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Original Article

DEVELOPMENT OF ACECLOFENAC LOADED MICROSPONGE GELS: A STATISTICAL QUALITY BY DESIGN (QBD) APPROACH TOWARDS OPTIMIZATION AND EVALUATION

RAKHIMOL K.[1], PRAJITHA BIJU[2*], SINDHOOR S. M.[3], NATASHA NAVAL AGGARWAL[4], SANDHYA V.[2], DEEKSHA RAI[5]

[1]Department of Pharmaceutics, College of Pharmacy Kannur Medical College, Kannur, Anjarakandy, India. [2]Department of Pharmaceutics, Yenepoya Pharmacy College and Research Centre, Karnataka-575018, Mangaluru, India. [3]Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), Mangalore-575018, Karnataka India. [4]Department of Pharmaceutical Chemistry, Yenepoya Pharmacy College and Research Centre, Karnataka-575018, Mangaluru, India. [5]Department of Pharmacognosy, Yenepoya Pharmacy College and Research Centre Deralakatte, Yenepoya Pharmacy College and Research Centre, Karnataka-575018, Mangaluru, India
[*]Corresponding author: Prajitha Biju; [*]Email: prajithabiju@yenepoya.edu.in

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ABSTRACT

Objective: The current research aims to deliver Aceclofenac in a controlled manner through a microsponges-loaded drug delivery system for the treatment of inflammation.

Methods: The formulations were prepared by the Quasi-emulsion solvent diffusion method and characterized for particle size and drug entrapment efficiency. For the optimization of the formulation through the Quality by Design (QbD) approach, Quality target product profiles (QTPP) were set up considering various key factors that affect the quality of the formulation. Further optimization of the important factors in relation to the major Critical Quality Attributes (CQAs) was conducted by applying full factorial design using the Design of Expert Software (11.0 software, Stat-Ease, Inc., USA). The optimized formulation was incorporated into the gel, and characterized for morphological analysis by Scanning Electron Microscopy (SEM), drug content, and *ex-vivo* permeation studies (DD solver, Version 2.0).

Results: It was found that process parameters such as drug-to-polymer ratio, the volume of the internal phase, and concentration of the emulsifier and polyvinyl alcohol (PVA), played a crucial role in improving the drug entrapment efficiency and particle size. On the other hand, stirring time did not significantly affect the particle size. Through Design of Expert (DOE) analysis, a PVA concentration of 0.641 mg/ml and an internal phase volume of 12.5 ml were identified to be the ideal concentrations to obtain the optimized microspongal gel formulation (MS4). Characterization studies were carried out on MS4, which displayed a drug encapsulation of 94%, with a C_{max} of 81.62 mg/ml, and a T_{max} of 12 h. Stability studies carried out as per the International Conference of Harmonization (ICH) guidelines confirmed no noticeable change in physical appearance and drug content.

Conclusion: Overall, this study focused on optimizing the formulation of microsponges for efficient dermal drug delivery, considering various critical variables and process parameters. The resulting optimized formulation demonstrated promising drug release and potential for the effective management of inflammation disorders.

Keywords: Microsponge, Quassi emulsion technique, Quality by design, Ishikawa fishbone diagram, Gel

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INTRODUCTION

Rheumatoid arthritis (RA) is a debilitating, chronic, inflammatory disease capable of causing joint damage and long-term disability [1]. Around the world, 18 million people suffer from this disorder. Rheumatoid arthritis affects over 70% of women and 55% of people over the age of fifty-five [2, 3]. When rheumatoid arthritis turns very severe, it involves multiple body systems: the joints of hands, wrists, feet, ankles, knees, shoulders, and elbows [4]. Overall, first-line treatment aims to relieve pain and decrease inflammation. Rheumatoid arthritis is frequently treated with nonsteroidal anti-inflammatory medications. These medications are fast-acting and work by inhibiting cyclooxygenase to prevent the synthesis of prostaglandins, prostacyclin, and thromboxanes [5]. Aceclofenac appears to have the potential to emerge as a favoured first medication in an individualized Non-steroidal anti-inflammatory drugs (NSAID) regimen for patients with rheumatic disorders. Aceclofenac reduces the Prostaglandins (PGs) to undetectable levels, thereby decreasing reactive oxygen species generation and nitrous oxide in human articular chondrocytes responsible for pain, swelling, and inflammation. Conversely, it is hypothesized that Aceclofenac will promote glycosaminoglycan synthesis in the adult osteoarthritic cartilage in synovial joints because of its high permeability properties [6]. The only drawback of this drug is that it lacks water solubility, which can cause reduced skin retention upon topical application.

Microsponges, tiny spherical particles made up of groups of even smaller spheres, can retain four times as much skin secretions as they weigh. Tiny, harmless microsponge particles do not penetrate the skin [7]. Instead, they gather in the skin's microscopic pores and release the drugs in a controlled manner. The size of microsponge varies from 5 to 300 µm, having an interior pore structure 10 feet long, giving it a total pore volume of around 1 ml/g [8], with an internal pore diameter of 0.25 µm which makes it impermeable to bacteria acts as self-sterilizing [9, 10]. The microsponge system may prevent drugs from accumulating too much in the dermis and epidermis. The microsponge technology has the potential to significantly lower the irritability of potent medications without compromising their potency. Hitherto, no microsponge-based products are commercially available, even though several advantages are reported. The change in structural viability during the encapsulation process prevents the product from scaling up. With this aspect, an in-depth analysis of Microsponges was done using the QbD (Quality by Design) approach to accelerate the formulation process. QbD approach included defining QTPP (Quality Target Product Profile), Risk identification and risk assessment, Primary and secondary screening with DOE [2^3 full factorial designs DOE software version 11.0 (Stat-Ease, Inc., USA)] [11]. Finally, as the formulation was targeted to treat pain associated with Rheumatoid arthritis, the Aceclofenac microsponge was incorporated into gel to make it easier for application. The transformation of Microsponges into gel resulted in considerably greater retention of drug on the skin [12].

MATERIALS AND METHODS

Aceclofenac and ethyl cellulose were procured from Balaji Drugs, Gujarat. Polyvinyl alcohol was obtained from Loba Chemie, Mumbai. Methyl paraben and propyl paraben were purchased from Ozone International, Mumbai. The solvents and excipients that were used were all of analytical quality.

Preparation of microsponges

Acelofenac-loaded microsponges were prepared using the Quasi-emulsion solvent diffusion technique, the active ingredient (Aceclofenac) is made to dissolve completely in the internal phase (ethanol) using a rotary shaker. The external phase was prepared by dissolving ethyl cellulose and polyvinyl alcohol in purified water maintained at 60 °C followed by the cooling mixture to room temperature. After that, the internal (dispersed phase) was slowly added to the external phase (water phase), placing the beaker on a magnetic stirrer maintained at 3000rpm for 6h for the evaporation of solvent to yield Microsponges. The obtained yield was filtered and washed with purified water and dried at 40 °C till the free-flowing powder was obtained [13].

QbD Approach for the optimization of aceclofenac-loaded microsponges

Quality target product profiles (QTTP)

Quality target product profiles (QTPP) were set up considering various key factors affecting drug product quality [13].

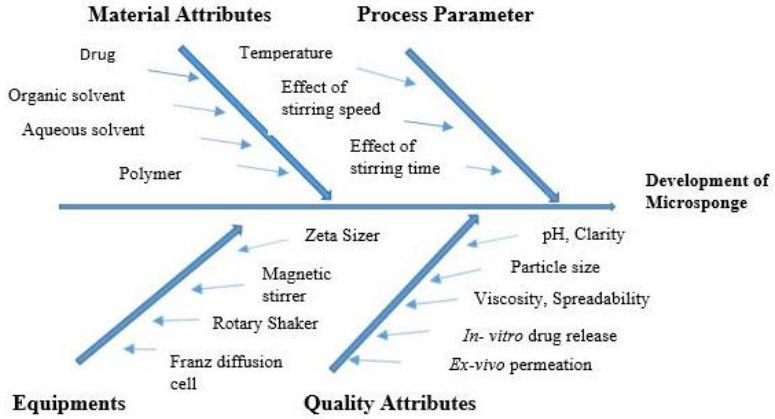


Fig. 1: **Ishikawa fishbone diagram for Aceclofenac loaded microsponges**

Risk assessment of critical quality attributes (CQA) from preliminary trial

A preliminary risk assessment was conducted to determine the elements that could have a significant impact on the product's quality. The formulation design variables are explained in table 2, and formulations containing different concentrations are given in table 1. The two categories considered in this study were CMAs (Critical Material Attributes) and CPPs (Critical Product Profiles). Table 3 lists the sixteen formulations tested for five critical elements and emphasizes the control elements studied using the described manufacturing methods. The quality attributes and manufacturing process control for the Microsponge dispersion were drug content, internal phase solvent, and 250 mg polymer (EC). Standard control parameters were maintained, like external phase temperature, 3000 rpm mixing speed, and 3600 sec total mixing time [14].

Table 1: Critical material attributes and Critical process parameters for Microsponges formulation

S. No.	Variables: CMAs and CPPs	Parameters
1	Effect of Drug: Polymer Ratio	2:1, 4:1, 6:1, 8:1
2	Effect of Polymer (PVA) concentration	0.25,0.5, 0.75, 1
3	Effect of internal phase volume	5, 7.5, 10, 12.5
4	Effect of external phase volume,	25, 50, 75, 100
5	Effect of Stirring Time	1, 2, 4, 6, 8

Optimization of microsponges by using DOE software

After the screening studies, optimization of the important factors in relation to the major CQAs, namely, particle size (Y1) and entrapment efficiency (Y2) was tried by applying full factorial design using the design of expert software version 11.0 software (Stat-Ease, Inc., USA) statistically. The different levels for the independent and dependent variables were denoted using the factors-1, and+1. The optimized formula given by the software helped in preparing microsponges of smaller particle size and high entrapment efficiency [16-18].

Characterization of microsponges

Particle size, analysis

The dynamic light scattering technique will be used to determine the particle size. The formulation will be diluted in MilliQ water prior to the analysis using Zetasizer Nano ZS, Malvern Instrument, and Worcestershire, UK. The particle size and the entrapment efficiency of Microsponges in varying concentrations of CMA and CPPs are represented graphically in fig. 1,2,3,4 and 5, respectively [15, 16].

Entrapment efficiency

About 5 ml of the sample was centrifuged at 15,000 rpm for 15 min, and the resulting supernatant layer was diluted with methanol and analyzed using UV–Visible spectrophotometer at 275 nm. This process will be repeated thrice to ensure that the free drug will be completely removed. The percentage of drug entrapment in Aceclofenac Microsponges was calculated using the formula mentioned below [17].

$$\text{Entrapment efficiency} = \left[\frac{\text{Total drug} - \text{Drug in supernatant}}{\text{Total drug}}\right] \text{X } 100$$

***In vitro* drug release studies**

The *in vitro* drug release studies were carried out utilizing cellophane membrane-enclosed vertical Franz diffusion cells (Mol wt cut off 83). With a 4.52 cm^2 effective molecular diffusion area, the previously calibrated volume of the formulation was placed in the donor compartment, and 8 ml of phosphate buffer (pH 6.8) was added to the receptor chamber, keeping it at 32 °±0.5 °C while being stirred by a magnetic stirrer at 100 rpm. After soaking it overnight, the cellophane membrane was sandwiched between the diffusion cells. One ml of aliquots was taken out of the sampling port and replaced with an equivalent amount of fresh buffer at predetermined intervals (1, 2, 4, 6, 8, 10, and 12 h) and analyzed at 275 nm using a UV-visible spectrophotometer. The *in vitro* drug release data is plotted using DD Solver and represented in fig. 7 [18].

Preparation and characterization of aceclofenac microsponges loaded topical gel

Method of preparation

About 100g of gel was prepared, dispersing 0.5% (w/v) of Carbopol 934P in water and allowed to hydrate it. Using a mechanical stirrer, the hydrogel was stirred until a lump-free dispersion was achieved. The homogenous dispersion was neutralized with Triethanolamine [18]. The composition of the acelclofenac-loaded gel is given in table 2.

Characterization of aceclofenac-loaded gel

Gels were evaluated for their Clarity, pH, Viscosity, Homogeneity, Extrudability, spreadability, drug content, and ex-vivo permeation studies.

Clarity

A visual examination was carried out under the black and white background to evaluate the clarity of different formulations.

Table 2: Composition of aceclofenac microsponges gel formulations

Composition	Activity	Composition w/w % (100 mg)			
Aceclofenac Microsponges	Anti-inflammatory	100	100	100	100
Carbopol 934 ((% W/V) gms)	Polymer base (1%)	0.5	0.5	0.5	0.5
Propylene Glycol	Viscosity enhancer		1	1	1
Menthol	Penetration enhancer	-	1	2	3
Propyl Paraben	Preservative	0.02	0.02	0.02	0.02
Water	Aqueous phase (q. s)	100	100	100	100

Polymer base 1% represents 1 gm of Carbopol in 100 ml of water.

pH

The pH value of Aceclofenac Microsponges Gel formulations (MS1-MS4) was measured with a Digital pH meter [18].

Homogeneity

All the developed formulations (MS1-MS4) were observed visually for clarity and homogeneity [18].

Viscosity measurement

Using an LV Brookfield, DV-E viscometer with spindle number 64rpm, the viscosity of Aceclofenac Microsponges gels was measured and recorded (in cps) at a controlled temperature of 35 ºC [18].

Spreadability

This method uses a circular mould plate of glass (diameter = 20 cm, width = 0.2 cm) with a central orifice of 1.2 cm diameter, which is placed on a glass support plate (20 cm x 20 cm) positioned over millimetric graph paper. The report on spreadability and viscosity is mentioned in table 8 [18].

Drug content

The microsponge gel was prepared with and without the drug; 1 ml of the sample was lysed with phosphate buffer pH 6.8 and diluted to 10 ml with phosphate buffer pH 6.8. The spectrum of both formulations was scanned from the range of 200-800 nm in the UV spectrophotometer. The spectrum showed no interference in the peak of the drug and polymer. Finally, considering the placebo formulation as blank, the drug content of the test formulation was determined [13, 18].

Scanning electron microscopy (SEM)

The surface morphology of optimized Aceclofenac Microsponges gel batch M4 was determined by scanning electron microscopy. The sample was made to run at 20 kV to observe the morphology of the Microsponges gel (M4). Platinum was applied to prepared Microsponges using an auto fine coater and ion sputtering. The images were captured using an SEM (JEOL-JSM 6390, Japan) under vacuum at room temperature while the Microsponges were held on the sample holder [13, 18].

***Ex-vivo* drug diffusion studies**

Vertical type of Franz diffusion cells using excised porcine skin was used to perform the *ex vivo* drug diffusion studies. The previously calibrated volume of the formulation was placed in the donor compartment, and 8 ml phosphate buffer (pH 6.8) was placed in the receptor compartment, the porcine skin of thickness of 2.6 mm exposing a surface area of 3.799 cm^2 was used. Subcutaneous fat content was cleaned from the excised porcine skin and placed between the diffusion cells. The *ex-vivo* diffusion studies were stopped after 240 min since the porcine skin loses its viability after a few hours when placed at room temperature. Samples were analyzed at 275 nm using a UV Spectrophotometer. The permeation profile was obtained by plotting a graph of cumulative drug permeation versus time. The flux (µg/cm^2/h), and permeability coefficient were calculated from the slope of the linear portion of the cumulative drug permeated (µg/cm^2) versus the time (h) profile [13, 18].

Table 3: Formulation design of trial batches for aceclofenac microsponges

Formulation code	Drug (g)	Ethyl cellulose (g)	Internal phase volume (ml)	PVA concentration (%)	External phase volume (ml)
I_1	0.5	0.25	12.5	0.5	50
I_2	0.5	0.25	10	0.5	50
I_3	0.5	0.25	7.5	0.5	50
I_4	0.5	0.25	5	0.5	50
E_1	0.5	0.25	5	0.5	25
E_2	0.5	0.25	5	0.5	50
E_3	0.5	0.25	5	0.5	75
E_4	0.5	0.25	5	0.5	100
P_1	0.5	0.25	5	0.25	50
P_2	0.5	0.25	5	0.5	50
P_3	0.5	0.25	5	0.75	50
P_4	0.5	0.25	5	1	50
D_1	0.5	0.25	5	0.5	50
D_2	1	0.25	5	0.5	50
D_3	1.5	0.25	5	0.5	50
D_4	2	0.25	5	0.5	50

I_1-I_4: Varying volume of internal phase, E_1-E_4: Varying volume of external phase, P_1-P_4: Varying PVA concentration, D_1-D_4: Varying concentration of drug.

Stability study of optimized formulation

Prepared Microsponges containing topical gel formulation (MS4) were tested for stability over a 30 d interval at a high temperature (40 °C) and 75% relative humidity. After 30 d, the sample was taken out and tested for factors like drug content.

The observations are shown in table 9 [13, 19].

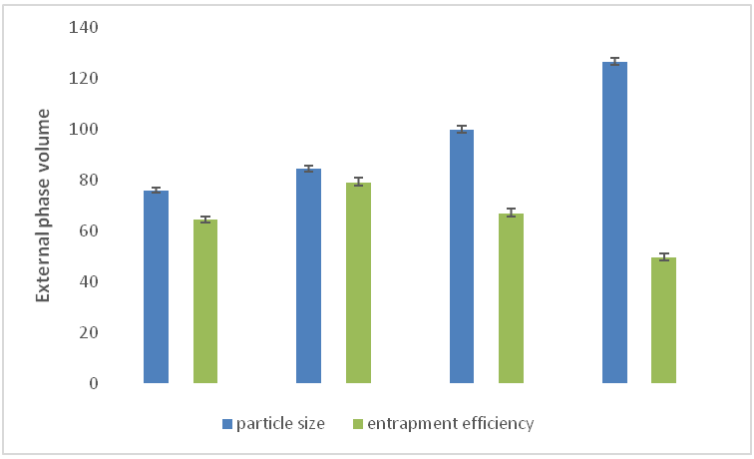


Fig. 1: Effect of Internal phase volume on the production of microsponges values represent mean±SD (n=5)

RESULTS AND DISCUSSION

Risk assessment of critical quality attributes from preliminary trial batches to develop QbD approach

Pharmaceutical Quality by Design is designed to enhance process efficiency and decrease product variability, which frequently causes flaws, rejections, and recalls. Robustly designed products and procedures are necessary for achieving this goal. Additionally, a better understanding of products and processes can make it easier to identify and control the variables affecting the quality of drug products.

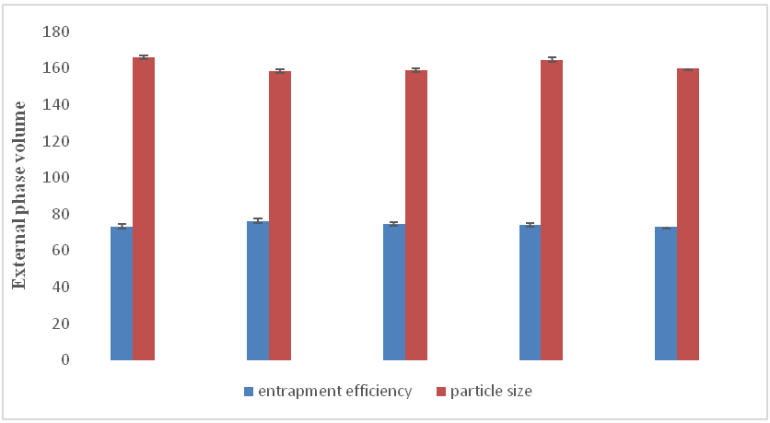


Fig. 2: Effect of external phase volume on the production of microsponges values represent mean±SD (n=5)

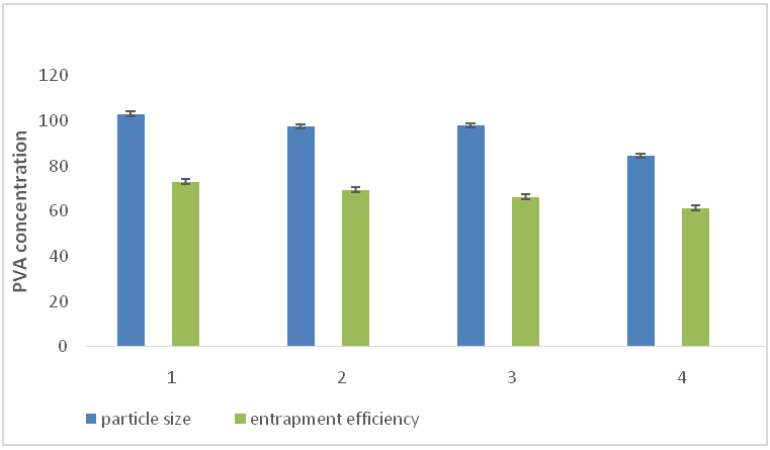


Fig. 3: Effect of PVA concentration on the production of microsponges, values represent mean±SD (n=5)

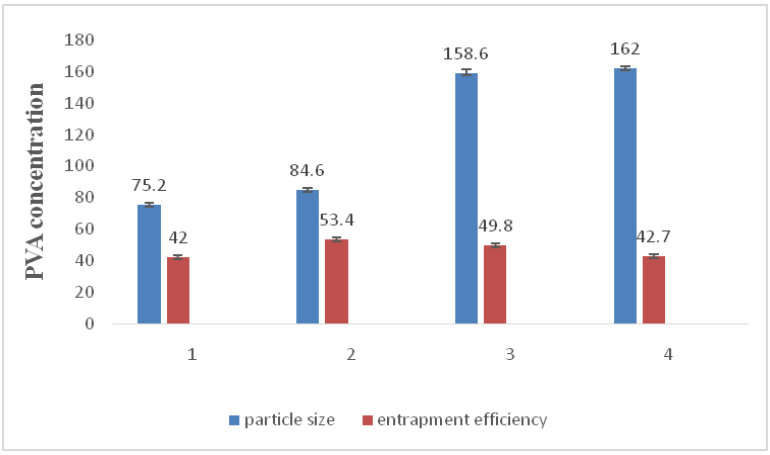


Fig. 4: Effect of stirring time on the production of microsponges, values represent mean±SD (n=5)

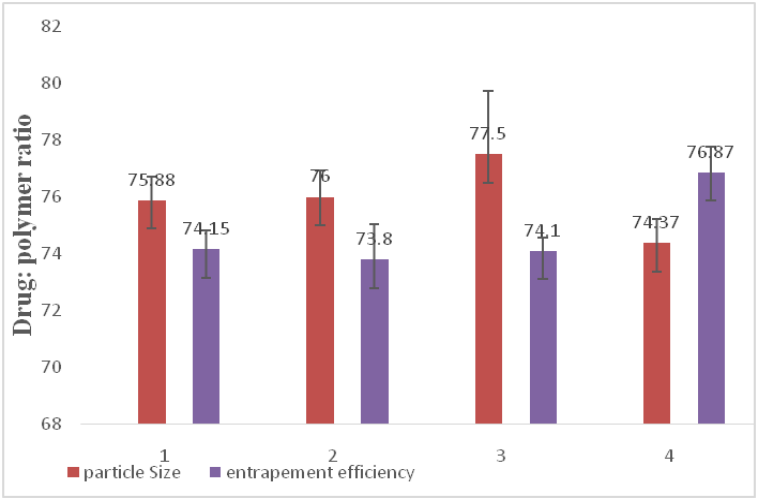


Fig. 5: Effect of drug: polymer ratio on the production of microsponges, values represent mean±SD (n=5)

Table 4: **Risk assessment to identify variables affecting drug product quality**

Variables: CMAs and CPPs	Effect of drug: polymer ratio (D)	Effect of polymer (PVA) concentration (P)	Effect of internal phase volume (I)	Effect of external phase volume (E)	Effect of stirring time
Particle size	Low	High	Medium	High	Low
Drug entrapment efficiency (%)	Low	Medium	High	Medium	Low

Low represents parameters that do not affect formulation, Medium represents the effect that must be considered upon formulation, and High represents the significant impact on the formulation.

In this work, the researchers focused on the formulation of microsponges, which are porous structures with increased drug-loading capacity and an occlusive effect on the skin. Increasing the drug-to-polymer ratio improved drug entrapment efficiency and particle size by enhancing drug molecule packing within the polymer bilayer. The volume of the internal phase was found to affect the particle size, with higher volumes leading to improved solubilization of drug particles, resulting in smaller particles. On the other hand, increasing the volume of the external phase, larger particles did not show significant microstructure formation and led to lower drug entrapment efficiency [19]. The concentration of the emulsifier, polyvinyl alcohol (PVA), played a crucial role in balancing the two phases. Higher PVA concentrations increased the viscosity of the continuous phase, resulting in larger particle sizes and affecting drug entrapment efficiency and product yield. Process parameters, such as stirring time, did not significantly affect particle size after 6 h [20-24].

Optimization of microsponges using design of experiment

Table 5: **Variables considered as independent and dependent for the DOE**

Independent variable	Low (-1)	High (+1)
Effect of Polymer (PVA) concentration(P)	0.25	0.75
Effect of internal phase volume(I)	5	12.5
Dependent variable		
Particle size(nm)	-	-
Drug Entrapment Efficiency (%)	-	-

Table 6: Three-level full factorial design to optimize the formulation parameters

Batch details	Design input (Independent variables)		Design output (Dependent variables)	
Run	Effect of polymer concentration (PVA)	Effect of internal phase volume (I)	Particle size (nm)	% Entrapment efficiency
1	0.5	8.75	290	98.09
2	0.5	14.05	275	83.68
3	0.5	3.44	273	82.76
4	0.25	5	276	84.8
5	0.85	8.75	278	86.98
6	0.75	12.5	270	79.05
7	0.25	12.5	270	79.97
8	0.14	8.75	289	97.3
9	0.5	8.75	299	99.34
10	0.5	8.75	294	99.7
11	0.5	8.75	290	98.1
12	0.75	5	293	98.07
13	0.5	8.75	273	81.06

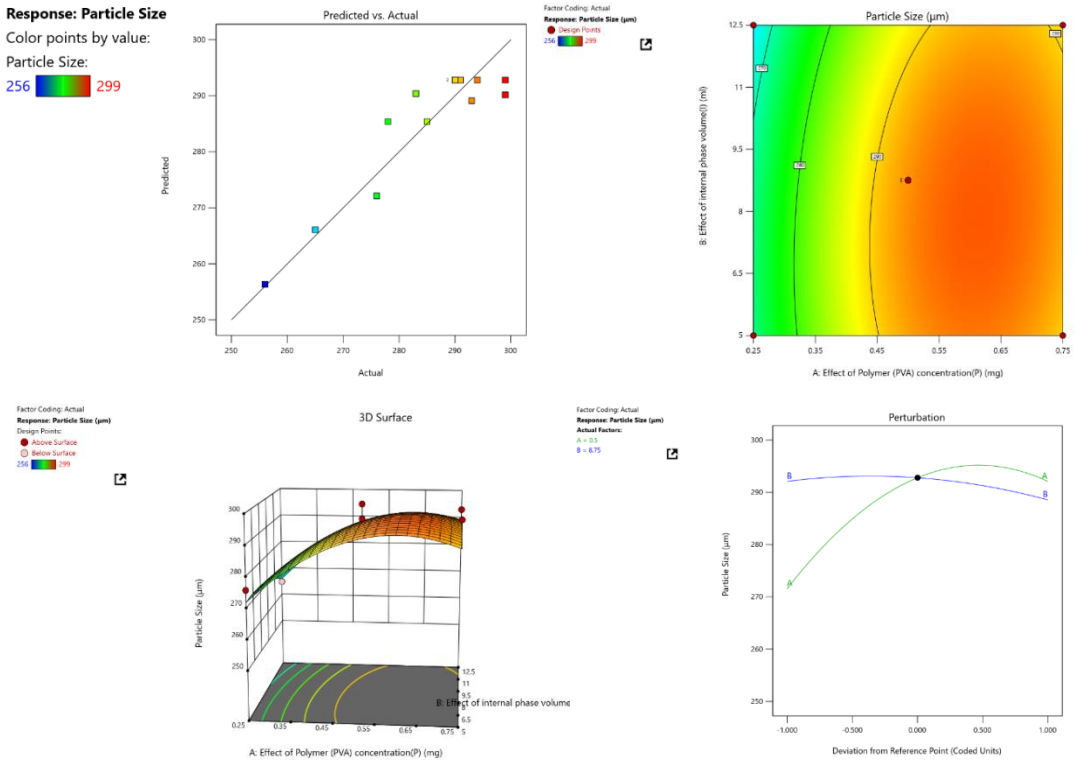


Fig. 6: Predicted vs. Actual graphs (A), Contour model graph (B), 3D surface graph (C), and Perturbation model graph (D) for particle size analysis

Table 7: Optimized formula obtained from DOE

Number	Effect of polymer (PVA) concentration (P)	Effect of internal phase volume (I)	Particle size	Entrapment efficiency	Esirability	
1	0.636	12.500	291.585	98.404	0.920	
2	0.634	12.500	291.588	98.402	0.920	
3	0.638	12.500	291.580	98.406	0.920	
4	0.641	12.500	291.574	98.407	0.920	Selected

To derive a relation between the independent variables with particle size and entrapment efficiency of micro sponges, different mathematical models like linear, 2FI, Quadratic, and cubic were analyzed using the Design Expert software. The design fits the quadratic model from the ANOVA analysis for particle size and entrapment efficiency. The Model F-value of 8.67 implies the model is significant. The Lack of Fit F-value of 4.96 implies nonsignificant. The Model F-value of 34.38 implies the model is significant. The Lack of Fit F-value of 2.53 implies the Lack of Fit is not significant for entrapment efficiency. The equation in terms of coded factors is used to make predictions about the response for given variables. Here, the independent variable is coded as *A* for the effect of PVA concentration and code *B* is the effect of internal phase volume. The coded equation was used to make predictions about the response (particle size, drug entrapment efficiency, and drug loading capacity) based on the values of the independent variables (coded factors). The positive coefficient for PVA concentration (+10.26) suggests that an increase in PVA concentration leads to an increase in particle size and drug entrapment efficiency (+6.32).

On the other hand, the negative coefficient for internal phase volume (-1.77) implies that an increase in the internal phase volume decreases particle size. The same was explained using the model graph 1) Perturbation curve 2) 3D surface curve and 3) Predicted vs Actual curve (fig. 6). In the Predicted vs. Actual curve, most points fall on the straight line, confirming that particle sizes and drug entrapment efficiency are well-correlated with the independent variables. The perturbation curve represents the hyperbolic curve, indicating that particle size directly affects PVA concentration and is inversely related to internal phase volume. This may be due to the lesser availability of polymer to entrap the drug, and the increase in mean particle size is due to increasing PVA concentration. The observed change in particle size with the change in surfactant concentration was similar to related works published.

Regarding drug entrapment efficiency, both PVA concentration and internal phase volume depicted a positive response. The 3D surface curve represents a visual model of the perturbation curve, providing a more comprehensive understanding of the relationship between the variables and the response. The difference between Adjusted and predicted R-squared was 0.2 suggesting a good fit. No significant differences between the obtained and the expected values were observed using this model, which concluded that the model accurately predicted the entrapment efficiency and particle size using the experimental design mentioned. Formulation D4 resulted in significantly higher entrapment efficiency and smaller particle size compared with formulation D1-D3 and was selected for use in a further study to optimize Aceclofenac-loaded microsponge based on the desired criteria of particle size and maximum entrapment efficiency. Formulation composition containing–drug (2g): Ethylcellulose (0.25g): internal phase volume (12.500), PVA concentration (0.636-0.641), external phase volume (50 ml), external phase temperature (40 °C), external phase volume: internal phase volume (1:4), mixing speed (3000 rpm) successfully developed a microsponges formulation with optimal particle size and drug entrapment efficiency.

In vitro drug release studies

Batch-to-batch variations in dissolution profiles are tested statistically using DD Solver 2.0. The *in vitro* drug dissolution is carried out for 12h, and the amount of drug dissolved is analyzed.

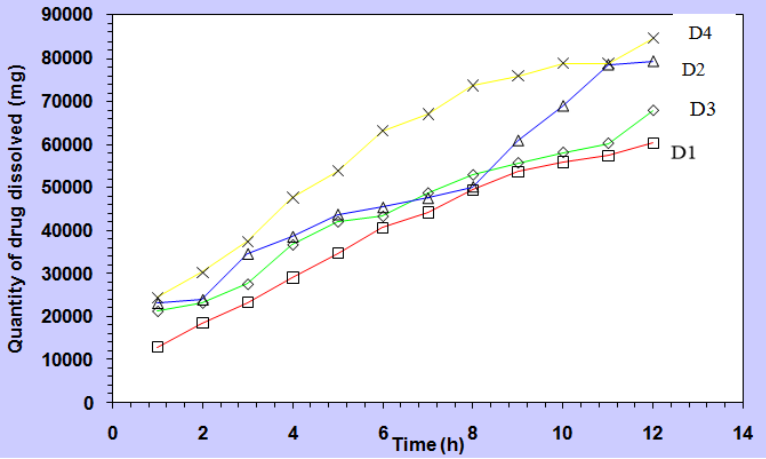


Fig. 7: *In vitro* drug release profile of AC-M batch (D1-D4), values represent mean (n=3)

The data showed that>80% of AC was released from Microsponge (D4) in 12 h compared to D3 (79.20%), D2 (67.79%), and D1 (60.17%) formulation. The release rate was further compared with the previously published report by Rahim H *et al.* fabricating AC-Nanocrystals and observed that>88% of Aceclofenac was released in the first ten minutes. Nanocrystals. The literature suggests that smaller particle size in nanosize increases the surface area thereby the dissolution is improved. Nanocrystals other than cubic are anisotropic showing different solubility in various directions along the crystal whereas Microsponges contain pores into which the drug molecule is entrapped. Aceclofenac drug exhibits polymorphism when condensed in water, heated, grinding in water, as well as suspended in water. Each polymorph may have distinct physical and chemical properties, including solubility and stability. It is also difficult to determine the crystal structure and molecular confirmations of different polymorphs of a single drug. Microsponges generally exhibited greater stability during storage compared to nanocrystals. The porous structure of microsponges protects the drug molecules from external factors, such as moisture and temperature fluctuations, which can degrade or alter the properties of the drug. The porous surface of the microsponge particles facilitated drug release based on concentration gradient and diffusion [25]. To facilitate application on the skin, the microsponges were incorporated into a hydrogel [26, 27].

Formulation of aceclofenac microsponge gel

The Microsponges were incorporated into the hydrogel to make it easier for application on the skin. However, it is also essential to have a dosage form that adheres to the skin and increases the residence time of Aceclofenac on the skin [28]. AC-M gel was obtained by the addition of 0.50 % Carbopol 972P.

Evaluation of aceclofenac microsponge gel

Gels were evaluated for their Clarity, pH, Viscosity, Extrudability, spreadability, Drug content, and *ex-vivo* permeation studies by using standard procedure.

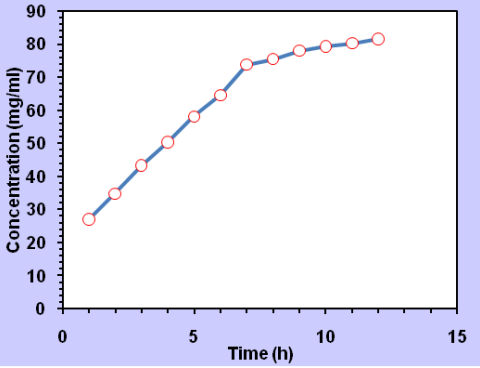
Table 8: Evaluation parameter of gel formulation

Formulation	Clarity	pH	Homogeneity	Viscosity (Cps)	Spreadability (Gm. Cm/Sec)	% drug content
MS_1	Clear	6.7	Good	5495±0.95	21.05±0.05	97.03±0.89
MS_2	Clear	6.8	Good	5890±0.73	16.00±0.35	95.18±0.75
MS_3	Clear	6.5	Good	6903±0.21	22.22±0.33	96.29±0.63
MS_4	Clear	6.8	Good	4105±0.56	26.66±0.68	99.88±0.41

Values represent mean±SD (n=3)

Ex-vivo permeation studies

The drug permeation profile (fig. 8) was obtained by placing optimized AC-M gel (Test formulation MS4) on the porcine membrane in the Franz diffusion cell.



Parameter	Unit	Value
Tmax	h	12
Cmax	mg/ml	81.62
Tlag	h	0
Clast_obs/Cmax		1
AUC 0-t	mg/mlh	706.12

Fig. 8: *Ex-vivo* permeation profile with reference product for M4 test formulation

According to the predicted values of the PK Solver, the maximum concentration of 81.62 mg/ml was attained at 12 h. This gives the impression that the prepared gel can sustain the release of a drug. Hence, the formulation MS4 of the drug (2g), ethyl cellulose (0.25g), internal phase volume (12.500), PVA concentration (0.636), external phase volume (50 ml) was found to be optimized, which suggests that AC-M gel has good topical application [29-31].

Surface morphology

SEM studies confirmed the sample had a porous and almost spherical nature. Scanning electron photomicrographs of Microsponges have provided additional evidence for the formation of smooth-surfaced micro-constructs with vesicular features and homogeneous size distribution.

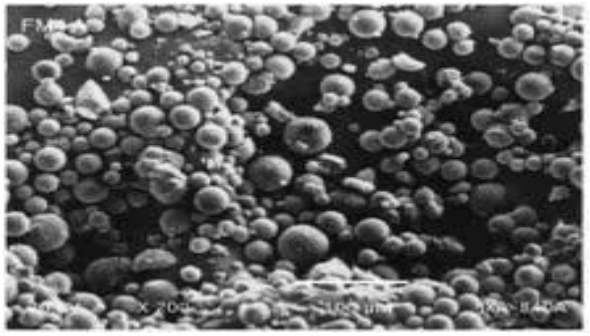


Fig. 9: SEM photograph of microsponge formulation with a magnification scale of 100 µm

These micro-constructs have unique properties due to their porous structure, which enables them to absorb or release substances effectively. In scanning electron photomicrographs, the smooth surfaces of the Microsponges are clearly visible. This suggests that the manufacturing process or synthesis method employed for their production resulted in a consistent and uniform surface texture. The vesicular features observed in the images indicate the presence of small, bubble-like structures within the Microsponges. These vesicles contribute to the material's porous nature and can be crucial for its desired properties. Additionally, the homogeneous size distribution seen in the photomicrographs implies that the Microsponges are relatively uniform in size. This uniformity is important for applications where precise control over particle size is required, such as in drug delivery systems, where it can affect the release rate or targeting efficiency [32].

Stability study of optimized formulation

After 30 d of storage, the Aceclofenac microsponge showed a decrease in particle size and entrapment efficiency. This reduction in particle size could be attributed to various factors, such as aggregation or fragmentation of the microsponge during storage. It is important to note that the specific reasons for this decrease would require further investigation. The stability studies of Aceclofenac Microsponges gel showed a small decline in drug content at 40 °C and 75% relative humidity. This finding suggests that the gel formulation may be sensitive to elevated temperature and humidity, leading to drug degradation or loss. The observations are shown in table 9.

Table 9: Stability study of optimized formulation

Factors evaluated	Before stability	After stability
AC-M	D4	D4
Particle size (nm)	101.8±0.34	111.8±0.44
Entrapment efficiency (%)	87.87±0.84	83.87±0.84
AC-M Gel	MS4	MS4
Drug Content(mg/ml)	83.88±0.21	78.90±0.18

ACM_ Aceclofenac microspongal gel, Batch MS4 subjected to stability studies, values represent mean±SD (n=3)

CONCLUSION

Transdermal therapy offers several advantages over medications with low oral bioavailability, including a larger skin surface area for drug absorption, non-invasiveness, avoidance of first-pass metabolism, reduced dose frequency, controlled drug distribution, and improved patient compliance. Microsponges were selected in this investigation due to their enhanced stability, reduced toxicity, and cost-effectiveness. Additionally, the microsponges exhibited increased superficial availability of Aceclofenac while reducing its permeation to the deeper layers of the skin. This selective drug release profile can be advantageous in targeting specific skin conditions or providing localized therapy. The study demonstrates the potential of microsponges loaded with Aceclofenac as a transdermal therapeutic option. The optimized formulation (D4) showed high entrapment efficiency, desirable particle size, and promising *in vitro* performance. Overall, this study focused on optimizing the formulation of microsponges for efficient dermal drug delivery, considering various critical variables and process parameters. The resulting optimized formulation demonstrated promising drug release and potential for the effective management of inflammation disorders.

ABBREVIATIONS

Non-steroidal anti-inflammatory drugs (NSAID), Rheumatoid arthritis (RA) Aceclofenac Microsponges (AC-M), Ethyl Cellulose (EC), Polyvinyl Alcohol (PVA), International Conference of

Harmonization (ICH), Quality by Design (QbD), Critical Quality Attributes (CQA), Critical Process parameters (CPP), Quality target product profiles (QTPP), Scanning Electron Microscopy (SEM), Design of Experiments (DoE).

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AUTHORS CONTRIBUTIONS

Rakhimol K: Methodology, Data curation, Writing-original draft, Prajitha Biju: Data curation, Investigation, Methodology, Writing-original draft, review and editing., Sindhoor S M: Investigation, Methodology, Natasha Naval Aggarwal: Writing-original draft, review and editing, Sandhya V: Methodology, Data curation, Deeksha Rai: Methodology, Data curation

CONFLICT OF INTERESTS

The authors declare there is no conflict of interest.

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