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Original Article

The Effect of Formulation Type on the Release of Benzoyl Peroxide from Microsponges

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Abstract

Benzoyl peroxide (BPO) is a first-line topical treatment in acne vulgaris, and it is superior to antibiotics, because the bacteria do not develop resistance to it. 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 effects while reducing percutaneous absorption. Therefore, the purpose of the present investigation was to prepare suitable controlled release formulations for BPO. This study examined whether the type of topical formulation (cream, gel and lotion) can affect the release behavior of BPO from microsponges. 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 stirring aqueous phase containing polyvinyl alcohol. The loading capacity of the drug content and the mean particle size of microparticles were determined. BPO microparticles were then incorporated into various formulations (creams, gels and lotions) for release studies. The micrograph of microsponges showed that they were spherical in shape and contained pores. It was shown that the drug:polymer ratio, stirring rate, volume of the 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 decrease in internal porosity of the microsponges. The release data showed that the highest release rate was obtained from lotions containing BPO microparticles and the lowest was obtained from cream formulations.

Keywords: Drug release; Drug:polymer ratio; Microsponge; Particle size; Porosity.
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1. Introduction

Benzoyl peroxide (BPO) is a first-line topical treatment in acne vulgaris. However, its use can cause mild skin irritation and dryness. BPO is an old and established treatment agent with keratolytic and antibacterial action. It was described as a therapeutic aid in the treatment of burns, ulcerations, and various cutaneous and mucous membrane infections, and it has been found to

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Table 1. Effect of drug:polymer ratio, stirring rate, concentration emulsifier, solvent and non-solvent amounts on the average diameter and drug content of BPO microsponges.

Parameter	Formulations	Theoretical drug content (%)	Mean drug drug loading (%)	Drug loading capacity (%±SD)
BPO: EC ratio	MDS*1 (1:1)	-	-	-
(rpm=4000)	MDS3 (3:1)	69.23	49.37	71.31±3.31
	MDS5 (5:1)	78.94	63.16	80.01±1.32
	MDS7 (7:1)	84.00	74.54	88.74±1.25
	MDS9 (9:1)	87.10	85.38	98.03±2.16
	MDS11 (11:1)	89.19	83.44	93.56±0.81
	MDS13 (13:1)	90.70	87.17	96.11±0.70
Dichloromethane	MDS13-A (5 ml)	-	86.95	95.87±4.05
volume (ml)	MDS13-B (10 ml)	90.70	72.21	79.61±3.89
	MDS13-C (15 ml)	90.70	66.67	73.51±3.74
Stirring rate (rpm)	MDS13-D (1000)	90.70	54.83	60.45±5.33
	MDS13-E (2000)	90.70	64.93	71.59±4.89
	MDS13-F (3000)	90.70	71.23	78.53±4.92

*MDS = Microsponge Delivery System

be among the most effective models of acne therapy [1, 2]. BPO is superior to antibiotics because the bacteria do not develop resistance to it, and it is preferred over keratolytic agents due to its bactericidal effect.

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 effects while reducing its percutaneous absorption. Encapsulation of BPO can reduce the side effects to a great extent [2, 3].

The encapsulated form has received increasing attention as a means for controlled release purposes [4]. Previous studies showed that controlled release formulations of BPO reduced the skin irritation due to the reduction in the release rate of the drug from formulation [5]. A popular method for the encapsulation of water-insoluble drugs within water insoluble polymers is the emulsification solvent diffusion method [6, 7]. The solvent diffusion process is easier to conduct and is less prone to agglomeration of the microsponges, and also is more economic. Solvent diffusion is a process by which microencapsulation can be readily performed in the laboratory without the need of specialized equipments. Selecting the appropriate method requires consideration of the physicochemical properties of the core material (drug and polymer) in conjunction with the characteristics of the process.

The prepared BPO microsponge formulations, can clearly increase the period of time that the active ingredient is in contact with the skin surface or within the epidermis, while minimizing its penetration through the dermis to the systemic circulation. This system provides maximum efficacy, minimum irritancy, extended product stability and improved aesthetic properties in an efficient and novel delivery system.

The purpose of the present investigation was to prepare BPO microsponges. We also investigated the factors affecting the particle size of microsponges. This study examined whether the type of topical formulation (cream, gel and lotion) can affect the release behavior of BPO from microsponges.

2. Matrials and methods

2.1. Materials

Benzoyl peroxide, polyvinyl alcohol (PVA; MW=10600–11000), dichloromethane, acetone, methanol, polyethylene glycol 400, and benzophenon, liquid paraffin, tri-ethanolamine, stearic acid, all were from Merck (Darmstadt, Germany). Ethyl cellulose was purchased from Sigma-Aldrich, carbomer

940 (BFG, USA). Silastic membrane was provided by Biogene, (Mashad, Iran). White beeswax was achieved from Thoton and Ross (Huddersfield, UK).

2.2. Preparation of microsponges

BPO microsponges were prepared by emulsion solvent diffusion method. To prepare the internal phase, BPO was dissolved in 20 ml of dichloromethane. In this procedure, dichloromethane was an effective solvent to dissolve both the drug and the polymer. While the external phase, 60 ml of an aqueous solution containing 5.6 g of 5% w/v PVA, was placed in the vessel and stirred with propeller type agitator at 4000 rpm, and the internal phase was poured into external phase. The system was thermally controlled at 25 °C in a water bath.

An agitation up to 30 min permits the formation of microsphere and after 8 h of stirring, the experiment was stopped as the dichloromethane was removed from the reaction. At this stage, the formed microsponges were filtered through the filter paper, washed with distilled water and tray dried at the room temperature and was weighted.

The effects of the process variables such as drug:polymer ratio, stirring rate and solvent volume on the mean particle size of the microparticles were investigated. BPO microspheres were prepared using various drug:polymer ratios (3:1, 5:1, 7:1, 9:1, 11:1 and 13:1), while keeping the other variables (stirring rate of 4000 rpm, emulsifier concentration 5.6 g of 5% w/v, solvent 20 ml and non-solvent 60 ml) constant. Similarly, to determine the effect of stirring rate on the mean particle size of microparticles, microsponges were prepared at various stirring rates (1000, 2000, 3000, 4000 rpm), while keeping the drug:polymer ratio at 13:1, emulsifier concentrations at 5.6 g, dichloromethane 20 ml and non-solvent 60 ml.

Microspheres were also prepared using different volumes of dichloromethane while keeping the drug:polymer ratio at 13:1, and stirring speed at 4000 rpm.

2.3. Scanning electron microscopy

The morphology and appearance of microparticles were examined by scanning electron microscopy (SEM). The prepared microspheres coated with gold platinum/ palladium alloy under vacuum. The coated samples were then examined using scanning electron microscope (LEO 440i, England) operating at 15 kV. Photomicrographs were taken of each sample at different magnifications.

2.4. Particle size distribution

The micrographs of microsponges were transferred into the software (Scion image analysis) for image analysis of microparticles. Each determination was carried out on a minimum of 100 particles. These data were converted to percent values using the initial total number of particles against particle size

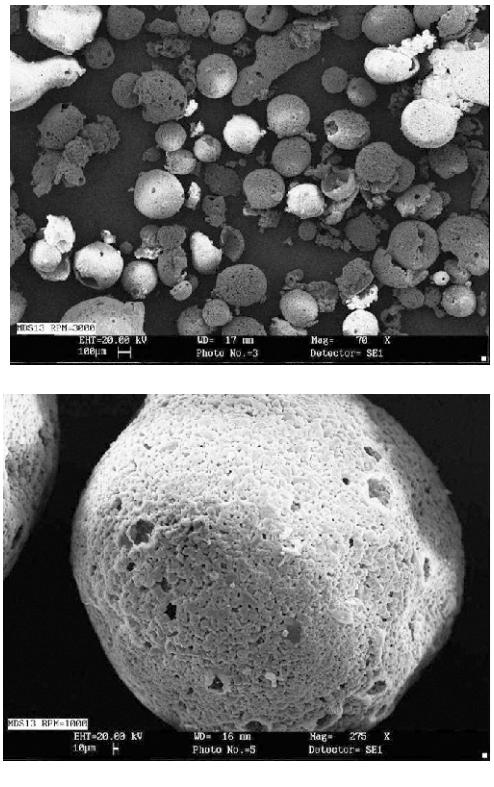

Figure 1. SEM of microsponges containing BPO at different magnifications.

Table 2. The effect of drug:polymer ratio on the release characteristics of BPO from different microsponges formulations.

Formulation code	Cream 2.5%				Cream 5%				Cream 10%			
	Flux[a] (mg/cm²h)	Intercept (mg/cm²)	r^2	Q_8[b] (mg/cm²h)	Flux[a] (mg/cm²)	Intercept (mg/cm²)	r^2	Q_8[b] (mg/cm²h)	Flux[a] (mg/cm²)	Intercept (mg/cm²)	r^2	Q_8[b] (mg/cm²h)
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	0.0240	0.14	0.933	0.354	0.0362	0.18	0.959	0.480
MDS13	0.0168	0.02	0.939	0.159	0.0200	0.10	0.947	0.275	0.0359	0.14	0.973	0.438
	lotion 2.5%				**lotion 5%**				**lotion 10%**			
Pure BPO	0.243	0.543	0.972	1.935	0.334	0.756	0.945	2.567	0.393	1.145	0.976	3.362
MDS3	0.188	0.900	0.971	2.090	0.261	1.315	0.991	2.932	0.272	2.084	0.850	3.548
MDS5	0.158	0.927	0.985	1.916	0.256	1.264	0.995	2.815	0.208	2.105	0.772	3.148
MDS7	0.146	0.819	0.987	1.651	0.271	1.136	0.985	2.717	0.298	1.595	0.877	3.156
MDS9	0.141	0.724	0.960	1.527	0.219	1.026	0.975	2.261	0.247	1.421	0.807	2.668
MDS11	0.123	0.689	0.902	1.371	0.168	0.828	0.952	1.825	0.223	1.162	0.921	2.407
MDS13	0.117	0.532	0.993	1.210	0.159	0.752	0.962	1.768	0.174	1.056	0.971	2.044
	gel 2.5%				**gel 5%**				**gel 10%**			
Pure BPO	0.1176	0.667	0.9727	1.331	0.126	1.094	0.9732	1.836	0.168	2.409	0.755	3.315
MDS3	0.1463	0.8772	0.9795	1.723	0.2197	1.5568	0.8973	2.811	0.3111	2.683	0.924	4.370
MDS5	0.1049	0.8115	0.9866	1.468	0.1908	1.4173	0.8802	2.452	0.3178	2.254	0.907	3.983
MDS7	0.0976	0.7193	0.9555	1.358	0.1699	1.3423	0.7128	2.185	0.2762	2.032	0.839	3.486
MDS9	0.0754	0.7043	0.9495	1.174	0.0959	0.936	0.9168	1.453	0.2011	1.735	0.923	2.814
MDS11	0.0966	0.5489	0.9616	1.154	0.0984	0.6691	0.9733	1.255	0.1218	1.055	0.926	1.737
MDS13	0.0762	0.5311	0.9542	0.965	0.0938	0.610	0.9204	1.116	0.1123	0.955	0.894	1.558

[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.

on probability scale. The probability plot directly gives the mean particle size values.

2.5. Determination of drug content

High-performance liquid chromatography (HPLC) was used to determine the amount of BPO in microsponges [5]. The HPLC system was a Shimadzu class VP series software, version 5.03 with two LC-10AT VP pumps, UV detector SPD-10A VP, RP C18 column (250 mm x 4.6 mm, particle size 5 nm, YMC, Inc., Wilmington, NC, USA). UV detection at 254 nm detected the eluent and the data were acquired, stored, and analyzed with the installed Shimadzu software, the mobile phase used was a mixture of methanol/distilled water (75:25), the filtered mobile phase was pumped at a flow rate of 1.2 ml/min. The retention times were 11.3 min and 7.2 min for BPO and benzophenone (the internal standard), respectively. A standard curve was constructed for BPO in the range of 1-200 µg/ml, using benzophenone as the internal standard. A good linear relationship was observed between the peak areas of BPO standard/internal standard in different concentration ratios with a correlation coefficient of 0.9943.

2.6. Determination of loading capacity

An accurately weighted quantity of BPO microsponges (equivalent to 10 mg of BPO) were digested in 10 ml of acetone by stirring for 30 min. The solution was filtered and 1 ml of the filtrate was added to 9 ml of dichloromethane. The solution was subjected to HPLC analysis as described previously. Each determination was made in triplicate. Incorporation efficiency was calculated using the following equation:

Incorporation Efficiency= (a/b) x 100

(where, a is the theoretical drug content and b is the entrapped drug).

2.7. Porosity studies

The pore analysis of microsponges was carried out using mercury intrusion porosimetry (Pascal 140, Italy). During the test, a round sampling of microsponges is placed in the vacuum chamber and submerged under a pool of mercury contained within a volume-calibrated cell. As pressure is gradually increased on the cell, mercury is forced into progressively smaller pores of the microsponges. Thus, the apparent volume of mercury within the calibrated cell is reduced as it penetrates into the microsponges. Changes in the surface area and pores diameter can be easily detected with the use of mercury intrusion porosimetry, providing a reproducible method to monitor these

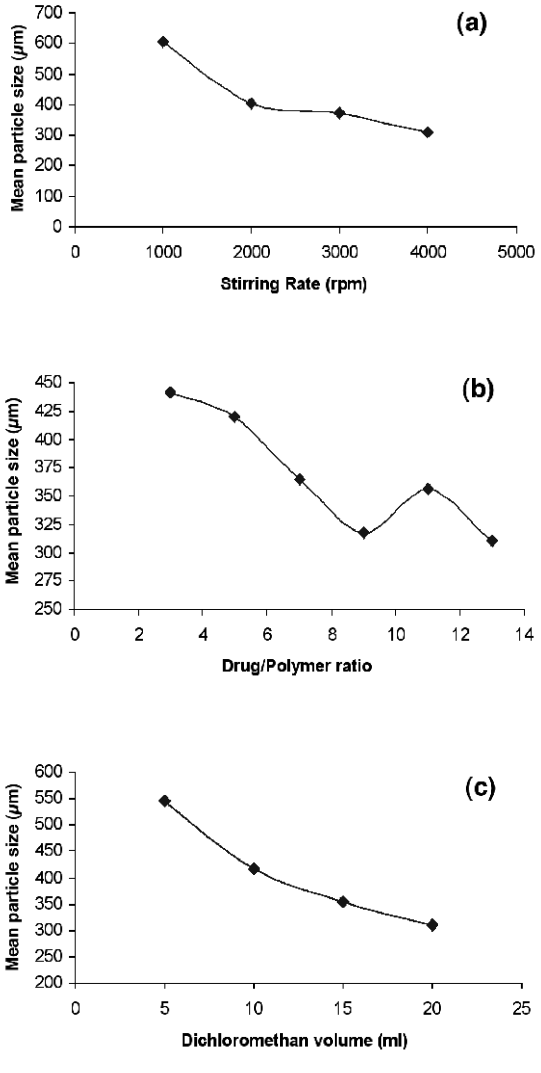

Figure 2. The effect of stirring rate (a), drug:polymer ratio (b), and dichloromethane volume (c) on the mean particle size of microsponges.

parameters consistently to correlate them with processing variables or rates ingredient from the MDS.

2.8. Viscosity measurement

A Brookfield rotational digital viscometer DVLV-II was used to measure the viscosity (cPs) of the internal and external phases at 25 ºC. The spindle number was rotated at 100 rpm.

2.9. Preparation of benzoyl peroxide microsponge creams, gels and lotions

Creams were prepared using a standard reverse emulsification method. Aqueous phase containing 5 g triethanolamine was added dropwise onto the oil phase containing stearic acid (20 g), liquid paraffin (5 g), white bees wax 3 g under a stirring rate of 400 rpm. Creams were prepared by melting the oil phase components at about 70 °C and then adding the aqueous phase at a similar temperature. Once the creams were prepared, the active component (pure BPO powder or microsponges containing BPO) was thoroughly mixed at the room temperature.

Gels were prepared by dispersing 1 g carbomer 940 in distilled water, adding BPO and neutralizing to a pH of 7 with tri-ethanolamine [8].

Lotions were prepared by dispersing the BPO powder or BPO microsponges into the PEG 400. PEG 400 was a good vehicle for this formulation because it dissolves the drug, but is unable to dissolve ethyl cellulose.

2.10. Drug release studies

Silastic membranes were mounted in static diffusion cells and the membrane surface dosed with 2.5, 5 and 10% BPO creams, gels and lotions containing BPO either freely dispersed or entrapped in ESD system. Receptor fluid composed of distilled water/acetone (1:1) was added to the cell and maintained at 25°C because of the exceedingly low solubility of BPO in either water or normal saline, a water/acetone mixture was selected as receptor fluid to provide adequate "sink" conditions after preliminary experiments showed no interactions of this mixture with either the membrane or the mixtures placed on the "donor" side. Drug flux through the membrane was determined by periodically withdrawing the receptor phase and analyzing for percent content by HPLC. HPLC condition was similar to HPLC analysis as described previously.

3. Results and discussion

Scanning electron microscopy of microsponges was shown in Figure 1. It is clear from the figure that microsponges have spherical shape and containing orifices. These orifices caused by the diffusion of the solvent (dichloromethane) from the surface of the microparticles. The type and concentration of emulsifier has a key role to play in the preparation of microspheres. Without the addition of emulsifier it is impossible to form microspheres.

The effect of drug:polymer ratio, the volume of dichloromethane and stirring rate on the mean particle size of BPO microsponges is shown in Figure 2. In order to investigate the effect of stirring rate on the physical characteristics of BPO microsponges, formulation MDS13 (the highest ratio of drug:polymer) was chosen and the stirring rate was altered in the ranging of 1000-4000 rpm. The dispersion of the internal phase of drug and polymer into the droplets in the aqueous phase depended on the agitation speed of the systems. As agitation speed increased, the size of microparticles was reduced. For example when the rate of stirring was increased from 1000 to 4000 rpm, the mean particle size was decreased from 603.9±58.4 to 310.3±34.3 μm. An increase in the mean particle size can be attributed to the tendency of globules to coalescence and aggregation at lower stirring rates. On the

other hand, at higher stirring rates, a vigorous, uniform, increased mechanical shear, is imposed and this results in a rapid division of the formed droplets which may have less chance of coalescing into bigger droplets [9].

Figure 2b shows that the ratio of drug to polymer played an important role in the particle size of microsponges. It is clear from the figure, generally, as the ratio of drug:polymer increased, particle size was decreased. This can be attributed to the increase in the viscosity of solutions (internal phase) with high drug content. In high drug:polymer ratios; the amount of polymer per microsponges is less than other formulations. When dichloromethane diffuses out, nearly all of the dispersed phase is converted to the form of solid microsponges and separated particles appear. Therefore, in high drug:polymer ratios less polymer amounts surrounded the drug and decreased the particle sizes of microsponges. When the dispersed phase with higher viscosity was poured into the dispersion medium bigger droplets were formed and mean particle sizes increased.

The effect of the amount of dichloromethane on the mean particle size of BPO microsponges was shown in Figure 2c. The results showed that increasing the solvent volume (dichloromethane) decreases the particle size of microsponges (compare formulations MDS13-A, MDS13-B and MDA13-C). When the viscosity of the internal phase of these formulations was investigated, it was found that the particle sizes of microsponges were proportional with the viscosity of the dispersed phase. The results showed that the viscosity of the polymer solutions containing 5, 10 and 15 ml of dichloromethane is 139, 52 and 33.3 $mN/m^2.S$, respectively. The viscosity of the external phase was 20.4 $mN/m^2.S$. When the dispersed phase with higher viscosity (MDS13-A 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 probably need more energy to divided into smaller particles and bigger droplets were formed and the mean particle sizes were increased. In other studies, Barkai et al. [10] and Pongpaibul et al. [11] showed that the particle size depends on the solvent volume and the drug:polymer ratio, when solvent diffusion method is utilized for preparing microspheres.

The incorporation efficiencies of BPO in the microspheres were between 60–96%. Incorporation efficiency data were compared. They were found to be significantly different depending on the variation of drug:polymer ratio (Table 1). The results of the loading efficiency (incorporation 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%. The use of higher amounts of BPO when preparing microsponges at higher drug:polymer ratios caused slightly an increase in the 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 capacity of these formulations can be explained through the fact that the amount of drug per unit polymer is greater than that in other formulations. Table 1 also showed that when the amount of dichloromethane increased from 5 to 15 ml, the efficiency of drug loading decreased. This is due to the low amount of the drug in higher volume of dichloromethane.

In order to investigate the effect of vehicle on the release of BPO from topical formulations, various formulations such as gel, creams and lotion containing pure dispersed BPO or BPO microsponges were prepared. The release profiles of BPO from gel, cream and lotion are shown in Figures 3,

Table 3. 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 (%)
MDS3 (3:1)	3.968	0.651	23.973	22.43
MDS5 (5:1)	2.448	0.518	17.080	15.39
MDS7 (7:1)	1.920	0.385	17.184	14.17
MDS9 (9:1)	1.764	0.420	17.599	12.13
MDS11 (11:1)	1.623	0.292	20.030	11.02
MDS13 (13:1)	1.447	0.265	24.488	9.87

4 and 5, respectively. Different percentages of BPO microsponges (2.5, 5 and 10% w/w) were incorporated in the cream, lotion and gel formulations and the drug release from these formulations was studied. These figures also show the effect of drug:polymer ratio on the release of the drug from cream, lotion and gel formulations. In order to better comparison between the release profiles of different formulations, a linear relationship between Q (the cumulative amount of drug penetrated through the unit surface area of the membrane) and the time was obtained after 1 h (see r^2 values in Table 2). The cumulative amount released increased with an increase in the concentration of active ingredient in the formulation. These figures also show that the amount of drug released at first hour is higher compared to the amount of drug release for the next hour. This could be due to the presence of non-encapsulated BPO in these formulations. When the free BPO was released, the flux remained constant for the next 7 hours. This flux represents 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 2). The flux results showed that, generally, the flux of drug from different formulations is as follows: lotions > gels > creams. In other words, the release of drug from lotions is the fastest. Comparing Q_8 (the amount of BPO released after 8 h) for different ratios of drug:polymer also showed that the Q_8 was lower for the microsponges with lower porosity of microsponges (see Tables 2 and 3).

In contrast to the other studies [12-14], the present study showed that generally an increase in the ratio of drug:polymer resulted in a reduction in the release of BPO from microsponges. They described that as the polymer amount increases, the matrix wall of microsponges becomes thicker. The formation of a thicker matrix wall leads to slower release rate of drug caused by longer diffusion path. Similar observations to our results were made for ketoprofen microsponges [13], but the authors did not provide an explanation for their observations.

In order to find the reason for the observation made in our studies, pore analysis of microsponges was carried out and the results are shown in Table 3. It has been reported that the pore diameter can have a significant effect on the release rate of the ingredient, and also affects 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 menthol in various MDS, when the release rate constant was plotted versus log pore diameter, a straight line was obtained; indicating that the rate of release is proportional to the cross-sectional area of the pore diameter [6]. We could not establish any relationship between pore diameters and the release rate of BPO from microsponges. Our results showed that apart from pore diameter, the number of pores is also important factor in controlling the release rate of BPO from microsponges. In order to show the impact effect of the number of pores on the release rate of BPO from microsponges, the total porosity of microsponges, total surface area

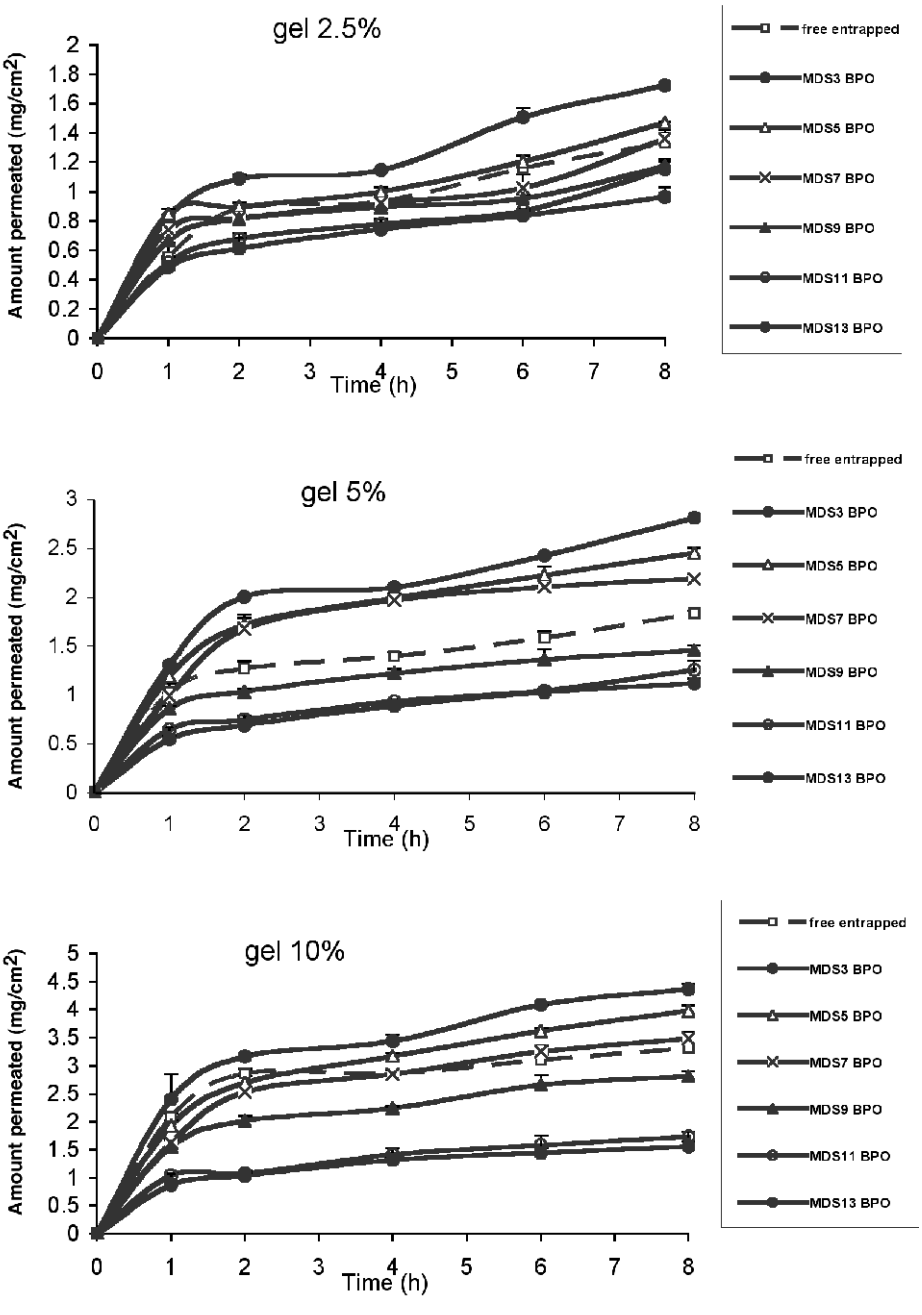

Figure 3. The release profiles of BPO from gel formulations containing different concentrations of BPO.

and total volume of pores of microsponges were calculated (Table 3). The results show that, generally, the lower release rate was obtained for microsponges with low porosity, low surface area and low volume. Therefore, a reduction in the release rate could be due to the low porosity of microsponges in MDS13 (Table 3). 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 2 and 3).

4. Conclusion

The main site of pharmacological action is the pilosebaceous canal [1]. BPO penetrates through the follicular opening, probably by dissolving into sebaceous lipids, and in this

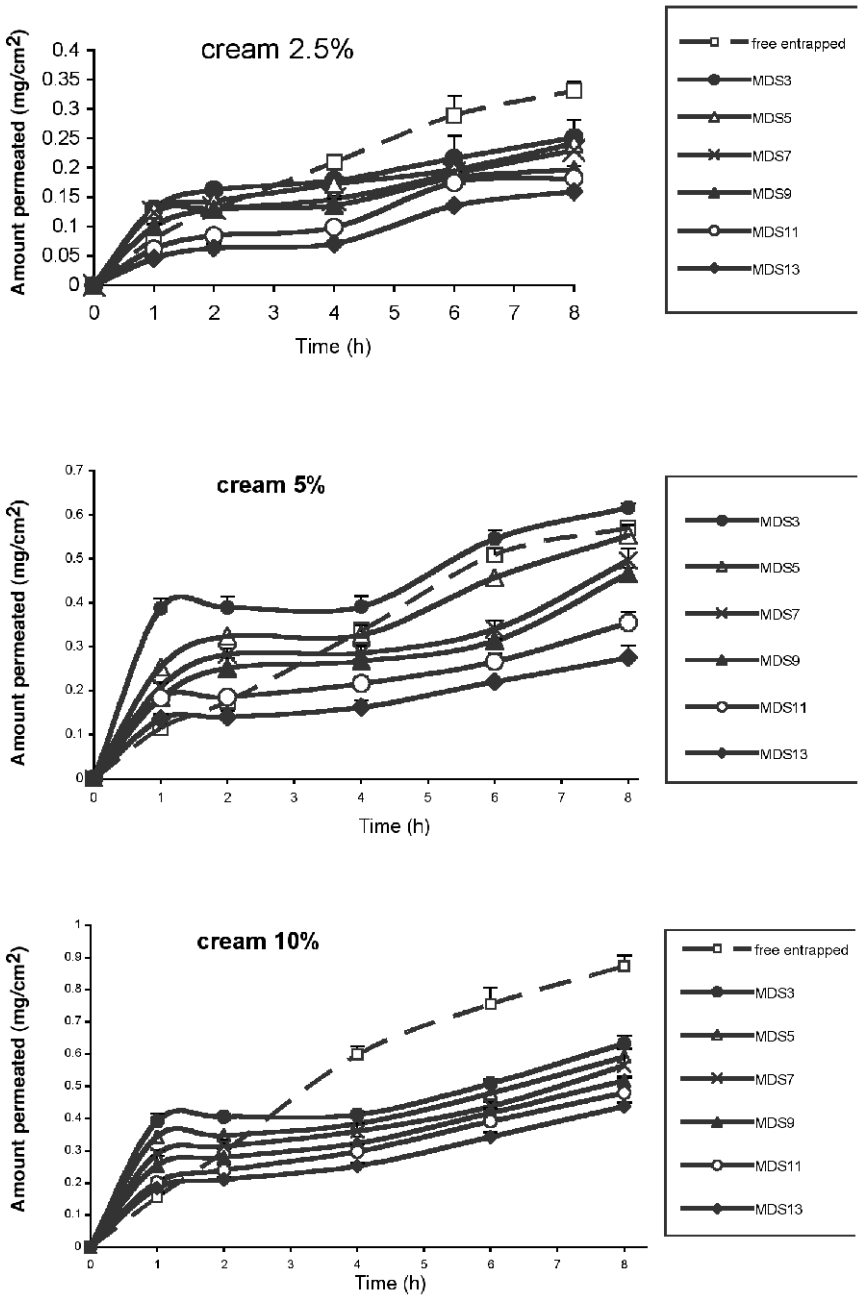

Figure 4. The release profiles of BPO from cream formulations containing different concentrations of BPO.

environment exerts its antimicrobial activity. Skin irritation is a common side effect, and a correlation exists between efficacy and irritation [1, 2]. The controlled release of BPO from a delivery system to the skin could alter this correlation by maintaining intrafolicular penetration while reducing percutaneous absorption. The microparticles are too large to pass through the stratum corneum, 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

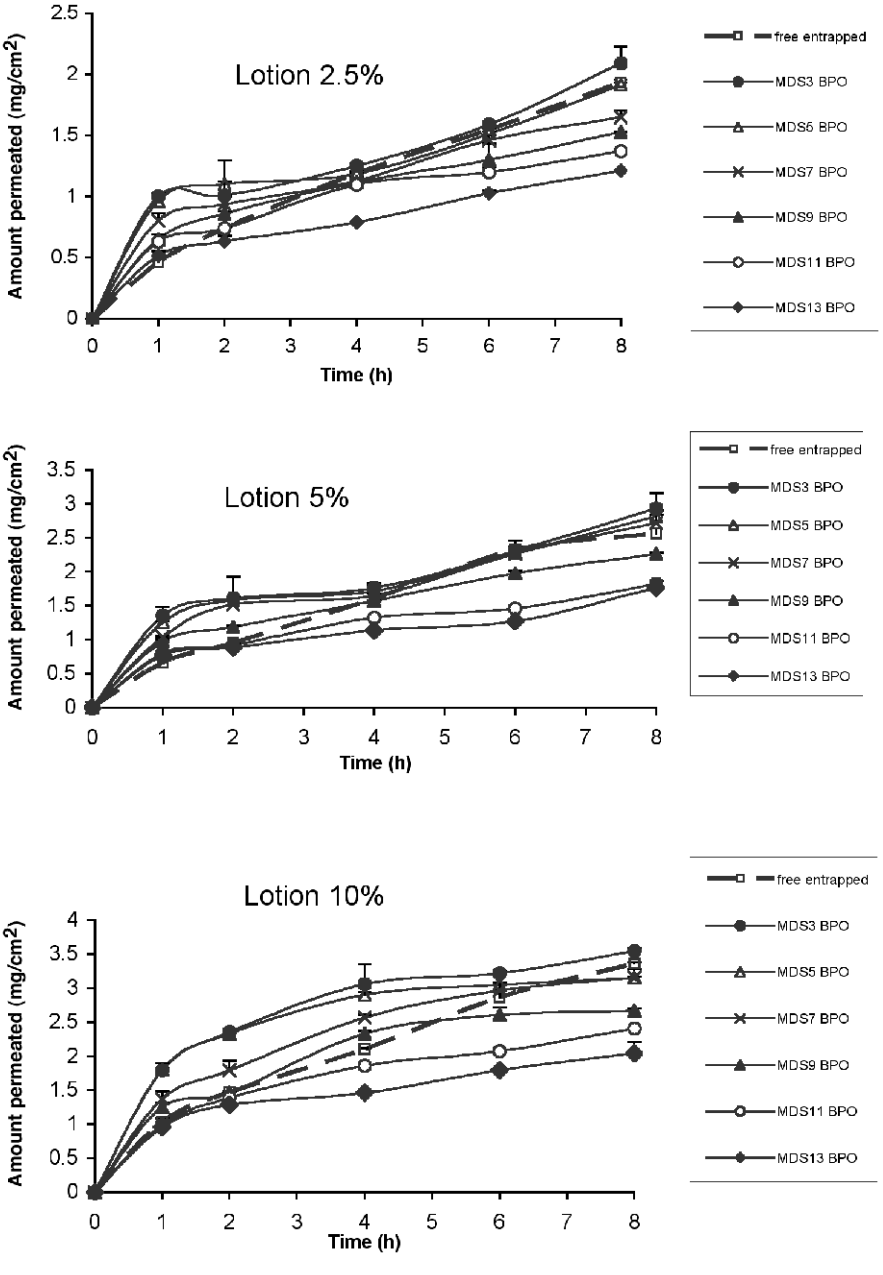

Figure 5. The release profiles of BPO from lotion formulations containing different concentrations of BPO.

containing uncapsulated BPO powders [5]. 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.

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