RESEARCH PAPER

Investigation Of Microsponges For Topical Delivery Of Halobetasol Propionate For The Management Of Psoriasis

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ABSTRACT: Halobetasol propionate (HBT) is a topical corticosteroid used to manage Psoriasis. The current studies investigate microsponges-loaded gels of Halobetasol propionate. The HBT Microsponge was prepared by QESD method. Based on a preliminary trial, the polymer, surfactant and plasticizer were selected respectively as Eudragit RS-100, Poloxamer 407 and Propylene glycol. Microsponge was optimized by Box-Behnken design by selecting independent factors the drug-to-polymer ratio (A), the concentration of surfactant (B), the concentration of plasticizer (C), and the Stirring speed (D). These parameters were chosen to investigate their impact on dependent parameters, including the percentage of encapsulation efficiency (%EE, Y1), particle size (Y2), and percentage yield (Y3). Optimized microsponge containing HBT was converted into gel employing HPMC K100M as gelling agent to impart viscosity to the preparation and maintain the drug's activity by extending residence duration. Optimized HBT loaded microsponge-gel evaluated for Spreadability, viscosity, pH, In vitro diffusion study, Ex vivo permeation study and stability study. %EE, Pa. size and % yield of optimized microsponge was found to be 84.87±0.87%, 89.58±1.99 micron, 93.65±0.47% respectively.The porous nature of microsponge structure was confirmed by SEM analysis. The Spreadability and viscosity of optimized microsponge-based gel (MSPG-2) was found to be 4.1±0.07 g.cm/sec and 9748±14.12 cps. respectively. The pH was found to be favorable to skin condition would not produce any skin irritation. The drug content of optimized gel was found to be 98.8±0.57%. From the in-vitro and ex-vivo drug diffusion study shows that at the end of 12 hours Microsponge loaded gel diffuse more through the membrane as compared to marketed formulation. The product was stable up to 3 months which is confirmed by stability study.

KEYWORDS: Microsponges, Halobetasol Propionate, Topical delivery, Box-Behnken design, Psoriasis

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INTRODUCTION:

Psoriasis is an autoimmune disease, characterized by marked epidermal proliferation with relapsing episodes of probably disabling inflammatory lesions and aberrant hyperkeratotic plaques.[1]

A microsponge delivery system is a uniform, spherical, porous, highly cross-linked polymeric microspheres or tiny sponge-like spherical particles with large porous surface.[1] They enhance stability, reduced side effects and modify drug release. It consists of micro-porous beads, typically 10-25 microns in diameter, loaded with active agents. Besides, they may enhance stability, modify drug release and reduce side effects favourably. Like a true sponge, each microsphere consists of a myriad of interconnecting voids of particles from 5-150µm within a non-collapsible structure, with a large porous surface.[2]

Microsponge systems are based on microscopic, polymer- based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated products such as a gel, cream, liquid or powder.

Microsponge drug delivery system can confer increased efficacy for topically active agents with

enhanced safety, improved aesthetic properties and extended product stability in a well-formed manner. A typical **25µm** sphere can have up to **2,50,000 pores** and providing a total pore volume of about **1ml/g** for extensive drug retention.[3]

Halobetasol Propionate is BCS Class II drug. These drugs often exhibit poor water solubility, limiting their availability for absorption. When used topically, the skin acts as a barrier, hindering drug penetration. There's a need to minimize systemic exposure while ensuring effective local drug delivery. Microsponges are sponge-like spherical particles with porous surfaces. They are designed to release drugs in response to external stimuli such as pH, temperature, or rubbing. Because of entrapment and adsorption of actives onto the polymeric cage, the release of actives is controlled over time. The porous structure facilitates drug penetration through the skin.[4] By localizing drug delivery, systemic exposure is minimized. Topical microsponges offer a promising approach for drug like Halobetasol Propionate, allowing targeted delivery while minimizing systemic exposure.[5-6]

MATERIALS AND METHODS:

Materials

Halobetasol Propionate was purchased from the Clickchem research lab., Ankleswar. Eudragit RS 100 was procured from Evonik Pharma. Ethylcellulose, chitosan, Polystyrene, Polyvinyl Alcohol, and PVP K 30 were procured from ChemDyes Chemical Ltd. Rajkot. Poloxamer 188 and Poloxamer 407 were procured from AnaChem Ltd. Dibutylphalathate, Polyethylene Glycol, and Propylene glycol were purchased from ChemDyes Chemical Ltd. Dichloromethane, Methanol, and Chloroform were purchased from AnaChem Ltd.

Methods

Solubility and Selection of Polymers:

For the selection of polymer various polymers like Eudragit RS100, Chitosan, Polystyrene and Ethylcellulose were taken. The solubility of polymers in different organic solvents were studied. The solubility study was done by quantitative method. In the fixed amount of solvent, (2 ml) polymers (1mg) were added until to get a saturated solution.[7]

Formulation of Microsponge by QESD Method and Preliminary trial for the selection of polymers:

To determine the most suitable polymers, trial batches of microsponges were formulated using Two distinct polymers: Eudragit RS 100 and Ethylcellulose based on solubility data of polymer. **Table:1** illustrates the composition for the preparation of Microsponge, wherein the drug-to-polymer ratio, concentration of surfactant, concentration of plasticizer, and speed remained constant. The Microsponge was fabricated employing the Quasi Emulsion solvent diffusion technique (QESD) and evaluated for parameters such as particle size, % yield and entrapment efficiency.[8]

Table:1 Preliminary trial for the selection of polymers

Batches	Drug: Polymer (mg)	Polymer	Surfactant PVA (%W/V)	Plasticizer Dibutylphalathate (%W/V)	Speed (RPM)
MSP-1	1:1	EUDRS-100	1	1	500
MSP-2	1:1	EC	1	1	500

Selection of Surfactant:

Polymeric surfactants are essential components in Microsponge formulation, playing a pivotal role in facilitating efficient drug encapsulation, improving drug solubility, regulating particle size, and fostering sustained release. To determine the most suitable surfactant, trial batches of microsponges were formulated using four distinct surfactants include Polyvinyl Alcohol (PVA), PVP K30, Poloxamer 188, and Poloxamer 407. **Table:2** illustrates the composition for the preparation of Microsponge, wherein the drug-to-polymer ratio, concentration of selected polymer, concentration of plasticizer, and speed remained constant. The Microsponge was fabricated employing the Quasi Emulsion solvent diffusion technique (QESD). Formulations incorporating these surfactants were meticulously evaluated for parameters such as particle size, % yield and entrapment efficiency.[9]

Table 2: Preliminary trial for selection of Surfactant

Batches	Drug: Polymer (mg)	Polymer	Surfactant (1 %W/V)	Plasticizer Dibutylphalathate (%W/V)	Speed (RPM)
MSP-3	1:1	EUDRS-100	PVA	1	500

MSP-4	1:1	EUDRS-100	PVP K 30	1	500
MSP-5	1:1	EUDRS-100	Poloxamer 188	1	500
MSP-6	1:1	EUDRS-100	Poloxamer 407	1	500

Selection of Plasticizer:

Plasticizers play a vital role in enhancing the flexibility and elasticity of the Microsponge matrix, crucial for maintaining its structural integrity. Furthermore, plasticizers can influence the release kinetics of the active ingredient. Additionally, plasticizers enhance drug encapsulation efficiency by fostering uniform dispersion within the Microsponge matrix, elevating drug-loading capacity and stability. Microsponges were prepared by utilizing variety of plastisizers examples Dibutylphalathate, Polyethylene Glycol, Propylene glycol, Triethyl Citrate with fixed drug to polymer ratio, surfactant and stirring speed. Evaluated for parameters such as %yield, particle size and entrapment efficiency. **Table:3** illustrates the composition for the preparation of Microsponge for selection of plastisizer.[10]

Table 3: Preliminary trial for selection of Plasticizer

Batches	**Drug: Polymer (mg)**	**Polymer**	**Surfactant (1 %W/V)**	**Plasticizer (1%W/V)**	**Speed (RPM)**
MSP-7	1:1	EUDRS-100	Poloxamer 407	Dibutylphalathate	500
MSP-8	1:1	EUDRS-100	Poloxamer 407	Polyethylene Glycol	500
MSP-9	1:1	EUDRS-100	Poloxamer 407	Propylene glycol	500
MSP-10	1:1	EUDRS-100	Poloxamer 407	Triethyl Citrate	500

Drug excipients compatibility by FTIR:

Identification Drug and compatibility studies of drug and excipient

To check the authenticity of API, drug was characterized by FTIR in which drug was mixed with the KBR in ratio of 1:1 and by using hydraulic press KBR disc prepared and analyse for FTIR spectra. The reference spectra were than compared with Sample spectra of Halobetasol.

Compatibility of Halobetasol Propionate, Eudragit RS-100, Poloxamer 407, Propylene glycol was recorded using FTIR **(**Nicolet 6700 model, Thermo Scientific) [11]

Optimization of HBT Microsponges by Box-Behnken Design:

several independent parameters: the drug-to-polymer ratio (A), the concentration of surfactant (B), the concentration of plasticizer (C), and the speed (D). These parameters were chosen to investigate their impact on dependent parameters, including the percentage of encapsulation efficiency (%EE, Y1), particle size (Y2), and percentage yield (Y3).[12] The factors with levels are shown in **Table:4**. The composition for the formulation of Microsponge using Box-Behnken Design give 24 batches which is shown in **Table:5.**

Table 4: Factors with level for optimization using Box-Behnken Design

Independent Parameters	**Levels**		
	-1	**0**	**+1**
Drug to Polymer ratio (mg) (A)	1:1	2:1	3:1
Concentration of Surfactant (%) (B)	0.5	1	1.5
Concentration of Plasticizer (%) (C)	0.5	1	1.5
Speed (RPM) (D)	400	600	800
Dependent Parameters	% Entrapment Efficiency (Y1) Particle Size (µm) (Y2) % Yield (Y3)		

Table 5: Composition for Optimization using Box Behnken Design

Batches	**Drug: Polymer (A)**	**Conc. Of Surfactant (%) (B)**	**Conc. Of Plasticizer (%) (C)**	**Speed (RPM) (D)**
MSP-11	2	0.5	1	800
MSP-12	1	1	1	400

Batches	Drug: Polymer (A)	Conc. Of Surfactant (%) (B)	Conc. Of Plasticizer (%) (C)	Speed (RPM) (D)
MSP-13	3	0.5	1	600
MSP-14	3	1	1.5	600
MSP-15	3	1.5	1	600
MSP-16	1	1.5	1	600
MSP-17	3	1	1	400
MSP-18	2	1	0.5	800
MSP-19	2	1.5	1	400
MSP-20	1	0.5	1	600
MSP-21	1	1	1.5	600
MSP-22	3	1	1	800
MSP-23	2	1.5	1	800
MSP-24	2	1.5	0.5	600
MSP-25	1	1	1	800
MSP-26	2	1	1.5	400
MSP-27	2	0.5	1.5	600
MSP-28	3	1	0.5	600
MSP-29	1	1	0.5	600
MSP-30	2	0.5	0.5	600
MSP-31	2	1	0.5	400
MSP-32	2	0.5	1	400
MSP-33	2	1	1.5	800
MSP-34	2	1.5	1.5	600

%EE:

The entrapment efficiency was assessed by processing a Microsponge (equivalent to 10mg of HBT). The Microsponge was weighed, crushed using a mortar and pestle, and dissolved in 10 ml of methanol. The solution was then filtered using Whatman filter paper, and the concentration of HBT was analyzed via UV-visible spectroscopy at 238 nm.[13]

$$\%\ Entrapment\ Efficiency = \frac{Experimental\ Amount\ of\ HBT}{Theorotical\ Amount\ of\ HBT}\ X\ 100$$

Particle Size Analysis:

Particle size of all the prepared batches of microsponge was determined using optical microscopy at 10X and 40X. The microsponges were placed on glass slide and observe under optical microscope with calibrated eyepiece. The size of 50-100 microsponges was measured using optical microscope. Then the Average particle size was calculated.[14]

Determination of production yield:

The production yield of the Microsponge was assessed by precisely calculating the initial weight of the raw materials and comparing it to the final weight of the obtained Microsponge. It can be calculated by following the formula.[15]

$$\%\ Production\ Yield = \frac{Practical\ Mass\ Of\ Microsponge}{Theorotical\ Mass\ of\ solid\ component}\ X\ 100$$

Checkpoint batch analysis:

Two checkpoint batches were prepared and assessed, with the observed values compared to the predicted values.

Optimization using the desirability function :

Optimization was conducted to determine the optimal levels of independent variables (A, B, C, and D) for achieving %EE, %Yield, and particle size data. During the formulation development stage, the responses were consolidated to design a product with the desired attributes. The primary role of the desirability function was to integrate all responses into a single experiment and predict the likelihood of achieving the highest levels for the independent variables.[16]

SEM of Optimized batch:

To observe the surface morphology optimized batch of Microsponge subjected to SEM analysis. The surface morphology shows the porous structure of Microsponge.

Formulation of Optimized Microsponges loaded Topical Gel:

Dose calculation and formulation of Microsponge-loaded gel:

- Optimized formulation contains Drug: Polymer ratio 2.15:1 (215 mg: 100 mg)
- It means the final formulation contains 215 mg HBT, 100 mg of Eudragit RS 100, 1.08 gm of poloxamer 407, and 1.5 gm of PG in 100 ml of solution.
- Theoretical yield is 2.895 gm.
- Based on the % yield (93.65%), the final weight of product is 2.711 gm.
- Based on the %EE (84.87%) it was observed that in the 2.711 gm of Microsponge, 182 mg of HBT present.
- For the preparation of gel 0.05% W/W of Microsponge loaded gel, 744 mg of Microsponge (50 mg of HBT) was used for 100 gm gel base.
- The Microsponge-based hydrogel (20gm) was constructed using the HPMC K100M gel matrix.
- The hydrogel was gradually combined with the 0.14 gm of Microsponges (10 mg HBT) while stirring. Ensure that the microsponge particles are evenly distributed throughout the gel by continuous stirring.
- The hydrogel was than filled in to collapsible tube.
- To get a suitable viscosity of Microsponge-based gel, several concentrations (1, 1.5, and 2%w/w), and the final concentration was chosen based on viscosity and Spreadability

Table 6: Composition of Microsponge loaded Gel

Ingredients	MSPG-1	MSPG-2	MSPG-3
Microsponge (10 mg HBT) (gm)	0.14	0.14	0.14
HPMC K 100 M (%)	1	1.5	2
Water (ml)	q. s	q. s	q. s

Evaluation Parameters of Microsponges loaded gel [16-18]

Viscosity and pH:

The viscosity was measured using a Digital viscometer. To determine the viscosity of microsponge-loaded gel, the spindle number 4 was dipped in the preparation and revolved at room temperature at 5, 10, 20, and 50 rpm. 100 g of microsponge-loaded gel was poured in a 250 ml beaker for viscosity measurement, and the viscosity was measured using Spindle number SPL4.

A digital pH meter was used to determine the pH. A microsponge-based gel (2.5 g) was precisely weighed and dispersed in 25 ml of distilled water. Before each usage, the pH meter was calibrated with buffer solutions of pH 4.0, 7.0, and 9.0. The pH of the formulation was measured in triplicate, and mean values were derived**.**

Spreadability test:

The two glass slides (10×10 cm) were placed in this apparatus. 0.5gm sample was kept in glass slides. 100 gm weight kept on upper slide and measure the diameter or length which was of pre-marked circle. The time required to spread the sample was recorded.[17]

Formula-

$S=MxL/T$

Where,

M= weight, L=length or diameter, T=time

Drug Content:

A Microsponge-based gel containing 10 mg of HBT was placed in a 10 ml volumetric flask with 5 ml methanol and agitated for 30 minutes. Methanol was used to make a volume of 10 ml. To get 10 µ/ml, 0.1 ml of the mentioned solution was diluted with 10 ml of methanol. The resulting solution was filtered using Whatman filter paper, and its absorbance at 238 nm was measured with a UV spectrophotometer.[18]

Comparison of In vitro drug permeation of optimized microsponge-based gel and HBT-Marketed gel:

The *in-vitro* drug permeation experiments were carried out utilizing a Franz diffusion cell and cellophane paper. The water jacketed recipient compartment held a total of 25 ml and featured two arms, one for sampling and the other for a thermometer. The interior diameter of the donor chamber was 2 cm. The donor compartment was positioned such that it only contacts the diffusion medium in the receptor compartment. The receptor compartment was filled with phosphate buffer saline (PBS) and kept at 37°C±1°C with 100 rpm stirring. The donor compartment was then treated with 1g of optimized microsponge gel containing HBT. At regular intervals, 1 ml of receptor medium was removed and the same amount of pure medium was immediately

introduced to the receptor compartment. The treatment was repeated for a total of 12 hours. All samples were filtered using Whatman filter paper and examined using a UV spectrophotometer set to 238 nm. The same procedure was performed for marketed HBT-gel (Psoricort H) 0.05%W/W.

Ex-Vivo Drug Permeation Study of Optimized Microsponge Based Gel:

Goat Skin was used for an Ex-vivo permeation of drugs from HBT-gel formulations. Skin thickness ranged from 0.28 to 0.06 mm on average. The open-ended diffusion was positioned with the stratum corneum facing the donor compartment and the dermal side facing the receiver compartment after the skins had hydrated for an hour. Same procedure followed as In vitro drug permeation of HBT-microsponge based gel.

Stability study:

The optimized microsponge-loaded gel was filled in to the collapsible tube and stored at 40℃± 1℃ and 75%RH for 3 months and samples were evaluated for physicochemical parameters like viscosity, Spreadability and drug content at 1 month interval.[18]

RESULT AND DISCUSSION:

Solubility of polymer:

Based on the solubility data presented in **Table:7**, it was noted that chitosan and polystyrene were insoluble in dichloromethane (DCM), methanol, and chloroform. Conversely, Eudragit RS 100 and Ethylcellulose demonstrated solubility in methanol and DCM, respectively. Eudragit RS 100 polymer has been extensively utilized for topical applications in numerous studies, and the FDA has approved polymethacrylates as safe and nontoxic polymers. So, Ethylcellulose and Eudragit RS 100 were selected as a polymer for the preparation of Microsponge.

Table:7 Solubility study of polymer

Solvents	Eudragit RS100	Chitosan	Polystyrene	Ethylcellulose
Dichloromethane	Sparingly Soluble	Not Soluble	Not Soluble	Soluble
Methanol	Soluble	Not Soluble	Not Soluble	Not Soluble
Chloroform	Not Soluble	Not Soluble	Sparingly Soluble	Soluble

Result for Selection of polymers for the preparation of Microsponge :

Based on the solubility data, Eudragit RS 100 and Ethylcellulose emerged as preferred polymers for the formulation of Microsponge. Analysis of the data presented in **Table:8** revealed that batch MSP-1 exhibited superior values for percentage encapsulation efficiency (%EE), percentage yield, and smaller particle size compared to MSP-2. Consequently, Eudragit RS-100 was selected as the polymer of choice for the Microsponge formulation

Table:8 Result of trial batches for selection of polymer

Batches	%EE	%Yield	Particle size
MSP-1	**68±0.54**	**70.4±0.47**	**212±1.71**
MSP-2	58±0.74	64.9±0.98	298±1.96

(Mean±SD, N=3)

Result for Selection of Surfactant:

Based on the data presented in **Table:9**, it was noted that MSP-6 exhibited the highest entrapment efficiency among all formulations, accompanied by the smallest particle size. Surfactants play a crucial role in particle size regulation; thus the selection criterion was based on achieving the minimum particle size. Consequently, Poloxamer 407 was chosen for subsequent processing steps.

Table:9 Result of trial batches for selection of Surfactant

Batches	%EE	%Yield	Particle size
MSP-3	55±0.88	71.5±0.97	210±1.42
MSP-4	57±0.56	73.6±0.35	345±1.65
MSP-5	59±0.43	70.4±0.73	225±1.78
MSP-6	**60±0.97**	**75.2±0.48**	**179±1.25**

(Mean±SD, N=3)

Result for Selection of Plasticizer:

As the concentration of the plasticizer increased, the plasticizer was selected based on achieving the highest percentage of encapsulation efficiency (%EE). Analysis of the results presented in the **Table:10** indicated that Propylene glycol exhibited the highest %EE of **68±0.74**% with a smaller particle size than other plasticizers. Therefore, Propylene glycol was identified as the most effective plasticizer among those tested.

Table:10 Result of trial batches for selection of Plasticizer

Batches	%EE	%Yield	Particle size
MSP-7	59±0.54	64.2±0.47	181±1.10
MSP-8	58±0.74	74.1±0.98	298±0.78
MSP-9	**68±0.74**	**78.5±0.32**	**185±2.85**
MSP-10	63±0.64	68.2±0.84	211±1.74

(Mean±SD, N=3)

Result for Drug Excipients Compatibility Study:

The FTIR spectrum of HBT and excipients was shown in **Figure. 1** and the interpreted data was depicted in **Table:11**. All major peaks available in spectrum confirm the availability of characteristic functional groups in molecule. Hence the API sample was found to be Halobetasol Propionate and the selected excipients were compatible with drug sample.

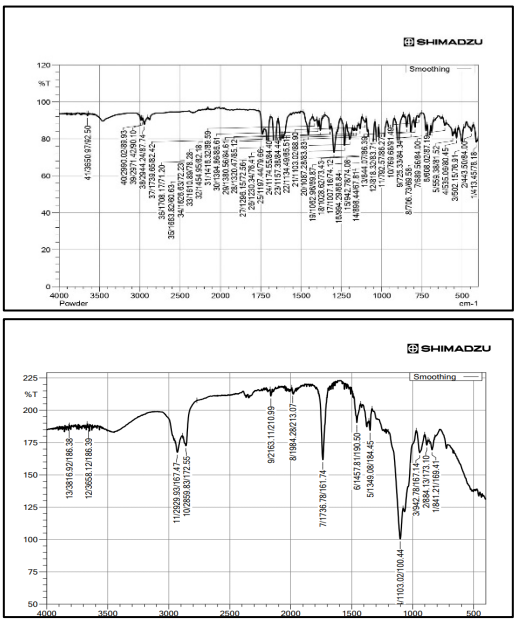


Figure:1 FTIR spectra of pure drug and drug with excipients

Table:11 FTIR interpretation data of drug and drug with excipients

Functional Group	HBT Spectra (cm-1)	MIXTURE
C=O STRECTHING	1739	1736.14
C=C STRECTHING	1610	1610.74
O-H STRETCHING	3650	3658.12
C-F STRETCHING	1394	1349.08

Optimization of Formulation:

Twenty-four batches were formulated using different combinations recommended by the Box-Behnken design. According to the data presented in **Table:12** the encapsulation efficiency (% EE) ranged from 60±0.47 to 92±0.22, the yield (%) varied between 63.9±0.15 and 96.3±0.57, and the particle size ranged from 85±1.25 to 163±0.98. Additional regression analysis was conducted using analysis of variance (ANOVA). This analysis examined the interaction effects between variables, and graphical presentations were generated to comprehend whether these effects were positive or negate

Table:12 Observation of prepared batches as per Box-Behnken design

Batches	Drug: Polymer (A)	Conc. Of Surfactant (%) (B)	Conc. Of Plasticizer (%) (C)	Speed (RPM) (D)	% EE (Y1)	Particle Size (µ) (Y2)	%Yield (Y3)
MSP-11	2:1	0.5	1	800	80±0.81	90±1.25	86.5±0.25
MSP-12	1:1	1	1	400	65±0.43	153±1.23	78.4±.047
MSP-13	3:1	0.5	1	600	74±0.33	142±1.45	71.5±0.82
MSP-14	3:1	1	1.5	600	78±0.57	126±1.36	70.8±0.64
MSP-15	3:1	1.5	1	600	73±0.34	150±1.58	71.9±0.42
MSP-16	1:1	1.5	1	600	64±0.24	149±1.63	65.7±0.67
MSP-17	3:1	1	1	400	73±0.61	152±0.45	70.9±0.24
MSP-18	2:1	1	0.5	800	84±0.47	85±1.25	95.4±0.67
MSP-19	2:1	1.5	1	400	91±0.49	170±1.36	83.8±0.43
MSP-20	1:1	0.5	1	600	65±0.38	140±1.84	63.9±0.15
MSP-21	1:1	1	1.5	600	69±0.67	123±0.36	66.2±0.54

MSP-22	3:1	1	1	800	74 ±0.57	85± 1.25	70.8 ±0.84
MSP-23	2:1	1.5	1	800	81 ±0.14	98± 1.74	87.7 ±0.91
MSP-24	2:1	1.5	0.5	600	92 ±0.12	145 ±1.65	89.8 ±0.45
MSP-25	1:1	1	1	800	65 ±0.68	85± 1.89	74.2 ±0.27
MSP-26	2:1	1	1.5	400	85 ±0.52	151 ±1.47	91.5 ±0.46
MSP-27	2:1	0.5	1.5	600	80 ±0.47	140 ±1.22	84.6 ±0.18
MSP-28	3:1	1	0.5	600	71 ±0.63	125 ±1.11	70.4 ±0.34
MSP-29	1:1	1	0.5	600	60 ±0.47	124 ±1.05	65.8 ±0.76
MSP-30	2:1	0.5	0.5	600	80 ±0.48	141 ±0.45	87.6 ±0.43
MSP-31	2:1	1	0.5	400	85 ±0.54	152 ±0.78	92.8 ±0.45
MSP-32	2:1	0.5	1	400	80 ±0.14	163 ±0.98	85.9 ±0.53
MSP-33	2:1	1	1.5	800	84 ±0.52	86± 1.54	96.3 ±0.57
MSP-34	2:1	1.5	1.5	600	92 ±0.22	148 ±1.47	95.4 ±0.61

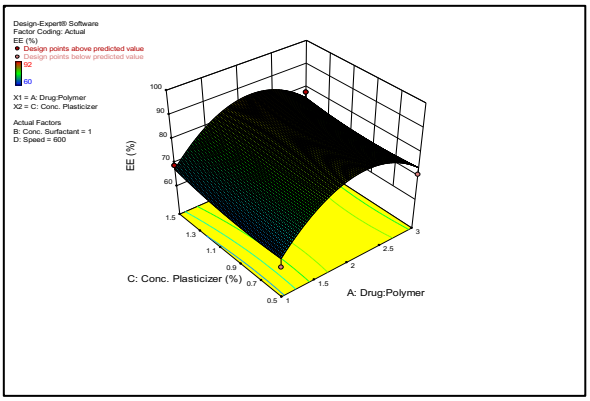
(Mean±SD, N=3)

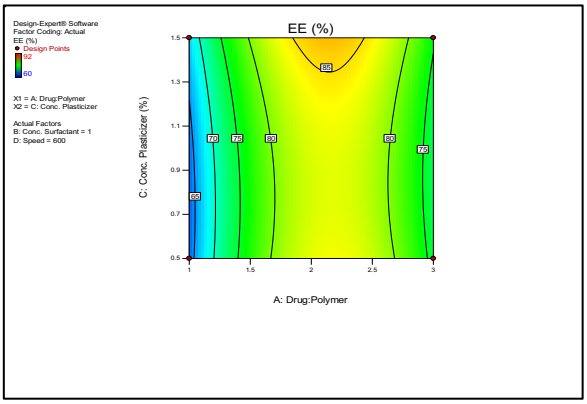
Regression Analysis:

For the Entrapment efficiency (%EE), the model's scientific significance was confirmed by an F-value of 9.15 In this model, terms A, B, and A^2 were identified as scientifically significant. Values greater than 0.1000 indicate a lack of scientific meaning. The adjusted R-squared value is 0.8216, while the predicted R-squared value is 0.8564. The difference between the adjusted and predicted R-squared values is less than 0.2, indicating reasonable agreement. Additionally, a signal-to-noise ratio greater than 4, which was 09.4, was achieved, supporting the utilization of the suggested model to operate within the design space

Polynomial equation for %EE

$$Y1 = +83.00 + 4.58 * A + 2.38 * B + 1.33 * C - 0.92 * D + 0.00 * AB - 0.50 * AC + 0.25 * AD + 0.00 * BC - 2.50 * BD + 0.00 * CD - 14.50 * A^2 + 0.63 * B^2 + 1.62 * C^2 + 0.00 * D^2$$





(A)

(B)

Figure:2 For % Entrapment Efficiency (A) 3-D response surface plot (B) Contour Plot

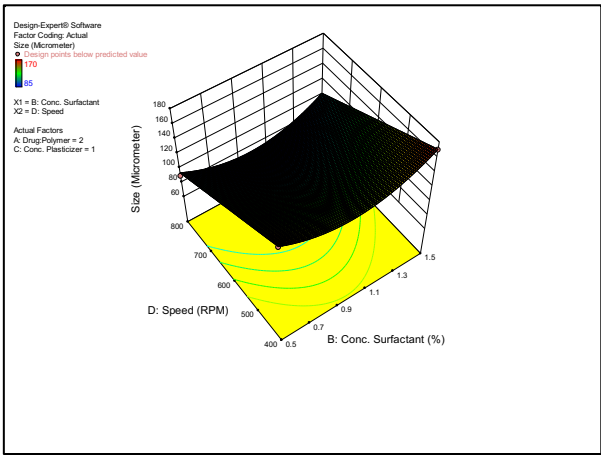
For the Entrapment efficiency (%EE), The relationship among factors influencing %EE was elucidated through a three-dimensional response surface plot and contour plot. It was noted that with an increase in the drug-to-polymer ratio, the entrapment efficiency (EE) also rises, up to a certain threshold. However, beyond this point, the entrapment efficiency begins to decline. This phenomenon is likely attributed to the reduced availability of polymer to effectively entrap the drug. The impact of plasticizer concentration was examined, revealing that as the concentration of plasticizer increases, there is a corresponding increase in entrapment efficiency. This phenomenon can be

attributed to the enhanced flexibility imparted to the Microsponge by the presence of the plasticizer

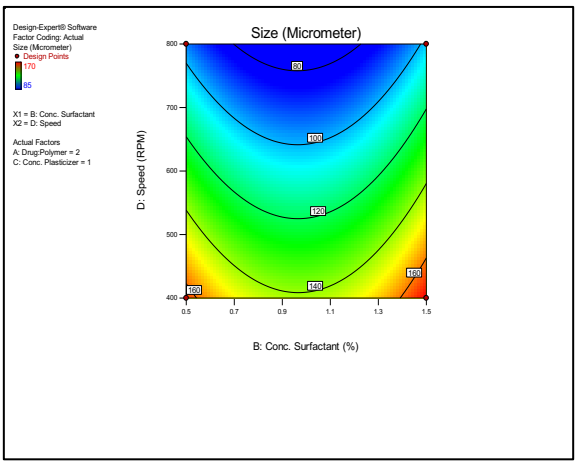
For particle size (Y2), The model's scientific validity was affirmed by an F-value of 106.13. Within this model, terms B, D, A^2, B^2, and C^2 were determined to be scientifically significant. Values exceeding 0.1000 signify a lack of scientific relevance. The "adjusted R-squared" value stands at 0.9834, while the "predicted R-squared" value is 0.9586. The discrepancy between the adjusted and predicted R-squared values is below 0.2, indicating reasonable consistency. Furthermore, a signal-to-noise ratio exceeding 4, recorded at 33.15, was attained, endorsing the use of the proposed model within the designated design parameters.

The polynomial equation for Particle size

$$Y2 = +107.25 + 0.50 * A + 3.67 * B + 0.17 * C - 34.33 * D - 0.25 * AB + 0.50 * AC + 0.25 * AD + 1.00 * BC + 0.25 * BD + 0.50 * CD + 10.50 * A^2 + 25.75\ B^2 + 9.50\ C^2 + 0.00D^2$$



(A)



(B)

Figure 1: For particle size (A) 3-D Response Surface Plot (B) Contour Plot

For particle size (Y2), it was observed that Lower concentrations of surfactant may result in larger particle sizes due to reduced stabilization of the dispersed phase. As the concentration of surfactant increases, it can lead to finer particle sizes by enhancing the stabilization of the dispersed phase and preventing aggregation. There might exist an optimum concentration of surfactant where the particle size of Microsponge is minimized. At this concentration, the surfactant molecules effectively coat the surface of the microspheres, preventing excessive aggregation while minimizing particle size. Beyond a certain concentration, further increases in surfactant concentration may not significantly affect the particle size, as the system becomes saturated with surfactant molecules. In the case of Speed, as the speed of rotation increases the particle size decreases.

For %Yield of Microsponges,

The scientific validity of the model was confirmed by an F-value of 22.03. In this model, terms A and A^2 were identified as scientifically significant. Values surpassing 0.1000 suggest a lack of scientific relevance. The "adjusted R-squared" value is 0.9224, while the "predicted R-squared value" stands at 0.8057. The difference between the adjusted and predicted R-squared values is less than 0.2, indicating reasonable consistency. Moreover, a signal-to-noise ratio exceeding 4, reaching 12.83, was achieved, supporting the utilization of the proposed model within the specified design parameters.

The polynomial equation for % Yield

$$Y3 = +89.92 + 2.94 * A + 1.19 * B + 0.23 * C + 0.88 * D - 0.35 * AB + 0.05 * AC + 0.27 * AD + 2.15 * BC + 0.83 * BD + 0.55 * CD - 21.74 * A^2 - 2.11 * B^2 + 1.90C^2 + 0.00D^2$$

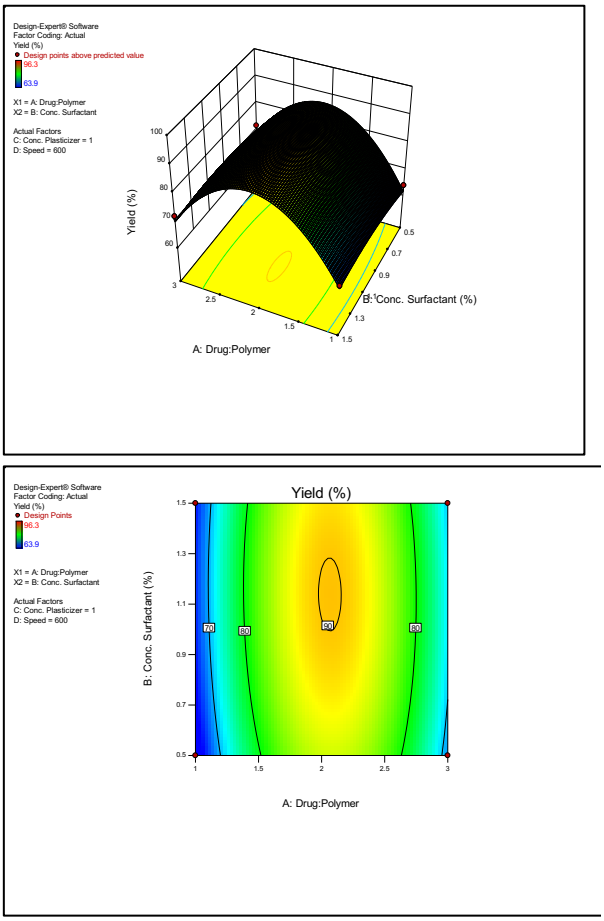


Figure 2: % yield (A) 3-D response surface plot (B) Contour plot

For % Yield (Y3) a gradual increase in % yield as the drug-to-polymer ratio rises. However, beyond an optimal point, further increases in the ratio lead to a decline in % yield. This decline is attributed to the limited capacity of the polymer to accommodate higher drug concentrations. Moreover, increasing the concentration of surfactant did not show any significant impact on % yield.

Checkpoint Batch Analysis

Examination of the data from **Table:13** indicated that the observed values align reasonably well with the predicted values.

Table:13 Checkpoint Batches results

Batches	Factor A	Factor B	Factor C	Factor D	Y1		Y2		Y3	
					Predicted	Observed	Predicted	Observed	Predicted	Observed
MSP-35	1.50	0.75	0.75	500	75.33	74.87±0.25	134.	138.47±1.25	82.67	80.47±0.68
MSP-36	2.50	1.25	1.25	700	83.16	81.56±0.41	104.25	110.54±1.47	87.92	85.96±0.36

Optimized batch using desirability function

To get the optimized product of Microsponge desirability function was utilized. The criteria were provided to the software to get optimized batch. Based on the criteria like Maximum %EE Minimum particle size and maximum % Yield, the desirability of 0.905 was found.

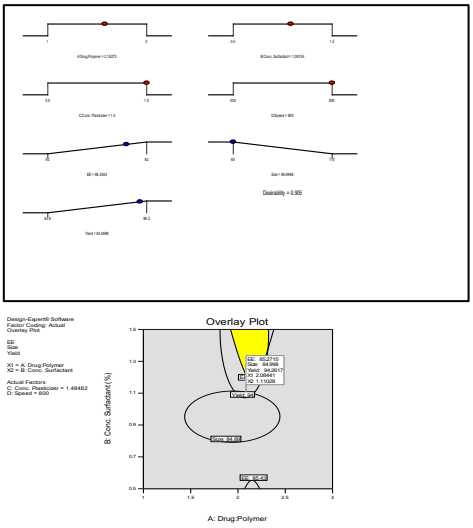


Figure:5 Optimized batch as per DOE

Batches	Factor A	Factor B	Factor C	Factor D	Y1 (% EE)		Y2 (Pa. Size) (µm)		Y3 (% yield)	
					Predicted	Observed	Predicted	Observed	Predicted	Observed
MSP-37	2.15	1.08	1.5	800	85.43	84.87±0.87	84.89	89.58±1.99	94.0	93.65±0.47

Table:14 Composition and results of Optimized batch of HBT- microsponges

(Mean±SD, N=3)

SEM of optimized batch

The Microsponge appears as a spherical object with a rough and porous surface. There are several small indentations and protrusions on the surface, which are characteristic of the porous nature of Microsponge

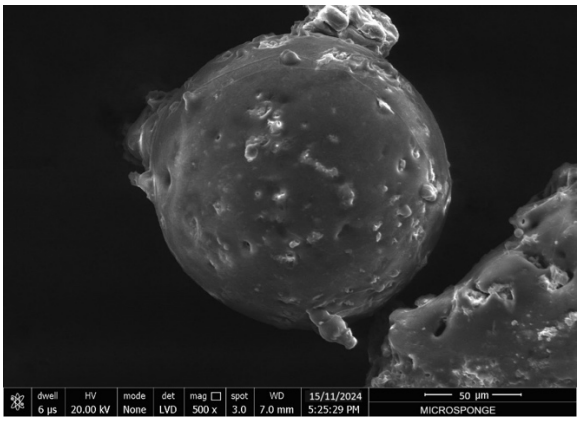


Figure:6 SEM Image of Microsponge

Result of Final optimized microsponge-based gel:

Evaluation of optimized gel:

For the preparation of microsponge-gel, optimized batch of HBT-microsponge (MSP-37) loaded into gel base containing HPMC K100M in three different concentrations (1, 1.5, and 2%w/w) formulated three batchs of HBT loaded microsponge-gel. it was observed that as the concentration of HPMC K100M increases the Spreadability decreases and the viscosity increases. Viscosity is resistance to flow, which is an important physicochemical property for topical preparations because it influences spreadability and drug release as well as jellification. Spreadability is shown as index of ease of application. The delivery of the correct dose of the drug depends highly on the spreadability of the formulation. The Spreadability and viscosity of optimized microsponge-based gel (MSPG-2) was found to be 4.1±0.07 g.cm/sec and 9748±14.12 cps. respectively. The pH was found to be favorable to skin condition would not produce any skin irritation. The drug content of optimized gel was found to be 98.8±0.57%. The results of drug content showed an appropriate selection of polymer, surfactant, and plasticizer

Comparison of In-vitro drug permeation study of optimized microsponge gel, marketed gel, and Ex-vivo drug permeation study of optimized gel:

Figure 7 shows the comparison of in vitro permeation of the produced optimized batch of HBT microsponge gel with marketed gel (Psoricort H) 0.05%W/W. and Ex-vivo permeation of produced optimized batch of HBT microsponge gel. After 12 h shows drug release 82.49±0.64%,46.82±0.07% and 80.14±0.73% respectively. Thus, prepared optimized formulations was detected with good in-vitro diffusion as compared to marketed. This is due to incorporation of surfactant and co-surfactant in the formulations.

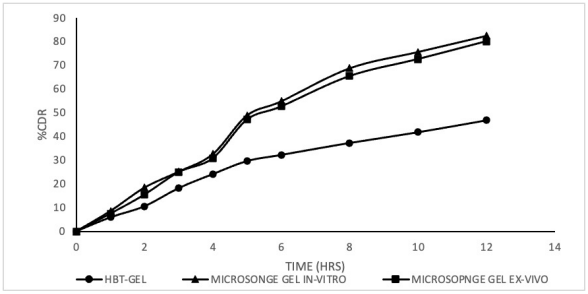


Figure 7: In-vitro and Ex-vivo Drug permeation study

Stability of Microsponge loaded Gel:

Optimized formulation of microsponge loaded gel (MSPG-2) was examined for accelerated stability. Finally, after 3 months of accelerated stability study, developed optimized formulation of HBT microsponge-gel detected with good stability and did not show any major change in Spreadability, drug content and Viscosity.

CONCLUSION

The HBT Microsponge was prepared by QESD method. From the Preformulation study Eudragit RS-100 as polymer, Poloxamer 407 as surfactant and Propylene glycol as plasticizer were selected. The formulation was optimized by using Box-Behnken design using DOE software. The optimized batch of Microsponge was selected based on the desirability 0.905 The optimized formulation contains 2.15:1 drug to polymer ratio, 1.08 % poloxamer and, 1.5% PG with rotation speed 800 rpm. The optimized batch MSP-37 was characterized by SEM which shows porous structure of Microsponge. The optimized batch was than loaded in Hydrogel with various concentration of HPMC K 100 M Based on the visual inspection MSPG-2 was selected which having optimum concentration of (1.5 %) HPMC K 100 M. The MSPG-2 was than evaluated for viscosity, Spreadability, pH and drug content. From the in-vitro and ex-vivo drug diffusion study shows that at the end of 12 hours Microsponge loaded gel diffuse more through the membrane as compared to marketed formulation. The product was stable up to 3 months which is confirmed by stability study.

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