

Formulation and evaluation of microsponges loaded topical gel for treatment of acne vulgaris

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ABSTRACT

The purpose of present study aims to design novel drug delivery system containing adapalene microsponges and to prepare microsphere gel. Adapalene is an anti-acne drug used in the treatment of acne infection having a poor aqueous solubility, side effects and adverse reactions. The microsphere delivery system is unique technology for controlled/sustained release of active agents. The microsponges were prepared by quasi-emulsion solvent diffusion method by using polymer Eudragit S-100 and Eudragit RS -100. All the formulated microsponges were subjected for various evaluation parameters such as production yield, encapsulation efficiency, particle size analysis and *in vitro* drug release study. The optimized microsphere formulation F4 and F8 were further formulated as gel formulation for topical delivery. Prepared gel was evaluated for physical parameters like pH, spreadability, viscosity, drug content and *in vitro* diffusion study and compared with the other formulation. The Differential scanning calorimetry (DSC), XRD, Zeta potential and Particle size of drug and excipient confirm compatibility. Results revealed that quasi-emulsion solvent diffusion method is a suitable technique for the preparation of microsponges as most of the formulations were discrete and spherical in shape with a good production yield of 51.88 % to 89.41% and the highest drug release for MGF4 and MGF8 formulation was found to be 87.77 % and 83.24 % respectively for the 8 h. The drug release of microsponges gel is 91.31%. The drug release data of optimized batch MGI (F4) were fitted into different kinetic models and showed that the drug release from gel formulation follows zero order release. As compared to conventional formulation, the prepared microsphere gel is expected to remain on the skin for a longer time, gradually releasing their contents over the time. Hence, adapalene microsponges and microsphere gel prepared in this study are promising as being more useful than conventional formulation therapy.

Keywords: Adapalene; Microsphere; Anti acne drug; Microsphere gel; Topical delivery

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INTRODUCTION

The novel drug delivery systems have been increasingly investigated to achieve targeted and controlled release of drugs as many of conventional delivery systems require high concentrations of active agents to be incorporated for effective therapy because of their low efficiency as delivery systems. Microsponges are highly cross-linked, patented, porous, polymeric microspheres that acquire the flexibility to entrap a wide variety of active ingredients that are mostly used for prolonged topical administration and recently for oral administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, elegance, flexibility in formulation, reduce side effects and modify drug release profile.

Adapalene (ADP) is a novel drug and unique drug that treats the most common dermatological disease and condition such as psoriasis, acne vulgaris and photoaged / sun-damaged skin. Adapalene (ADP); 6-[3-(1-adamantyl)-4-methoxyphenyl] naphthalene-2-carboxylic acid. It is a third-generation retinoid derivative. It is extremely hydrophobic, exhibits higher stability to light and oxidation compared to other retinoid. ADP mechanism of action mainly involves selective binding to retinoic acid receptor (RAR). As a result, it attains several dermatological effects [1]. Acne vulgaris is a common inflammatory pilosebaceous condition affecting more than 85% of adolescents and young adults. A complex interplay of four factors, follicular hyperkeratosis, hyperseborrhea, dysbiosis of the cutaneous micro biome and inflammation together describe the pathogenesis of acne. Retinoid are effective first-line treatment for acne, and, according to some reports, ADP has been the most powerful retinoid. Used for treating acne vulgaris skin disease.

Adapalene is a topical retinoid that is FDA-approved for treating acne vulgaris. Additionally, adapalene and adapalene analogs are investigated for potential antimicrobial, anti-cancer, and neuroprotective effects. Adapalene, a naphthoic acid, is a synthetic retinoid that possesses some of the biologic activities of tretinoin, but with distinct physicochemical properties. The most distinctive of these properties is its increased chemical and light stability, rigidity, and high lipophilicity. Adapalene was initially FDA-approved in 1996 for acne in patients 12 years of age or older. The FDA-approved adapalene 0.1% gel as an over-the-counter acne treatment in patients 12 and older in 2016. Formulations of adapalene 0.1% lotion, cream, and 0.3% gel are available by prescription only [2].

The microsp sponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. These products are typically presented to the consumer in conventional forms like creams, gels or lotions and they contain relatively high concentration of active ingredients. Microsponges are polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective. There have been concerns related to the conventional topical dosage forms such as lotions, creams, ointments and powder in terms of drug diffusion or release from the vehicle and delivery through the skin.

The primary objective of this research was to produce a topical formulation of ADP via using microsp sponge technology to control the drug delivery and consequently decrease the ADP local size effects. Microsponges were prepared by changing several factors to highlight the effect of many formulation variables on the microencapsulation efficiency. Taking into consideration the need for obtaining an aesthetic product, the optimized microsponges formula was intended to have a particle size no larger than 30 µm (to prevent any rough sensation) and to be incorporated into and into vehicle base like aqueous Carbopol 934 gel [3].

MATERIALS AND METHODS

Materials

Adapalene was procured from Taj Pharmaceutical Ltd, India Eudragit S-100; Eudragit RS -100 was obtained from Evonik India Pvt. Ltd, Mumbai. Carbapol-934 and polyvinyl Alcohol was purchased from S D fine chem. Ltd, Mumbai respectively. All other reagents used were of analytical grade. The microsponges were prepared by the quasiemulsion solvent diffusion method.

Method of preparation of microsponges

The microsponges of respective composition, as shown in table 5.3, were designed using Eudragit S-100, Eudragit RS-100 as a polymer, and polyvinyl alcohol as a stabilizer. Batches were designed for a different drug: polymer ratios and for different concentrations of polyvinyl alcohol at stirring speed of 1500 rpm. The microsponges containing Adapalene were prepared by a quasiemulsion solvent diffusion method using Eudragit S-100, Eudragit RS-100 as a polymer. To prepare the inner phase, the polymer is added to ethyl alcohol and the drug is added to methyl alcohol. Polymer solution and drug solution dissolved under ultra-sonication at 35 °C. This solution made inner

phase. The inner phase was poured into the PVA solution in water (external phase). Following 2 h stirring at 1500 rpm, the mixture is filtered to separate the microsponges. The microsponges are dried in an air heated oven at 40 °C for 12 h and weighed to determine production yield (PY) (Tab.1.) [4].

Evaluation of adapalene microsponges

Microscopy: Motic digital microscopy for morphology and surface topography, prepared microsponges can be placed on a glass slide at room temperature and then the surface morphology of the microsponges can be studied by Motic Digital Microscopy (B1 advanced series). Motic Digital Microscopy of a fractured microsp sponge particle can also be taken to illustrate its ultrastructure. The morphology of Adapalene microsp sponge was examined with a Motic Digital Microscopy. The samples were mounted on a glass slide and observed under 10X object with the magnification power 2048 x 1536 [5].

- Determination of production yield:** The production yield of the microsponges was determined by calculating accurately the initial weight of the raw materials and the final weight of the microsponges obtained.

$$\% \text{ production yield} = \frac{\text{Practical mass of Microsp sponge}}{\text{Theoretical mass (polymer + Drug)}} \times 100$$

- Actual drug content and encapsulation efficiency:** A sample of dried microsponges equivalent to 10 mg was taken into mortar and pestle and add little amount of phosphate buffer of pH 7.4 and allowed to stand for 24 h. Then transfer content into 100 ml volumetric flask and make up volume to 100 ml with phosphate buffer of pH 7.4. The solution was filtered through Whatman filter paper (No.41). From the resulting solution take 1 ml into 10 ml volumetric flask and then make up volume to 10 ml with phosphate buffer of pH 7.4. Drug content was determined by UV spectrophotometer (Dynamica, Halo DB-20) at 320 nm [6].

$$\% \text{ Entrapment efficiency} = \frac{\text{Actual Drug Content} - \text{Free drug Content}}{\text{Actual Drug Content}} \times 100$$

The drug content and encapsulation efficiency were calculated using the following formula.

$\% \text{ Encapsulation Efficiency} = \frac{\text{Actual drug content in Microsp sponge}}{\text{Theoretical drug content}} \times 100.$

$\% \text{ Actual drug content} = \frac{\text{Nact}}{\text{Nms}} \times 100$

Where Nact is the actual adapalene content in weighed quantity of microsponges, Nms is the weighed quantity of

Tab. 1. Composition of Adapalene Microsponges.

INGREDIENTS (mg)	FORMULATION CODE							
	F1	F2	F3	F4	F5	F6	F7	F8
Adapalene (mg)	100	100	100	100	100	100	100	100
Eudragit S-100(mg)	200	500	750	1000	1000	500	500	-
Eudragit RS-100(mg)	-	-	-	-	1000	500	1000	1000
Ethanol (ml)	5	5	5	5	5	5	5	5
Methanol (ml)	5	5	5	5	5	5	5	5
PVA% w/v	0.5	0.5	0.5	0.5	0.75	0.75	0.75	0.75
Distilled Water	100	100	100	100	100	100	100	100

powder of microsponges.

- 3. Particle size analysis:** Particle size analysis of prepared microsponges was carried out by using Motic digital microscope particle size analyzer [B1 advanced series. Microsponges were dispersed on the slide before running the sample in the instrument, to ensure that the light scattering signal, particle size was measured, which is within instrument's sensitivity range.
- 4. Zeta potential:** Zeta potential is an indicator of particle surface charge and particle stability. Particles will not adhere to each other if the value of zeta potential is above +30 or below -30 mV. Zeta size A Zetasizer was used to determine the particle size distribution of the given samples. Malvern software was used to analyze the intensity distribution data of particles of different size ranges, and a graphical representation was obtained. The peak on the graph indicates the size of most particles present in the sample.
- 5. X-ray diffraction (XRD):** XRD analysis of pure drug, polymer and formulation of TCM-containing microsponges was conducted to evaluate the nature of drug particles alone as well as in the form of formulated microsponges.
- 6. Morphology determination by scanning electron microscopy (SEM):** Scanning electron microscopy (SEM) was used to determine the Morphology of the prepared microsponges. SEM is useful for characterizing the morphology and size of microscopic specimens with particle size as low as 10 -10 to 10 -12 grams. The sample was placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that, when detected, are used to form images and provide elemental information about the specimens. It was observed. That the microsponges were spherical and uniform with no drug crystals on the surface, the shape of the microsponges affects the surface area and surface area per unit weight of spherical microsponges. The irregular shape of the particles may affect dissolution rate present in dissolution environment [7].

Preparation of ADP microsphere gel

A gel of ADP microsphere was prepared using under the moderate stirring, Carbopol 934 was added to a mixture of water and glycerine. Parabens and edentate disodium were dissolved in water and mixed with the prior mixture. After that, this mixture was neutralized by adding triethanolamine with gentle mixing. Finally, ADP

microsponges (equivalent to 0.1% w/w of ADP) were incorporated to obtain homogenous ADP microsphere-loaded gels (Tab. 2.).

Evaluation of adapalene gel

- 1. Visual inspection:** The prepared gel formulation of microsponges was inspected visually for their color, texture and appearance.
- 2. pH measurement:** The pH of gel formulation was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of the formulation was done.
- 3. Spreadability studies:** One of the criteria for a gel to meet the ideal qualities is that it should possess good spreadability. It is the term expressed to denote the extent of the area to which gel readily spreads on application to the Skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel placed in between the slides under the direction of certain load. Lesser the time is taken for separation of two slides, better the Spreadability. Spreadability was determined by glass slides and a wooden block, which was provided by a pulley at one end. By this method, spreadability was measured on the basis of Slip and Drag characteristics of gels. A ground glass slide was fixed on this block [8].

An excess of gel (about 1 gm) of different formulations was placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Excess of the gel was scrapped off from the edges. The top plate was then subjected to pull of 20 Gms; lesser the time is taken for separation of two slides better the spreadability.

Spreadability was then calculated using the following formula:

$$S = M \times L/T \dots$$

- 4. Viscosity measurement:** The viscosity of the different gel formulations was determined using a Brookfield viscometer with spindle no. 4 at 100 rpm at temperature 25°C. The viscosity of the optimized formulation was determined as such without dilution using Brookfield Viscometer (Model-LVDV-E). Brookfield Viscometer consists of a cup, which is stationary and a spindle which is rotating. Different sized rotating spindles are used and immersed in the test material. For liquids with low viscosity, large size spindles (large diameter and surface area) are used while for higher viscosity

Tab. 2. Displays ADP microsphere gel compositions.

INGREDIENTS	MGF4 MICROSPONGES GEL	MGF8 MICROSPONGES GEL
Microsponges (mg)	equivalent to 100 mg of drug	equivalent to 100 mg of drug
Carbopol 934 (g)	0.5	0.5
Glycerine (g)	5	5
Triethanolamine	q.s	q.s
Methyl Parabens (g)	0.18	0.18
Propyl Parabens (g)	0.02	0.02
EDTA (g)	0.05	0.05
Distilled water (g)	q.s 100	q.s 100

liquids small spindles (small diameter and surface area) are used. Rotate the spindle in the microsp sponge gel till we get a constant dial reading on the display of the viscometer. This procedure is repeated three times for reproducible results [9].

5. **Drug content:** 1 gm. of Adapalene microsp sponge gel was accurately weighed and dissolved using methanol, sonicated for a period of 10-15 min and made up to the mark in 100 ml volumetric flask with methanol. From this 10 ml was pipetted out and diluted to 100 ml with methanol and the final dilution was made using distilled water to get a concentration within Beer's range. The absorbance was measured by UV spectrophotometer (Dynamica, Halo DB-20) at 320 nm against blank gel treated in the same manner as a sample [10].

6. **In vitro drug release tests:** A vertical Franz diffusion cell with a reservoir capacity of 9.5 mL was used for in vitro release investigations. Between the compartments of the diffusion cell, a cellulose nitrate membrane with an effective diffusion area of 2.54 cm² was inserted. The receptor medium was composed of a mixture of water and ethanol (50:50, v/v), and it was kept at 32±0.1 °C and swirled constantly. Each formulation weighing 0.5 g of microsp sponge-based gel was placed on the donor side. 2 mL of the sample was taken from the receiver fluid and replaced with an equal volume of fresh receptor fluid at predefined time intervals. Collected samples were assayed by a 320 UV-Vis spectrophotometer after a suitable dilution.

7. **In vitro drug release kinetic study:** To determine the drug release mechanism and to compare the release profile differences among microsp sponge gel formulations, the data obtained from the drug released amount and time were used. The drug release kinetics was analyzed with mathematical models like Zero order, First order, Higuchi matrix, and Hixson Crowell and Korsmeyer-peppas model. Several kinetic models have been proposed to describe the release characteristics of a drug from the matrix. The three parameters were used to study the release mechanism i.e. release rate constant (k), correlation coefficient (R), and release exponent (n) and determine the best fit model for optimized formulation. The release data was analyzed with the following mathematical models:
Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be presented by the following equation:

$$Q = K_0t \dots \text{Eqn (1)}$$

Where Q is the amount of drug released at time t, K₀ is the zero order rate constant expressed in units of concentration/time and t-is the time in hours. The pharmaceutical dosage forms following this profile, release the same amount of drug by a unit of time. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First order kinetics: This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis.

$$Q_1 = Q_0 e^{-K_1 t} \text{ or } \text{Log } Q_1 = \text{Log } Q_0 - K_1 t / 2.303 \dots (2)$$

Where Q₁ is the amount of drug released in time t, Q₀ is the initial amount of drug in the solution and K₁ is the first order release constant. The pharmaceutical dosage form following this dissolution profile, such as water soluble drugs in porous matrices releases the drug in such a way that is proportional to the amount of drug remaining in its interior, in such a way that the amount of drug released by a unit of time diminishes.

Higuchi matrix model: This model is used to study the release of water soluble and low soluble drugs incorporated in semisolid and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. It describes drug release as a diffusion process based on the Fick's law, square root time dependent.

$$Q = KH t^{1/2} \dots \text{Eqn (3)}$$

Where Q is the amount of drug release in time t, KH is the Higuchi dissolution constant. Korsmeyer-peppas model: Korsmeyer developed a simple, empirical model, relating exponentially the drug release to the elapsed time (t).

$$F_t = a \cdot t^n \dots \text{Eqn (4)}$$

Where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism and function of t is Mt/M_∞ (fractional release of drug) .

Hixson-Crowell model: Hixson and Crowell (1931) recognized that the particles regular area is proportional to the cube root of its volume. They derived the equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa t \dots \text{Eqn (5)}$$

Where W₀ is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface volume relation. The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets. To study the release kinetics, data obtained from in vitro drug release studies were plotted as the cube root of drug percentage remaining in matrix versus time.

8. **Stability testing:** Formulation F4 was subjected to stability studies according to ICH guidelines. The formulations were monitored for up to 6 months at 40±2°/75±5%. At 1, 2, 3, 4, 5, and 6 months, the appearance, pH, viscosity, drug content, and drug release of the gel were evaluated.

RESULTS AND DISCUSION

Microscopy: Microscopic image A of ADP microsponges & Microscopic image B of ADP microsponges gel (Fig. 1).

Determination of production yield: The production yield of all batches was ranged from 51.88±0.01% to 89.41±0.3.8 %. It was found that production yield was greatly affected by drug: polymer ratio as well as by concentration of

polyvinyl alcohol. It was indicated that increasing polymer concentration, increased production yield while increasing polyvinyl alcohol concentration, decreased production yield.

Actual drug content and encapsulation efficiency: Shows 72.84%EE, F4 shows 98.65 %, F5 shows 44.16 % EE, F6 shows 81.44%EE , F7 shows 52.76%EE and F8 shows 95.78%EE and Drug Content was, F1 shows 87.18 %, F2 shows 78.57%, F3 shows 72.84%, F4 shows 98.65%, F5 shows 44.16 % ,F6 shows 81.44%, F7 shows 52.76% and F8 shows 95.78% From this study, The F4 shows more entrapment efficiency, and Drug content was also more than other batches. So that F4 batch was optimized batch. The results of % Drug entrapment efficiency are shown in Table no 6.6 the formulation of F5 shows the least entrapment about 44.16 % and higher drug entrapment was shown by F4 formulation, The results shown in Table no 4 (**Tab. 3.**) [11].

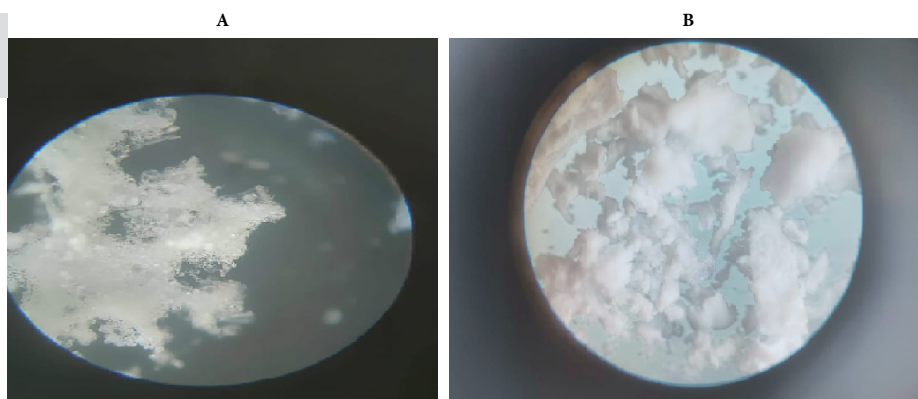
Particle size analysis: The particle size ADP microsponges' formulation is tabulated in Table 5 and graph 1, the particle size of the microsp sponge was determined by optical microscopy and the microsponges were found to be uniform in size 5-300 μm . The average particle size of all formulations ranges from $20.34 \pm 1.12 \mu\text{m}$ to $78.5 \pm 1.20 \mu\text{m}$ which is in increasing order due to the increase in the concentration of polymer but after certain concentration

it was observed that as the ratio of drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high drug to polymer ratio, the amount of polymer available per microsp sponge was comparatively less. Probably in high drug-polymer ratios less polymer amounts surround the drug and reducing the thickness of polymer wall and microsponges with smaller size were obtained. By performing the particle size analysis, it is concluded that the formulation has the particle size varies with the concentration of polymer drug ratio. On other hand, the particle size of adapelene decrease with the increase in PVA concentration (**Tab.4.** and **Graph.1.**).

Zeta potential and zetasizer: The zeta potential graph plot showed a peak at -40.1 mV , of F4 Formulation which meant that most of the microsp sponge particles in formulation had this charge, showing that the particles had an affinity for each other. Results shown are **graph 2** and **Table 5 (Graph. 2.)**.

X-ray diffraction study: A clear difference was observed in the diffract grams of pure drug and the prepared formulation in figure. Crystallinity of the pure drug was masked when it was captured in microsponges, indicating that ADP was present in the form of solid solution of drug in excipients. While the diffract grams of ADP microsp sponge shows sharp peaks at 17° , 18° , 23° (2θ) with decreased intensity which indicates decrease in crystalline nature of the microsp sponge. Results are shown in the (**Graph. 3.**) [12].

Fig. 1. Microscopic image A of ADP microsponges & Microscopic image B of ADP microsponges gel.



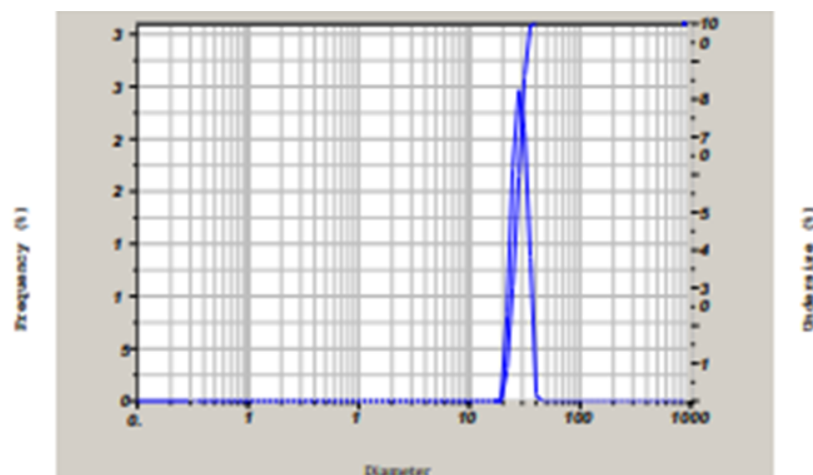
Tab. 3. Result of %yield & Actual drug content and Encapsulation efficiency.

Batches	Production yield (%)	Encapsulation efficiency (%)	Actual drug content (%)
F1	69.05 \pm 0.18	87.18	87.18
F2	89.41 \pm 03.8	78.57	78.57
F3	70.87 \pm 0.29	72.84	72.84
F4	54.34 \pm 0.27	98.65	98.65
F5	58.28 \pm 0.39	44.16	44.16
F6	70.33 \pm 0.15	81.44	81.44
F7	52.79 \pm 0.19	52.76	52.76
F8	51.88 \pm 0.01	95.78	95.78

Tab. 4. Result of adapelene base microsponges particle size and Zeta seizer.

Batch	Particle size (μm)	Zeta potential (mV)
F1	31.3 \pm 1.25	-27.2
F2	29.4 \pm 1.23	-25.9
F3	20.34 \pm 1.12	-18.5
F4	78.5 \pm 1.20	30.1
F5	28.7 \pm 1.03	-18.3
F6	27.6 \pm 125	22.3
F7	23.9 \pm 125	-28.5
F8	37.3 \pm 1.33	-40.1

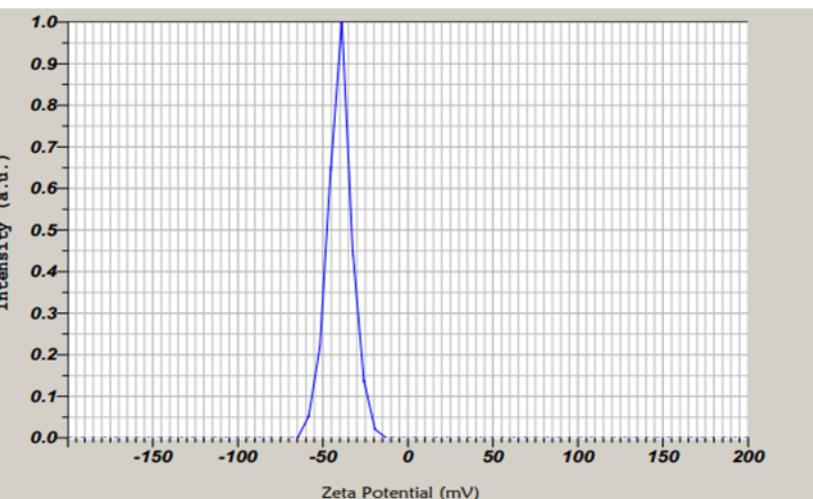
Graph 1. Result of particle size image of F4 formulation.



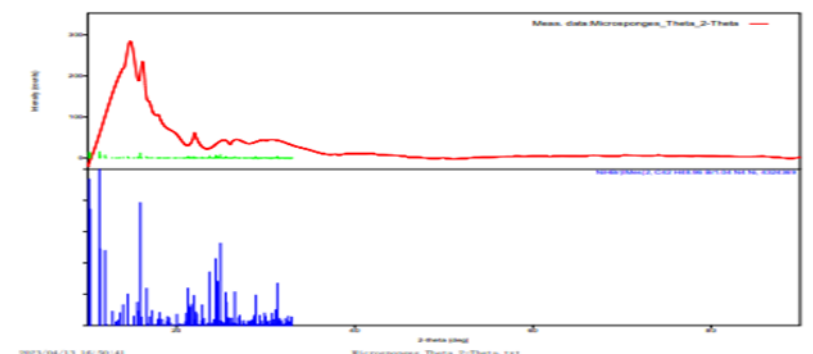
Tab. 5. Results of microsponges gel Visual Inspection PH, Spredability, Viscosity, %Drug Content.

Formulation of MS gel	Visual Inspection	PH	Spredability	Viscosity	Drug Content (%)
MG4	Pearl White	6.8±7.2	7.43±0.04	1000±3	99.31
MG8	Pearl White	6.7±0.04	5.1±0.26	1011±2	95.1

Graph 2. Result of graphical presentation of zeta potential distribution.



Graph 3. Displays the X-ray diffraction spectra of ADP F4 microsponge formulation.



Scanning electron microscope (SEM): The representative SEM photographs of the microsponge formulations F4 are shown in fig. 6.16 SEM images showed the microsponges were spherical and devoid of aggregation. Therefore, they would easily disperse into the gel formulation. In addition, the drug crystals were not seen on the surface of the microsponges. This indicates the dispersion of the drug inside the polymeric matrix which is interpreted in DSC (Fig. 2 & 3).

Evaluation of ADP microsponge gel

Visual inspection: The prepared gel formulations of Adapalene microsponges were inspected visually for their color, texture and appearance. All prepared formulations were pearl white, viscous preparations with a smooth texture and showed good homogeneity with the absence of any lumps and syneresis. Results are shown in the table No 6 (Fig. 4.).

pH measurement: The pH value of all prepared

Graph 3. Displays the X-ray diffraction spectra of ADP F4 micro sponge formulation.

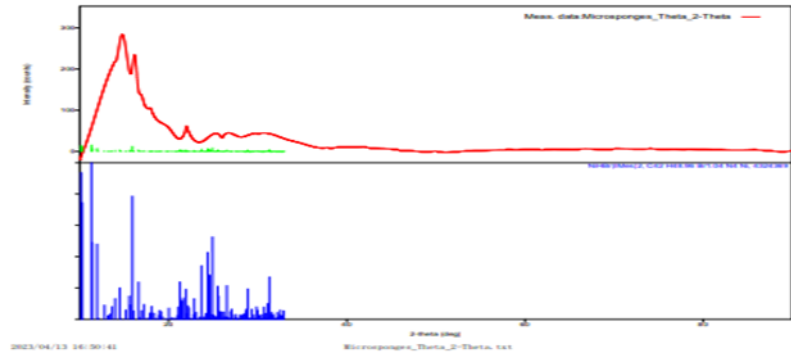


Fig. 2. SEM image of ADP MS.

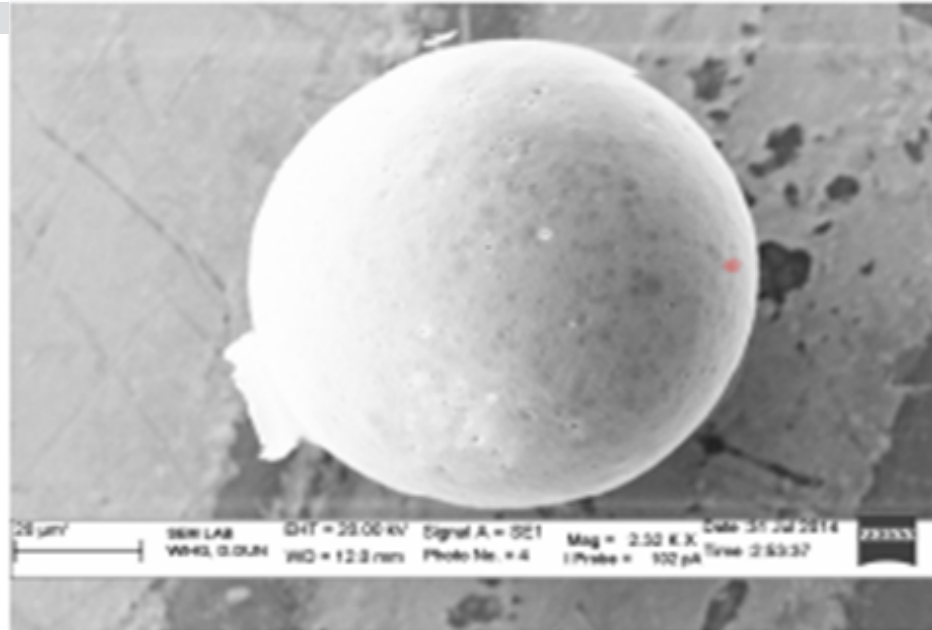
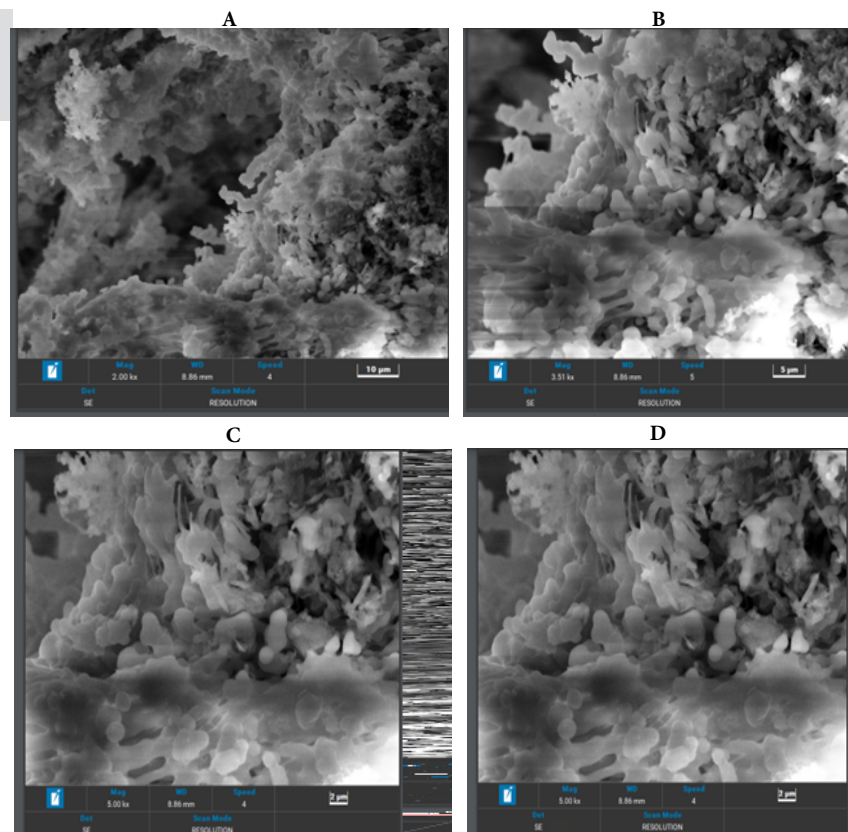


Fig. 3. SEM image of (A) F4 formulation, 2kx (B) F4 formulation, 3.51kx (C) F4 formulation, 500x (D) F4 formulation, 5.00kx.



formulations was found to be in the range of 6.8 to 7.2, which was considered to be acceptable to avoid the risk of irritation upon application to the skin. Results are shown in the table no 6 [13].

Spreadability study: The values of spreadability indicated that the gel was easily spreadable by a small amount of shear. Spreadability of microspunge gel (MGF4) was found to be 7.4g. Cm/sec; indicating that spreadability of drug loaded microspunge gel was good. Results are shown in the table no 6.

Viscosity studies: The viscosities studies for microspunge formulations were carried out. The viscosities of all formulations are shown in table 6.9.From above result, microspunge gel (MGF4) has required viscosity. Results are shown in the table no 6.

Drug content studies: Drug content studies for

microspunge formulations were carried out. Drug content of F4 formulations are shown in table 6.9 the drug content of the formulations showed that the drug was uniformly distributed in the gels. From above result, microspunge gel (MGF4) has higher drug content i.e. 99.31%.Results are shown in the table no 6 (Tab. 5.) [14].

In vitro diffusion study: The cumulative percent drug release for formulation batch MG4 to be higher i.e. 88.77% after 8 hours. Hence the formulation was optimized and MGF4 batch was finalized from the above study for the evaluation of gel, cumulative % drug release of MGF4 batch was more than MGF8 batches show 83. 24% these results are shown in Figure 4 and Table 7 (Tab. 6. and Graph. 4.).

Drug release kinetic study of optimized formulation MGF4: To determine the kinetics of release, drug diffusion data were treated with different kinetic equations.

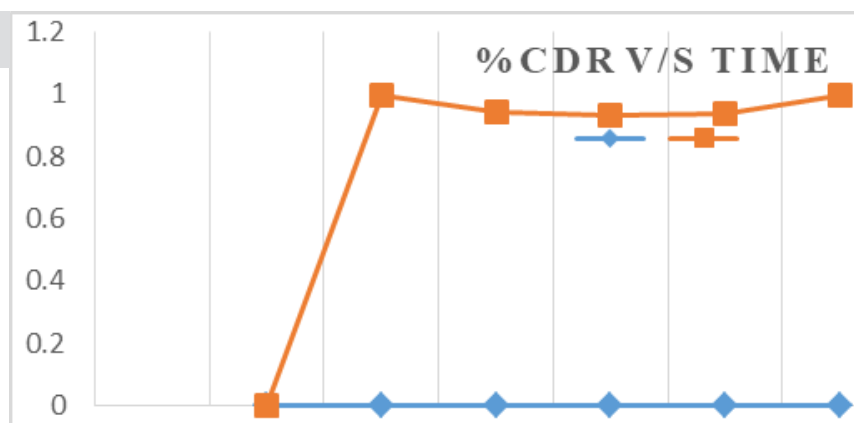
Fig. 4. Image of microsponges gel.



Tab. 6. Results of % CDR of selected formulation of microsponges.

Time in hr.	% CDR	
	MG4	MG8
0	0	0
1	4.44	3.45
2	12.71	8.22
3	20.55	15.63
4	26.64	28.09
5	37.56	45.72
6	43.57	68.81
7	62.81	78.53
8	87.77	83.24

Graph 4. Times in hr. vs. % cumulative drug release.



Tab.7. Release kinetics of optimized formulation (F4) MGf4 Model Formulation code.

Model	Formulation code
Zero order	0.9987
First order	0.9432
Higuchi matrix	0.932
Hixson Crowell	0.9386
Korsmeyer peppas	0.9943

Obtained drug diffusion data was fitted to Zero order, First order, Higuchi matrix model, Hixson Crowell model and Korsmeyer-peppas model. The three parameters were used to study the release mechanism i.e. release rate constant (k), correlation coefficient (R), release exponent (n). Correlation coefficient (R), release rate constant (k), of optimized formulation F4 (MG4), is reported in table. The model that fits the release data was selected based on the correlation coefficient (R) value in various models. The model that gave the high 'R' value was considered as the best fit of release data. Korsmeyer peppas model best described the sustained release of optimized (MG4) formulation and the diffusion exponent (n) value was found to be 0.9134 suggesting that the Fick's law of diffusion was not followed. From the result, the best fit model for optimized formulation F4 (MG4) is Zero order (Tab. 7.) [15].

Stability study: The batch F4 was subjected to 3-month stability study at accelerated conditions and was analyzed for physical appearance, in vitro drug release and FTIR spectroscopy. After 3 months, the formulation was found with no significant change in its appearance. The in vitro percentage drug release came out to be 99.31% similar and also the FTIR spectra revealed no sign of instability. Thus, all these parameters suggested that the formulation F4 may have good shelf life [16].

CONCLUSION

The purpose of this work was to formulate an ADP-based microsphere gel with acceptable physicochemical properties and sustained release for improved drug tolerance. Eight formulations of ADP-loaded microsponges, F1, F2, F3, F4, F5, F6, F7, and F8, were produced using the quasi emulsion solvent diffusion method with two types of solvents (ethanol and methanol), types of surfactants (PVA), two concentrations of polymer Eudragit S100 and Eudragit RS 100 two concentrations of surfactant PVA (0.5% and 0.75%). These microsponges were then analyzed for production yield, entrapment efficacy and particle size. F4 and F8 formulations showed high yield and entrapment efficacy, and they achieved a particle size less than 30 μm , making them appropriate for cutaneous application.

The gel containing microsponges showed the viscous modulus. This study concluded that microsponges prepared with Eudragit RS-100 and Eudragit S-100 in the 1:10 (F4)

were more efficient to give drug release which released the 87.77% and 83.24% drug at the end of 8 h. Microsphere formulation F4 and F8 showed good physical parameter study and was used for formulating into gel, incorporated in the Carbopol. The microsphere gel prepared with Eudragit S-100 in the batch MGf4 (F4) was showed good physical parameters and more efficient to give sustained drug release which released the 87.77 % drug at the end of 8 h. The optimized formulation MGf4 (F4) followed Zero order kinetics and non-fiction diffusion. As compared to conventional formulation, these microsphere gels are expected to remain on the skin for a longer time, gradually releasing their contents over the time. Hence, adapalene microsponges and microsphere gel prepared in this study are promising as being more useful than conventional formulation therapy.

MDS holds significant potential in both pharmaceutical as well as cosmetic industries because of its release technique is novel and its ease of administration with fewer side effects; more research works are carried out to optimize its efficacy for the therapy. It is a unique technology for the sustained release of topical agents which act locally. It is originally developed for topical delivery of drug like anti-acne, anti-inflammatory, anti-fungal, anti-dandruff, antipruritic, and rubefacients, Microsphere's delivery system that can release its active ingredient on stimuli. Therefore, a microsphere has got a lot of potential in drug delivery technology today.

Future prospects: A Microsphere consists of a myriad of interconnecting voids with in non-collapsible structure that can accept a wide variety of substance. The outer surface is typically porous allowing the flow of substance into and out of the sphere, scientist are more concentrating on delivery of anti-acne, sunscreen, antidandruff, agents which can also use in delivery of thermo labile substance such as vaccines, proteins, peptides, and DNA based therapeutics, now-a-days, it is also used in tissue engineering and in controlled drug delivery for therapeutic agents, which requires long duration of therapy Optimization techniques are carried out in these studies to get best out come from various formulation. Hence it requires lot of skills for developing novel formulation for the tropical diseases. Some Microspheres based products are already approved; several others are currently under development and clinical assessment.

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