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Original Article

DEVELOPMENT OF GEL-LOADED BASED MICROSPONGES OF CLARITHROMYCIN FOR THE TREATMENT OF TOPICAL DELIVERY

SUNNY DHIMAN[1], NISHANT SHARMA[1], REENA THAKUR[1], INDER KUMAR[1*], BHUMIKA THAKUR[2], ANKITA SHARMA[2], VANDANA THAKUR[3], KIRAN KUMARI[3]

[1]School of Pharmacy, Abhilashi University, Mandi, HP India, [2]Shiva Institute of Pharmacy, Bilaspur, HP India, [3]Abhilashi College of Pharmacy, Nerchowk, Mandi HP India
*Email: inder.93kumar@gmail.com

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ABSTRACT

Objective: The purpose of the present study aims to design a novel drug delivery system containing clarithromycin microsponges and to prepare microsponge gel.

Methods: The microsponges were prepared by quasi-emulsion solvent diffusion method using polymer eudragit RS-100. All the formulated microsponges were subjected to various evaluation parameters such as production yield, encapsulation efficiency, particle size analysis, and *in vitro* drug release study.

Results: *In vitro* drug release of all the formulations was found to be 47.36% to 87.32%. Formulations F2, F3, and F4 show the best drug release from all formulations within 480 min. The optimized microsponge formulations F2, F3, and F4 were further formulated as gel formulations for topical delivery. Prepared gel was evaluated for physical parameters like pH, spreadability, viscosity, drug content, *in vitro* diffusion study, and stability study. All gel formulations showed drug release of 63.18±0.52%, 76.4±0.51%, and 72.93±0.42% from formulations GF1, GF2, and GF3, respectively, within 480 min. The microsponge gel formulation GF2 showed the controlled release of clarithromycin for 480 min, which was 76.4±0.51%. The stability study shows no significant changes in all parameters.

Conclusion: With the revealed results by different evaluation parameters, it is concluded that the microsponges drug delivery system has become a highly competitive and rapidly evolving technology and more and more research is carried out to optimize the cost-effectiveness and efficacy of the therapy.

Keywords: Microsponges, Clarithromycin, Eudragit RS 100, Acne Vulgaris, Controlled release

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INTRODUCTION

Acne vulgaris, commonly known as acne is a ubiquitous disease affecting about 80% of individuals in which the hair follicles get clogged with dead skin cells, oil, sebum, and dirt. Acne occurs only where there is a high region of the pilosebaceous unit, which contains oil glands such as the face, neck, upper chest, back, and trunk [1]. It is a common disease in the world, ranking 8th worldwide, affecting around 660 million people globally. Acne occurs in adolescence affecting about 80 to 90% of the teenagers in the world and persists in about 3% of middle-aged adults [2]. Acne is termed a universal disease because it occurs in a major population irrespective of race and area affecting about 95% of boys and 83% of girls. Although the major cause of acne is genetics, many other factors that contribute to breakouts are changes in hormonal levels, infections, diet, and stress [3]. Inflammatory as well as non-inflammatory lesions initially including comedones and further papules, pustules, nodules, and cysts respectively, characterize it [4].

The major depiction of Acne is done by the appearance of comedones by the excessive oily sebum production, inflammatory lesions, and the presence of bacteria such as *Propionibacterium acnes* and *Staphylococcus aureus* in the pilosebaceous unit [5]. Pathogenesis of acne is thought to be occurred by many factors but the proliferation of bacteria, mainly *Propionibacterium acne* plays a massive role in the formation of comedones and inflammation of lesions. *P. acnes* activate the native immune response and various chemotactic factors involving inflammatory cells such as monocytes, macrophages, neutrophils, and keratinocytes [6]. Treatment for acne vulgaris includes changes in lifestyle, the inclusion of medications, and medical procedure. But the acne treatment should help in achieving the aim to reduce both severities as well as re-occurrence of the skin lesions for the improvement of appearance also [7].

Clarithromycin is a broad-spectrum antibiotic, a member of the macrolide family, which is active against both gram-negative as well as gram-positive bacteria like *Staphylococcus aureus, E. coli, Klebsiella and Proteus.* It is used to treat skin and soft tissue infections. It is also used to treat both upper and lower respiratory tract infections as well as *Helicobacter pylori* infections. Clarithromycin is best known as an anti-infective but also exerts other important pharmacological actions such as immunosuppressant and immune modulation and apoptosis-inducing effect in addition to the antimicrobial role. It is also capable of inhibiting cytokine production by human monocytes as interleukin-1α, interleukin-6, tumor necrosis factor-α, or TNF-α, thus reducing inflammation further. It acts by binding to the 50 S bacterial ribosomal subunits and blocks the translocation of aminoacyl transfer-RNA and polypeptide synthesis [8-10].

Many topical formulations of clarithromycin are available in the market, including creams, ointments, and gels but these conventional formulations of topical drugs are meant to act on external layers of the skin. To minimize irritations and side effects, there is a need for a drug delivery system that enhances the time of active ingredients to retain on the surface of the skin but minimizes the transdermal penetration of the drug. Recently, it has been found major interest in the development of novel microsponges which is one of the most useful devices to deliver material effectively and safely to achieve targeted and sustained release of drugs.

Hence, in the present study, an attempt has been made to design, develop and evaluate the clarithromycin microsponges, which are further incorporated into a gel for topical treatment of acne, which extends the release of the drug thereby overcoming the disadvantage of the conventional dosage form.

MATERIALS AND METHODS

Clarithromycin drug was obtained as a gift sample from Lark Laboratories. Carbopol 940, glycerine, ethanol, methyl, eudragit RS

100, polyvinyl alcohol, dichloromethane, sodium carbonate, potassium dihydrogen phosphate, disodium hydrogen phosphate, etc. were purchased from CDH (p) Ltd. And HiMedia Laboratories Pvt. Ltd. All the chemicals were used in AR grades.

Formulation of microsponges

The method of preparation for the microsponges for the hydrophobic drug was reported as a quasi-emulsion solvent diffusion method by a two-step process.

Preparation of internal phase

This phase has consisted of the drug (clarithromycin), polymer (Eudragit RS 100), and solvent (ethanol and dichloromethane in ratio 1:1). To prepare for this phase, Eudragit RS 100 was dissolved in a mixture of solvents and then the drug was further added to it and dissolved under ultrasonication.

Preparation of external phase (aqueous phase)

For the preparation of the aqueous phase, weighed quantity of Polyvinyl alcohol was taken and dissolved in 50 ml of water in a beaker. The internal organic phase was poured into the external phase drop-wise. The mixture was allowed to stir until the foam settled down and after the complete evaporation of dichloromethane, the mixture was filtered with whatmann filter paper (0.45 µm). The formed microsponges were separated and air-dried for 24 h and kept for further evaluation [11-13].

Table 1: Formulation of microsponges

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Clarithromycin: Eudragit RS 100	1:1	1:1.5	1:2	1:2.5	1:3	1:3.5	1:4	1:4.5	1:5	2.0
DCM: Ethanol (5 ml)	1:1	1:1	1:1	1:1	1.1	1:1	1:1	1:1	1:1	1:1
PVA (mg)	500	500	400	300	300	200	100	100	100	100
Distilled water (ml)	50	50	50	50	50	50	50	50	50	50

*DCM = Dichloromethane, PVA = Polyvinyl alcohol

Evaluation of microsponges

Morphology and surface topography

SEM (Digital Scanning Electron Microscope-JSM 6100 (JEOL) was used for prepared formulations. Microsponges were taken and coated with gold-palladium under an argon atmosphere placed at room temperature and then the surface morphology was studied [14].

Particle size

The Particle size analysis of the microsponges was determined by the optical microscopy method. The optical microscope was fitted with a stage micrometer by which the size of microsponges could be determined. The mean diameter of about 100 dried microsponges was noted [15].

Drug content and Encapsulation efficiency

A sample of dried microsponges equivalent to 10 mg was taken into mortar and pestle and a little amount of phosphate buffer of pH 5.5 was added and allowed to stand for 24h. Then transfer the content to a 10 ml volumetric flask and the volume was made up to 10 ml with phosphate buffer of pH 5.5. The solution was filtered through whatmann filter paper. From the resulting solution, 1 ml of solution was taken into a 10 ml volumetric flask and then followed the same procedure as mentioned in the estimation procedure and allowed to stand for 20 min for completion of the reaction. Drug content was determined at 760 nm [8, 16].

***In vitro* drug release**

In vitro release studies were carried out using a modified Keshary-Chien diffusion cell. The Himedia dialysis membrane 70 (soaked in pH 5.5 for 24 h before use) was fixed to one end of the cylinder with the aid of an adhesive to result in a permeation cell. Weighed quantity of 10 mg of microsponges was taken in the cell (donor compartment) and the cell was immersed in a beaker (500 ml) containing drug-free phosphate buffer pH 5.5 (300 ml) as the receptor compartment. The cell was immersed to a depth of 1 cm below the surface of phosphate buffer in the receptor compartment and was agitated using a magnetic stirrer and a temperature of 37 °C±1 °C was maintained. 5 ml of dissolution medium was withdrawn from the receptor compartment at various intervals of time (30, 60, 90, 120, 180, 240, 300, 360, 420, 480 min) over 8 h and then estimated calorimetrically using a UV spectrophotometer at 760 nm. The volume withdrawn at each time was replaced with drug-free phosphate buffer. The amount of clarithromycin released at various intervals of time was calculated and plotted against time [17].

Table 2: Preparation of gel containing microsponges

S. No.	Formulation embodiments	GF1	GF2	GF3
1	Clarithromycin microsponges	254.45 mg	343 mg	497 mg
2	Carbopol 940	2%	2%	2%
3	Glycerine (ml)	3.5	3.5	3.5
4	Triethanolamine (ml)	2.5	2.5	2.5
5	Methyl paraben (ml)	0.1	0.1	0.1
6	Alcohol (ml)	1.0	1.0	1.0
7	Distilled water	q. s.	q. s.	q. s.

*Equivalent to 1% w/w of clarithromycin concentration

Evaluation of gel

The prepared gel was evaluated for various parameters such as; physical appearance, pH, drug content, viscosity, spreadability, *in vitro* diffusion study, data analysis, and stability studies.

Drug content

An accurately weighed quantity of gel (about 100 mg) was taken in 10 ml of phosphate buffer of pH 5.5. The gel was shaken to dissolve the drug in a solvent. These solutions were transferred to a volumetric flask and appropriate dilutions were made with the same buffer solution. The solution was filtered through whatmann filter paper. The filtrate was pipetted out and suitably diluted if desired and further following the same colorimetric procedure quoted earlier. UV Spectrophotometrically analysed the sample against a similarly treated blank at 760 nm [18, 19].

Viscosity measurement

The viscosity of the prepared gel was determined by using Brookfield Viscometer. The speed of spindle no. 6 was adjusted at 20 rpm at 25 °C and readings were recorded [20].

Spreadability study

This was determined by measuring the diameter of 1 g gel placed between horizontal plates of wooden block glass slides apparatus. The top plate was subjected to pull particular weight with the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of at least 5 cm be noted [18]. Spreadability was measured using the equation

$$S = \frac{M}{T} \times L$$

Where, M= weight (gm) taken, L= length of the slide, T= time (sec) taken

***In-vitro* diffusion study**

The release of clarithromycin from various gel formulations was studied using a modified Keshary-Chien diffusion cell. The Himedia dialysis membrane 70 (soaked in pH 5.5 for 24 h before use) was fixed to one end of the cylinder with the aid of an adhesive to result in a permeation cell. One gram of gel was taken in the cell (donor compartment) and the cell was immersed in a beaker containing 300 ml phosphate buffer (pH 5.5) as the receptor was agitated using a magnetic stirrer and maintaining a temperature of 37 °C±1 °C. 5 ml of dissolution medium was withdrawn from the receptor compartment at different intervals and then estimated colorimetrically using UV spectrophotometer at 760 nm [21-23].

Stability studies

Stability studies of the gel formulations were conducted for three months by storing the gel at ambient temperature (30°C and 40°C). Gel formulations were evaluated for color, after-feel effects, viscosity, drug content, spreadability, and pH after 3 mo [24].

RESULTS AND DISCUSSION

Absorption maximum (λ_{max}) of clarithromycin

The λmax of clarithromycin was determined by colorimetric procedure utilizing 0.1 N HCl and it was observed at 760 nm. The calibration curve showed a regression coefficient (R^2) of 0.995.

Compatibility studies

The FTIR spectrum of clarithromycin revealed the presence of peak at 1691 cm^{-1} refers to O-C=O stretching vibration from the ketone group, 1732 cm^{-1} refers to O-C=O stretching vibration in the lactone ring, 1051 cm^{-1}, 1171 cm^{-1}, and 1107 cm^{-1}, refers to the-O-ether functional bands, and at 2939 cm^{-1} refers to the Alkyl-CH_3 substitution bands and H-bond at 3468 cm^{-1} [25].

The FTIR spectrum of drug, polymer, physical mixture and other excipients did not show any significant change in the characteristic peaks of the drug, which proved the excipient were compatible with each other (fig. 1).

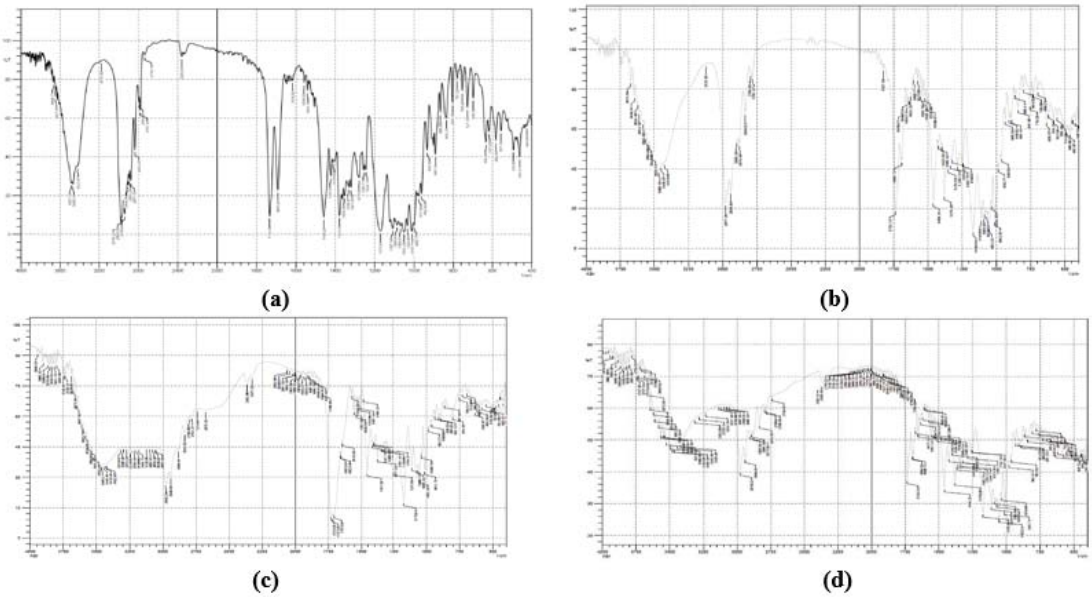

Fig. 1: FTIR spectrum of (a) clarithromycin (b) clarithromycin and eudragit RS 100 (c) clarithromycin and carbopol 940 (d) clarithromycin and polyvinyl alcohol

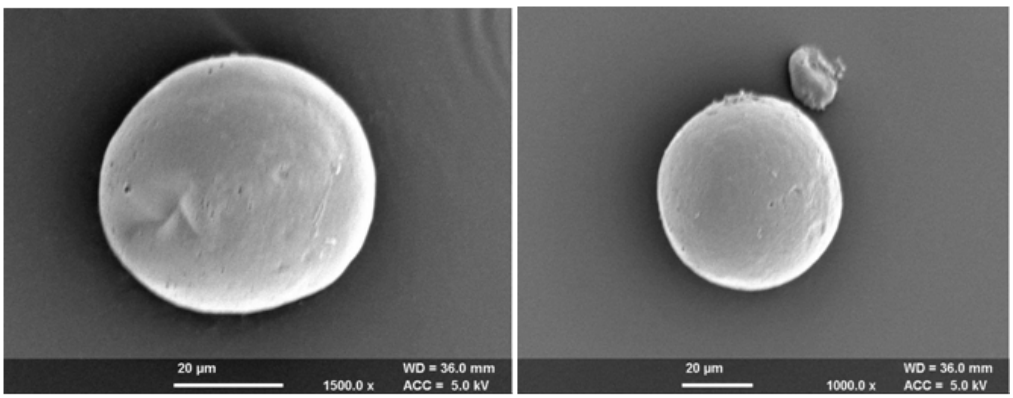

Fig. 2: SEM images of the clarithromycin microsponges

Evaluation of microsponges

Morphology and surface topography

The morphological evaluation was done by visual inspection and from the Scanning Electronic Microscope (SEM) images of formed microsponges as well as fractured microsponges to illustrate its ultrastructure are shown in fig. 2. The images obtained from SEM revealed that the particles were spherical with a porous structure which indicates that microsponge formulations were properly prepared. Fractured images showed that due to evaporation of solvent from the surface of microsponges, pores were induced.

Particle size analysis of microsponges

Particle size analysis of microsponges is shown in table 3. The particle sizes were found in the range from 103 µm to 145 µm, which follows the literature that the average particle size of microsponges should be in the range of 5-300 µm. The visual inspection of all batches using the optical microscope for particle size revealed that particle size had increased with an increase in drug: polymer ratio. This may be due to the reason because of the higher drug: polymer ratio, the polymer available was in more quantity, thereby increasing the wall thickness, which led to increasing in the size of microsponges. The production yield of all the formulations was 62.53±0.33% to 90.32±0.55%. Data of particle size and production yield are tabulated in table 3.

Drug content and encapsulation efficiency

Drug content and encapsulation efficiency of microsponge formulation are shown in table 4. Drug content was found to be lesser than the theoretical value for every drug: polymer ratio. Formulation F2 shows a higher drug content of 59.06±0.40% and formulation F9 shows a drug content of 15.32±0.33%. The drug content of the formulation was found to decrease with an increase in the drug to polymer ratio, while Encapsulation efficiency reflected that with the higher drug: polymer ratios, greater drug loadings up to certain limits (F6) occurred and then decreased further from F7 to F10. Data are tabulated in table 4 [26].

***In vitro* diffusion release**

The drug release was observed to decline within a range of 89.32% to 47.36% for the rise in drug to polymer ratio from 1:1 to 2:0. The highest drug release was found to be in the formulation F3, which was 89.32% at a ratio of 1:2 while the lowest was 47.36% for F10 at a ratio of 2:0. Higher release in the initial formulation F2 and F4 may be due to less polymer matrix or may be due to non-encapsulated drug at the lower drug to polymer ratio. Data are tabulated in table 5 and fig. 3.

Table 3: Particle size and production yield of microsponge formulations

S. No.	Formulation code	Particle size (µm)	Production yield (%)
1	F1	106.48±0.42	62.53±0.33
2	F2	110.18±0.78	68.30±0.48
3	F3	113.22±0.45	78.28±0.63
4	F4	118.44±0.65	83.36±0.88
5	F5	118.48±0.35	86.72±0.54
6	F6	119.33±0.85	88.65±0.42
7	F7	123.35±0.65	83.92±0.65
8	F8	120.56±0.35	90.32±0.55
9	F9	135.26±0.56	81.37±0.65
10	F10	142.12±0.35	86.55±0.45

*Mean+SD, n=3, SD = Standard Deviation

Table 4: Drug content and encapsulation efficiency of microsponge formulations

S. No	Formulation code	Drug content (%)	Encapsulation efficiency (%)
1	F1	43.15±0.50	80.82±0.21
2	F2	59.06±0.40	83.12±0.30
3	F3	52.13±0.84	87.32±0.52
4	F4	48.21±0.68	85.51±0.71
5	F5	36.31±0.33	78.61±0.12
6	F6	32.80±0.55	70.48±0.31
7	F7	28.46±0.44	61.16±0.51
8	F8	16.35±0.25	65.18±0.53
9	F9	15.32±0.23	50.32±0.33
10	F10	18.14±0.73	42.17±0.41

*Mean+SD, n=3, SD = Standard Deviation

Table 5: *In vitro* diffusion release of microsponge formulations

Time (min)	Cumulative percent release (%CPR)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0
60	11.21	13.84	18.28	9.17	10.47	8.71	0	0	0	0
90	22.91	15.13	26.91	12.15	17.74	15.32	12.54	13.64	20.65	14.33
120	33.24	26.49	35.69	22.60	25.58	29.84	15.56	13.38	20.86	21.38
180	38.75	38.74	45.48	32.93	36.59	42.55	27.36	37.74	28.22	23.63
240	48.15	45.66	55.33	42.38	49.85	47.07	35.46	41.89	30.56	29.15
300	62.12	59.41	62.65	55.43	59.78	59.28	40.35	42.64	36.12	30.47
360	71.02	67.25	75.18	59.42	68.3	64.54	48.2	47.9	43.2	35.34
420	73.12	82.22	81.29	76.18	75.89	72.27	56.49	53.37	45.93	40.35
480	75.76	85.46	87.32	84.58	80.39	74.47	68.34	56.45	51.64	47.36

*% CPR = Cumulative percent release

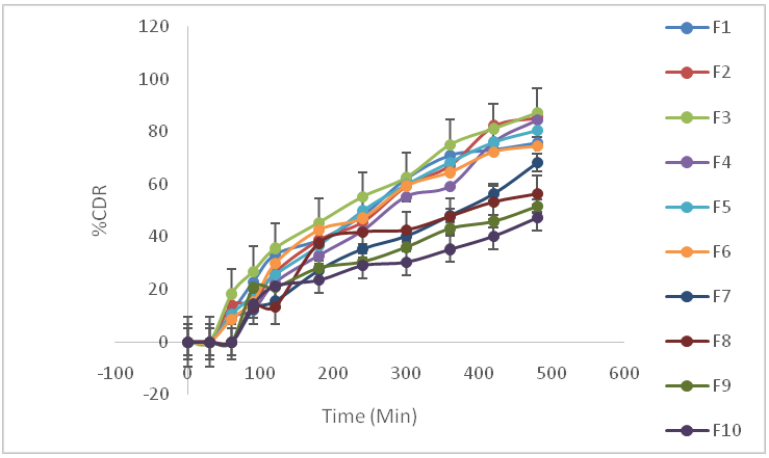

Fig. 3: *In vitro* diffusion profile of microsponge formulations. Error bars indicate SD of n=3

Optimized formulation of clarithromycin microsponges for gel

Based on the evaluation of microsponges specifically encapsulation efficiency and *in vitro* drug release, the optimized batches for the gel formulation of clarithromycin microsponges were found to be F2, F3, and F4 having encapsulation efficiency of 83.12±0.30%, 87.32±0.52%, 85.51±0.71%, and *in vitro* drug release of these formulations was 85.46%, 87.32%, and 84.58%.

Evaluation of microsponges gel formulations

The prepared gels of formulations F3, F4, and F5 named GM1, GM2, and GM3 were evaluated for the visual inspection for color, texture, appearance, consistency of the gel, pH of the formulation, homogeneity, Drug content, Spreadability, and viscosity. The drug content of all gel formulation were 93.1±0.24 %, 91.3±0.21 %, 92.2±0.18 % of formulation GF1, GF2,and GF3 respectively. The spreadability of all the gel formulations were GF1 (26.94±0.66±0.56), GF2 (22.156±0.45), and GF3 (19.43±0.38), respectively. The parameters evaluated are shown in table 6.

***In vitro* diffusion study of clarithromycin microsponges gel formulations**

The release of microsponges gel formulation is shown in table 7. It was found that the conventional gel released 99.88±0.42% of the drug in 300 min while the microsponges gel formulation drug released was found between 63.18±0.52%, to 76.4±0.51% in 480 min. The *in vitro* release of the gel GF1 was found to be 63.18±0.52%, GF2 76.4±0.51%, and GF3 72.93±0.42%. The release of the drug from formulations showed GF1 released the drug in a confined manner while Gel GF2 and GF3 showed a better release profile (fig. 4) [27].

Table 6: Evaluation parameters for microsponges-loaded gel formulations

Parameter	Pure gel	GF1	GF2	GF3
Carbopol strength	2%	2%	2%	2%
Color	Transparent	Transparent	Transparent	Transparent
After feel effects	Smooth	Smooth	Smooth	Slightly rough
Consistency	good	good	good	Residue remaining
Homogeneity	good	good	good	good
pH determination	6.84±0.12	6.75±0.22	6.65±0.14	6.48±0.10
Drug content	98.8±0.11 %	93.1±0.24 %	91.3±0.21 %	92.2±0.18 %
Spreadability	28.10±0.56	26.94±0.66	22.156±0.45	19.43±0.38
Viscosity (cps)	1725±0.42	1730±0.41	1761±0.48	1743±0.58

*Mean+SD, n=3, SD = Standard Deviation

Table 7: *In vitro* diffusion release of the formulated gel by using dialysis membrane

Time (min)	Cumulative percent release (%CPR)			
	Pure gel	GF1	GF2	GF3
0	0	0	0	0
30	23.18±0.32	09.45±0.44	12.44±0.49	8.32±0.51
60	38.40±0.44	16.74±0.32	19.48±0.31	10.44±0.62
90	45.90±0.56	20.34±0.31	27.28±0.52	15.63±0.59
120	64.50±0.35	26.58±0.43	32.54±0.45	26.24±0.53
180	88.55±0.50	34.82±0.36	42.55±0.61	38.98±0.54
240	99.58±0.62	42.94±0.42	50.42±0.42	48.74±0.31
300	99.88±0.42	48.62±0.39	59.59±0.11	58.64±0.52
360	-	52.80±0.74	66.12±0.56	64.17±0.54
420	-	58.73±0.61	72.64±0.58	69.29±0.69
480	-	63.18±0.52	76.4±0.51	72.93±0.42

*mean±SD, n = 3, SD = Standard Deviation

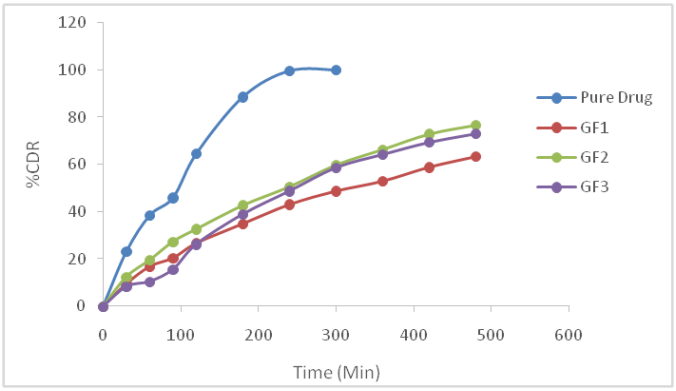

Fig. 4: *In vitro* diffusion profile of pure gel and microsponge gel formulations

Stability studies

The stability studies showed that there were no significant changes in the pH, drug content, spreadability, and viscosity. There were no changes in the color and feel of the gel. All formulations showed a pH range between 6.2±0.005 to 6.3±0.003. Drug content, spreadability, and viscosity all showed no significant changes in the optimized formulations. The results are shown in table 8.

Table 8: Stability studies of gel formulations

Parameters	Initial stage			After three months		
	GF1	GF2	GF3	GF1	GF2	GF3
Color and after-feel effect	Transparent and smooth	Transparent and smooth	Transparent and rough	Transparent and smooth	Transparent and smooth	Transparent and rough
pH	6.3±0.002	6.4±0.001	6.4±0.006	6.2±0.005	6.3±0.003	6.3±0.002
Drug content	97.10±0.012	96.30±0.010	95.20±0.013	96.50±0.011	95.7±0.014	94.80±0.015
Spreadability (g. cm/sec)	22.09±0.018	20.10±0.015	17.40±0.014	22.00±0.014	19.50±0.016	16.80±0.014
Viscosity (cps)	1720±0.018	1721±0.017	1723±0.011	1719±0.013	1720±0.018	1721±0.018

*mean±SD, n = 3, SD = Standard Deviation

CONCLUSION

The microsponges were prepared by quasi emulsion method and were evaluated for their different parameters, which revealed many interesting results for efficient preparation of the microsponges. The formulations F2, F3, and F4 showed better results than the other seven formulations. F2, F3, and F4 have encapsulation efficiency of 83.12±0.30%, 87.32±0.52, and 85.51±0.71%. The gel-loaded microsponges were evaluated and show significant results. The formulation GF2 show 76.4±0.51% drug release within 480 min. The stability study shows no significant changes in all parameters. With the revealed results by different evaluation parameters, it is concluded that the microsponges drug delivery system has become a highly competitive and rapidly evolving technology and more and more research is carried out to optimize the cost-effectiveness and efficacy of the therapy.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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