RESEARCH ARTICLE

Optimization of Clotrimazole-Loaded Ethyl Cellulose and Natural Gum Facilitated Microsponges: Formulation and Characterization

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ABSTRACT

This study aimed to optimize Clotrimazole-loaded microsponges using a 4^2factorial design, incorporating ethyl cellulose and natural gum derived from *Onosma Bracteatum* leaves. The microsponges were formulated using an emulsion solvent diffusion method, with ethyl cellulose concentration and natural gum concentration as independent variables. DSC and FTIR spectroscopy confirmed that clotrimazole has good compatibility with excipients and excellent interactions and stability. Spherical microsponges were seen to have a porous surface using scanning electron microscopy. The optimized formulation demonstrated a particle size of 74.55 ± 1.07 µm, entrapment efficiency of 62.52 ± 1.84 %, and % yield of 52.63 ± 1.13. A design of experiments (DOE) approach identified significant model terms, enabling predictive optimization through mathematical models and visual analysis via contour and 3D plots. The optimized microsponges demonstrated extended drug release, achieving 86.44% release over 10 hours with gum incorporation, compared to 76.85% without gum. This sustained release was attributed to non-collapsible structural formations. These findings underscore the potential of clotrimazole-loaded microsponges as an effective platform for sustained drug delivery. This research highlights the potential of combining ethyl cellulose and natural gum in microsponge formulation for enhanced drug delivery of Clotrimazole, offering a promising approach for topical antifungal therapy.

Keywords: Clotrimazole, Microsponges, Topical Drug Delivery, design of experiment, *Onosma bracteatum*

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INTRODUCTION

The potential of topical drug delivery systems (TDDS) to treat localized conditions while reducing systemic side effects has led to their considerable popularity in contemporary medicine. These systems are designed to administer therapeutic chemicals directly to the skin or mucosal surfaces, making them particularly effective for treating dermatological issues, localized infections, and inflammatory diseases. Topical medication administration has many benefits over systemic approaches, which is why it is becoming more and more common in clinical practice.[1] Topical Drug Delivery Systems (TDDS) offer several advantages, including: reduced systemic side effects, improved localized treatment[2,3], increased patient compliance[4], faster onset of action[5,6], and minimal drug degradation.[7,8] These systems deliver drugs directly to the site of action, reducing the risk of side effects linked to systemic absorption.[9] They also provide greater medication concentrations at the intended location, which is beneficial for diseases like psoriasis, eczema, and fungal infections.[2,3] Topical formulations are often easier to apply and follow, making them more likely to be followed. TDDS also offer a faster onset of action, especially in urgent situations requiring quick relief.[5,6] Topical formulations also protect sensitive active pharmaceutical ingredients (APIs) from degradation during systemic circulation, preserving their efficacy.[7,8] TDDS can be customized to meet unique treatment demands and patient preferences, offering a variety of forms to meet individual treatment needs.[7,10] Microsponges are a novel drug delivery system that can be customized to meet specific treatment needs and patient preferences. They can be manufactured in various forms, such as gels, creams, ointments, and patches.[11,12] Microsponges have a controlled release mechanism, preserving medication levels at the site of action, reducing the need for repeated administrations and enhancing patient adherence.[2] Their porous shape expands the surface area for drug absorption, potentially improving the bioavailability of medications that are not very soluble.[13] Encapsulated drugs in micro sponges can also minimize skin irritation, making them ideal for long-term treatment or sensitive skin.[14] The versatility in formulation allows for the use of different polymers, such as natural gums and synthetic compounds like ethyl cellulose, to create formulations that address various skin types and ailments.[15,16] Additionally, micro sponges can be used to co-encapsulate multiple drugs, enhancing therapeutic efficacy and reducing resistance, particularly in the treatment of infections.[15,16] The imidazole class of antifungals includes the broad-spectrum antifungal drug clotrimazole. It is mostly used to treat a variety of superficial fungal infections, such as those brought on by yeasts, dermatophytes, and certain moulds.[17,18] By preventing the production of ergosterol, a

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crucial part of fungal cell membranes, clotrimazole damages the integrity of the cell membrane and causes cell death. Because of its mode of action, it effectively combats a variety of fungal infections, such as Microsporum canis, Trichophyton rubrum, and Candida albicans.[17,18]

Clotrimazole is used for treating various skin infections, including dermatophyte-caused infections like jock itch, ringworm, and athlete's foot, Candida species-caused infections like oral thrush and vaginal yeast infections, and tinea versicolor, a skin disorder caused by Malassezia yeast excess.[18,19] Improved clotrimazole formulations are needed to enhance effectiveness and patient compliance. Techniques include nanoparticle delivery systems, microsponges with sustained release, combination therapies, and patient-centric formulations.[19] Nanoparticles increase solubility and bioavailability, microsponges reduce application frequency, and combination therapies lower resistance. Patient-centric formulations, such as gels or patches, can reduce side effects and enhance therapeutic results.[18,19] Ethyl cellulose (EC) is a popular polymer in

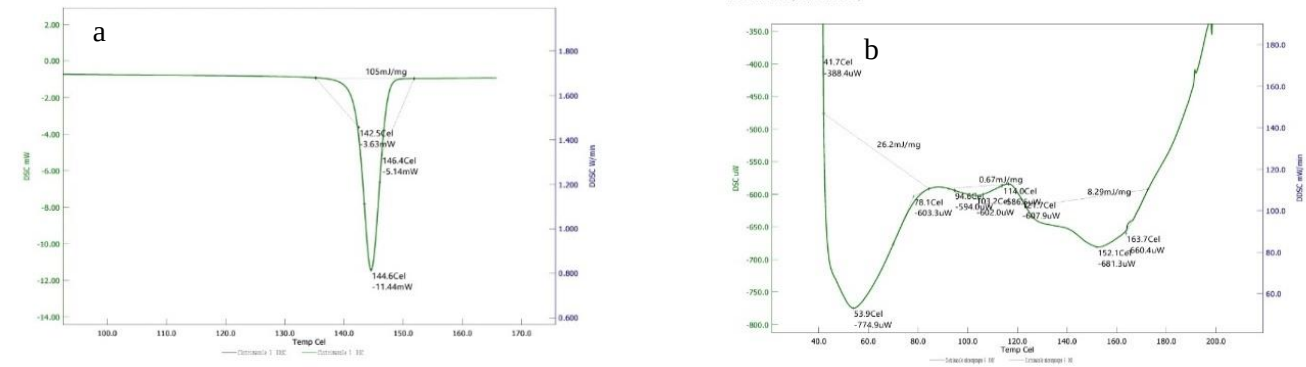

Figure1: DSC thermograms of clotrimazole individually (a) and along with excipients (b)

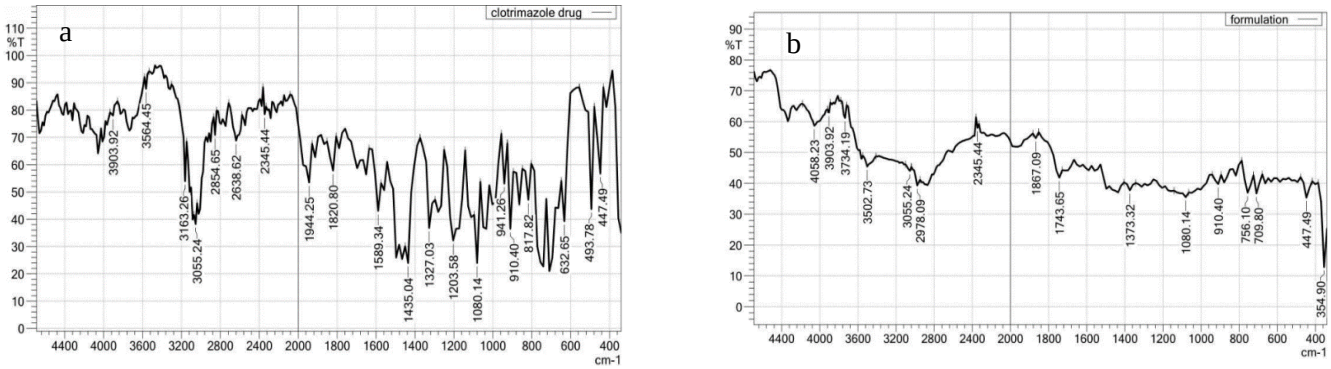

Figure 2: FTIR spectrum of Clotrimazole alone (a) and its combination with excipients used (b)

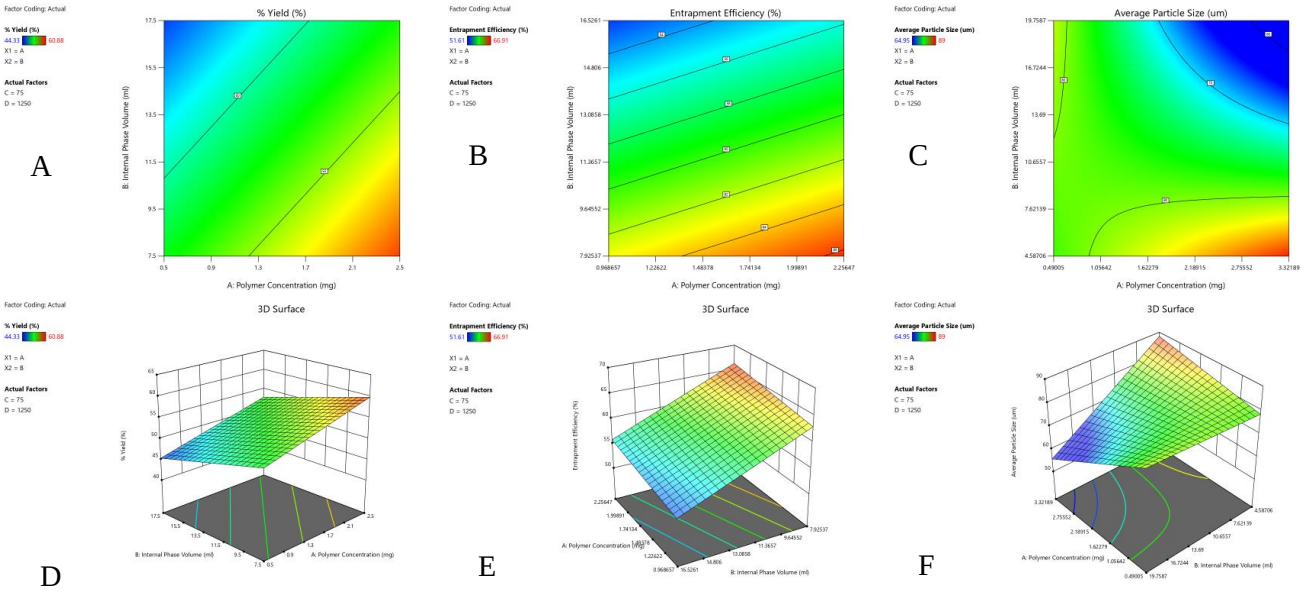

Figure 3: Contour plots illustrate the responses of A) % Yield B) entrapment efficiency, and C. Average Particle Size while 3D plots depict the responses of D) % Yield E) entrapment efficiency, and F) Average Particle Size

Table 1: Composition of Clotrimazole Microsponges

Run	Independent Variables				Dependent Variables		
	X1 A:Polymer Conc.(g)	X2 B:Internal Phase Volume (ml)	X3 C:PVA Conc (mg/ml)	X4 D:Stirring Speed (rpm)	Y1 Yield (%)	Y2 Entrapment Efficiency (%)	Y3 Average Particle Size (um)
1	1	10	100	1500	52.24	59.45	72.13
2	1	15	100	1500	48.77	52.42	64.95
3	1	10	50	1000	52.66	62.57	73.45
4	1	15	50	1000	49.19	55.54	78.34
5	1	15	50	1500	53.63	56.35	80.5
6	1	10	50	1500	57.1	63.38	81.65
7	1	10	100	1000	47.8	58.64	89
8	1	15	100	1000	44.33	51.61	87.86
9	2	15	100	1500	52.55	55.95	66.1
10	2	15	100	1000	48.11	55.14	70.98
11	2	15	50	1500	57.41	59.88	79.48
12	2	10	100	1500	56.02	62.98	72.3
13	2	15	50	1000	52.97	59.07	74.47
14	2	10	50	1000	56.43	66.1	75.62
15	2	10	100	1000	51.57	62.17	82.34
16	2	10	50	1500	60.88	66.91	81.82

Table 2: The equations for Y1, Y2, and Y3 for the linear model

% Yield	+51.79000+3.77750 Polymer Concentration -0.693500 Internal Phase Volume -0.097200 PVA Concentration +0.008885Stirring Speed
Entrapment Efficiency	+70.15750 +2.57500 Polymer Concentration -1.21500 Internal Phase Volume -0.059500 PVA Concentration +0.003530 Stirring Speed
Average Particle Size	-7.44188 -1.49500 Polymer Concentration +3.56800 Internal Phase Volume +1.37835 PVA Concentration +0.039775Stirring Speed -0.823500Polymer Concentration * Internal Phase Volume -0.098350 Polymer Concentration * PVA Concentration +0.012855Polymer Concentration * Stirring Speed -0.026130Internal Phase Volume * PVA Concentration -0.000811 Internal Phase Volume * Stirring Speed -0.000763 PVA Concentration * Stirring Speed

pharmaceutical formulations due to its biocompatibility, stability, and controlled-release matrix formation. It ensures patient safety by preventing negative reactions when in contact with biological tissues. EC's stability is crucial for maintaining the effectiveness of active pharmaceutical ingredients (APIs) and preserving the formulation's integrity. Its ability to create a consistent and long-lasting release profile is particularly beneficial for medications with limited therapeutic index or long-lasting effects.[20] Onosma bracteatum leaves, a naturally occurring polymer, has shown promise in pharmaceutical formulations, particularly in drug delivery microsponges.[8] Its biocompatibility ensures patient safety, and its hydrophilic nature improves the solubility of medications. Gum's gel-forming ability allows for encapsulation within microsponges, enhancing stability and regulated release. It also enhances drug retention, allowing for extended interaction with the target site and potentially better therapeutic results. Gum can also control the release mechanism of encapsulated medications, creating a sustained release environment. It can work with synthetic polymers like ethyl cellulose to maximize microsponges' properties while maintaining release profiles.[21] Making Clotrimazole-loaded microsponges with ethyl cellulose and natural gum from *Onosma bracteatum* leaves utilizing the 4^2Factorial design design method with the aid of Design Expert software is the goal of this study. The formulation seeks to improve the efficacy and stability of medication delivery.[22,23] By analyzing the drug-to-polymer ratio, gum concentration, and preparation technique, factorial design is used to optimize the formulation's properties. To make sure a sizable amount of Clotrimazole stays inside the microsponges, performance is evaluated using entrapment efficiency measures and *in vitro* drug release experiments.[23-25]

MATERIALS AND METHODS

Materials

The main pharmaceutical ingredient in this investigation was clotrimazole, which was kindly provided by Unijules Life Sciences, Kalmeshwar, Nagpur. Maradwar Ayurveda in Wardha supplied the *Onosma bracteatum* leaves, while Loba Chemie in Mumbai supplied the ethyl cellulose, dichloromethane, and polyvinyl alcohol. Each and every additional chemical used in the experiment was of AR grade. The plant material was identified and authenticated by analysing organoleptic, microscopic and pharmacognostic characteristics.[26] The specimen with accession no: 10737 was submitted to the herbarium of the Botany Department, Rastrasant Tukdoji Maharaj Nagpur, University Nagpur Maharashtra (India).

Isolation and Purification of Gums and Mucilage's [26,27]

Table 3: Confirmation locations solution given by design of experiment software

locations	Predicted Mean	Predicted Median	Observed
% Yield	52.6575	52.6575	52.63 ± 1.13
Entrapment Efficiency (%)	61.1375	61.1375	62.52 ± 1.84
Average Particle Size (um)	75.8281	75.8281	74.55 ± 1.07
Polymer Concentration (g)	1		
Internal Phase Volume (ml)	10		
PVA Concentration (mg/ml)	50		
Stirring Speed (rpm)	1000		

Solvent precipitation, heating and microwave-assisted extraction are some means of extracting gum from plant components. The simplest technique is solvent precipitation.[26] This process involves selecting the portion of the plant that contains gum mucilage, then drying, grinding, and screening that portion of the plan.[26-28] After being collected, the fresh plant materials were cleaned with water to get rid of any dirt or debris and then dried. To preserve its qualities, plant material is either dried in the sun (ideally) or in an oven set at 105˚C.[28,29] Usually, the plant contains pigments or chlorophyll, which need be eliminated before the gum is isolated. Plant material must first be cleaned of pigments and chlorophyll by treatment with petroleum ether and then chloroform, and finally rinsed with distilled water.[29]

Gum / mucilage extraction has two stages.

Step 1: Extraction of gum

The maximize extraction of gum and mucilage was carried out by Response Surface Methodology. Leaves of plant were soaked in different portions of distilled water (1:10 to 1:30). Continuous stirred with heated at various temperatures from room temperature to 60°C for 6-8 Hrs. It has filtrated through muslin cloth and cool at 4°C to 6°C.[26,30]

Step2: Isolation of *and Purification* gum

Solvent for precipitation has been selected and extracted gum is allowed to precipitate with it, and finally supernatant and precipitating solvent of thrice the volume is brought together in continuous stirring.[30] It permits filtration through muslin cloth. The marc from the solution was removed by washing with acetone and squeezing the gum mucilage from an essentially eight-folded muslin cloth. This was further dried to constant weight at 35–45°C in hot air oven.[30,31] The hard gum mucilaginous cake obtained was grinded and sieved through sieve #22 and kept in desiccator for further use.[26,31,32]

Preparation of microsponges

Internal phase

An emulsion was formed using ethyl cellulose from a solution in DCM as the organic internal phase, to which *O. bracteatum* gum was added, along with clotrimazole.[33-35] The gum and the polymer can be dissolved by the most effective solvent used is dicloromethane.[33]

External phase

The above internal phase was emulsified in into aqueous solution containing polyvinyl alcohol and placed in a beaker and stirred by a magnetic stirrer at 1000 and 2000 rpm for 2 hr.[36] Organic phase evaporated and microsponges were separated, filtered and air dried.[22,36] The dried structures were observed under Motic Microscope for structure development and sizes.[22]

Formation of quasi emulsion

Ethylcellulose, gum, and Clotrimazole are dissolved in dichloromethane to produce the organic internal phase. The external phase, distilled water containing the emulsifying agent polyvinyl alcohol, is then progressively mixed with this solution. The formation of the emulsion required for microsponges depends on this stage.[22]

Stirring process

A magnetic stirrer is used to agitate the mixture for about 60 minutes at a temperature of 35°C at a speed of 1000–1500 rpm. By removing dichloromethane, this churning facilitates the formation of microsponges as the solvent diffuses out.[34]

Filtration and washing

Whatman® filter paper no. 41 is used to filter the created microsponges after they have been stirred. After that, they are cleaned with distilled water to remove solvent or unencapsulated medication.[37]

Drying

For 12 hours, the microsponges are dried at 40°C. In order to guarantee that the microsponges are dry and prepared for additional analysis, this step is crucial[38]. A total of 16 formulations were prepared using the 4^2 factorial design Design method, facilitated by Design Expert software 13 (Trial version) (Table 1).

Drug estimation

Absorbance at 263 nm is measured using a UV spectrophotometer to estimate the free clotrimazole in the filtrate.This step is crucial for determining the drug concentration and ensuring the quality of the microsponges.[39]

Compatibility studies by DSC and FTIR

To evaluate the compatibility between the drug and polymers, samples were judged by DSC. The drug alone and its combination with the excipient were heated from 30 to 300°C. DSC analysis is a common technique for assessing the thermal behavior of materials, enabling the detection of interactions and compatibility between components. By comparing the thermal profiles of the drug alone and in combination with the excipient, any changes in melting points, enthalpy, or other thermal parameters can be observed, indicating potential interactions. This method provides valuable insights into the suitability of polymers for formulating the drug and ensuring the stability and efficacy of the final product.[39] Further, Fourier Transform Infrared (FTIR) spectroscopy was employed. The IR spectra were captured utilizing a spectrophotometer over a wavelength range spanning from 4000 to 400 cm^{-1}. This

analytical approach helps to analyze chemical bonds and efficient groups present in both the drug and the polymers, thereby determining their compatibility.[39]

Optimization of clotrimazole loaded microsponges by 4^2 factorial design

Utilizing a 4^2factorial design, this research will systematically evaluate the effects of various formulation parameters on the characteristics of the microsponges. Key variables such as the drug-to-polymer ratio, emulsifier concentration, and solvent volume will be altered to identify optimal conditions that maximize drug entrapment efficiency and ensure consistent release rates.[40] Employing Design-Expert software, 16 experimental runs were generated, implementing a nonlinear quadratic model equation. The model considered various coefficients, including linear, interaction, and quadratic, along with the intercept. Independent variables (IV), i.e., Polymer Concentration (X_1), Internal phase volume (X_2), polyvinyl alcohol concentration (X_3), and stirring speed (X_4) were studied against dependent variables (DV), including Yield (Y_1), entrapment efficiency (EE) (Y_2), and Average particle size (Y_3).

Yield calculation

Microsponge production yield (PY) is determined by the following formula.[41]

PY (%) = Practical mass (micro sponges)/ Theoretical mass (polymer + drug) × 100

Entrapment efficiency

Ten milliliters of phosphate buffer (pH 7.4) were used to dissolve a precisely weighed quantity of drug-loaded microsponges (10 mg), stirring occasionally.[42] A blank was made of phosphate buffer solution 7.4, and 1 ml of the aforementioned sample was roughly diluted to 1 ml, and the absorbance was measured at 263 nm.[42] Using the following formulae, the drug content and loading efficiency were estimated for each batch[22,39,42-46]

Entrapment efficiency = M_{act} / M_{the} x 100

Where,

M_{act} = Actual drug content in microsponges

M_{the} = Theoretical drug content in microsponge

Particle size analysis

The microscopic analysis of drug-loaded microsponge was done and the mean diameter of 100 dried microsponges was determined with the help of DIGITAL MICROSCOPE (MOTIC DM111 6120084) IMAGE PLUS MICROSCOPE.[39]

RESULTS AND DISCUSSION

Compatibility results

In this study, clotrimazole and the excipients interacted and the DSC thermograms of the mixture revealed several findings relevant to the compatibility of the components and potential benefits of the formulation. The mixture with excipients gave a peak at 152. 1 ° C while clotrimazole alone had a distinct endothermic peak at 144. 6 ° C. The shift in the thermograms indicates that there is a good solubility and compatibility between clotrimazole and the excipients. This change in the peak temperature is an indication that there has been a change in the thermal behaviour of the drug – excipient mixture hence enhancing their compatibility. Taken together, our results support the idea that clotrimazole and excipients can interact effectively, which is essential for creating reliable and effective drug delivery systems. (Figure 1). The FTIR investigation revealed that even when coupled with the excipients, the particular peaks and stretches in the FTIR spectra of clotrimazole remained unchanged (Figure 2). This suggests that neither the chemical structure of the drug nor its functional groups were significantly altered by the interactions between clotrimazole and excipients. The presence of these characteristic peaks proved that the excipients were safe for use with clotrimazole and there were no changes or interactions that could affect the molecular structure of the drug. This emphasizes the suitability of excipients for creating products containing clotrimazole while maintaining their medicinal qualities.

Percentage yield, entrapment efficiency, and average

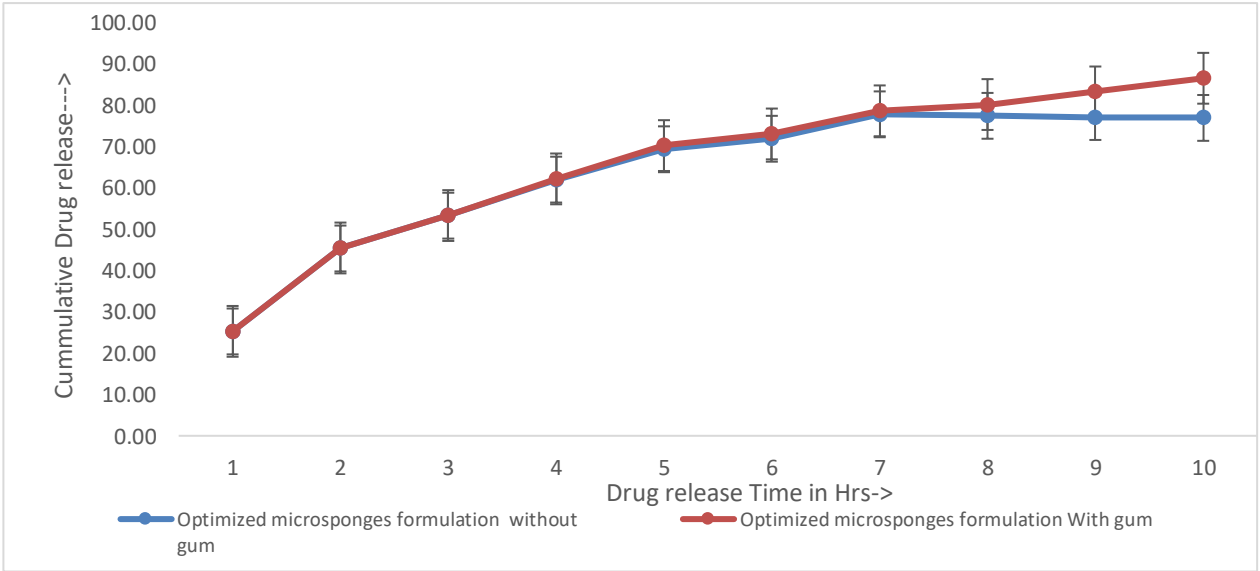

Figure 4: Cumulative drug release profile of optimized clotrimazole loaded microsponges with and without gum *Onosma bracteatum*

particle size results

The % yield of microsponges lies in the 44.33-60.88% range. Additionally, the % Entrapment Efficiency ranged from 51.61 to 66.91%, suggesting differences in the effectiveness of encapsulating the drug within the vesicles across various formulations. Microsponges should average in the range of 5 to 250 µm in particle size. In the present work, At least 100 particles of microsponges were counted for precise size distribution. The average particle size of clotrimazole-loaded microsponge ranged from 64.95 µm to 89 µm. The mean particle size significantly increased with increasing polymer.

These findings highlight the heterogeneity in yield, drug entrapment, and size, which may influence their performance and suitability for drug delivery applications.

Effect of IV on the responses

The model's F value of 7.66 is significant at the 1% level and noise has less than 1 % probability of producing a higher F value. Terms are considered significant if the P.value is less than 0.0500 (significant at the 5% level). In this case A, B, C and D are important model terms. (A stands for polymer concentration, B for internal phase volume, C for PVA concentration, and D for stirring speed). It implies the model has a significance of 15.21. A chance of 0.0002% exists that an F-value this large could be due to noise. All model terms with P value <0.0500 are considered significant. In this case A, B, C and D are significant model terms. F Value of the model is indicated by its 5.79. That is, the probability that this F value is due to noise is 3.31%. We consider the model terms significant when P(value) < 0.0500. In this case, CD is a key model term. (Results are depicted in figure 3)

Equations of the responses

The provided equations in table 2, represent mathematical models describing the association between the IV (X1, X2, and X3) and the DV (Y1, Y2, and Y3) in the experimental design. These equations are derived from experimental data and are useful for predicting the DV based on specific combinations of the IV. Each equation consists of various coefficients representing the linear, interaction, and quadratic effects of the IV on the DV. By analyzing these equations, one can understand how changes in the IV affect the responses of interest, providing valuable insights for optimizing the experimental conditions to achieve desired outcomes. The contour plots presented in Figures 3A, 3B, and 4C provide a graphical representation of the relationship between the IV and DV. These plots offer valuable insights into how changes in the levels of the IV influence the values of the DV. By analyzing the contour plots, one can identify regions of the parameter space where the DVs are optimized, facilitating the selection of optimal situations for achieving desired outcomes. In addition, the 3D plots depicted in Figures 3D, E, and F offer a visual depiction of the interaction between multiple IV and their impact on the DV. These plots provide a full indulgent of the association between the variables by illustrating how changes in one or more IVs affect the behaviour of the DV. By examining the 3D plots, researchers can identify complex patterns of interaction between the variables and pinpoint optimal parameter settings for maximizing % yield, entrapment efficiency, and average particle size.

Optimization

The design of experiment software suggested solution of 75 responses as confirmation locations along with predicted mean and median. (table 3). The observed values are significantly matches with the predicted mean and median values, hence confirm the optimized location for the formulations of microsponges. Finally optimized formulations *in vitro* drug release profile was comparatively studied without use of gum formulation. The incorporation of gum not only extend the drug release but also helps in releasing drug clotrimazole release to a maximun 86.44% as compared to microsponges prepared without gum i.e., 76.85% in 10 Hrs. This is due to formation of non-collapsible structural mydriatic spaces due to incorporation of gum during microsponge formation. The results were decapitated in Figure 4.

Surface morphology of optimized formulations

The surface morphology of optimized formulations were recorded with and without gum *Onosma bracteatum*.. The surface of microsponges was non-collapsible with maximum mydriatic regions on the surface indicating its application for the release of drug through these tiny cracks. Thus resulting in slow extended and maximum drug release as compared to microsponges prepared with only ethyl cellulose.

CONCLUSION

The findings of this study emphasize the successful development of clotrimazole-loaded microsponges with optimized characteristics suitable for drug delivery. Results of studies using Fourier Transform Infrared (FTIR) Spectroscopy and Differential Scanning Calorimetry (DSC) showed the compatibility of clotrimazole with specific excipients allowing efficient interactions without loss of chemical integrity of the drug. The shifts in DSC thermograms and preserved FTIR peaks collectively suggest the formulation's stability and miscibility.The experimental data on percentage yield, entrapment efficiency, and particle size demonstrated significant variability, driven by key formulation parameters. Higher polymer concentration improved both yield and entrapment efficiency, while stirring speed and PVA concentration influenced particle size. The design of experiments (DOE) approach validated significant model terms, providing predictive equations that facilitated the optimization process. Contour and 3D plots further aided in visualizing the interplay of variables, helping identify optimal formulation conditions. The optimized microsponges exhibited controlled drug release, with formulations incorporating gum achieving extended release (86.44% over 10 hours) compared to non-gum formulations (76.85%). This extended release can be attributed to the formation of stable, non-collapsible structures in the presence of gum, enhancing the sustained release profile. In conclusion, the optimized clotrimazole-loaded microsponges offer a promising platform for sustained drug delivery, demonstrating significant potential for improved therapeutic efficacy. Future studies should focus on *in vivo*

evaluations and stability testing to further validate these findings and support clinical translation.

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REFERENCES

1. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: A review. Biomaterials research. 2021;25(1):24. https://doi.org/10.1186/s40824-021-00226-6
2. Kadam Chetan Y., Ashok Muchandi., Pratiksha P Alabade., Prashant P Narwade., Sumit R Khandwe. TRANSDERMAL drug delivery system: a painless method for healthy skin-a review. International Journal of Scientific Development and Research. [Internet]. 2022;7(4):123-130. Available from: www.wjpps.com
3. Rangari AT, Ravikumar P. Polymeric nanoparticles based topical drug delivery: an overview. Asian Journal of Biomedical and Pharmaceutical Sciences. 2015;5(47):5-12.
4. Agrawal MB, Patel MM. Optimization and in vivo evaluation of quetiapine-loaded transdermal drug delivery system for the treatment of schizophrenia. Drug development and industrial pharmacy. 2020;46(11):1819-1831. https://doi.org/10.1080/03639045.2020.1821051
5. Ayalasomayajula LU, Kumari MK, Earle RR. An Insight into delivery of drug through the skin: Transdermal drug delivery system. Research Journal of Topical and Cosmetic Sciences. 2021;12(1):4-12.
6. Kharat R, Bathe RS. A comprehensive review on: transdermal drug delivery systems. International Journal of Advanced Biological and Biomedical Research. 2016;7(4):147. http://dx.doi.org/10.7439/ijbar.v7i4.3131
7. Prabhakar D, Sreekanth J, Jayaveera KN. Transdermal drug delivery patches: a review. Journal of Drug Delivery and Therapeutics. 2013;3(4):231. Available from: http://jddtonline.info
8. Shingade SP, Kakde RB, Pimpale AD. ONOSMA bracteatum wall: a review of its phytochemical constituents and therapeutic potential, International Journal of Modern Pharmaceutical Research. 2015;6. Available from: www.ijmpronline.com
9. SHINGADE GM. Review on: recent trend on transdermal drug delivery system. Journal of drug delivery and therapeutics. 2012;2(1). Available from: http://jddtonline.info
10. Kumar VM, Veena NM, Manjula BP. Formulation and evaluation of microsponges for topical drug delivery of mupirocin. International Journal of PharmTech Research. 2013;5(3: 1434-1440,
11. Resmi DS, Mathew P, Dev AP, Abraham E. Formulation and evaluation of topical econazole nitrate microsponge loaded hydrogel. Ijppr. 2018;12(1):27-64. Available from: www.ijppr.humanjournals.com
12. Veena S, Kaur S, Kulkarni G. Formulation and evaluation of antifungal cream of chlorphenesin. International Journal of Current Pharmaceutical Research. 2021;13(5):76-81.
13. J Jacob S, Nair AB, Shah J, Gupta S, Boddu SH, Sreeharsha N, Joseph A, Shinu P, Morsy MA. Lipid nanoparticles as a promising drug delivery carrier for topical ocular therapy—an overview on recent advances. Pharmaceutics. 2022;14(3):533. https://doi.org/10.3390/pharmaceutics14030533
14. Zhao L, Song J, Du Y, Ren C, Guo B, Bi H. Therapeutic applications of contact lens-based drug delivery systems in ophthalmic diseases. Drug Delivery. 2023;30(1):2219419. https://doi.org/10.1080/10717544.2023.2219419
15. Raina N, Rani R, Thakur VK, Gupta M. New insights in topical drug delivery for skin disorders: from a nanotechnological perspective. ACS omega. 2023;8(22):19145-19167. https://doi.org/10.1021/acsomega.2c08016
16. Charyulu NR, Joshi P, Dubey A, Shetty A. Emulgel: A boon for enhanced topical drug delivery. Journal of Young Pharmacists. 2021;13(1):76.
17. Kumar S, Khan R, Sharma B. CLOTRIMAZOLE: a review of its structure, therapeutic class and pharmaceutical properties, pharmaceutical dosage forms and administration and analytical study. World journal of pharmacy and pharmaceutical sciences. 2021;10(9): 325-338.
18. Bhargava S, Chakrabarty S, Damodaran RT, Saikia PK, Shenoy M, Bangale B. Rising burden of superficial fungal infections in india and the role of clotrimazole for optimal management. Indian Journal of Clinical and Experimental Dermatology. I2023;9(1):1–16. https://doi.org/10.18231/j.ijced.2023.001
19. Issa AJ , Muhammed AI, Mohamed M, Jabar R. Clotrimazole for treatment of fungal skin infections disease. Iraqi Journal of Industrial Research IJOIR. 2023;10(1):131–7. https://doi.org/10.53523/ijoirVol10I1ID328
20. Ahmadi P, Jahanban-Esfahlan A, Ahmadi A, Tabibiazar M, Mohammadifar M. Development of ethyl cellulose-based formulations: A perspective on the novel technical methods. Food Reviews International. 2022;38(4):685-732. https://doi.org/10.1080/87559129.2020.1741007
21. Ansari Z, Goomer S. Natural gums and carbohydrate-based polymers: Potential encapsulants. Indo Global Journal of Pharmaceutical Sciences. 2022;12:01-20. https://doi.org/10.35652/IGJPS.2022.12001
22. Gusai T, Dhavalkumar M, Soniwala M, Dudhat K, Vasoya J, Chavda J. Formulation and optimization of microsponge-loaded emulgel to improve the transdermal application of acyclovir—a DOE based approach. Drug delivery and translational research. 2021;11:2009-2029. https://doi.org/10.1007/s13346-020-00862-w
23. Shah C, Shah D. Design and optimization of fluconazole microsponges containing ethyl cellulose for topical delivery system using quality by design approach. Pharma Science Monitor. 2014;5(3):95-133.
24. Dineshmohan S, Gupta VR. Formulation and in vitro evaluation of fluconazole loaded microsponge gel for

topical sustained delivery. IOSR Journal of Pharmacy and Biological Sciences. 2015;10:15-20. DOI: 10.9790/3008-10631520

25. Crcarevska MS, Dimitrovska A, Sibinovska N, Mladenovska K, Raicki RS, Dodov MG. Implementation of quality by design principles in the development of microsponges as drug delivery carriers: Identification and optimization of critical factors using multivariate statistical analyses and design of experiments studies. International journal of pharmaceutics. 2015;489(1-2):58-72. https://doi.org/10.1016/j.ijpharm.2015.04.038
26. Choudhary PD, Pawar HA. Recently investigated natural gums and mucilages as pharmaceutical excipients: an overview. Journal of pharmaceutics. 2014;2014(1):204849. https://doi.org/10.1155/2014/204849
27. Ramu Samineni DR, Sujala DP, Anwar Khan DS, Babu MR, Yanadaiah P. A Prospective Review on Novel Strategies for Preparation and Evaluation of Nanosponge Tablets. European Chemical Bulletin. 2023;12(5):2482-2496.
28. Malabadi RB, Kolkar KP, Chalannavar RK. Natural plant gum exudates and mucilage: pharmaceutical updates. International Journal of Innovation Scientific Research and Review. 2021;3(10):1897-1912.
29. Farooq U, Malviya R, Sharma PK. Extraction and characterization of okra mucilage as pharmaceutical excipient. Academic Journal of Plant Sciences. 2013;6(4):168-72. DOI: 10.5829/idosi.ajps.2013.6.4.82292
30. Farooq U, Malviya R, Sharma PK. Design and development of multi particulate system for targeted drug delivery using natural polymer. Pharm. Anal. Acta. 2015;6:366. http://dx.doi.org/10.4172/2153-2435.1000366
31. Farooq U, Malviya R, Sharma PK. Extraction and characterization of okra mucilage as pharmaceutical excipient. Academic Journal of Plant Sciences. 2013;6(4):168-172. DOI: 10.5829/idosi.ajps.2013.6.4.82292
32. Gunasheela S, Chandrakala V, Srinivasan S. Development and evaluation of microsponge gel of an antifungal drug. International Journal of Current Pharmaceutical Research, 2023;15(1):30-41, doi:10.22159/ijcpr.2023v15i1.2069.
33. Kaity S, Maiti S, Ghosh AK, Pal D, Ghosh A, Banerjee S. Microsponges: A novel strategy for drug delivery system. Journal of advanced pharmaceutical technology & research. 2010;1(3):283-90. *DOI:* 10.4103/0110-5558.72416
34. Maiti S, Kaity S, Ray S, Sa B. Development and evaluation of xanthan gum-facilitated ethyl cellulose microsponges for controlled percutaneous delivery of diclofenac sodium. Acta Pharmaceutica. 2011;61(3):257-270. https://doi.org/10.2478/v10007-011-0022-6
35. Wadhwa G, Kumar S, Mittal V, Rao R. Encapsulation of babchi essential oil into microsponges: Physicochemical properties, cytotoxic evaluation and anti-microbial activity. Journal of food and drug analysis. 2019;27(1):60-70. https://doi.org/10.1016/j.jfda.2018.07.006
36. Tile MK, Pawar AY. Microsponges: a novel strategy for drug delivery. International Journal of Pure and Applied Bioscience. 2015;3(1):224-35.
37. Osmani RA, Aloorkar NH, Ingale DJ, Kulkarni PK, Hani U, Bhosale RR, Dev DJ. Microsponges based novel drug delivery system for augmented arthritis therapy. Saudi pharmaceutical journal. 2015;23(5):562-72. https://doi.org/10.1016/j.jsps.2015.02.020
38. Shukla AK, Yadav A, Vishwakarma RK, Mishra SK. Applications, isolation and characterization of fenugreek seed gum as pharmaceutical excipient. Journal of Medical Pharmaceutical and Allied Sciences. 2020 May;9(2):920. DOI: 10.22270/jmpas.v9i2.920
39. Kumar PM, Ghosh A. Development and evaluation of metronidazole loaded microsponge based gel for superficial surgical wound infections. Journal of Drug Delivery Science and Technology. 2015;30:15-29. https://doi.org/10.1016/j.jddst.2015.09.006
40. Sharma S, Sharma S, Kaur C, Baba AS, Jujhar AS. MICROSPONGES: as a topical drug delivery system. International Journal of Pharmaceutical Sciences and Research. 2020;11(2):524–534. http://dx.doi.org/10.13040/IJPSR.0975-8232.11
41. Bhatia M, Saini M. Formulation and evaluation of curcumin microsponges for oral and topical drug delivery. Progress in biomaterials. 2018;7:239-48. https://doi.org/10.1007/s40204-018-0099-9
42. Jelvehgari M, Siahi-Shadbad MR, Azarmi S, Martin GP, Nokhodchi A. The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies. International journal of pharmaceutics. 2006;308(1-2):124-32. https://doi.org/10.1016/j.ijpharm.2005.11.001
43. Boorugu R, Radha GV. Development and Evaluation of Eplerenone Microbeads as Floating Drug Delivery System using Design of Experiment. International Journal of Pharmaceutical Quality Assurance. 2023;14(4):837-846. DOI: 10.25258/ijpqa.14.4.02
44. Chauhan R, Singh B, Singh MP, Malik A. Pharmacokinetic Study of Aloin Nanoparticulate: Enhanced Oral Formulation Bioavailability. International Journal of Pharmaceutical Quality Assurance. 2024;15(1):94-100. DOI: 10.25258/ijpqa.15.1.14
45. Nandini, Yadav HKS, Jasmine, Punianib S. Formulation, Development & Evaluation of Mallotus philippensis Extract Loaded NLCS based Nanogel for Psoriasis. International Journal of Drug Delivery Technology. 2024;14(3):1269-1277. DOI: 10.25258/ijddt.14.3.04
46. Singh S , Sahu D. A Review on Novel Drug Delivery System: Microsponges. International Journal of Drug Delivery Technology 2017; 7(4); 298-303 doi : 10.25258/ijddt.v7i04.10652