Formulation & Evaluation of Benzoyl Peroxide Gel

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Abstract

Benzoyl peroxide (BPO) is a first-line topical treatment in acne vulgaris .It 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 Eudragit L 100 microparticles containing BPO which were able to control the release of BPO to the skin.
Microspheres were prepared by Solvent Evaporation Technique. Microspheres are optimized on the basis of their properties like Entrapment efficiency, % drug loading, % yield & Particle size. Polymers Ethyl cellulose, Eudragit L100, Eudragit RS 100 were used in the formulations of Microspheres & the optimized batch incorporate in Gel preparation.

Key Words: Microspheres, Ethyl cellulose, Eudragit L100, Eudragit RS 100, Benzoyl peroxide Gel.

Introduction

Benzoyl peroxide (BPO) is a first-line topical treatment in acne vulgaris. It is commonly used in topical formulations for the treatment of acne and athletes foot. Benzoyl peroxide (BPO) is superior to antibiotics, because the bacteria do not develop resistance to it. Skin irritation is a common side effect. The degree of irritation is believed to be related to the amount of BPO present in the skin, which can be reduced by the encapsulation, to a great extent because the controlled release of BPO results in reduced amount of BPO at the skin site at a particular time. The controlled release of drug from a formulation containing microspheres incorporated in gel. such that the drug remains primarily localized at the epidermis with only a restricted amount entering the systemic circulation. This 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.

From a microbiological perspective, BPO is a vital component of acne therapy, exhibiting marked suppression of ***Propionibacterium acnes*** and reduced proliferation and emergence of antibiotic-resistant *P. acnes* strains with both "leave on" and wash formulations.BPO is not associated with resistance to its own antimicrobial properties. Multiple studies have confirmed the therapeutic benefit of BPO, both alone and in combination with other agents, such as topical antibiotics and topical retinoids. In fact, BPO is considered to be an integral component of first-line therapy for acne vulgaris, based on its ability to markedly reduce inflammatory acne lesions and its ability to moderately reduce comedonal acne lesions. It may also be used successfully as a component of long-term maintenance therapy.

Material and Methods:

Materials

Benzoyl peroxide (BPO) was obtained from ****** ***** Pvt .Ltd, Mumbai**, Ethyl cellulose, Eudragit L100, Eudragit RS 100,Carbopol 934, Hydroxypropyl methyl cellulose- 15 cps (Central Drug house, Delhi) was used.

Preparation Of Microsphere

Benzoyl peroxide microspheres were prepared by dissolving the drug in polymers (Eudragit L100, Eudragit R S 100, and Ethyl Cellulose), which was previously dissolved in the methanol. The resulting solution was added to the aqueous phase containing 0.1 g of span80 or 5 g of 5% w/v PVA as an emulsifying agent and the mixture was then agitated using a propeller with the rotation speed 500 rpm and 1000 rpm .The dispersed drug & eudragit (L 100 ,RS 100) or ethyl cellulose were immediately transformed into fine droplets, which subsequently solidified into rigid microspheres due to solvent evaporation the particles were collected by filtration and washed with dematerialized water & desiccated at room temperature for 24 hr (table 1).

Table 1: Formulations Optimization

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Benzoyl peroxide	1	1	1	1	1	1	1	1	1	1	1	1
Ethyl celullose	1	2	3	4	-	-	-	-	-	-	-	-
Eudragit L 100	-	-	-	-	1.5	2.5	3.5	1	-	-	-	-
Eudragit R S 100	-	-	-	-	-	-	-	-	1	2	3	4
PVA (5 % w/v)	-	-	-	-	5	5	5	5	5	5	5	5
Span 80	0.1	0.1	0.1	0.1	-	-	-	-	-	-	-	-
Methanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Determination of Physicochemical Parameters

Microspheres are optimized on the basis of their properties like Entrapment efficiency, % drug loading, % yield & Particle size (table2).

Table 2: Physical Parameters of Microspheres

Formulation code	Drug : Polymer:PVA:SPAN	Entrapment	Percentage drug	Yield (%) of	Particle size(µm
F1	1 : 1 : 0 : 0.1	67.46±0.248	40.35±0.060	41.21±0.005	105.98+23.7
F2	1 : 2 : 0 : 0.1	71.42±0.287	27.18±0.39	44.6±0.005	132.79+22.1
F3	1 : 3 : 0 : 0.1	73.35±0.268	20.11±0.39	51.25±0.005	144.84+35.5
F4	1 : 4 : 0 : 0.1	74.58±0.19	16.76±0.081	56.67±0.005	117.86+29.7
F5	1 : 1.5 : 5 : 0	87.93±0.130	36.98±0.081	44.03±0.01	127.46+26.2
F6	1 : 2.5 : 5 : 0	88.46±0.056	27.8±0.068	46.07±0.01	99.7+20.5
F7	1 : 3.5 : 5 : 0	89.01±0.056	21.06±0.068	51.11±0.056	93.40+29.5
F8	1 : 1 : 5 : 0	89.34±0.051	46.37±0.68	65.57±0.017	91.63+22.3
F9	1 : 1 : 5 : 0	84.72±0.051	46.56±0.68	40.54±0.015	112.09+46.2
F10	1 : 2 : 5 : 0	87.56±0.051	32.08±0.68	47.56±0.005	128.89+25.2
F11	1 : 3 : 5 : 0	88.08±0.020	23.71±0.68	53.82±0.011	134.56+20.6
F12	1 : 4 : 5 : 0	84.23±0.026	18.58±0.068	42.88±0.005	147.78+35.9

Morphological Characterization of Microspheres

The surface morphology of microspheres was investigated using **SEM (Scanning Electron Microscope)**. To prepare specimens for the polarizing, the microsphere (**Optimized F8 Batch**) was first taken on the slide as powder form and placed it on the base plate. Vacuum was created through the system to reduce the conduction. Specimens were ready to be viewed on the SEM. Images were scanned at different magnifications (fig 1).

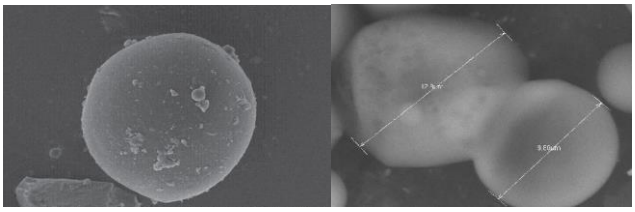

Figure 1: Microsphere SEM at 1800 resolution & SEM at 9000 resolution

Preparation of Gel Containing Drug Loaded Microspheres

Purified Water (60 ml) was heated to 75 to 80ºC and Methylparaben, Propylparaben and Disodium Edetate were dissolved into it, then Carbopol 934 was added and dispersed into it under stirring to form a uniform dispersion and cooled to room temperature. Drug Benzoyl peroxide in microsphere form was added and dispersed into the solution under stirring for 10-15min, then Propylene Glycol and Silicone Oil were added and mixed. Finally, the weight was adjusted with Purified Water with continued stirring for 15 min (table3).

Table 3: Formulation Details Of Gel Containing Methanol Based Microspheres (%w/w)

Ingredient	Optimized Formulation of Benzoyl peroxide Gel					
	A1	A2	A3	A4	A5	A6
Benzoyl peroxide Microspheres (Prepared by using Eudragit L 100)	5	5	5	5	5	5
Carbopol 934	1	1.5	2	-	-	-
Hydroxy propyl methyl cellulose	-	-	-	1	2	3
Methylparaben	0.2	0.2	0.2	0.2	0.2	0.2
Propylparaben	0.02	0.02	0.02	0.02	0.02	0.02
Disodium Edetate	0.1	0.1	0.1	0.1	0.1	0.1
Silicone Oil	-	1ml	5ml	-	1ml	5ml
Propylene Glycol	-	5 ml	5 ml	-	5 ml	5 ml
Purified Water	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

Table 4: Physical Parameters Of Gel Containing Methanol Based Microspheres (%w/w)

Batch no	pH	Spreadability	Viscosity	Consistency	Homogeneity	Skin irritation	(%)Drug
A1	4.9	5.8	0.94×10^{-3}	6mm	Good	Nil	90.0±0.09
A2	5.1	5	1.6×10^{-3}	6mm	Good	Nil	92.76±0.06
A3	5.1	6.3	1.6×10^{-3}	5mm	Very good	Nil	98.97±0.12
A4	4.5	5.8	1.7×10^{-3}	6mm	Good	Nil	91.56±0.02
A5	5.1	5.8	1.6×10^{-3}	6mm	Good	Nil	90.21±0.01
A6	5.5	5.9	1.7×10^{-3}	6mm	Very good	Nil	97.46±0.005

In-Vitro Release Permeability Studies by Franz Diffusion Cell

Phosphate buffer of pH 5.5 was used for in vitro release as a receptor medium. The pretreated skin of albino mice was used in Franz diffusion cell. The gel sample was applied on the skin and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer (100ml) of pH 5.5. The temperature of diffusion medium was thermostatically controlled at 37º ± 1º by surrounding water in jacket and the medium was stirred by magnetic stirrer at 500 rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 222nm against their respective blank (fig 2, 3, 4).

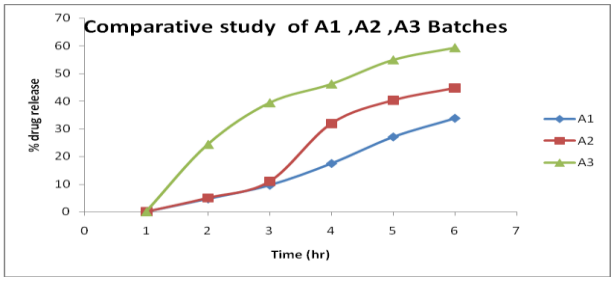

Figure 2: In-Vitro Comparative Drug Release Profile of A1, A2, A3 Formulation

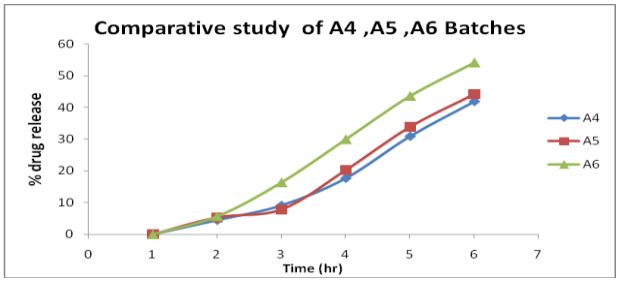

Figure 3: In-Vitro Comparative Drug Release Profile of A4, A5, A6 Formulation

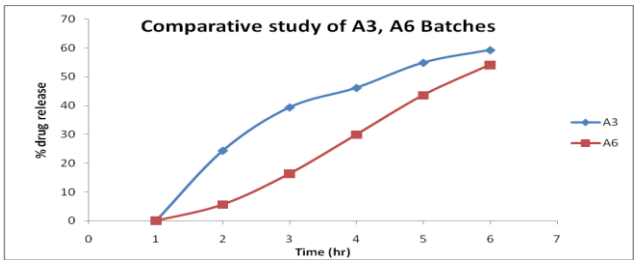

Figure 4: In-Vitro Comparative Drug Release Profile of A3, A6 Formulation

Rheological Studies

Rheological behavior of the gel (A3 batch) was evaluated using a viscometer (Brookfield DV-E, USA) by applying increasing values of the shear rate (rpm) in order to reveal the possible flow behavior of the gel. All rheological measurements were performed at 30±0.2^{0}C (table 5, fig 5).

Table 5: Rheological Study Profile of A3 Batch Gel

S.NO.	INCREASING ORDER		DECREASING ORDER	
	rpm	Viscosity (cP)	rpm	Viscosity (cP)
1	0.3	85600	30	2440
2	0.5	74900	20	3312
3	0.6	66800	12	4940
4	1	51040	10	5720
5	1.5	28160	6	4640
6	2	23800	5	10060
7	2.5	18110	4	12100
8	3	15570	3	15470
9	4	13100	2.5	18050
10	5	10800	2	21640
11	6	8710	1.5	28160
12	10	5670	1	40080
13	12	4973	0.6	64100
14	20	3324	0.5	74700
15	30	2472	0.3	105300

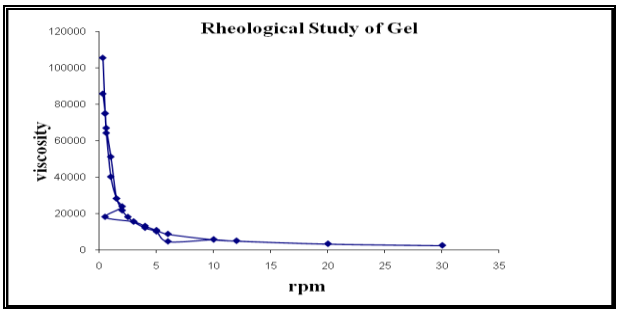

Figure 5- Rheological Study of Gel

Results and Discussion

The microspheres formulation batches were prepared by solvent evaporation method .It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulation may be due to microspheres lost during the washing process. Percentage yield of all formulations varies from 40.54±0.015 % to 65.57±0.017 %, the best one is F8 as given in Table 3.2. Percentage drug loading of drug in microsphere was evaluated, they varies from 16.76±0.081 to 46.56±0.68. Entrapment Efficiency of drug in microsphere was evaluated, the drug was entrapped & they varies from 67.46±0.248 to 89.34±0.051.

The F8 batch is better then all formulation batches because of Entrapment Efficiency (89.34±0.051), Percentage drug loading (46.37±0.68) and % Yield of Microspheres (65.57±0.017) are greater then all batches. So the F8 batch of microsphere is used for the preparation of Gel.The microspheres of Benzoyl Peroxide prepared by solvent evaporation were found to be almost spherical, free-flowing, white or almost white in color.

The pH value of all developed batches A1, A2, A3, A4, A5 and A6 were found to be 4.9, 5.1, 5.1, 4.5, 5.1 and 5.5 respectively. The values of Spreadability indicate that the gel is easily spreadable by small amount of shear. Spreadability of all batches A1, A2, A3, A4, A5 and A6 were found to be 5.8, 5, 6.3, 5.8, 5.8 and 5.9 respectively. Spreadability of A3 batch is 6.3g.cm/sec, indicating spreadability of carbopol -934 containing Benzoyl Peroxide gel was good as compared to the other batches.

The Viscosity shows the optimum flow property of gel formulation. Viscosity of all batches A1, A2, A3, A4, A5 and A6 were found to be 0.94 $x10^{-3}$, 1.6 $x10^{-3}$, 1.6 $x10^{-3}$, 1.7 $x10^{-3}$, 1.6 x 10^{-3} and 1.7 $x10^{-3}$ respectively. The Consistency reflects the capacity of the gel, to get ejected in uniform and desired quantity when the tube is squeezed. Consistency in terms of distance travel by cone was 5mm of A3 batch as compared to 6mm of all developed batches. Consistency is inversely proportional to the distance traveled by falling cone. Hence, the consistencies of carbopol -934 containing Benzoyl Peroxide gel were better as compared with all developed batches.

The A1, A2, A4, A5 gel showed good homogeneity and A3, A6 batch shows very good homogeneity with absence of lumps. The developed preparations were much clear and transparent. The skin irritation studies of developed gel were carried out on human volunteers and that confirmed the absence of any irritation on the applied skin. Percentage Drug Content of all developed batches A1, A2, A3, A4, A5 and A6 were found to be 90.0±0.09, 92.76±0.06, 98.97±0.12, 91.56±0.02, 90.21±0.01 and 97.46±0.005 respectively. On the basis of their Drug content, consistency, Homogenity, pH and Spreadibility, formulation A3 and A6 are two optimized formulations which shows better release profile than that of other formulation. On the comparative study of optimized batches the A3 batch shows the releases 46.12 % drug in 2 hr in a sustain manner and releases almost 59.23 % drug in 6 hr & A6 releases the 54.13 % in 6 hr ,so we are selecting A3 gel formulation .

The optimized A3 batch of gel shows non- Newtonian flow and exhibited pseudoplastic behavior, suggesting that gel do not flow at low shear stress and room temperature.The results of Antimicrobial Susceptibility Testing showed that both the formulated gel (A3 batch) and marketed gel have inhibitory effect on *Staphylococcus aureus* (ATCC- BAA 1026) with zone of inhibition 17.3 and 16.6 mm, respectively, it shows the formulated gel (A3 batch) possesses greatest inhibitory effect on the *Staphylococcus aureus* (ATCC- BAA 1026).

Conclusion

The main purpose of the study was to prepare controlled release formulation for reducing skin irritancy and incompatibility of drugs comprised of porous polymeric microspheres by using non-biodegradable polymers like Ethyl cellulose, Eudragit L 100, Eudragit RS 100. The method used to formulate these microspheres was Solvent Evaporation technique. Preciously optimized recipe was studied with different emulsifying agent SPAN -80, PVA and percentage yield, average particle size, and entrapment efficiency was determined. Surface morphology was observed with scanning electron microscopy. Gel was prepared with anti acne absorbed polymeric Microspheres. In-vitro release study by using Franz Diffusion Cell was performed on controlled release gel formulations comprised of porous polymeric microspheres containing acne treatment substance.

Gel containing carbopol -934 as gelling agent was found to have a balance between the adhesion and release of the drug through Microspheres and therefore, 2 g is considered as the optimum conc. of carbopol-934 to make best formulation.A3 & A6 batches both are comparatively good but A3 is better then all batches because of consistency ,Homogenity, pH,Spreadibility & release of drug. The A3 batch is best than all batches because there is No inflammation, No redness & No irritation, so when we applied to skin it gives Better result. A3 batch give the good release, so it maintains the drug in sustained manner. Hence improves patient compliance.

References

1. Van Abbe N J, Spearman R I C, Jarrett A. Pharmaceutical and Cosmetic Products for Topical Administration. 1st Edition, London: William Heinemann Medical Books Ltd, 1969: 5 - 65.

2. Walters K A, Roberts M S. The structure and fundtion of skin. In: Dermatological and transdermal formulations. Eds K.A.Walters, New York: Marcel Dekker, 2002: 1 - 40.

3. Trivedi Parul, Verma A M L, Garud N. Preparation and characterization of Aceclofenac microspheres. Asian Journal of Pharmaceutics 2008: 110-115.

4. Gohel M C, Sheth M N, Patel M M. Design of chitosan microspheres containing diclofenac sodium. Indian Journal of Pharmaceutical Science 1994; 56(6): 210-214.

5. Kosaraju S L, D'ath L, Lawrence A. Preparation and characterization of chitosan microspheres for antioxidant delivery. Carbohydrate Polymers 2006; 64: 163-167.

6. Nokhodchi Ali, Jelvehgari M, Siahi M R, Dastmalchi Siavoosh. The effect of formulation type on the release of Benzoyl Peroxide from microsponges. Iranian Journal of Pharmaceutical Sciences 2005; 1(3): 131-142.

7. Jelvehgari M, Siahi-Shadbad M R, Azarmi S, Dray Martin P, Ali Nokhod Chi. The Microsponge Delivery System of benzoyl peroxide: Preparation , Characterization and release studies. International Journal of Pharmaceutics 2006; 308 (1-2):124-132.

8. Shivhare U D, Jain K B, Mathur V B, Bhusari K P, Roy A A. Formulation development and evaluation of diclofenac Sodium gel using water soluble polyacrylamide polymer. Digest Journal of Nanomaterials and Biostructures 2009; 4(2): 285 – 290.

9. Gupta A, Mishra A K, Singh A K, Gupta V, Bansal P. Formulation and evaluation of topical gel of diclofenac sodium using different polymers. Drug Invention Today 2010; 2(5): 250-253.

10. Winfield A J. External Preparatoins. 3rd Edition, Eds Winfield A J, Richards R M E, New York: Churchill Livingstone, 2004: 206 - 217.

11. http://www.blackwellpublishing.com/content/BPL_Images/Content_store/Sample_chapter/0632064293/DermChap3.pdf.

12. Elias J J. The Microscopic Structure of the Epidermis and Its Derivatives. In: Percutaneous Absorption, 2nd Edition, Eds Bronaugh R L, Maibach H I, New York: Marcel Dekker, Inc, 1989:3 - 12.

13. Becher P. Encyclopedia of Emulsion Technology. New York: Dekker, 1983: 212-224.

14. Cohen S, Bernstein H. Microparticulate system for the delivery of protein and vaccines. New York: Marcel Dekker ,1996: 413-425.