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Microsponges Loaded Topical Drug Delivery System for the Effective Management of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disease associated with severe joint pain. Herein, we report aceclofenac (ACF)-loaded cellulosic microsponge gel formulation with sustained anti-inflammatory effects that are required to manage arthritic pain. The microsponges were formulated using quasi-emulsion solvent diffusion method. The optimized formulation was dispersed into Carbopol gel. Further, the optimized formulation was evaluated for pH, viscosity and spreadability, drug content, and kinetic drug release profile. The optimized microsponges loaded topical gel showed R^2 value of 0.9930 which was nearest to one which revealed that formulation obeyed Higuchi kinetic model and n value was found to be 0.48 which depicts Fickian transport of drug diffusion. The prepared optimized formulation showed no signs of irritation when applied on hairless skin of rats along with inhibitory effect on inflammation was observed in *in vivo* studies in animals, hence, ACF-loaded topical drug delivery is considered as a potential platform for the management of RA.

Keywords: Aceclofenac, Rheumatoid Arthritis, Quasi-emulsion solvent diffusion, Anti-inflammatory

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Introduction

Aceclofenac (ACF) is a nonsteroidal anti-inflammatory drug used in the management of pain and inflammation due to rheumatoid arthritis (RA), osteoarthritis, and ankylosing spondylitis.[1] ACF is chemically 2-[(2,6-dichlorophenyl) amino] phenyl acetoxyacetic acid, a non-selective COX inhibitor that stimulates glycosaminoglycan in human osteoarthritic. In addition, through suppression of metalloprotease production and proteoglycan release in rheumatoid synovial cells, it shows chondroprotective effects.[2] A previous study showed that the ACF and its metabolite (4'-hydroxyaceclofenac) have a significant impact on COX-2 and have less effect on COX-1.[3] In comparison to diclofenac, oral and parenteral administration of ACF is well tolerated with minimal gastrointestinal side effects.[4,5] However, ACF has a low water solubility and a low mean plasma elimination half-life (about 4 h). Frequent dosing is needed which have been associated with various side effects including gastrointestinal irritation and gastrointestinal bleeding.[6,7]

To overcome these limitations, transdermal delivery of ACF through microsponges could be a promising strategy.[8,9] Microsponges are a sponge-like porous polymeric system with a size range of 5–300 μm.[10] The microsponges prepared to date, showed excellent tolerability against a wide range of temperature (up to 130°C) and pH (1-11). In addition, they are non-allergenic, non-mutagenic, and non-irritating and have greater entrapment efficiency and excellent compatibility with a wide range of excipients.[11-14] As compared to conventional formulations, microsponges required less amount of API and able to release the entrapped drug in a sustained manner.[15] With respect to liposomal formulations, microsponges have greater entrapment efficiency, simple processing, and extended stability.[16]

Materials and Methods

ACF was received as a gift sample from Orison Pharma International (Kala Amb, HP); ethyl cellulose and polyvinyl alcohol were purchased from SD Fine Chemicals, Mumbai. All other chemicals and reagents used were of analytical grade.

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Preparation of Drug-Loaded Microsponges

Drug-loaded microsponges were developed using quasi-emulsion solvent diffusion method. Briefly, the internal phase was prepared by dissolving ACF (100 mg) ethyl cellulose (300 mg) in ethanol (10 mL) followed by bath sonication (5 min) for complete solubilization. For the external phase, polyvinyl alcohol (100 mg) was dissolved in distilled water (150 mL). The internal phase was then added dropwise to external phase with continuous stirring (1000 rpm) for 2.5 h. Finally, the solution was filtered, and the microsponges were separated and dried at room temperature, kept in a glass vial, and stored in a desiccator before further analysis. The developed microsponges were examined under a microscope for their shape and size.

Preliminary Trial Batches of Topical Gel

Preliminary trials were performed to develop Carbopol gel. The different concentrations of Carbopol 934 were taken which are illustrated in Table 1.

Method of Preparation ACF Microsponges loaded Topical Gel

The best optimized Carbopol 934-P gel estimated from trial batch was considered and weighed amount of Carbopol was liquefied in 100 mL of distilled water for 2 h soaking and with speed of 600 RPM agitation after that penetration enhancer was incorporated into the formulated gel which helps in preventing the gel from being getting dried. To this formulation, aqueous solution of triethanolamine was slowly added with gentle agitation and continuous stirring. The ACF-loaded microsponges were then added into the formulated gel.

Characterization of Topical Gel

Physical evaluation

Physical evaluation of gel was performed to study the organoleptic characteristics, occlusiveness along with washability of gel.

Measurement of pH of gel

The pH of the formulated gel was checked using a calibrated digital pH meter.

Viscosity study of gel

For viscosity studies, Brookfield viscometer was used. In this, 50 g of formulated gel was kept in suitable beaker and spindle groove was allowed to dip at specific RPM in the viscometer. The reading was taken in triplicate and calculated mean was considered as mean viscosity.

Spreadability of gel

For checking spreadability of gel, accurately weighed quantity gel (1 g) was pushed between two slides and left untouched for approximately 5 min. Diameters of spread circles were calculated in cm and were considered as comparative values for spreadability until no further spreading is obtained. The readings were taken in triplicate and mean of three determinations was calculated.

Homogeneity and grittiness

To check the consistency of formulated gel, the gel was pressed between the thumb and the index finger. Minor amount gel was wiped on skin from the back of hand to identify the homogeneity and grittiness of the gel.

Drug content

For calculation of drug content, 1 g of each gel formulation was dissolved in 20 mL of methanol contained in volumetric flask for continuous stirring of 30 min. Finally, the solution further was diluted and filtered. After that, further dilution was made up to 10 mL with methanol and again 1 mL of sample was withdrawn and diluted to 10 mL with alcohol. The area was calculated using HPLC at a wavelength of 275 nm.

Table 1: Preliminary trial of ACF gel

Ingredient	*AC gel 1*	*AC gel 2*	*AC gel 3*	*AC gel 4*
Carbopol 934 (%w/v)	1	1.5	2	2.5
Propylene glycol (mL)	5	5	5	5
Methyl paraben	0.1	0.1	0.1	0.1
Propyl paraben	0.05	0.05	0.05	0.05
Triethanolamine (mL)	0.25	0.25	0.25	0.25
Water (mL)	100	100	100	100

ACF: Aceclofenac

In vitro diffusion profile

In vitro diffusion studies were carried out using cellophane membrane which was priorly activated for 24 h in glycerin. The membrane was kept on the donor compartment of Franz diffusion cell. The donor chamber was fixed by clamp with the receiver chamber. In the receiver chamber, phosphate buffer of pH 7.4 was filled. The assembly was kept for magnetic stirring after that 1 g of gel was kept on the donor compartment. The starting time was noted down. The samples were withdrawn and were filtered and % cumulative drug release was calculated by taking area at λmax 275 nm using HPLC.

Kinetics of drug release

The kinetic release profile of the formulation was studied by fitting the data obtained into different kinetic equations depicted in Table 2 and release kinetic mechanism is shown in Table 3.

Stability Study of the Optimized Microspongic Gel

The quality of the formulation is affected with due course of time under the impact of changed temperature, humidity variation, and light effects, which is determined by performing stability testing studies. It's studies were carried out for 3 months with

Table 2: Different kinetic equations

Kinetic model	*Kinetic equation*
Zero-order kinetic	Qt = Q0 + K0t Qt = amount of the drug dissolved in time t Q0 = initial amount of drug in the solution K0 = zero-order release constant expressed in units of concentration/time
First-order kinetics	Log C = Log C0 - Kt/2.303 C0 = initial concentration of drug K = first-order rate constant, and t = time
Higuchi model	Q = KH × t1/2 KH = Higuchi dissolution constant Plot: Cumulative percentage drug release versus square root of time
Hixson-Crowell model	WO 1/3 – Wt 1/3 = κ t where W0 = initial amount of drug in the pharmaceutical dosage form, Plot: Cube root of drug percentage remaining in matrix versus time
Korsmeyer–Peppas model	Mt / M∞= k tn Mt / M∞ = fraction of drug released at time t, k = release rate constant and n = release exponent. Plot: Log cumulative percentage drug release versus log time

Table 3: ICH specification for stability studies

Study type with duration	*Storage condition*
Long period (12 months)	25°C±2°C/60% RH±5% RH and 30°C±2°C/65% RH±5% RH
Intermediate period (12 months)	30°C±2°C/65% RH±5% RH
Accelerated period (12 months)	40°C±2°C/75% RH±5% RH

conditions 25°C ± 2°C/60% RH ± 5% RH and 40°C ± 2°C/75% RH ± 5% RH. Samples were normally withdrawn at every 0th, 30th, 60th, and 90th day and were again analyzed for physical appearance including pH, spreadability, and drug content. ICH specification for stability studies is shown in Table 3.

Animal Studies

All the experimental processes were conducted in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animal (CPCSEA) guidelines with the Regn. No. 1669/GO/abc/12/CPCSEA.

Primary Skin Irritation Study

To check the formulation for skin irritation studies, the formulated optimized formulation was applied on the hairless skin of the Wistar rats. A total of 12 rats were used out of which three were untreated and were considered normal control (Group I) and three were treated with the prepared optimized formulation (Group IV). Rest Group II and Group III were treated with pure drug gel of ACF and marketed formulation of the ACF. Animals were inspected at different time points for possible sign of irritation. Through visual inspection possible sign of irritation such as redness and inflammation was evaluated.[17] The protocol of primary skin irritancy study is shown in Table 4 and standards score of irritancy studies is depicted in Table 5.

Ex vivo Permeation Studies of Microsponge Loaded Gel

For performing *ex vivo* permeation studies, the abdominal skin of the rat was used as dialysis membrane. For experiment, Wistar rat

Table 4: Protocol of primary skin irritancy study

Groups	*Route of drug administration*	*No. of animals*
Group-I: Normal control	Untreated	3
Group-II: Pure drug gel treated	Topical	3
Group-III: Marketed formulation of ACF treated	Topical	3
Group-IV: Optimized microspongic AC gel 1 treated	Topical	3

ACF: Aceclofenac

Table 5: Standard score for skin irritancy

Skin reaction	*Standard score*
Erythema and eschar formation	
No erythema formation	0.5
Very slightly erythema	01
Well-defined erythema	02
Moderate-to-severe erythema	03
Severe erythema	04
Total possible erythema score (a)	05
Edema formation	
No edema formation	0.5
Very slight edema	01
Slight edema	02
Moderate edema	03
Severe edema	04
Total possible edema score (b)	05
Total possible score for primary skin irritation (a+b)	10

good in health was selected and anesthetized using chloroform. The hair from the abdominal region was properly shaved using safety razor and was cleaned with cotton dipped in water to remove the stitched hairs on the skin. The rat was then sacrificed and clean skin was excised properly with the help of surgical blade. The skin procured was cleaned thoroughly in distilled water and was further stored in Ringer solution with proper aeration. The permeation study of microsponges loaded gel was performed using Franz's diffusion cell. Phosphate buffer (pH 7.4) was filled in the receptor compartment. Abdominal skin of rat was used as dialysis membrane. The skin was tied to the donor compartment of the Franz diffusion cell so that stratum corneum might be in direct contact with the release surface of prepared optimized gel incorporated in the donor cell. Phosphate buffer solution of pH 7.4 (20 ml) was put into the donor compartment before being mounted on the diffusion cell. A specified quantity of formulated gel was applied on to the Wistar rat skin which with continuous stirring. The entire system was properly maintained at a temperature of 37 ± 1°C. An aliquot of 2 mL sample was withdrawn at specific time points up to 8 h and was further estimated using HPLC at a wavelength of 276 nm. Equal amount of fresh diffusion medium was replaced after every withdrawal. The percentage of drug permeation was calculated for every interval of time in hour at different time. The data obtained from % cumulative drug release was used to determine the Flux and permeation coefficient.[18]

In vivo Studies-Adjuvant Arthritis Model

In vivo studies in Wistar rats were done to check the efficiency of prepared formulation for managing the inflammation and pain during arthritis. Complete Freund's adjuvant (CFA) was used to induce the arthritis in rats. For studies rats were divided into four groups, each group consisted of six animals.

Group I – Normal control (non-arthritic).
Group II – Arthritic control (0.1 mL CFA).
Group III – Treated with prepared optimized gel formulation
Group IV – Treated with conventional marketed formulation
Group V – Treated with pure drug gel

Group I was regarded as normal control, and to this group, vehicle 2.5% w/v of Tween 20 was applied. After that, arthritis was induced in Groups II, III, IV, and V by injecting subcutaneously 0.1 mL of CFA at a dose concentration of 1 mg/mL on the plantar surface of the right hind paw of the rat.[19] Group II will not receive any treatment and hence was considered as arthritic control. From Groups II to V were allowed to develop arthritis. Group III was optimized gel formulation treated group, Group IV was marketed formulation treated group, and Group V was pure drug gel treated group. During the experiment periodically, rat paw volume of control along with the treatment groups was measured on initial 0 day, 5th, 12th, and 21st day. Marketed ACF gel, pure drug gel along with that optimized formulation was applied topically for 21 days on inflamed area. On 0 day, 5 days, 12 days, and 21 days, paw volume of rat was measured and percentage inhibition of inflammation using different formulation in groups was determined.[20] The animals were properly maintained under standard environmental conditions and were allowed to fed with standard pellet diet along with water *ad libitum*. All the experimental process was been conducted in accordance with Committee for the Purpose of Control and Supervision of Experiments on Animal (CPCSEA) guidelines with the Regn. No. 1669/GO/abc/12/CPCSEA. The

anti-inflammatory effect was checked by calculating % inhibition of inflammation using the formula,

% Inhibition=100 (1-Vt/Vc),

Where, Vc represents edema volume in control

Results and Discussion

Characterization of Preliminary Trial Batch

The preliminary trial batch of topical gel using Carbopol 934 evaluation parameters is depicted in Table 6.

First of all, topical gel was prepared using Carbopol 934. After that, they were characterized for different parameters including color, odor, pH, viscosity, and spreadability. The AC gel 1 shows good spreadability and viscosity when compared with other prepared gels. Hence, it was considered as optimized formulation and a promising alternative to develop microspongic loaded gel. Now, prepared optimized microsponges were dispersed in the Carbopol gel and were further compared with pure drug gel as well as the conventional gel of ACF purchased from the market. The AC gel 1 shows good spreadability and viscosity. Hence, it was considered as optimized formulation for formulating further promising alternative to microspongic loaded gel.

Characterization of microsponges loaded topical gel

The ACF microsponges loaded topical gel was prepared and evaluated for following parameters which are shown in Table 7.

The formulated microsponge loaded gel was evaluated for different parameters such as clarity, pH, viscosity, drug content, and spreadability and was compared with pure drug gel and marketed formulation to check the effectiveness of the formulation. From the observation, it was concluded that ACF-loaded microspongic topical gel prepared from ethyl cellulose revealed greater drug content and showed more spreadability and hence the optimized formulation AC gel 1 is considered promising to be use on animals to study the skin irritation effects. Table 5.29 shows the data for clarity, pH, viscosity, drug content and spreadability of pure drug gel, marketed formulation gel, and prepared optimized microsponges loaded gel.

Table 6: Characterization of trial batch of topical gel

Batch code	*Color*	*Odor*	*pH (Mean±SD) (n=3)*	*Viscosity spindle no.: 62 (Mean±SD) (n=3)*	*Spreadability (g.cm/sec) (Mean±SD) (n=3)*
AC Gel 1	Colorless	Odorless	6.91±0.004	9236±58	11.38±0.73
AC Gel 2	Colorless	Odorless	6.7±0.04	9556±72	11.20±1.15
AC Gel 3	Colorless	Odorless	6.76±0.047	14491±44	10.4±1.22
AC Gel 4	Colorless	Odorless	6.83±0.094	12620±81	10.1±1.54

Table 7: Characterization of microsponges loaded topical gel

Parameter	*Pure drug gel*	*Marketed ACF gel*	*AC gel 1*
Dose	100 mg	0.50%	100 mg
Strength	15 g	15 g	15 g
Clarity	Transparent	Transparent	Transparent
Odor	Odorless	Odorless	Odorless
pH (Mean±SD (*n*=3)	6.81±0.57	6.96±0.02	6.92±0.03
Spreadability (Mean±SD) (*n*=3)	10.6±0.79	11.28±1.03	11.86±0.08
Viscosity (Mean±SD) (*n*=3)	9478±123 cps	9896±43 cps	9471±23 cps
% drug content (Mean±SD) (*n*=3)	88.11±0.78	93.58±1.56	90.87±0.81

ACF: Aceclofenac

In vitro Diffusion Studies and Release Kinetics

The *in vitro* diffusion studies data reveal drug release profile at different time interval which is illustrated in Table 8 and diagrammatic representation is shown in Figure 1.

After evaluating for different parameters, the optimized formulation was characterized for *in vitro* release. From the data of *in vitro* diffusion studies of pure drug gel, conventional gel purchased from the marketed and drug-loaded microspongic gel, it was found that the prepared topical gel AC gel 1 showed retarded release of about 71.33% for a period of about 8 h, whereas the comparative conventional formulation releases almost same amount of drug in 6 h and got exhausted. Optimized formulation showed controlled release of drug from the microsponges which specify that the formulation is capable of releasing the drug in a retarded controlled fashion and is efficient enough.

Kinetic Release Profile

The release kinetic profile in different kinetic models is illustrated in Table 9.

The % cumulative drug release of the optimized AC gel formulation and both comparative studies was fitted into different kinetic models and slope along with R^2 value was calculated. Formulation showed R^2 value of 0.99330427, nearest to 1. Hence, this depicts that formulation was best fitted in Higuchi model and showed Fickian transport mechanism as the value of n was found to be 0.48.

Stability Studies of the Optimized AC Gel 1

The stability studies for three months were done and data are illustrated in Table 10.

When optimized formulation of drug AC gel 1 was subjected to stability studies at 40°C ± 2°C/75% RH ± 5% RH conditions for 3 months, it was found that formulation does not show any significant changes in pH, viscosity, spreadability, and drug content at time different time interval. Hence, the formulation is stable.

Table 8: Drug release data of conventional gel and microspongic gel

Time in hours	*Pure drug gel (Mean±SD) (n=3)*	*Marketed ACF gel (Mean±SD) (n=3)*	*Optimized AC gel 1 (Mean±SD) (n=3)*
0	0	0	0
1	20.23±1.23	23.69±1.43	12.24±1.62
2	31.21±2.49	34.37±1.28	20.61±1.25
3	40.32±1.82	48.88±1.72	35.17±1.84
4	50.87±1.57	52.33±2.18	41.62±1.35
5	58.24±1.72	62.73±2.26	48.45±1.23
6	67.25±1.23	71.29±1.25	54.31±1.86
7	71.25±2.16	82.31±1.57	63.81±1.34
8	80.45±2.75	92.41±3.14	71.39±1.07

ACF: Aceclofenac

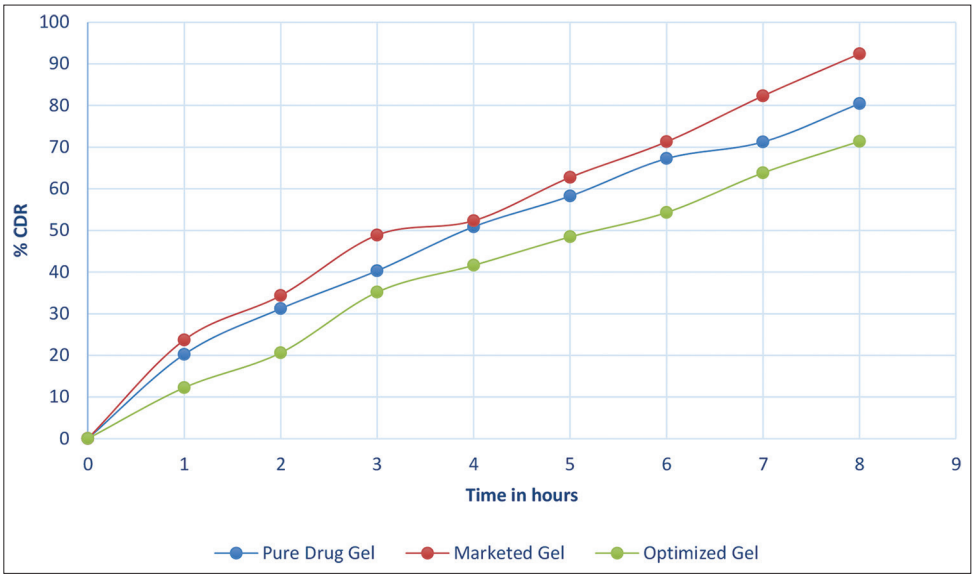

Figure 1: Drug release profile

Table 9: Release kinetic of ACF conventional and microspongic gel

Model	*Parameter*	*Pure drug gel*	*Marketed aceclofenac gel*	*Optimized AC gel 1*
Zero order	R2	0.9509	0.9504	0.9266
	Slop	8.135	8.347	7.927
	Intercept	12.67	13.69	12.98
First order	R2	0.9629	0.9972	0.9805
	Slop	0.152	−0.162	−0.1616
	Intercept	4.47	4.51	4.1
Higuchi model	R2	0.9581	0.9974	0.9933
	Slop	26.64	26.76	26.554
	Intercept	1.79	1.85	1.71
Hixson-Crowell	R2	0.8583	0.8469	0.8767
	Slop	0.876	0.82	0.88
	Intercept	2.9321	2.71	2.98
Korsmeyer-Peppas	R2	0.4423	0.4309	0.4297
	Slop	0.52	0.59	0.58
	Intercept	−0.64	−0.61	−0.62

ACF: Aceclofenac

Table 10: Stability studies data

Parameter	*Optimized ACF microsponges loaded gel AC gel 1*			
	40°C±2°C/75% RH±5% RH			
	0 Day	*30 days*	*60 day*	*90 day*
Clarity	Transparent	Transparent	Transparent	Transparent
Odor	Odorless	Odorless	Odorless	Odorless
pH	6.92	6.92	6.92	6.92
Spreadability	11.86	11.86	11.86	11.86
Viscosity	9471	9474	9475	9478
% Drug content	90.87	90.81	90.56	90.30

ACF: Aceclofenac

Primary Skin Irritation Study

The primary skin irritation studies were done and scoring was done visually and depicted in Table 11 and photographs are shown in Figures 2-4, respectively.

Primary skin irritation study results revealed that the formulation showed no possible signs of irritation when inspected for erythema and edema. Pure drug gel and conventional marketed formulation were used to compare the results of irritation.

Table 11: Skin irritation studies data at t time and after 24 h

Formulation	*Score*	
	Day 1	*Day 2*
Control group	0	0
Pure drug gel treated	0.5	0.5
Marketed ACF gel treated	0.5	0.5
Optimized AC gel 1	0.5	0.5

ACF: Aceclofenac

Microsponges loaded gel was capable of increasing the viscosity of the prepared formulation and formed a structured network which reduces the contact chances between skin layer and microsponges. Hence, there exist least chances of irritation using microspongic gel formulation. Hence, it can be used effectively for topical application.

Ex vivo Permeation Studies in Animals

J-flux and permeability coefficient are shown in Table 12.

Ex vivo permeation studies were performed using abdominal skin of rat in Franz diffusion cell. The flux is the amount of permeant that is crossing the membrane per unit area, and in case *ex vivo* permeation, it is the accumulation of permeant which is crossing the membrane in a specified time. The diffusion rate of drug for the 1st h was elevated in comparison to later hours which show that unentrapped drug was released first due to which flux was affected after that flux was decreased for next hours which depicts that entrapped drug was releasing at a retarded rate.

In vivo Studies

The *in vivo* studies data of rat paw with different treatment groups are shown in Figure 5. The paw volume of rat for different days is represented in Figure 6. The percent inhibition of inflammation is calculated at different days and graph is shown in Figure 7.

In vivo activity in Wistar rats was calculated using Tukey HSD test. The paw volume after induction of CFA in all the five groups was measured using plethysometer: Group I – Normal

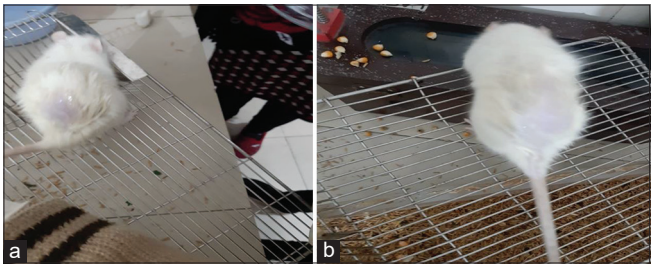

Figure 2: Treated with pure drug gel (a) at 0 h, (b) after 24 h

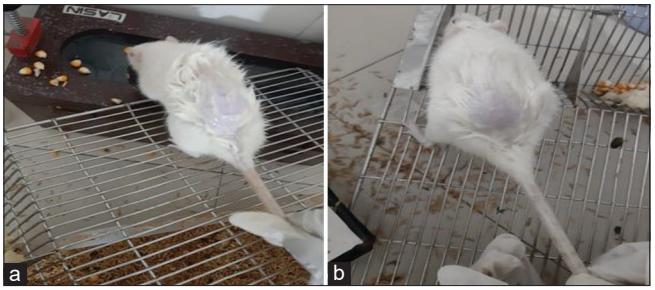

Figure 3: Treated with marketed aceclofenac gel (a) at 0 h, (b) after 24 h

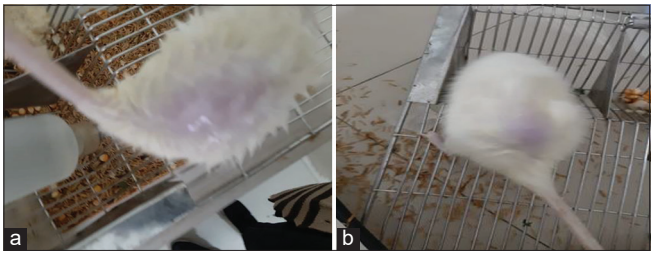

Figure 4: Treated with optimized microspongic gel (a) at 0 h, (b) after 24 h

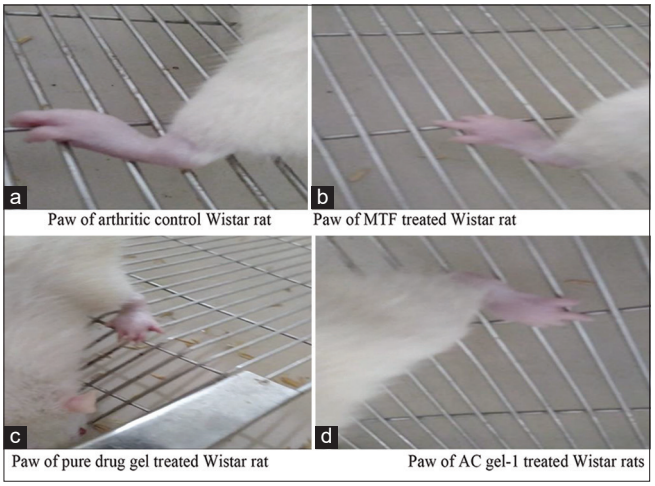

Figure 5: (a-d) Paw of Wistar rats with different treatment groups

control (non-arthritic), Group II – Arthritic control (0.1 mL CFA), Group III – Treated with AC gel 1, Group IV – Treated with marketed formulation, and Group V – Treated with prepared pure drug gel.

The results were found significant from *P* value and were concluded that at 95% confidence interval, $P < 0.05$ was considered.

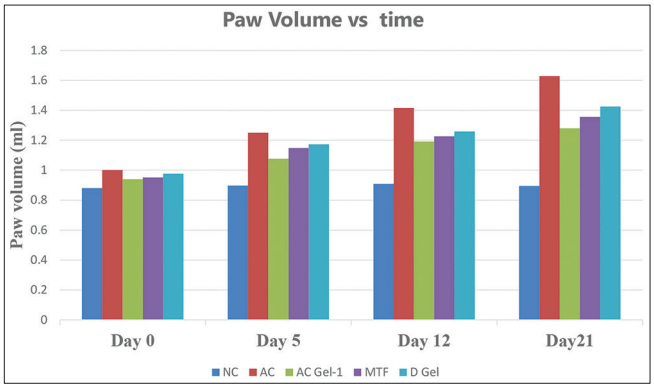

Figure 6: Rat paw volume on different days with different formulation

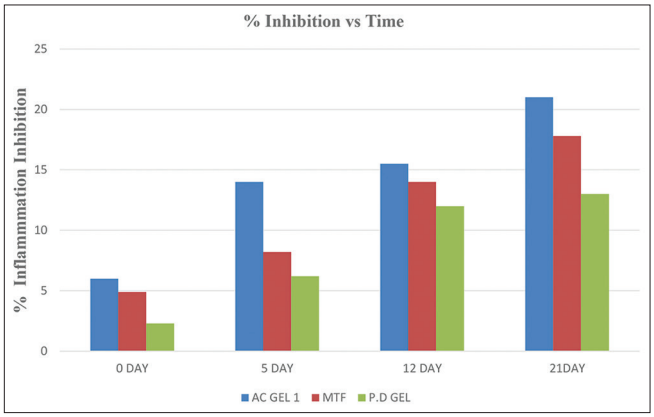

Figure 7: % inhibition of inflammation with different formulation

Table 12: J-flux and permeability coefficient

Time in hours	*Flux J (mg/cm²/h)*	*Permeability coefficient (Kp)*
0	0	0
1	1.8556	0.0247334
2	2.5545	0.0365421
3	1.7431	0.026534
4	0.1723	0.0024623
5	0.1534	0.002312
6	0.3659	0.0051
7	1.1347	0.0153
8	0.1224	0.001657

This shows that anti-inflammatory activity was significantly improved in case of microsponges loaded topical gel (AC gel 1) when compared to conventional marketed gel of ACF. The paw volume of Wistar rats after induction of CFA at different days 0, 12, 15, and 21 days along with the % inhibition of inflammation in the paw depicted in the aforementioned tables and figures. Percentage inhibition of inflammation was also found significant which indicates the progress of AC gel 1. Further clinical studies can enlighten and strengthen the use of microsponges loaded gel for controlled release for the management of pain in the persons suffering from joint inflammatory disorders.

Conclusion

The microsponges prepared by incorporating ethyl cellulose were found to have good physical, morphological characteristics along with the % encapsulation higher and hence the formulation was

dispersed in the Carbopol gel. The trial batch of Carbopol gel was characterized for pH, viscosity, and spreadability studies. AC gel 1 showed good viscosity and spreadability and so this formulation was considered optimized and microsponges loaded gel was prepared using the same gel. The microsponges loaded gel was evaluated for drug release profile studies by comparing with pure drug gel and conventional gel purchased from the market. The optimized gel showed controlled release of 71.33% in 8 h which revealed that formulation prepared is releasing drug at a controlled manner with no possible signs of irritation on skin of rats. When the data of the drug release were fitted into different kinetics models, it was found that formulation obeyed Higuchi model as the value of R^2 was nearest to one and showed Fickian transport mechanism. The optimized formulation did not show any significant changes when subjected to stability study analysis.

From the study, it was concluded that it is possible to design a topical polymeric microsponges formulation for effective management of RA using ACF which is capable of increasing efficiency along with patient compliance which is prime requirement of the patients. However, *in vivo* experiments conducted on Wistar rats revealed that prepared formulation gives promising results and can be used for further clinical studies for the management of arthritis induced through CFA in rats.

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