10.37021/ijper.v1i2.4

RESEARCH ARTICLE

Formulation and Evaluation of a Microsphere Loaded Topical Gel for Acne vulgaris containing Benzoyl Peroxide

Neeru Sharma[1*], Azhar Danish Khan[2], Vipul Upadhyay[1], B P Singh[1], Sanjeev Tripathi[1]

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 the controlled release of BPO from a delivery system to the skin could reduce the side effect while reducing percutaneous absorption. Therefore, the present study aimed to produce Eudragit L 100 microparticles containing BPO, which were able to control the release of BPO to the skin. Solvent Evaporation Technique prepared microspheres. Microspheres are optimized based on their properties like Entrapment efficiency, % drug loading, % yield, and particle size. Polymers Ethylcellulose, Eudragit L100, Eudragit RS 100 were used in the formulations of Microspheres & the optimized batch incorporate in Gel preparation.

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

How to cite this article: Sharma, N., Khan, A.D., Upadhyay, V., Singh, B.P. and Tripathi, S. (2019). Formulation and Evaluation of a Microsphere Loaded Topical Gel for Acne vulgaris containing Benzoyl Peroxide. Int. J. Pharm. Edu. Res., 1(2):42-46.

Source of support: Nil

Conflict of interest: The authors declare that they have no competing interests.

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.[1] 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 of the controlled release of BPO results in a reduced amount of BPO at the skin site at a time. The controlled release of drugs from a formulation containing microspheres incorporated in the gel, such that the drug remains primarily localized at the epidermis with only a restricted amount entering the systemic circulation.[2] 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.[3] BPO is not associated with resistance to its 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. The 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 reduce comedonal acne lesions moderately. It may also be used successfully as a component of long-term maintenance therapy.

[1]Research and Development Centre, Sanat Products Ltd. Sikandrabad, Bulandshar, India

[2]Ram Eesh Institute of Vocational and Technical Education, Greater Noida, India

Corresponding author: Neeru Sharma, Sanat Products Ltd., B-8, Industrial Area, Sikandrabad, Bulandshar, U.P. 203205, India, email: neerurkgit@gmail.com, Ph. No: 7838110993

MATERIAL AND METHODS

Materials

Benzoyl peroxide (BPO) was obtained from Loba Chemie Pvt. Ltd, Mumbai, Ethylcellulose, Eudragit L100, Eudragit RS 100, Carbopol 934, Hydroxypropyl methylcellulose-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 RS 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 ethylcellulose 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 hours[4,5,6] (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 cellulose	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, and Particle size (Table 2).

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. A 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.[7] (Figure 1).

Preparation of Gel Containing Drug Loaded Microspheres[8,9,10]

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 minutes (Table 3).

In-Vitro Release Permeability Studies by Franz Diffusion Cell

Phosphate buffer of pH 5.5 was used for in vitro release

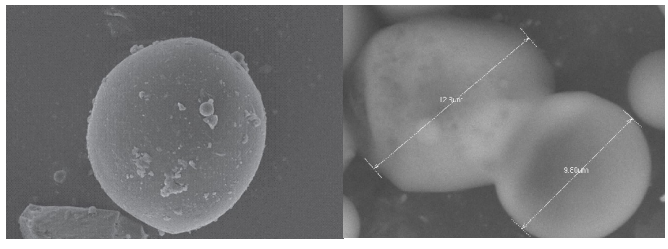

Figure 1: Microsphere SEM at 1800 and 9000 resolution

Table 2: Physical Parameters of Microspheres

Formulation code	*Drug : Polymer:PVA: SPAN*	*Entrapment Efficiency*	*Percentage of drug loading*	*Yield (%) of Microspheres*	*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

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

	Optimized Formulation of Benzoyl peroxide gel					
Ingredient	*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	-	-	-
Hydroxypropyl methylcellulose	-	-	-	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	-	1m				L
Propylene Glycol	-	5 m				L
Purified Water	100 m					L

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 the donor and receptor compartment of the diffusion cell. The receptor compartment contained phosphate buffer (100ml) of pH 5.5. The temperature of the diffusion medium was thermostatically controlled at 37° ± 1° 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 an equal volume of fresh fluid.[11,12] The samples withdrawn were spectrophotometrically estimated at 222nm against their respective blank (Figures 2-4).

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.[13] All rheological measurements were performed at 30±0.2^{0}C (Table 5, Figure 5).

RESULTS AND DISCUSSION

The microspheres formulation batches were prepared by a 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. The 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 drugs in the microsphere was evaluated; they vary from 16.76 ± 0.081 to 46.56 ± 0.68. Entrapment Efficiency of a drug in the microsphere was evaluated, the drug was entrapped, and they vary from 67.46 ± 0.248 to 89.34 ± 0.051.

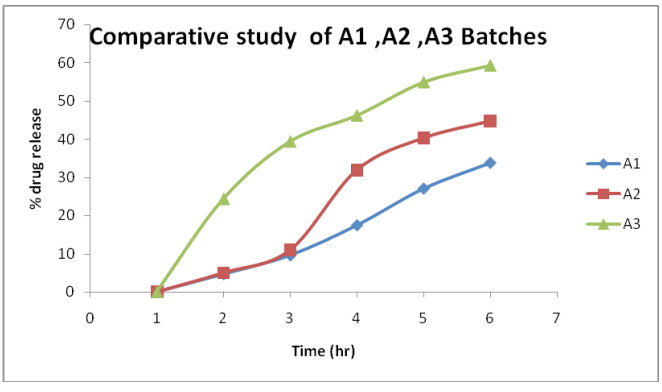

Figure 2: In-Vitro Comparative Drug Release Profile of A1, A2, A3 Formulation

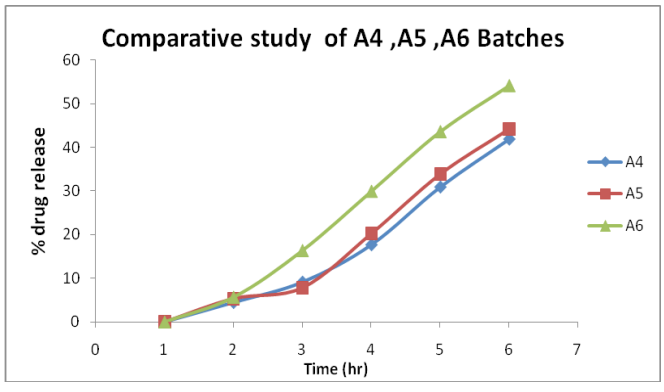

Figure 3: In-Vitro Comparative Drug Release Profile of A4, A5, A6 Formulation

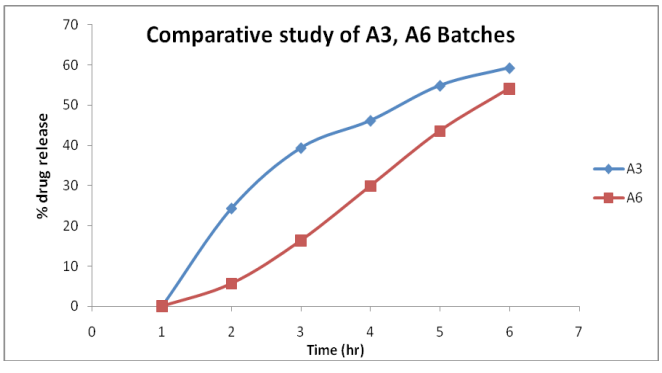

Figure 4: In-Vitro Comparative Drug Release Profile of A3, A6 Formulation

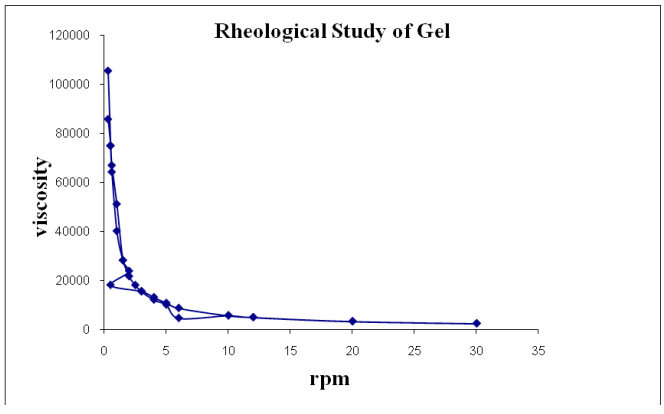

Figure 5: Rheological Study of Gel

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

Batch no	*pH*	*Spreadability g.cm/sec*	*Viscosity (dyn·s/cm^2)*	*Consistency (60 sec)*	*Homogeneity*	*Skin irritation*	*(%)Drug Content*
A1	4.9	5.8	0.94 x 10^{-3}	6mm	Good	Nil	90.0 ± 0.09
A2	5.1	5	1.6 x 10^{-3}	6mm	Good	Nil	92.76 ± 0.06
A3	5.1	6.3	1.6 x 10^{-3}	5mm	Very good	Nil	98.97 ± 0.12
A4	4.5	5.8	1.7 x 10^{-3}	6mm	Good	Nil	91.56 ± 0.02
A5	5.1	5.8	1.6 x 10^{-3}	6mm	Good	Nil	90.21 ± 0.01
A6	5.5	5.9	1.7 x 10^{-3}	6mm	Very good	Nil	97.46±0.005

Table 5: Rheological Study Profile of A3 Batch Gel

	INCREASING ORDER		DECREASING ORDER	
S.NO.	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

The F8 batch is better than 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 than all batches. So the F8 batch of the 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 a 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. The spreadability of A3 batch is 6.3g.cm/sec, indicating the 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 an 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. Based on their Drug content, consistency, Homogeneity, pH, and Spreadability, 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 hours in a sustained manner. It releases almost 59.23 % drug in 6 hr & A6 releases the 54.13 % in 6-hour, 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 Ethylcellulose, Eudragit L 100, Eudragit RS 100. The method used to formulate these microspheres was the solvent Evaporation technique. The 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. The 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 than all batches because of consistency, homogeneity, pH, spreadability, and 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 results. A3 batch give the good release, so it maintains the drug in a sustained manner. Hence improves patient compliance.

REFERENCES

1. Hayashi N, Akamatsu H, Iwatsuki K.Guidelines for the treatment of acne vulgaris Japanese J Dermatol 2016; 26: 1045–1086.
2. Hayashi N, Higaki Y, Kawamoto K, Kamo T, Shimizu S, Kawashima M. A cross-sectional analysis of quality of life in Japanese acne patients using the Japanese version of Skindex-16. Journal of Dermatology 2004; 31: 971–976.
3. Nakase K, Nakaminami H, Noguchi N, Nishijima S, Sasatsu M. First report of high levels of clindamycin-resistant Propionibacterium acnes carrying erm(X) in Japanese patients with acne vulgaris. Jornal of Dermatology 2012; 39: 794–796.
4. Liu J, Meisner D, Kwong E, Wu XY, Johnston MR. A novel trans-lymphatic drug delivery system: implantable gelatin sponge impregnated with PLGA-paclitaxel microspheres. Biomaterials, 2007; 28(21): 3236-3244.
5. Mathew Sam T, Devi Gayathri S, Prasanth VV, Vinod B. Suitability of factorial design in determining the processing factors affecting entrapment efficiency of albumin microspheres, Journal of Pharmacy Research.2010; 3(5): 1172- 1177.
6. Sudhamani T, Reddy N, Ravi Kumar V, Revathi R, Ganesan V. Preparation and evaluation of ethyl cellulose microspheres of ibuprofen for sustained drug delivery. International Journal Pharmaceutical Research and Development 2010;2: 119-125
7. Chuanbin W, Jame W, Mcginity WJ. Influence of ibuprofen as a solid-state plasticizer in Eudragit RS 30 D on the physicochemical properties of coated beads. Journal of Pharmaceutical Science and Technology 2001; 2:1-7.
8. Yang JH, Yun MY, Kim DK, Kim MJ, Kim Y, Kim TY, et al. Preparation and evaluation of ketorolac tromethamine gel containing genipin for periodontal diseases. Arch Pharm Res. 2007;30(7):871-875. 26.
9. Zia H, Nasseri AA, Aboofazeli R, Needham TE. Lecithin-stabilized microemulsion- based organogels for topical application of ketorolac tromethamine. In vitro release study. Iranian Journal of Pharmaceutical Research. 2003; 2:117-123.
10. Basarkar GD, Shirsath GN, Patil S.B. Development of microspheres containing diclofenac diethylamine as sustained release topical formulation. Bulletin of Pharmaceutical Research. 2013;3(1):14-22.
11. Ganesh S, Kumar SD, Kumar SB, Abhilash R, Bharadwaj SP, Mohammed I, et al. Controlled release formulation and evaluation of idarubicin microsphere using biodegradable hydrophilic and hydrophobic polymer mixtures. Asian Journal of Pharmaceutical and Clinical Research. 2010;3(3):179-182. 20.
12. Avachat MA, Bornare NP, Dash RR. Effect of process parameters Sustained release microspheres of ropinirole hydrochloride. Acta Pharmakon. 2011 ;61(21): 363-376.
13. Dhoka VM, Pande VA, Vaidya DP, Arora A. In vitro and in vivo evaluation of ethyl cellulose-based floating microspheres of cefpodoxime proxetil. International Journal of Pharmaceutical and Biomedical Research. 2010;1(4):122-128.