



PREPARATION AND CHARACTERIZATION OF FLUTICASONE PROPIONATE LOADED MICROSPONGE BASED GEL

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Volume 6, Issue 15, Sep 2024

Received: 15 July 2024

Accepted: 25 Aug 2024

Published: 05 Sep 2024

doi: [10.48047/AFJBS.6.15.2024.3133-3147](https://doi.org/10.48047/AFJBS.6.15.2024.3133-3147)

ABSTRACT

This purpose of this study to deliver fluticasone propionate (FP) in a controlled manner to minimise the side effects in the form of microsp sponge based gel. Using the quasi-emulsion solvent diffusion method, FP containing microsp sponge as the active constituent (API) in several formulations was effectively developed by altering the amounts of drug, polymer (Eudragit RL100), and Poly vinyl alcohol. The physical characteristics and particle size of these formulations were examined. The spherical and porous nature of the microsp sponge was seen by scanning electron microscopy (SEM) pictures. According to the physical characterization the microsp sponge formulation F4 and F6 showed a higher loading efficiency and production yield. This formulation of microsponges was made as a gel in carbopol 934 and its pH, viscosity, spreadability and invitro release have been studied. The viscosity of the GM1 and GM2 microsp sponge formulation gel was 24039% and 23614%, its spreadability was 23.44 and 25.66 cm/s, and its drug content was 80% and 82% respectively. The drug release profiles shown by the FP microsp sponge gel formulations were acceptable. At 8 hours, 92% of the drug was released by F4. Fourier transform infrared spectroscopy did not reveal any significant interactions between the drug and excipients.

KEY WORDS: Microsp sponge, Topical, Gel, Fluticasone propionate.

1. INTRODUCTION

The capacity of novel drug delivery systems to provide targeted and regulated medicine release has attracted a lot of attention. Because traditional distribution systems are inefficient, they frequently need for substantial dosages of active drugs. Conversely, highly cross-linked, porous polymeric microspheres make up the advanced, patent-protected technology known as

microsponges. These microsponges are especially well suited for sustained topical treatments and, more recently, oral administration due to their remarkable effectiveness in encapsulating a broad variety of active substances. Microsponge systems provide several advantages, including as controlled drug release, fewer side effects, increased stability, flexible and attractive formulations, and effective delivery of active medicinal components at lower dosages. [1,2]

To stop too much material from building up in the dermis and epidermis, the microsphere system was created. Consumer may typically get these items in conventional formats like lotion, gel, and cream, which frequently have rather high active ingredient concentration. Polymeric delivery system called microsphere and these are composed of porous microspheres that may hold a wide range of active substances, such as sunscreens, essential oils, emollient, and agents with anti-inflammatory, anti-fungal, and anti-infective qualities.[3]

Traditional topical dose forms including lotions, creams, ointments, and powder have drawn challenges especially when it comes to skin delivery and drug diffusion from the vehicles. Because of their base insufficient drug release and quick skin clearance, cream and lotion frequently have low bioavailability. Patients find non-hydrophilic ointment to be oily and oleaginous whereas topically applied medicinal powders have a brief skin residence duration. Conversely, gels are semisolid systems in which a three-dimensional network of interlaced particles or solvated macromolecules of the dispersed phase limits the mobility of the dispersion medium. The semisolid state is produced by this interlacing because internal friction increases viscosity. Gels may also have wrapped up, matted strands that form both crystalline and amorphous region throughout the system because they are held together by stronger Van der Waals forces. By prolong the duration of drugs residence on the skin, gel can be used as a delivery system to increase bioavailability. Gel have a number of benefit, such as improved drug release, longer skin residence time, patient compliance, non-greasy texture, and ease of application. [4]

Topical glucocorticoids are the frequently prescribed by dermatologists due to their anti-inflammatory, immunosuppressive, and antiproliferative characteristics, which are essential for the treating a variety of skin condition. Due to its breakdown into an inactive carboxylic acid, one such synthetic carbothioate corticosteroid, fluticasone propionate (FP), is known for its great clinical effectiveness and low risk of systemic or local side effect. FP is offered in ointments and cream preparations with 0.005% and 0.05% concentrations. The itchy and inflammatory symptoms of corticosteroid-responsive dermatoses are reduced with topical FP formulation. After approximately a week of treatment, a sustained reaction is usually seen. Although both regimens are equally effective, a twice-daily schedule may have a somewhat quicker start of action than a once-daily schedule. As a result, FP is a useful addition to the variety of topical corticosteroids for treating skin disorders such vitiligo, atopic dermatitis, and psoriasis due to its benefit of once-daily treatment and minimal risks of systemic toxicity.[5-8]

2. MATERIALS AND METHODS

2.1. Materials

Fluticasone propionate was procured from Intas Pharmaceuticals, Ahmedabad. Eudragit RL100, Ethanol, Dichloromethane, Poly vinyl alcohol, Glycerol, Carbopol 934, Dibutyl phthalate and Triethanolamine from CDH Private Limited.

2.2. Equipment

Table 1: List of instruments

S. No.	Instruments	Manufacturer
1	UV Spectrophotometer	Shimadzu
2	Infrared Spectrophotometer	PerkinElmer spectrum
3	Mechanical Stirrer	Bezif
4	Magnetic Stirrer	Bezif
5	Ultrasonicator	PSI Industries
6	Brook Field Viscometer	Richmond scientific
7	Hot air oven	Metrex
8	Single Pan Electronic Balance	Paras Engineers (Delhi)
9	pH-Meter	Paras Engineers
10	Motic Digital microscope	Dewinter Technologies
11	In-vitro dissolution apparatus	Datasheet Dissolution apparatus

2.3. Method

2.3.1. Formulation Design of Fluticasone Propionate by Box-Behnken Design

Design-Expert® software (trial version 12.0.3.0, Stat-Ease) was used to implement the design, and 17 run in total were produced.

A response surface method, three-factor, three-level Box-Behnken design was employed for the last optimization of fluticasone propionate microsponges. % entrapment efficiency, drug release, % yield and % particle size were regarded as dependent responses, where as the drug and polymer ratio was taken into consideration as an independent component. Tables 2 and 3 provide the factors, levels and summary.

Table 2: Factor and their levels used in Box Behnken Design

Factor	Lower level(-1) (mg)	Upper level(+1) (mg)
A	30	50
B	130	150
C	36	40

A = Fluticasone propionate(mg), B = Eudragite RL100(mg), and C = PVA(mg)

Table 3: Summer by Design Expert Software (version 12.0.3.0)

Study type	Response surface
Design type	Box Behnken
Sub type	Randomize
Design model	Quadratic
Runs	17

2.3.2. Preparation of fluticasone propionate (FP) microsponges

The microsponges containing fluticasone propionate were made with eudragit RL-100 as the polymer via a quasi-emulsion solvent diffusion technique. The drug is added to the polymer along with ethanol and dichloromethane (1:1) to prepare the inner phase. At 35 °C, the drug and polymer solutions were dissolved by ultrasonication, this result created an internal phase and external phase was prepared by mixing PVA in 75 ml of distilled water by using magnetic stirrer. The inner phase was introduced drop by drop with the help of micro pipette and stirring at 1400 rpm for 90 min, in the PVA solution as outer phase. The mixture was filtered, then dried in hot air oven at 40 °C for 12 h and weighed to determine production yield.[9,10]

2.4. CHARACTERIZATION OF MICROSPONGE

2.4.1. Determination of production yield

Accurate calculations of the starting weight of the raw materials and the end weight of the produced microsponges were used to calculate the production yield of the microsponges.[11]

$$\text{Production yield} = \text{Practical mass of microsp sponge} / \text{Theoretical mass (polymer + drug)} \times 100$$

2.4.2. Determination of entrapment efficiency

Spectrophotometry was used to determine the level of drug of the microsp sponge at a wavelength of 240 nm. A 10 mg sample of fluticasone propionate microsponges was dissolved in a freshly prepared 100 ml phosphate buffer (pH 7.4). The drug content was calculated using a calibration curve and presented as loading efficiency.[12]

$$\text{Drug entrapment} = \text{Mass of drug present in microsp sponge} / \text{Theoretical mass} \times 100$$

2.4.3. Zeta potential

Using zeta potential, particle stability and surface charge have been evaluated. Particles cannot stick to one another if the zeta potential is greater than +30 mV or lower than -30 mV.[13]

2.4.4. Particle size analysis

The particle size distribution of the supplied materials was examined using a Zetasizer. The intensity distribution data of particles of various sizes was analyzed using Malvern software to provide a graphical picture. The graph's peak represents the size of particles that predominate in the sample.[13,14]

2.4.5. Scanning electron microscopy (SEM)

Scanning electron microscopy was use to determine the surface morphology of the fluticasone propionate microsp sponge formulation for optimization. Double-sided adhesive tape was used to adhere the sample to the SEM sample holder. Images were taken with an acceleration voltage of 10 kV at different magnifications.[15]

2.4.6. In vitro dissolution studies

The USP type II dissolving test apparatus was used to conduct an in vitro drug release research. The 900 ml 7.4 phosphate buffer dissolving medium was kept at 37±1 °C and stirred at 50 rpm. After extracting samples (5 ml) in small amounts over an average of 6 hours, they were filtered

through Whatmann filter paper and a volume of 10 ml was gained by adding 7.4 phosphate buffer. A UV-visible spectrophotometer was used to measure the sample at 240 nm.[16]

2.4.7. Fourier Remodel Infrared Spectroscopic Analysis (FT-IR)

It has been measured by utilizing the KBr pellet method via a Fourier Transform Infrared Spectrophotometer. The wavenumber range of 4000 to 400 cm^{-1} was used to capture the fluticasone propionate FTIR spectra, as well as the microsphere formulation and physical mixture(s) of fluticasone propionate and eudragit RL-100. [17,18]

2.5. Formulation of Microsphere Loaded Fluticasone Propionate Gel

Microspheres with excellent characteristics (made using a solvent quasi-emulsion process) the formulation of microsphere F4 and F6 was used. Preparation of fluticasone propionate microsphere loaded gel was prepared by under stirring, Carbopol 934 was accurately measured and dissolved in small amount of distilled water and allowed to swell and form gel for two hours. Then glycerine, Parabens and EDTA were dissolved in water and mixed with the previously prepared mixture. After that, triethanolamine was added and gently mixed into this mixture to neutralize it. Lastly, FP microsphere (the equivalent to 0.05% w/w of FP) was added to obtain homogenous FP microsphere loaded gels and stored for further study in airtight container.[9,19,20]

Table 4: Formulation of Microsphere Loaded Fluticasone Propionate Gel

Ingredients	GM1	GM2
Corbapol (mg)	300	300
Glycerine (ml)	03	03
Methyl Paraben (mg)	180	180
Propyle Paraben (mg)	20	20
EDTA (mg)	50	50
Triethanol Amine (ml)	q.s	q.s
Water (ml)	q.s	q.s

2.6. Charecterization of fluticasone propionate microsphere based gel

2.6.1. Appearance

The prepared gel bases were examined visually to ensure they were clear, colored, and free from any particles. Microspheres filled with carbopol gel displayed translucent gel.

2.6.2. Measurement of pH:-

The pH of formulations was determined by using digital pH meter. After dissolving 1gm of each formulation in 25 ml of distilled water.[21]

2.6.3. Spreadability studies

The spreadability of semisolid gel preparation is crucial for administering a dose of preparation to the skin. It's measured in seconds and involves evenly spreading the gels on two sets of 7.5 cm glass slides. The gel is then compressed and sandwiched between the slides. A weight of 100g is placed on the upper slide and the weight is removed and 20g is tied to the upper slide. The slides are tilted so that only the upper slide slips off. The time interval between the upper slide and

lower slide is measured. The test is repeated in triplicate, and the mean value is considered. The lower the time interval, the better the spreadability. The spreadability study uses a formula to determine the optimal time interval for the spreadability of the preparation.[22]

$$S = ML/T$$

Where S is spreadability, M is weight tied to upper slide, L is length of glass slide and T is time taken by the slide to separate from.

2.6.4. Rheological Study

Several gel compositions were tested for viscosity by using a Brookfield viscometer (spindle number 64). It had been set to spin at 100 rpm at 25 °C. A Brookfield Viscometer (Model-LVDV-E) was used to evaluate the viscosity of the new formulation without diluting it. This apparatus is made comprised of a fixed cup and a spinning spindle. The viscosity of the test material is measured by using spindles of different sizes- larger spindles with a greater surface area and diameter are utilized for liquids with low viscosities while smaller spindles are utilized for liquids with higher viscosities.

To measure viscosity, insert the chosen spindle into the microsp sponge gel and rotate it until the viscometer display displays the same dial reading on the dial. To ensure that the results were reproducible, this procedure was done three times.[23]

2.6.5. Drug content

After dissolving one gram of the chosen gel formulation in a pH 7.4 phosphate buffer solution, the mixture was stirred with a magnetic stirrer for 12 hrs. Spectrophotometry was used to measure the drug content after filtering the resultant dispersion at a wavelength of 240 nm.[24]

2.6.6. In vitro release study

The study examined the in vitro release of fluticasone propionate from gel formulation including microsp sponge, utilizing a Franz diffusion apparatus. A Teflon-coated magnetic bead was utilized at 100 rpm to stir the dissolving solution. To maintain ideal sink conditions, a small volume was taken out at pre-set intervals of 60, 120, 180, 240, 300, 360 and 420 minutes and replaced with an equivalent volume of fresh receptor medium. Using neutralized buffer as the blank, the resultant small amounts were properly diluted with the receptor medium and evaluated at 240 nm using a UV-visible spectrophotometer.[25]

3. RESULTS AND DISCUSSION

3.1. Zeta potential

Plot peaks from -23.5 to -26.7 mV show that most of the microsp sponge particles in the formulation had this charge, suggesting a strong affinity between the particles.

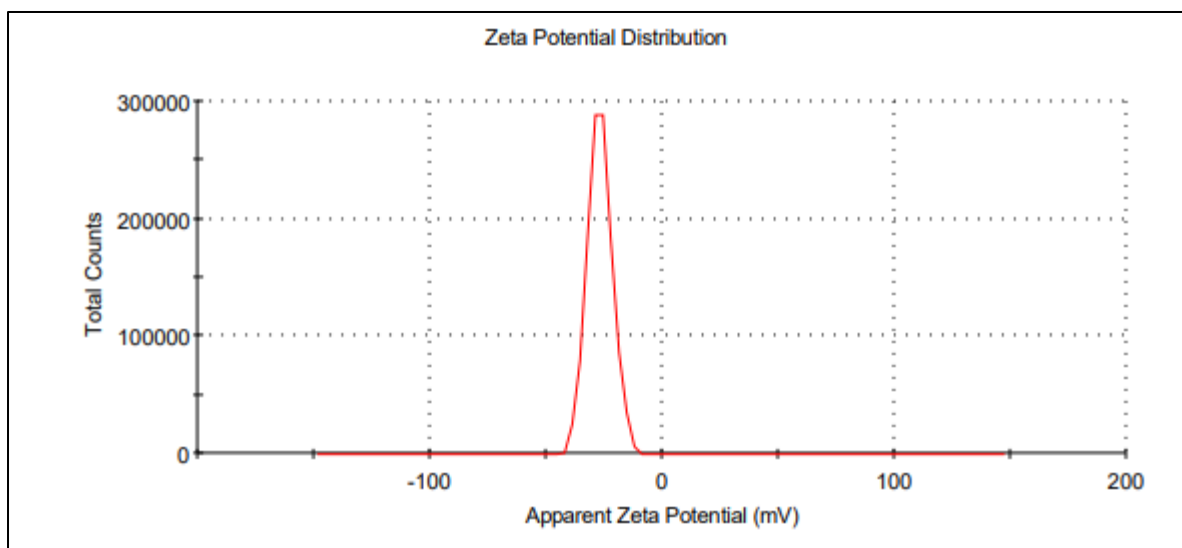


Fig. 1: Zeta potential

3.2. Particle size analysis

By using the zetasizer approach, the average particle size of the microsponges was found. These microsphere lowest and maximum mean diameters were reported to be 21 μ m and 28 μ m respectively.

3.3. Determination of Percentage yield and encapsulation efficiency

Table 5 displays the production yields for the fluticasone propionate microsphere formulation. The calculated production yield for each microsphere varied between 71.71 and 98.67%. According to the fluticasone propionate microsphere formulation's production yields, the production yield rose as the drug:polymer ratio was raised.

Table 5 lists the loading efficiency of several formulations of fluticasone propionate microsphere. All microspheres had loading efficiencies that ranged from 72.35 to 89.5 percent. The MS F4 formulation, which had more drug encapsulation, had the highest loading efficiency. Greater the amount of drug encapsulated, the higher the loading efficiency.

3.4. In vitro dissolution studies

At pH 7.4 PBS, fluticasone propionate was found to be released in vitro from microspheres. Table 5 displays the profile for the cumulative percentage of fluticasone propionate drug release from optimized microspheres at pH 7.4. For the microspheres, a sustained release pattern of drug release was noted.

Table 5: Showing results of different parameters of microspheres

Run	Drug (mg)	Eudragit RL100 (mg)	PVA (mg)	Particle size (μ m)	Drug Entrapment (%)	% Yield (%)	% Drug Release(%)
1	40	150	36	26.23	73.4	98.67	70
2	50	140	40	22.56	84.15	88.69	80

3	30	130	38	24.63	72.35	71.71	76
4	30	140	40	27.88	89.6	89.52	92
5	40	150	40	20.26	86.5	89.13	60
6	40	130	36	21.2	82.25	81.55	88
7	30	150	38	23.55	77.4	82.56	70
8	50	140	36	26.35	81.5	96.46	73
9	50	130	38	24	83.14	85.32	82
10	40	140	38	23.54	82.6	89.90	74.8
11	40	140	38	28	88.6	87.61	70.2
12	40	140	38	27	81.15	84.86	78
13	30	140	36	23	72.5	76.69	71.5
14	50	150	38	22.85	84.5	89.91	66
15	40	130	40	25.61	87.5	90.95	83
16	40	140	38	27	82.4	90.82	70
17	40	140	38	25.25	80.2	88.99	71.5

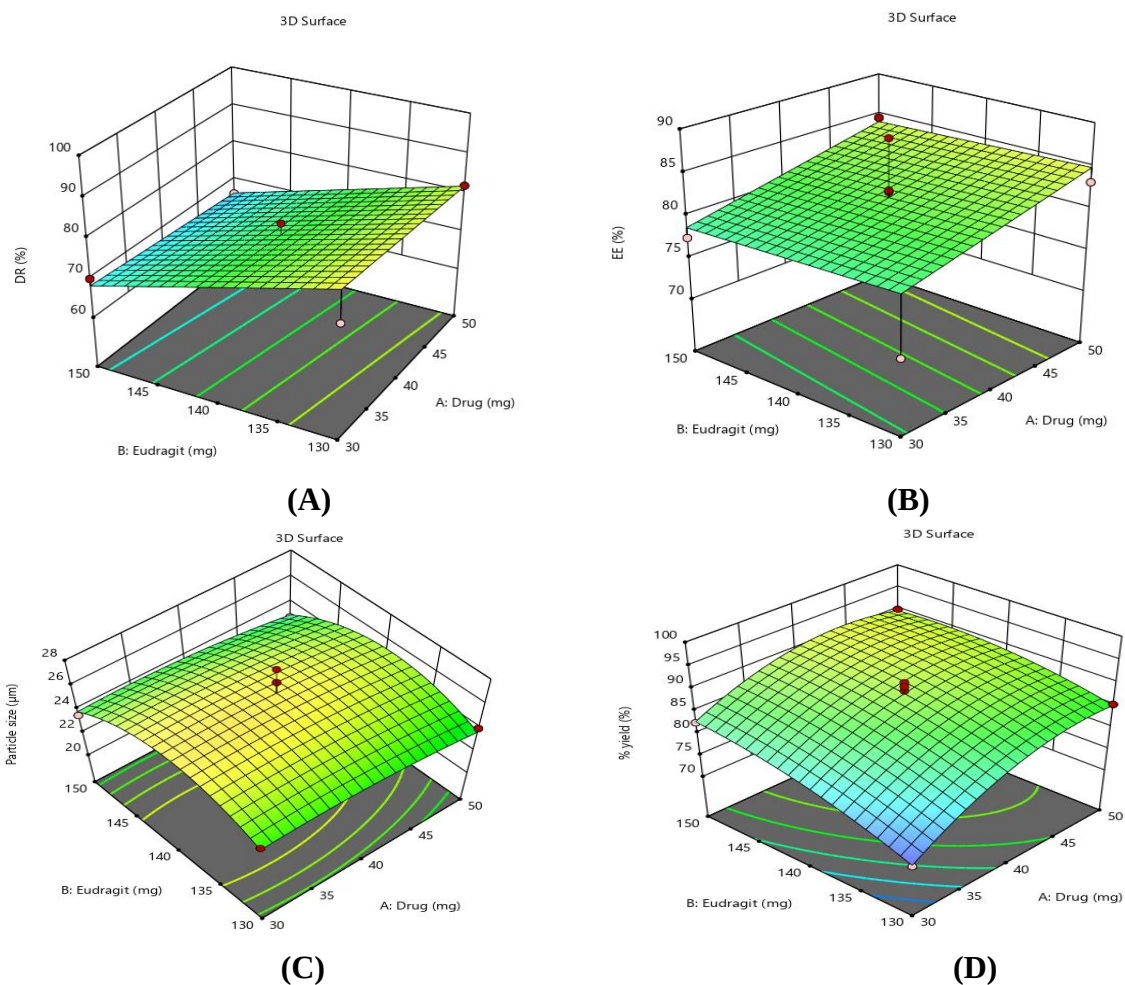


Fig. 2: Model analysis of (A) Drug release, (B) Drug entrapment, (C) Drug release, and (D) % yield

3.5. Scanning electron microscopy

Scanning electron microscopy was used to study the morphology of microsphere. This displayed a spherical form with a sponge-like structure where the drug was entrapped, as well as a rough surface which Seen in fig 3.

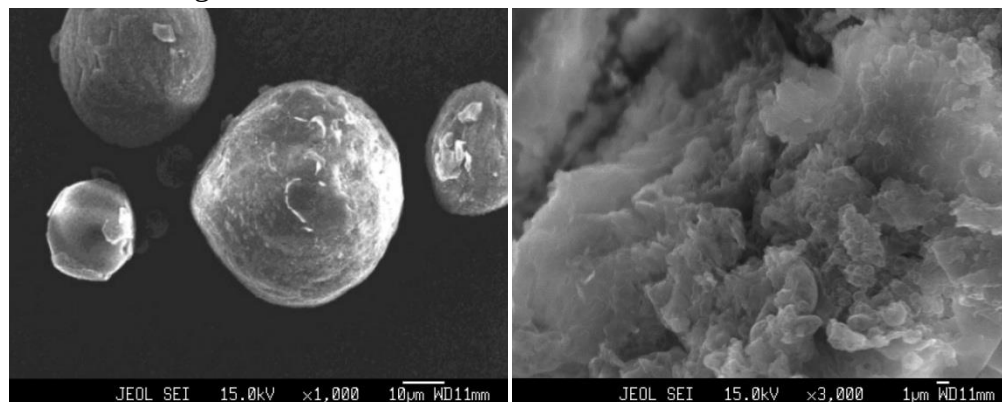


Fig 3: SEM image of FP loaded microsphere

3.6. Drug-excipient interaction study by FTIR spectrum

The IR spectra of the physical mixture and loaded microsponges during the compatibility analysis revealed that fluticasone propionate was compatible with various polymers and excipients. This indicates that fluticasone propionate is compatible with specific polymers and stable in microsponges which shown in fig. 6 and 7.

Spectrum

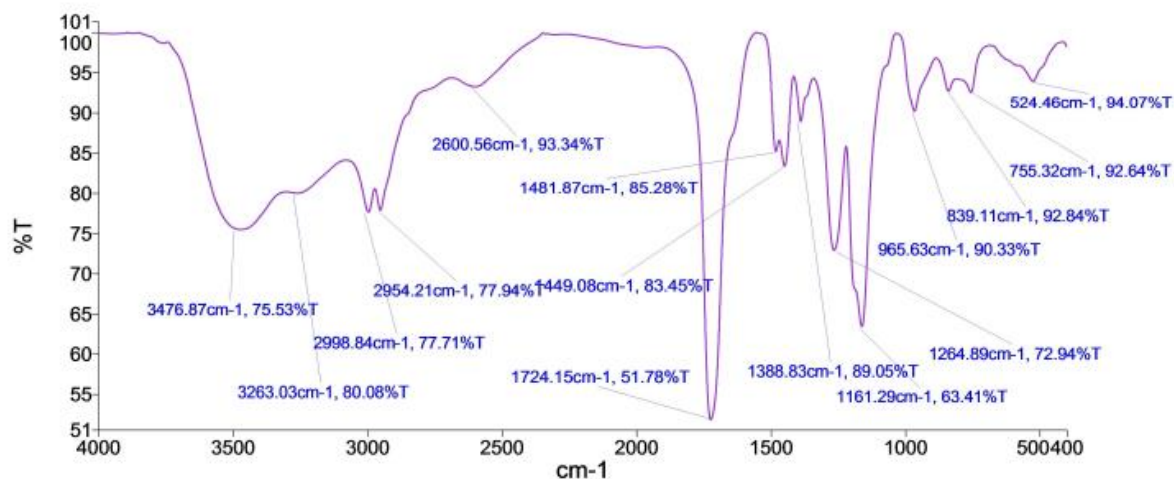


Fig. 4: Polymer (Eudragit RL100)

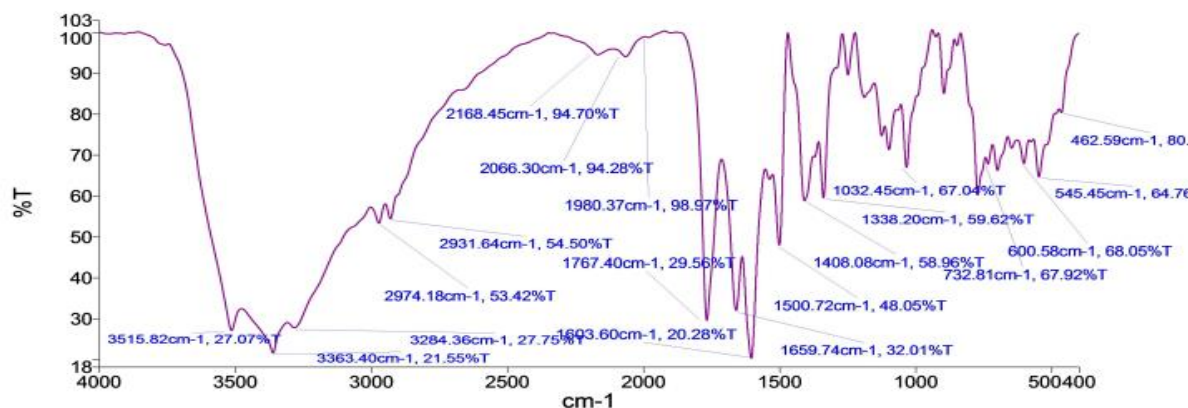


Fig. 5: Pure Drug (FP)

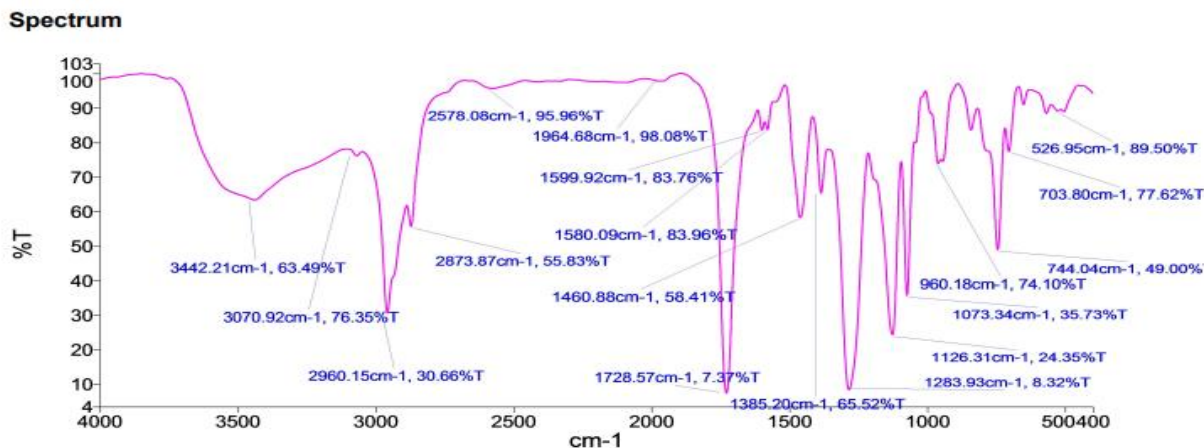


Fig. 6: Drug loaded microsphere A

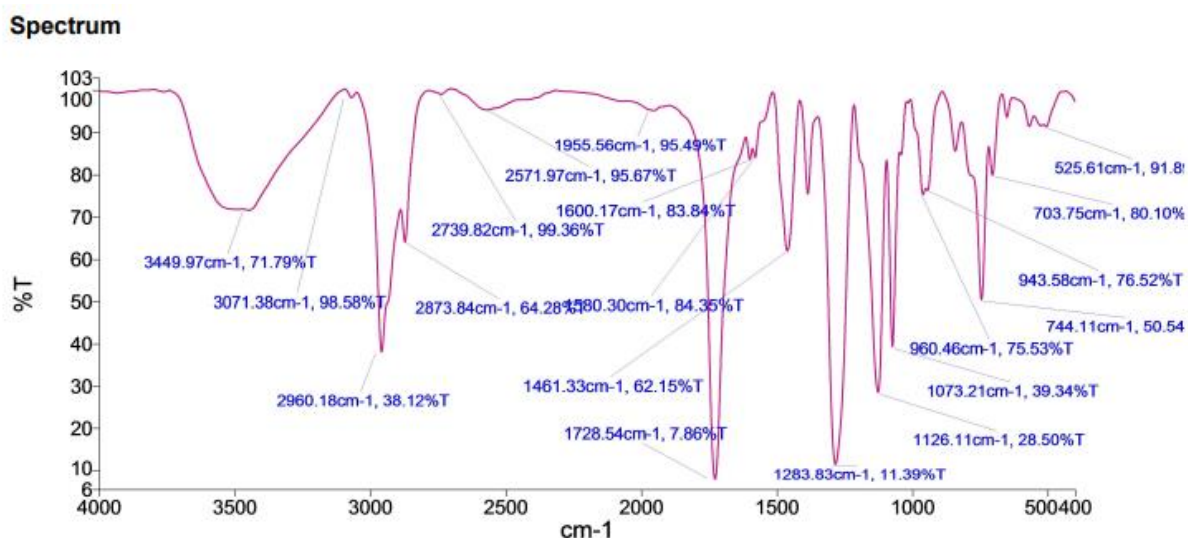


Fig. 7: Drug loaded microsphere B

3.7. Charecterization of Fluticasone propionate microsphere based gel

We examined the pH, drug concentration, spreadability, drug content, and viscosity of the produced gels of formulations GM1 and GM2. Table 6 displays the parameters studied.

Tabale 6: Showing results of different parameters of FP microsphere based gel

S.No	Formulation code	pH ±S.D	Drug content (%)	Viscosity (cps) at 25 °C	Spreadability studies (gm-cm/s)
1	GM1	6.5±0.05	80	24,039±22	23.44
2	GM2	6.7±0.06	82	23,614±36	25.66

3.7.1. Appearance

The produced gel formulations containing fluticasone propionate microspheres were assessed for their appearance, texture, and color. Every formulation showed (Table-7) excellent

homogeneity and a smooth texture with a consistent glossy white look and thick consistency. Additionally, no lumps were seen.

Table 7: Appearance of Gel

Formulation code	Homogeneity	Appearance	Consistency
GM1	Good	Translucent	Good
GM2	Good	Translucent	Good

3.7.2. In vitro diffusion study

PBS (pH 7.4) was used for in vitro diffusion experiments for each formulation. The in vitro diffusion of formulations GM1 and GM2 is shown in Table 8.

Table 8: In vitro diffusion profile

S.No.	Time (h)	GM1	GM2
1	00	00	00
2	01	16	18
3	02	22	26
4	03	35	32
5	04	49	45
6	05	55	57
7	06	68	64
8	07	72	75

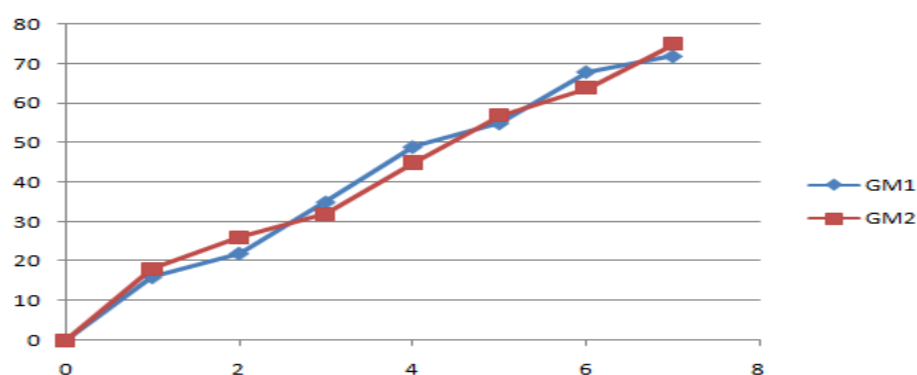


Fig. 8: In-vitro drug release graph

4. CONCLUSION

The quasi-emulsion method was used to produce the FP loaded microsponges and the formulations were assessed for various parameters, revealing several intriguing results that contributed to the efficient preparation of the microsphere. In comparison to the other formulations, the F3 and F6 formulations demonstrated better results. The microsponges prepared with eudragit RL-100, F3 and F6 were better efficient to give extended drug release which released the 92% and 88% respectively drug at the end of 8 h. The microsphere formulations F3 and F6 show excellent physical parameter study and were therefore used in the carbapol 934 formulation process for making a gel. Prepared microsphere gel batches MGI-F3 and MG2-F6 shown good physical properties and performed more effective for providing extended drug release, releasing 72% and 75% of the drugs, respectively at 7 hours. The stability examination shows no significant changes in any of the parameters and the evaluation of the gel loaded microsphere showed significant results. Due to the rapid onset of action and also their anti-inflammatory effects of topical corticosteroids, these drugs are most widely used for the treatment of different skin disorders. It concludes that the fluticasone propionate gel based on microsphere can be more effective delivery system for the treatment of dermatitis based on the results obtained from various evaluation parameters.

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