927.
E-mail address: a.nokhodchi@gre.ac.uk (A. Nokhodchi).

0378-5173/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2005.11.001

cles which may be greasy, sticky and may cause discolorations, since this can result in the lack of patient compliance (Embil and Nacht, 1996).

The selection of a particular encapsulation method is primarily determined by the solubility characteristics of the drug and polymer (Rainer and Bodmeier, 1990). A popular method for the encapsulation of water-insoluble drugs within water insoluble polymers is the diffusion solvent method (Kawashima et al., 1988; Perumal et al., 1999b). This method can be both readily performed in the laboratory but has scale up potential such that large volumes of water can be handled.

When finally developing a microencapsulation procedure then finally selected method should ideally produce (Fong, 1988) (a) high yields of microparticles and free of extensive agglomeration, (b) a high of encapsulation of the core material, (c) a reproducible release profile from batch to batch, and (d) an ability to modify in vitro release rates by varying process parameters in order to prepare microparticles with the desired in vivo release characteristics.

The purpose of the present investigation was to (a) prepare BPO microparticles using ethyl cellulose with different drug:polymer ratios using an emulsion solvent diffusion method, (b) study the effect of drug:polymer ratio, solvent:polymer ratio, stirring rate and emulsifier concentrations on the physical characteristics of the microparticles, and (c) compare the release rate and flux of BPO from microparticles incorporated in topical formulations with that of the same formulations prepared with pure BPO.

2. Materials and methods

2.1. Materials

The following materials were used in the study: benzoyl peroxide, poly vinyl alcohol (MW = 1,06,000–1,10,000 Da), dichloromethane, acetone, methanol, benzophenone, liquid paraffin, triethanolamine, stearic acid, all obtained from Merck (Darmstadt, Germany). Ethyl cellulose 46 cP (5% w/w solution in 80/20 toluene/ethanol) was purchased from Sigma–Aldrich (St. Louis, USA). Silastic membrane was provided by Biogene (Mashad, Iran). Filter papers with the pore size of 0.45 μm were purchased from Millipore (Maidstone, UK) and white beeswax was supplied by Thorton and Ross (Huddersfield, UK). All other chemicals and solvents were of analytical grade.

2.2. Preparation of microparticles

BPO microparticles were prepared by an emulsion solvent diffusion method. In this method, the organic internal phase containing BPO and ethyl cellulose in 20 ml dichloromethane was gradually added into 60 ml distilled water which contained different concentrations of polyvinyl alcohol (PVA) as emulsifying agent. The mixture was stirred for 8 h, at 25 °C to remove dichloromethane from the reaction flask. The formed microparticles were filtered and washed with distilled water before being tray-dried at room temperature. For the evaluation of the effect of drug:polymer ratio on the physical characteristics of microparticles, different weight ratios of drug to ethyl cellulose (1:1, 3:1, 5:1, 7:1, 9:1, 11:1, 13:1) were employed. In all these formulations, the total amount of polymer and emulsifier were kept constant. To optimize the particle size, size distribution and the drug release from the microparticles, an individual formulation was selected (MDS13) and a series of the microsponges were prepared using different stirring rates. However, for optimizing the preparation method, the concentration of polyvinyl alcohol, type and volume of organic solvent and volume of aqueous phase were changed, and the characteristics of the prepared microparticles were evaluated.

2.3. Viscosity measurement

A Brookfield rotational digital viscometer DVLV-II was used to measure the viscosity (cP) of the internal and external phases at 25 °C. Spindle number 1 was rotated at 100 rpm.

2.4. Scanning electron microscopy (SEM)

The morphology of microparticles was examined with a scanning electron microscope (LEO 440i, UK) operating at 15 kV. The samples were mounted on a metal stub with double adhesive tape and coated with platinum/palladium alloy under vacuum.

2.5. Particle size analysis

Scanning electron micrograph images of particles were obtained. The size of a minimum of 100 randomly selected particles were processed from the acquired SEM images using an image analysis software package (Scion image analysis). These data were converted to size percent values using the total number of particles and then plotted as a function of particle size on a probability scale. The probability plot directly provides the mean particle size values.

2.6. Pore volume and pore size determination of MDS

Pore analysis of microparticles was carried out using mercury intrusion porosimetry (Pascal 140, Italy). During the test, a sample of microparticles was placed in vacuum chamber and submerged under a pool of mercury contained within a volume-calibrated cell. As pressure was gradually increased on the cell, mercury was forced into progressively smaller pores of the micropartiles. Thus, the apparent volume of mercury within the calibrated cell was reduced as it penetrated into the microsponges.

2.7. Determination of true density

The true density of microparticles and BPO was measured using an ultrapycnometer 1000 (Quantachrom, USA) under helium gas and was calculated from a mean of five determinations.

2.8. Determination of drug content

The quantitative determination of BPO in microparticles was carried out using a reversed phase isocratic HPLC (Shimadzu HPLC Class VP series) with two LC-10AT VP pumps, UV–vis Detector SPD-10A VP, and RP C-18 column (250 mm × 4.6 mm, particle size 5 μm; YMC Inc., Wilmington, NC, USA). The HPLC system was equipped with Class-VP series software, version 5.03 (Shimadzu, Japan).

A mixture of methanol/distilled water (75:25) was used as the mobile phase. The filtered mobile phase was pumped at a flow rate of 1.2 ml/min and the eluent was monitored using a UV detector at 254 nm. Data were acquired, stored and analyzed with the Class-VP series software, version 5.03. Benzophenone was used as internal standard in the concentration of 50 μg/ml and the retention times were found to be 7.2 and 11.3 min for benzophenone and BPO, respectively. A good linear relationship was found to exist between the peak areas of BPO standard/internal standard in different concentration ratios. Studies were carried out to estimate the precision and accuracy of this HPLC method for analysis of BPO. The standard curve was used to estimate the concentration of BPO in microsponges and each determination was calculated in triplicate and the mean of concentrations reported.

2.9. Determination of loading efficiency and production yield

The loading efficiency (%) was calculated according to the following equation:

$$\text{loading efficiency} = (\text{actual BPO content in microparticles} / \text{theoretical BPO content}) \times 100$$

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges obtained (Kilicarslan and Baykara, 2003). All the experiments were performed in triplicate and the mean of the values was reported.

2.10. Preparation of benzoylperoxide microsponge creams

Creams were prepared using a standard reverse emulsification method. Aqueous phase containing 5 g triethanolamine was added dropwise into an oil phase containing stearic acid 20 g, liquid paraffin 5 g, and white bees wax 3 g while the mixture was stirred at 400 rpm. The temperature of the aqueous phase and oil phase was adjusted to 70 and 65 °C, respectively. The mixture was stirred, while allowing it to cool to room temperature and whilst a cream formed. At this point either BPO powder or BPO microparticles was added to the formulation and mixed to prepare a homogenous cream.

2.11. Drug release studies

Three different cream formulations containing 2.5, 5 and 10% w/w either BPO powder or BPO microparticles were prepared. The release studies were conducted using Franz diffusion cells (ERWEKA, Germany). Silastic membrane was fitted into place between the two chambers of cells. The receptor phase composed a mixture of acetone:water (50:50) and the temperature was maintained at 37 °C. The exceedingly low solubility of BPO in either water or normal saline solution necessitated the use of a water–acetone mixture so as to provide adequate "sink" conditions. Preliminary experiments showed no interactions of the receptor phase mixture with either the membrane or the formulations placed on the "donor" side. The receptor phase was stirred at 700 rpm during the study. A pre-determined amount of cream was mounted on the donor side of Franz cell. Samples were withdrawn at different time intervals and these were analyzed using HPLC according to the method outlined above. Each test was carried out in triplicate and the mean of three observations was reported.

3. Results and discussion

3.1. The effect of drug:polymer ratio on the produced microparticles

SEM images showed the microparticles to be porous and to have spherical shape (Fig. 1). The pores were induced by the diffusion of the solvent from the surface of the microparticles (Crotts and Park, 1995). The appearance of the particles was such that they were termed microsponges. The results of the effect of drug:polymer ratio on production yield, drug loading efficiency and mean particle size are shown in Table 1. As can be seen from this table, the production yield, loading efficiency and mean particle size of microsponges can be greatly affected by the drug:polymer ratio. When drug:polymer ratio was 1:1, the production yield was very low (less than 15%), therefore, no further investigations were carried out on this ratio. Generally, increasing the drug:polymer ratio increased the production yield, however, when the ratio of the drug–polymer increased from 11:1 to 13:1 the increase in the production yield was not significant. This showed that the highest production yield was obtained when the ratio of drug:polymer was 11:1 or 13:1. The reason for increased production yield at high drug:polymer ratios

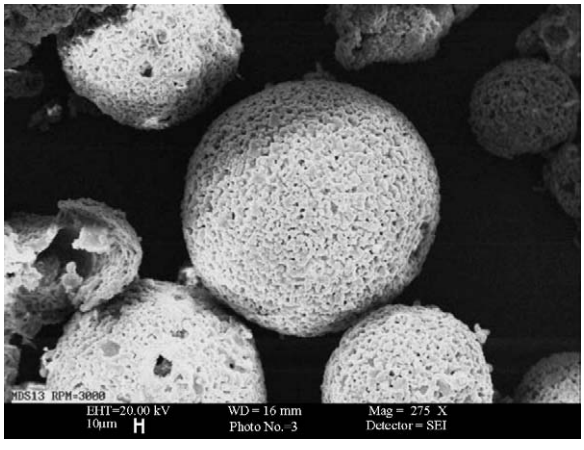

Fig. 1. SEM of a spherical microsponge containing BPO.

Table 1
Effect of drug:polymer ratio on drug loading efficiency, production yield and particle size of benzoyl peroxide microsponges (microsponges were prepared under a stirring rate of 4000 rpm)

Formulations	Drug:polymer ratio	Production yield (% ± S.D.)	Theoretical drug content (%)	Mean amount of drug entrapped (%)	Drug loading efficiency (% ± S.D.)	Mean particle size (μm ± S.D.)
MDS1	1:1	<15	–	–	–	
MDS3	3:1	51.55 ± 1.24	69.23	49.37	71.31 ± 3.31	442.2 ± 50.3
MDS5	5:1	55.38 ± 1.91	78.94	63.16	80.01 ± 1.32	419.7 ± 79.2
MDS7	7:1	60.01 ± 3.53	84.00	74.54	88.74 ± 1.25	364.5 ± 39.1
MDS9	9:1	63.21 ± 0.79	87.10	85.38	98.03 ± 2.16	317.6 ± 47.0
MDS11	11:1	67.48 ± 1.17	89.19	83.44	93.56 ± 0.81	356.3 ± 74.4
MDS13	13:1	67.84 ± 2.10	90.70	87.17	96.11 ± 0.7	310.3 ± 34.3

MDS: microsponge delivery system.

could be due to the reduced diffusion rate of dichloromethane from concentrated solutions into aqueous phase. This provides more time for the droplet formation and may improve the yield of microparticles (Lee et al., 1999). At all ratios of drug–polymer employed, the mean amount of drug entrapped in the prepared microsponges was lower than the theoretical value, since the drug loading efficiency did not reach 100%. This can be accounted for by dissolution of some drug in the solvent or aqueous phase employed. The results of loading efficiency showed that the higher drug loading efficiencies were obtained at the higher drug:polymer ratios. For example, for MDS9, MDS11 and MDS13 the drug loading efficiencies were above 90%. Use of the higher amounts of BPO when preparing microsponges at higher drug:polymer ratios caused slightly an increased viscosity of the dispersed phase. When dichloromethane diffuses out, nearly all of the dispersed phase is converted to the form of solid microsponges and separated particles appear. The highest drug loading efficiency of these formulations can be explained through the fact that the amount of drug in per unit polymer is greater than that in other formulations. Table 1 also shows that the ratio of drug to polymer played an important role in the formation of the resultant microsponges. It was found that

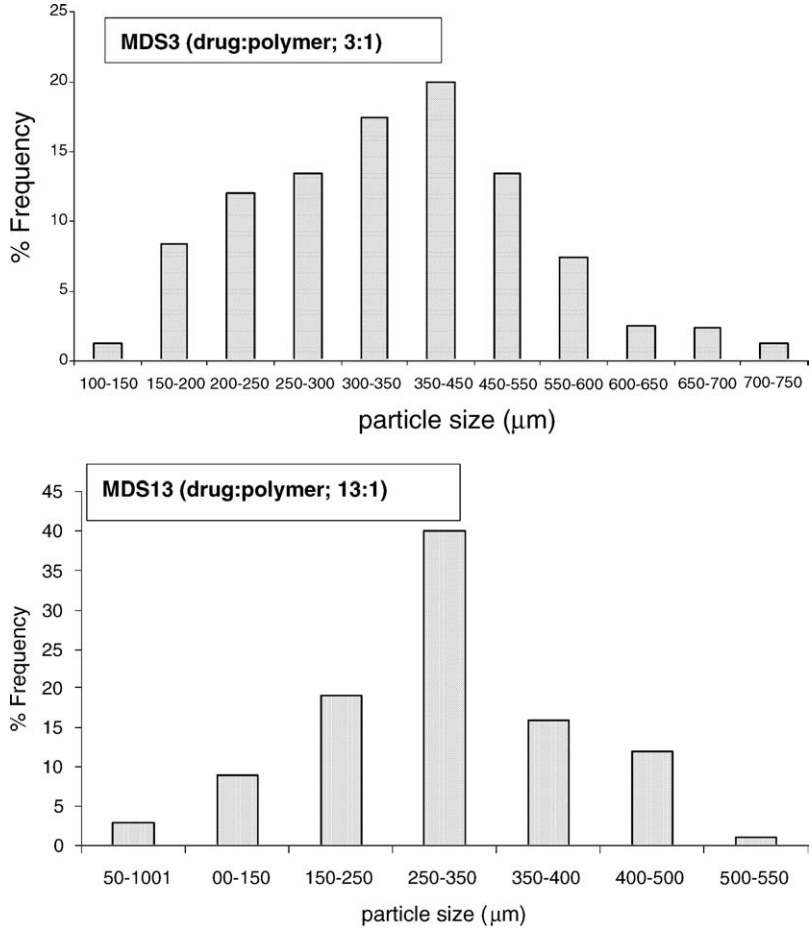

Fig. 2. Particle size distribution of microsponges produced with different ratios of drug:polymer.

Table 2
Effect of stirring rate on the drug content, production yield and particle size benzoyl peroxide microsponges, prepared using a drug:polymer ratio of 13:1

	Stirring rate (rpm)			
	4000	3000	2000	1000
Mean diameter ± S.D. (μm)	310.3 ± 34.3	374.2 ± 42.3	402.9 ± 46.6	603.9 ± 58.4
Drug content (%)	87.17 ± 2.21	71.23 ± 4.02	64.93 ± 5.74	54.83 ± 4.8
Production yield (%)	31.96 ± 1.73	41.07 ± 1.50	48.93 ± 2.90	55.00 ± 3.1
Theoretical drug content (%)	90.70	90.70	90.70	90.70

by increasing the drug:polymer ratio, the mean particle size was decreased. For example, when the ratio of drug:polymer increased from 3:1 to 13:1 the mean diameter of microsponges was decreased from 419.7 to 310.3 μm.

In order to better analyses the effect of drug:polymer ratio on particle size of microsponges, the resultant particle size distribution for each formulation was constructed. As examples the particle size distribution of MDS3 (ratio of drug:polymer was 3:1) and MDS13 (ratio of drug:polymer was 13:1) are shown in Fig. 2. The particle size distribution for higher drug:polymer ratio was found to be narrower than that of the lower drug:polymer ratio. The mean particle size of original BPO powders is about 613 μm which is larger than most of produced microparticles (Table 1).

3.2. Effect of stirring rate

The effect of stirring rate on the physical characteristics of the formulated microsponges was examined for formulation MDS13. The results of stirring rate on the mean particle size diameter of microsponges, drug content and production yield are listed in Table 2. The results showed that increasing the stirring rate from 1000 to 4000 rpm decreased the production yield but the drug content increased from 54.83 to 87.17%. This indicates that the drug loss was decreased as the stirring rate was increased. It was found that the drug loss was reduced linearly as the stirring rate was increased (Fig. 3). It was observed that at the higher stirring rates employed, due to the turbulence created within the external phase, polymer then adhered to the paddle and production yield decreased. Table 2 also shows that the stirring rate employed had a marked effect on particle size diameter. It has been reported that the stirring rate of the emulsion at the time of manufacture influences the particle size (Barkai et al., 1990) and,

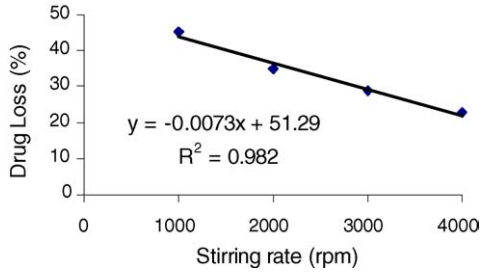

Fig. 3. Linear relationship between percentage drug loss and stirring rate.

in some cases, the size distribution of the prepared microparticles (Nixon and Hassan, 1980). Hence, a suitable stirring rate to optimize particle size, size distribution and subsequent drug release from microsponges was needed. Our study showed that an increase in the stirring rate resulted in a reduction in mean particle size. Any increase in mean particle size at lower stirring rates can be attributed to the increased tendency of globules to coalescence and aggregate. On the other hand, at higher stirring rates, a vigorous, uniform, increased mechanical shear, is imposed and this results in a rapid dispersion of the formed droplets which may have less chance of coalescing into bigger droplets. This suggests that the size of the droplets formed during the encapsulation process may therefore be closely related to the size of the final microsponges produced (Perumal, 2001).

3.3. Effect of the composition of internal and external phases on the produced microparticles

Table 3 shows the effects of internal phase and external phase compositions on the particle size, percentage yield, and drug content of different formulations. The results show that

Table 3
The effect of internal and external phases composition on microsponge properties

Formulation Code	Internal phase composition			External phase composition		Yield (%)	Mean diameter μm ± S.D.	Drug content (%)	Theoretical drug content (%)
	BPO amount (g)	Polymer amount (g)	Dichloromethane (ml)	Water (ml)	PVA (g)				
MDS13-A	2.6	0.2	20	60	–	–	–	–	–
MDS13-B	2.6	0.2	20	60	2.8	53.57 ± 0.7	237.6 ± 27.2	93.26 ± 0.6	90.70
MDS13-C	2.6	0.2	20	60	11.2	47.50 ± 0.4	330.5 ± 74.2	77.87 ± 0.9	90.70
MDS13-D	2.6	0.2	20	30	5.6	28.93 ± 0.2	248.2 ± 31.7	76.23 ± 0.8	90.70
MDS13-E	2.6	0.2	20	120	5.6	58.21 ± 0.5	348.7 ± 40.3	83.87 ± 0.6	90.70
MDS13-F	2.6	0.2	5	60	5.6	59.29 ± 0.7	545.2 ± 115.9	86.95 ± 0.8	90.70
MDS13-G	2.6	0.2	10	60	5.6	57.50 ± 0.6	416.4 ± 49.5	72.21 ± 0.8	90.70
MDS13-H	2.6	0.2	15	60	5.6	47.85 ± 0.4	353.7 ± 33.5	66.67 ± 0.6	90.70

decreasing the solvent volume (dichloromethane) increases the particle size of microsponges (comparing formulations MDS13-F, MDS13-G and MDS13-H). When the viscosity of the internal phase of these formulations was investigated it was found that particle sizes of microsponges were directly proportional to the apparent viscosity of dispersed phase. The results showed that the apparent viscosities of the polymer solution containing 5, 10 and 15 ml of dichloromethane were 139, 52 and 33.3 mPa s. The apparent viscosity of the external phase was 20.4 mPa s. It is apparent that the larger the difference between the apparent viscosity of the dispersed and continuous phases the larger mean particle sizes of microsponges. When the dispersed phase with higher viscosity (MDS13-F containing 5 ml dichloromethane) was poured into the continuous phase (external phase), due to the higher viscosity of the internal phase, the globules of the formed emulsion can hardly be divided into smaller particles and bigger droplets were found and mean particle sizes increased. In other studies, Barkai et al. (1990) and Pongpaibul et al. (1984) showed that the particle size depends on the solvent volume and the drug:polymer ratio, when the solvent diffusion method is utilized for preparing microparticles. Table 3 also shows that when the amount of dichloromethane was increased from 5 to 15 ml the production yield and drug content of microsponges decreased. This is due to the lower concentration of the drug in the higher volume of dichloromethane. The effect of dichloromethane volume on the morphology of microsponges was also investigated. SEM of microsponges showed that the content of dichloromethane affected the morphology of the microsponges with a greater sphericity being obtained when the amount of dichloromethane was 15 ml (Fig. 4).

It was found that a decrease in the volume of external phase (water), resulted in decreases in the production yield, mean particle size and drug content (comparing MSD13-D and MSD13-E in Table 3). The type and concentration of emulsifier has a key role to play in the preparation of microspheres (Perumal et al., 1999a). Without the addition of emulsifier it is impossible to form microspheres (MDS13-A). When the concentration of emulsifier was decreased, the production yield, and drug content increased whereas the mean particle size of microsponges decreased (comparing formulations MDS13-B and MDS13-C in Table 3). The emulsifier employed was non-ionic and molecules can associate away from the oil-water interface at higher concentrations. Such alternative hydrophobic region can dissolve some portions of drug resulting in a reduction in drug content and production yield within the microsponge formulations. An increase in mean particle size of microsponges with an increase in the emulsifier concentration can be attributed to an increase in apparent viscosity at increased emulsifier concentrations. Such increased viscosity would result in larger emulsion droplets and finally in greater microsponge size (the apparent viscosities of formulations containing 2.8 or 11.2 PVA were 15.7 or 18.9 mPa s, respectively).

3.4. In vitro release studies

Different weights of BPO microsponges (2.5, 5 and 10% w/w) were incorporated into the cream formulation and

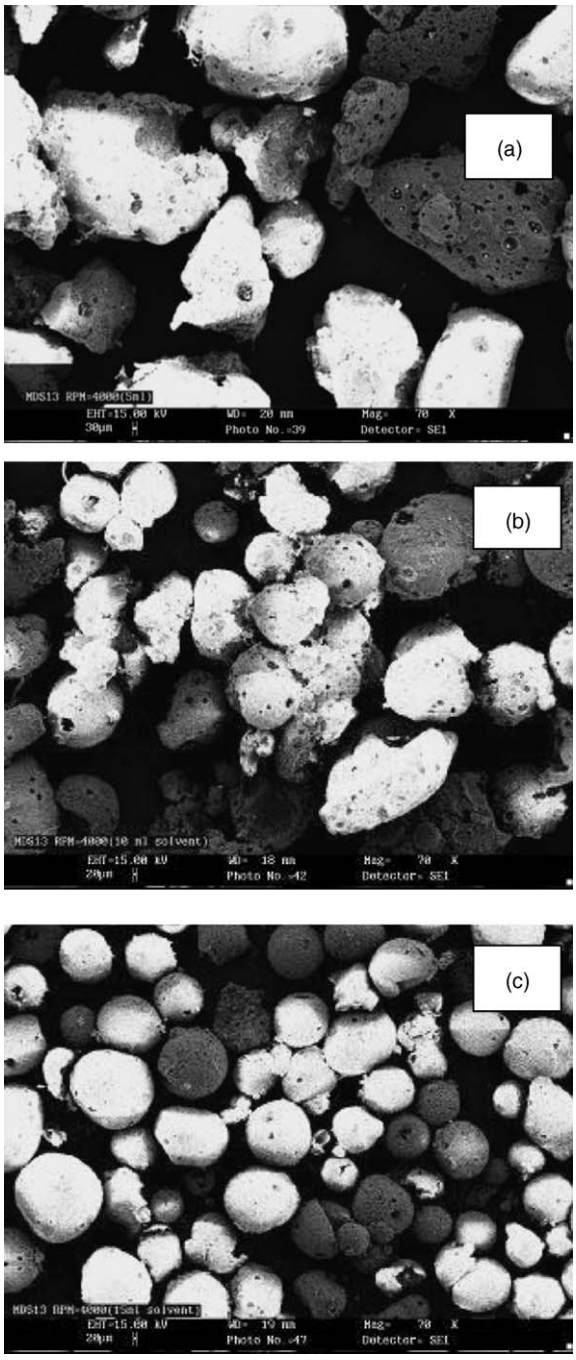

Fig. 4. The effect of dichloromethane volume on the morphology of BPO microsponges: (a) 5 ml; (b) 10 ml; (c) 15 ml.

the drug release from the resultant formulations was studied. The effect of drug:polymer ratio on the release of the drug from cream formulations containing 2.5, 5 and 10% microsponges are shown in Figs. 5–7, respectively. Different kinetic models (first-order release, Higuchi equation, Weibull model and zero-order release) were employed to fit the data relating to the kinetics of the release of BPO from microsponges. The results showed that the release kinetics on the basis of the highest r^2 values best-fitteda zero-order kinetic model. Analysis of variance showed that these correlations are statistically significant ($p < 0.05$). So, in all graphs, a linear relationship between Q (the cumulative

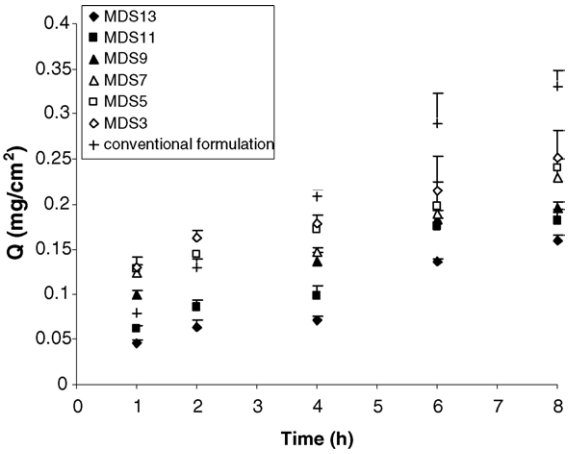

Fig. 5. The effect of ratio of drug:polymer on the release rate of BPO from cream formulations containing 2.5% microsponges.

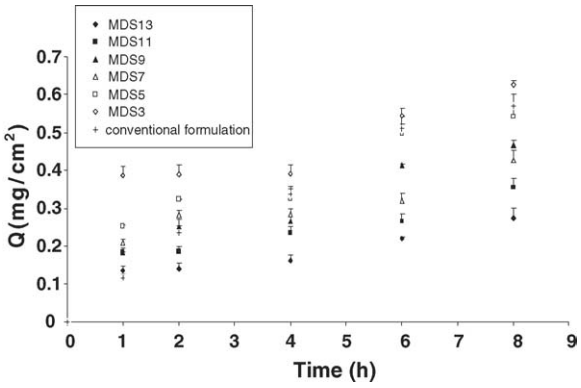

Fig. 6. The effect of ratio of drug:polymer on the release rate of BPO from cream formulations containing 5% microsponges.

amount of drug penetrated through the unit surface area of the membrane) and time was obtained after 1 h (see r^2 values in Table 4). The cumulative amount released increased with an increase in concentration of active ingredient in the formula. The rate of drug released over the first hour was higher compared to the rate of drug release over the second hour (Figs. 5–7). This could be due to the presence of non-encapsulated BPO in these formulations. When the free BOP was released, the flux remained constant for the next 7 h and this slower flux is likely to indicate the release of entrapped drug from microsponges. Slopes of the linear portion of the release profiles were calculated. These slopes represented the rate of release or flux of BPO from different formulations (Table 4). The table shows the rate of release of BPO or flux (mg/cm^2 h) is a function of its concentration in the formula. For example, the fluxes for cream formulations (MDS13 formulations in Table 4) containing 2.5, 5 and 10% w/w BPO microsponges were 0.0168, 0.020 and 0.0359 mg/cm^2 h, respectively. Previously published data (Yeung et al., 1983) have shown similar findings. In contrast to the other studies (Kilicarslan and Baykara, 2003; Pongpaibul et al., 1984; Comolu et al., 2003; Kim et al., 1994) the present study showed that generally an increase in the ratio of drug:polymer resulted in a reduction in release of BPO from microsponges. This is in contrast to other studies which have been suggested that the formation of a thicker matrix wall in microsponges with smaller drug:polymer ratios lead to a longer diffusion path, and consequently slower drug release rates. Similar observations to our results have been made previously for ketoprofen

Table 4
The effect of drug:polymer ratio on the release characteristics of BPO from different microsponge formulations

Formulation code	Cream 2.5%				Cream 5%				Cream 10%			
	Flux[a] (mg/cm^2 h)	Intercept (mg/cm^2)	r^2	Q_8[b] (mg/cm^2)	Flux (mg/cm^2 h)	Intercept (mg/cm^2)	r^2	Q_8 (mg/cm^2)	Flux (mg/cm^2 h)	Intercept (mg/cm^2)	r^2	Q_8 (mg/cm^2)
Pure BPO	0.0365	0.054	0.984	0.331	0.0689	0.05	0.980	0.571	0.1038	0.10	0.933	0.873
MDS3	0.0162	0.11	0.979	0.251	0.0394	0.21	0.960	0.503	0.0461	0.30	0.963	0.645
MDS5	0.0156	0.11	0.989	0.241	0.0397	0.18	0.958	0.490	0.0463	0.26	0.945	0.614
MDS7	0.0156	0.11	0.989	0.230	0.0351	0.18	0.871	0.496	0.0380	0.23	0.954	0.564
MDS9	0.0136	0.09	0.947	0.196	0.0346	0.15	0.888	0.466	0.0413	0.19	0.951	0.551
MDS11	0.0184	0.04	0.927	0.182	0.024	0.14	0.933	0.354	0.0362	0.18	0.959	0.480
MDS13	0.0168	0.02	0.939	0.159	0.020	0.10	0.947	0.275	0.0359	0.14	0.973	0.438

[a] Flux was obtained from regression analysis between the amount of drug release per unit surface area and time.
[b] Q_8 is the amount of drug release per unit surface area after 8 h.

Table 5
Results obtained from porosimetry experiments carried out on different microsponge formulations

Ratio of drug: polymer	Total cumulative volume (cm^3/g)	Total specific surface (m^2/g)	Pore radius (μm)	Porosity (%)	Bulk density (g/cm^3)	True density (g/cm^3)
MDS3 (3:1)	3.968	0.651	23.973	22.43	0.125	1.662
MDS5 (5:1)	2.448	0.518	17.080	15.39	0.129	1.146
MDS7 (7:1)	1.920	0.385	17.184	14.17	0.178	1.490
MDS9 (9:1)	1.764	0.420	17.599	12.13	0.206	1.346
MDS11 (11:1)	1.623	0.292	20.030	11.02	0.219	1.382
MDS13 (13:1)	1.447	0.265	24.488	9.87	0.378	1.241

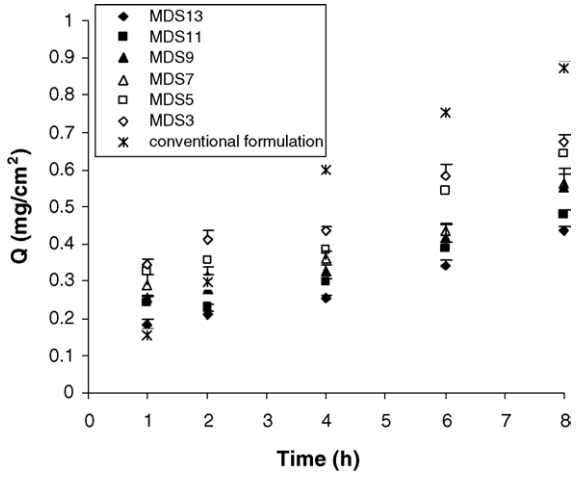

Fig. 7. The effect of ratio of drug:polymer on the release rate of BPO from cream formulations containing 10% microsponges.

microsponges (Comolu et al., 2003), but no simple explanation is apparent. The retarding effect apparent when higher percentages of drug were employed in this study shows that other parameters other than matrix wall thickness are involved in controlling the release rate of BPO from microsponges. Pore analysis of the microsponges produced in this study was carried out (Table 5). It has been reported that the pore diameter can have a significant effect on the release rate of the ingredient, and can also affect the migration of the active ingredient from the microsponge particle into the vehicle in which the material is dispersed. As an example, it has been reported that for menthol in various MDS, a linear relationship was obtained when the release rate constant was plotted as a function log pore diameter, indicating that rate of release was proportional to the cross-sectional area of the pore diameter (Embil and Nacht, 1996). Such a relationship between pore diameters and the release rate of BPO from microsponges in this study was not appeared. The results indicated that in addition to pore diameter, the number of pores may be an important factor in controlling the release rate of BPO from microsponges. In order to seek to determine the effect of the number of pores on release rate of BPO from microsponges, the total porosity of microsponges, total surface area and total volume of pores of microsponges were calculated (Table 5). The results show that generally, the lower release rate was obtained for microsponges with a low porosity, low surface area and low volume. Therefore, a reduction in release rate could be due to the low porosity of microsponges in MDS13 (Table 5). The results also show that the Q_8 values (i.e. the amount of BPO released after 8 h) were lower for the microsponges with lower porosity of microsponges (see Tables 4 and 5).

The main site of pharmacological action is the pilosebaceous canal (Nacht, 1981). BPO penetrates through the follicular opening, probably by dissolving into sebaceous lipids, and in this environment exerts its antimicrobial activity (Leyden et al., 1980). Skin irritation is a common side effect, and a correlation exists between efficacy and irritation (Fulton and Bradley, 1974). The controlled release of BPO from a delivery system to the skin could alter this correlation by maintaining intrafollicular penetration while reducing percutaneous absorption. The microparticles are too large to pass through the stratum corneum and hence they would be expected to remain on the skin surface, gradually releasing their contents over time. This release pattern prevents excessive accumulation of active agent in the epidermis and, as a result, may enhance the safety of any topically applied drugs. For example it has been shown that encapsulated BPO has a lower irritation effect on the skin in comparison to the formulations containing uncapsulated BPO powders (Wester et al., 1991). Because the pharmacological activity of BPO is as a consequence of its ability to penetrate into the skin preferentially through the follicular openings, a controlled-release topical delivery system might reduce the percutaneous absorption of BPO without affecting its intrafollicular penetration, thereby reducing the irritancy of the drug without sacrificing efficacy.

Acknowledgment

The financial support from the research council of Tabriz University of Medical Sciences is greatly acknowledged.

References

Arabi, H., Hashemis, A., Fooladi, M., 1996. Microencapsulation of alloporinol by solvent evaporation and controlled release investigation of drugs. J. Microencapsul. 13, 527–532.

Barkai, A., Pathak, Y.V., Benita, S., 1990. Polyacrylate (Eudragit Retard) microspheres for oral controlled release of nifedipine. I. Formulation design and process optimisation. Drug Dev. Ind. Pharm. 16, 2057–2075.

Chellquist, E.M., Gorman, W.G., 1992. Benzoyl peroxide solubility and stability in hydric solvents. Pharm. Res. 9, 1341–1347.

Comolu, T., Nonul, N., Baykara, T., 2003. Preparation and in vitro evaluation of modified release ketoprofen microspones. Il Farmaco 58, 101–106.

Crotts, G., Park, T.G., 1995. Preparation of porous and non-porous biodegradable polymeric hollow microspheres. J. Contr. Release 35, 95–105.

Embil, K., Nacht, S., 1996. The Microsponges® Delivery System (MDS): a topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. J. Microencapsul. 13, 575–578.

Fares, H.M., Chatterjee, S., Hayward, M., 1996. In vitro permeation and irritation of benzoyl peroxide-containing products. Int. J. Pharm. 333, 215–222.

Fong, J.W., 1988. Microencapsulation by solvent evaporation and organic phase separation processes. Contr. Release Syst.: Fabr. Technol. I, 82–83.

Fulton, J.E., Bradley, S., 1974. Studies on the mechanism of action of topical benzoyl peroxide in acne vulgaris. J. Cutan. Pathol. 1, 191–194.

Kawashima, Y., Niwa, T., Takeuchi, H., Iwamoto, T., Ito, Y., 1988. Preparations of controlled releases microballoons of ibuprofen with acrylic polymer by novel quasi-emulsion solvent diffusion method. Proc. Int. Symp. Contr. Rel. Bioact. Mater. 15, 185–186.

Kilicarslan, M., Baykara, T., 2003. The effect of the drug/polymer ratio on the properties of verapamil HCl loaded microsoheres. Int. J. Pharm. 252, 99–109.

Kim, C.K., Kim, M.J., Oh, K.H., 1994. Prepartion and evaluation of sustained release microspheres of terbutaline sulfate. Int. J. Pharm. 106, 213–219.

Lee, J.H., Park, T.G., Choi, H.K., 1999. Development of oral drug delivery system using floating microspheres. J. Microencapsul. 16, 715–729.

Leyden, J.J., McGinley, K.J., Mills, O.H., 1980. Topical antibiotics and topical antimicrobial agents in acne therapy. In: Juhlin, L.A., Rossman, H., Strauss, J.S. (Eds.), Proceedings of the Symposium. Lund, Uppsala, Sweden, pp. 151–164.

Nacht, S., 1981. Methods to assess the transepidermal and intrafolicular penetration of anti-acne agents. In: The Proprietry Association (Ed.), Proceedings of the 1980th Research and Scientific Developments Conference. New York City, pp. 88–91.

Nixon, J.R., Hassan, M., 1980. The effect of preparative technique on the particle size of thiabendazole microcapsules. J. Pharm. Pharmacol. 32, 856–857.

Perumal, D., 2001. Microencapsulation of ibuprofen and Eudragit® RS 100 by the emulsion solvent diffusion technique. Int. J. Pharm. 218, 1–11.

Perumal, D., Dangor, C.M., Alcock, R.S., Hurbans, N., Moopanar, K.R., 1999a. Effect of formulation variables on in vitro drug release and micromeritic properties of modified release ibuprofen microspheres. J. Microencapsul. 4, 475–487.

Perumal, D., Dangor, C.M., Alcock, R.S., Hurbans, N., Mooparnar, K.R., 1999b. Effect of formulation variables on in vitro release and micromeritic properties of modified release ibuprofen microspheres. J. Microencapsul. 16, 475–487.

Pongpaibul, Y., Price, J.C., Whitworth, C.W., 1984. Preparation and evaluation of controlled release indomethacin microspheres. Drug Dev. Ind. Pharm. 10, 1597–1616.

Puranik, P.K., Manekar, N.C., Dorle, A.K., 1992. Preparation and evaluation of abietic acid microcapsules by a solvent evaporation technique. J. Microencapsul. 9, 425–435.

Rainer, A., Bodmeier, R., 1990. Encapsulation of water soluble drugs by a modified solvent evaporation method. J. Microencapsul. 7, 347–355.

Wester, R.C, Patel, R., Nacht, S., Leyden, J., Melenders, J., Maibach, H., 1991. Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy. J. Am. Acad. Dermatol. 24, 720–726.

Yeung, D., Nacht, S., Bucks, D., Maibuch, 1983. Benzoyl peroxide: percutaneous penetration and metabolic disposition. II. Effect of concentration. J. Am. Acad. Dermatol. 9, 920–924.