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Research Article

Formulation and Evaluation of Nicotinamide Microsponges – The First Step Towards the Development of a Novel Topical Dosage Form

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ABSTRACT

The objective of this work was to formulate and analyze microsponges of nicotinamide. The said formulation was created using the emulsion solvent diffusion technique, and a 3 level two factor-based factorial design was applied to optimize the effect of the stabilizer (X_1), as well as drug (X_2), amounts on the entrapment efficiency (Y_1) and average particle size (Y_2). Various parameters, such as flow characteristics, percentage yield, drug concentration, *in-vitro* drug release tests, entrapment efficiency, and scanning electron microscopy (SEM), were evaluated. All parameters were found to be within the acceptable range. Design Expert 13 was employed to optimize the microsponges, and the optimal batch was determined by examining the desirability data. From this analysis, the optimal amounts of drug and stabilizer were found to be 302.87 and 59.71 mg, respectively. The reliability of the preparation and evaluation of the optimized batch was confirmed by a less than 5% discrepancy between the observed and predicted values of parameters. SEM images revealed that the microsponges were prepared with uniform and spherical morphology. The study concluded that nicotinamide microsponges were successfully prepared and evaluated. Further steps will involve incorporating this formulation into a novel topical dosage form.

INTRODUCTION

Developing new topical medication delivery methods has been one of the core competencies of the field of pharmaceutical research. Recently, exploring novel dose forms as a means of improving therapeutic effectiveness and patient compliance has been a prime focus of the researchers.^[1] Microsponges have surfaced as a potentially effective medication delivery platform that may be tailored to specific needs. These address a number of issues with traditional drug delivery methods and a flexible way to provide therapeutic drugs under strict control has also been explored as a part of the research in this specific formulation.^[2] Nicotinamide, sometimes referred to as vitamin B3 or niacinamide is a water-soluble substance having established medical benefits. Because of its potential to be an active component in a variety of pharmaceutical and dermatological formulations, it has attracted a lot of interest in the medical and cosmetic

industries.^[3] Because of its proven anti-inflammatory, antioxidant, and anti-aging properties, nicotinamide is a great option for treating dermatological diseases like rosacea, acne, and photoaging.^[4]

The most prevalent skin condition, acne vulgaris, or acne as it is commonly known, affects around 80% of people between the ages of 11 and 30 years. It may have detrimental effects on psychosocial development that include emotional problems, social disengagement, and hopelessness. It can cause deformity and lasting scars that last for years. The etiology of acne is complex, but a large number of its component elements are now targets for therapeutic intervention. Millions of people worldwide suffer from acne, a common skin problem that usually flares up in adolescence but can often linger into adulthood.^[5] It is distinguished by the development of blackheads, whiteheads, and occasionally even cysts on the skin. Since the density of oil glands is larger in these

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skin portions - the face, neck, chest, back, and shoulders - these blemishes frequently appear there.^[6]

Acne comes in different forms, from moderate to severe, such as comedones. Blackheads and whiteheads are examples of non-inflammatory acne, which is caused by clogged hair follicles that are not inflamed.

Papules

Tiny, elevated, red lumps brought on by irritated hair follicles.

Pustules

Similar to papules but with a whitish or yellowish core packed with pus.

Nodules

Large, painful, firm aggregated just below the epidermis of skin caused by deeper, more severe inflammation.

Cysts

Painful, deep, pus-filled tumors that may leave scars.^[7] For mild to moderate acne, over-the-counter topical medicines containing alpha hydroxy acids, salicylic acid, or benzoyl peroxide may be helpful. In more severe cases, dermatologists may prescribe oral or topical antibiotics, retinoids, or hormonal therapy (for females) to control hormone levels.

Microsponges are porous microspheres with several interconnecting gaps with a particle size of 5 to 300 μm . These microsponges can be applied topically as a carrier system for a large number of active ingredients, such as anti-infectives, essential oils, antifungals, emollients, sunscreens and anti-inflammatory agents. Moreover, these porous microspheres containing active chemicals offer numerous benefits and are incorporated into a diversity of formulations, such as powders, gels, lotions, and creams.^[8,9]

Controlling the rate of delivery of active drugs to a particular site in the body has proven as one very challenging problem that pharmaceutical scientists are facing. There has been the development of many advanced techniques for systemic medicine distribution under the general heading of transdermal delivery systems (TDS), in which the skin is employed as a portal of entry. It enhanced the safety and effectiveness for numerous medications, which might get absorbed better via the skin. However, TDS is not feasible for anything which is to be residing on the skin. A challenging thing is the medication delivery to the skin under-regulated settings that enhance the localization of the drug and not considerably let it in the systemic circulation. Hence, the current study attempts to create and assess nicotinamide microsponges as a preliminary measure toward the creation of an innovative topical dose form for the management of vulgaris acne.^[9,10]

He Y *et al.* (2018) conducted a thorough evaluation that demonstrates the many advantages of microsphere

technology in terms of increasing medication efficacy, boosting patient compliance, and reducing side effects. Microsponges are porous polymeric particles with a high surface area-to-volume ratio and porosity that allow for the controlled release and trapping of pharmaceuticals.^[11] Microsphere formulations enable controlled release, increased stability, targeted distribution, and better patient compliance, making them a flexible and promising method for pharmaceutical drug delivery. These benefits highlight how promising microsphere technology is for resolving issues with traditional medication delivery methods and promoting the creation of safe and effective treatments.

MATERIALS AND METHODS

Materials

Nicotinamide was procured from Agro Cool Ind. Ltd., New Delhi. Polyvinyl alcohol (cold water soluble) was obtained from ChemDyes Corporation Rajkot. Ethyl cellulose was procured from Asha Cellulose, Baroda. All other chemicals were laboratory reagents.

Preparation of Microsponges

Quasi-emulsion solvent diffusion technique was implemented to prepare the micro sponges. The drug was nicotinamide and the matrix-forming polymer was ethyl cellulose for the micro sponges. Dichloromethane was used as the solvent for the internal phase. To prepare it, the medication and polymer were dissolved in the solvent. To prepare the external phase, the stabilizer, polyvinyl alcohol, was dissolved in a suitable quantity of distilled water. The internal phase was added gradually to the external phase while being continuously agitated for a predefined period of time. The solvent from the internal phase diffuses in the external phase, causing the drug as well as the polymer to precipitate simultaneously. Additional solvent diffusion encourages the components to solidify, which forms the micro sponges. Following filtration, the produced microsponges were dried for 12 hours at 40°C.^[12]

Preliminary Studies for the Determination of Processing Variables

Numerous processing parameters, like drug:polymer ratio, time of stirring, speed of stirring, the volume of internal phase, stabilizer dosage, etc., are included in the formulation of microsponges. The production yield, entrapment efficiency, flow characteristics, and other crucial quality aspects of the microsponges can all be impacted by the aforementioned elements.^[13,14] For the preliminary studies, the three factors, namely, the stirring speed, stirring time and internal phase volume, were considered and the remaining factors were kept constant while studying each one of these as per Table 1.

Table 1: Preformulation batches for determination of processing variables

Batch	Nicotinamide (mg)	Ethyl cellulose (mg)	Pva (mg)	Stirring rate (rpm)	Stirring time (minutes)	Internal phase volume (mL)	External phase volume (mL)
F1	500	250	75	1000	60	5	30
F2	500	250	75	2000	60	5	30
F3	500	250	75	3000	60	5	30
F4	500	250	75	1000	30	5	30
F5	500	250	75	1000	60	5	30
F6	500	250	75	1000	120	5	30
F7	500	250	75	1000	60	5	30
F8	500	250	75	1000	60	7.5	30
F9	500	250	75	1000	60	10	30

(When modifying one parameter, the others were kept constant)

3² Factorial Design for the Optimization of the Microsponges

The quadratic response surface approach is used in the statistical design of 3² factorials. The design is rotatable, independent, and quadratic. It offers a significantly cheaper technique in comparison to the existing approach for the formulation & dosage form optimization because it requires less number of runs (nine trials for two variables) and the required time is also much less. None of the components are ever concurrently set to their greatest or lowest values because it lack axial points. The usefulness of such designs are in avoiding testing in unfavorable conditions where subpar results could occur. This technique optimizes the main, interaction, and quadratic effects.^[15]

Considering preliminary studies, the amount of stabilizer (X_1) and drug (X_2) were selected as factors which are also known as the independent variables. The responses in this design were entrapment efficiency (Y_1) and average particle size (Y_2). The statistical analysis for this design was executed by Design Expert 13. Below is the model equation for the design:

Here, Y is the observed response, b_0 is constant, b_1 and b_2 are coefficients for factors X_1 and X_2 , respectively, b_{12} is the interaction coefficient, b_{11} and b_{22} are quadratic terms coefficients and E is an error. X_1 and X_2 depict the mean output when there is a change in one factor from its low to a high value at a given time, as per Table 2. When two factors are simultaneously changed, the response changes is demonstrated by X_1X_2 and it is also called the interaction term. To look at nonlinearity, X_1^2 and X_2^2 were added and they are called the polynomial terms.

Evaluation Parameters

Numerous assessment measures, including entrapment efficiency, production yield, drug content, *in-vitro* drug release, physicochemical characterization, etc., can be used to assess the development of nicotineamide-loaded microsponges.^[13] Nevertheless, the current work's

Table 2: Formulation of 3² factorial design batches

Batch	Amount of stabilizer (X_1)		Amount of drug (X_2)	
	Coded	Actual (mg)	Coded	Actual (mg)
B1	-1	30	-1	250
B2	0	60	-1	250
B3	+1	90	-1	250
B4	-1	30	0	500
B5	0	60	0	500
B6	+1	90	0	500
B7	-1	30	+1	750
B8	0	60	+1	750
B9	+1	90	+1	750

Y_1 = Entrapment Efficiency (%), Y_2 = Average Particle Size (μm)

scope is restricted to the creation of nicotineamide microsponges alone—not the final result. As a result, several assessment parameters that aren't relevant for this kind of intermediate formulation are left out of the analysis.

Flow properties

The flow characteristics are anticipated to be crucial in the process of integrating the improved nicotineamide microsponges formulation into a novel target dosage form. Studying the prepared microsponges' flow characteristics is, therefore, essential. Hausner's ratio, Carr's index and the angle of repose for all the batches were studied.^[13] All the evaluations were measured in triplicates.

Angle of repose

The fixed funnel technique was employed to determine the angle of repose. This method included positioning a funnel with its tip at a height 'h' above a level of graph paper placed horizontally. The powder was slowly poured until the peak of the pile just touched the funnel's tip.^[13] Subsequently, the following equation was used to determine the angle of repose:



Carr's index

The ratio of the tapped and bulk densities difference to tapped density times 100 is the percentage compressibility index, also known as Carr's index.

Hausner's ratio

The ratio of tapped density to bulk density is known as Hausner's ratio, which is determined by using the following equation:

Production yield

The dried microsponges of the optimized batch were measured in weight and the following equation was used to calculate the %production yield.^[13]

Drug content

The amount of microsponges that were prepared, containing 100 mg equivalent weight of nicotinamide, was dissolved in methanol and then filtered. The UV-visible spectrophotometer was used to detect the absorbance at 262 nm following an appropriate dilution.^[13] Three copies of the absorbance measurement were made. To determine the drug content afterward, here's the equation that was used:

Where, M_1 is the measured drug content and M_2 is the weighted quantity of microsponges.

Entrapment efficiency

The entrapment efficiency was calculated using the following equation.^[13] All the evaluations were measured in triplicates.

Where, M_{act} is actual microsponges drug content and M_{the} is theoretical microsponges drug content.

In-vitro Drug Release Study

A study on drug release (*in-vitro*) was conducted by the basket method (Type I) specified in United States Pharmacopoeia. An accurately weighed sample of 200 mg nicotinamide containing microspunge was used. It was added in pH 5.5 phosphate buffer solution at $37 \pm 1^\circ\text{C}$ and kept rotating at 100 rpm. About 5 mL aliquot was collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours.^[13] The samples were assayed at 262 nm with a UV-visible spectrophotometer ($n = 3$).

Scanning Electron Microscopy

Scanning electron microscopy (SEM) is one of the most useful methods for studying the morphology of optimized formulation. If the sample is not conductive, it can be covered with a thin layer of metal and placed on a conducting stub. After that, it enters a vacuum chamber to be scanned by a concentrated electron beam. The way the electrons interact with the sample is detected by detectors, which provide information about the sample's composition, surface characteristics, and shape.^[13] The sample of the optimized batch was sent to the Department of Biotechnology, Junagadh Agricultural University, Junagadh, Gujarat for surface morphology.

Accelerated Stability Study

The accelerated stability study was performed on the optimized batch as per the guidelines issued by ICH and WHO. It was sealed in aluminum foil and placed in the stability chamber. $40 \pm 2^\circ\text{C}$ temperature and $75 \pm 5\%$ relative humidity were set as the conditions for 6 months duration. The drug content and particle size were analyzed on day 0, at 1 month and at 6 months.^[13]

Evaluations of Optimized Batch

The optimized batch of nicotinamide microspunge was evaluated for the average particle size, %entrapment efficiency, yield (%), flow properties, drug content (%), and scanning electron microscopy.

RESULTS AND DISCUSSION

The purpose of this work was to formulate and evaluate nicotinamide microsponges that are optimized for particle size and other suitable parameters. The microsponges design batches and all of the early batches were created using the emulsion solvent diffusion method. The initial investigations were conducted in order to ascertain specific processing parameters, such as volume of internal phase, time of stirring, and speed of stirring. To ascertain the ideal concentrations of the chosen independent variables—the dosage of medication and the dosage of stabilizer—a 3^2 -factorial design was implemented. Optimization was carried out by Design Expert 13 and the optimized batch was then evaluated for certain characteristics and the conclusion of the study was derived on the basis of the obtained results of all of these studies.

Preliminary Studies for the Determination of Process Variables

Various batches of nicotinamide microsponges were formulated using a specific set of parameters to determine whether certain processing variables had any significant effect on the quality of the prepared microsponges. While changing one parameter, all the others were set as unchanged so that the effect of that particular parameter can be determined easily without any combination effects. The formulation batches F1, F2 and F3 were focused on assessing the effect of stirring speed, which was set to 1000, 2000 and 3000 rpm, respectively. The batches F4, F5 and F6 were formulated to check if stirring time affects the properties of microsponges and the stirring time was set to 30, 60 and 120 minutes, respectively. At last, the remaining three batches F7, F8 and F9, were aimed at the determination of internal phase volume, which was kept at 5, 7.5 and 10 mL, respectively.

The impact of various parameters on the %yield, particle size and entrapment efficiency of microsponges is detailed in Table 3.

In the preliminary studies, the influence of stirring speed, stirring time, and volume of internal phase on the percentage yield, entrapment efficiency, and

Table 3: Results of pre-formulation batches for determination of processing variables

Batch	Parameter	Production yield (%)	Entrapment efficiency (%)	Average particle size (μm)
Stirring speed (rpm)				
F1	1000	62.24 \pm 2.96	93.69 \pm 1.41	97.34 \pm 1.72
F2	2000	56.61 \pm 2.85	90.85 \pm 1.66	85.79 \pm 3.19
F3	3000	48.07 \pm 2.54	88.68 \pm 1.32	127.68 \pm 2.86
Stirring time (minutes)				
F4	30	52.57 \pm 1.65	86.14 \pm 1.57	94.23 \pm 2.61
F5	60	60.71 \pm 1.76	93.89 \pm 1.47	82.63 \pm 1.34
F6	120	67.11 \pm 1.47	92.57 \pm 1.27	75.59 \pm 2.79
Internal phase volume (mL)				
F7	5	62.86 \pm 2.18	96.4 \pm 1.13	78.67 \pm 3.2
F8	7.5	56.24 \pm 2.33	92.52 \pm 1.67	88.58 \pm 4.46
F9	10	50.25 \pm 2.25	88.97 \pm 1.57	115.29 \pm 3.15

(All the parameters are given as Mean \pm S.D. and n = 3)

average particle size of the produced microsponges were investigated. Nine batches (F1-F9) were prepared with varying combinations of these parameters.

It was observed that there was a decrease in the production yield and entrapment efficiency with increasing stirring speed (F1 > F2 > F3). This might be attributed to the fact that excessively high shear forces during high-speed stirring might disrupt particle formation and lead to increased particle loss.^[9,12] Conversely, it was observed that there was a decrease in the average particle size with the increase in the stirring speed (F1 < F2 < F3), indicating a potential role of high shear in promoting particle size reduction.^[12,16] Production yield and entrapment efficiency appeared to improve with extended stirring time (F4 < F5 > F6). This can be because of the fact that sufficient time allows for better particle formation and encapsulation of the internal phase.^[12] However, excessively long stirring times (F6) could show a slight reduction in average particle size, potentially due to

particle aggregation or breakage. Internal phase volume: Percentage yield and entrapment efficiency decreased as the volume of the internal phase increased (F7 > F8 > F9). This could be attributed to limitations in material availability for particle formation with a larger internal phase volume.^[9,13] Interestingly, average particle size increased with increasing internal phase volume (F7 < F8 < F9). The presence of a larger volume of internal phase material hindering particle compaction during production can be the reason for this. The stirring parameters and internal phase volume significantly influence all three parameters of the produced particles.^[17]

Results of Optimization Study Using 3² Factorial Design

For nicotinamide microsponges, nine batches were prepared in the said design. 1000 rpm stirring speed, 60 minutes stirring time and 5 mL as the internal phase volume were the optimized parameters from the

Table 4: Results of 3² factorial design batches

Batch	Stabilizer (mg)	Drug* (mg)	Entrapment efficiency (%)	Average particle size (μm)
B1	30	250	87.24 \pm 1.63	102.47 \pm 4.89
B2	60	250	89.18 \pm 1.42	98.73 \pm 3.94
B3	90	250	91.35 \pm 1.17	94.92 \pm 2.78
B4	30	500	85.71 \pm 2.38	114.52 \pm 5.41
B5	60	500	87.84 \pm 1.92	109.37 \pm 4.18
B6	90	500	90.12 \pm 1.54	104.21 \pm 3.72
B7	30	750	83.47 \pm 3.19	127.84 \pm 6.21
B8	60	750	85.29 \pm 2.87	123.17 \pm 5.79
B9	90	750	87.04 \pm 2.51	118.50 \pm 4.92

(*In all the batches, the polymer was fixed at 500 mg in order to vary the Drug: Polymer ratio)



preliminary studies. The values of the variables in the actual and coded forms are shown in Table 2. Version 13 of the Design Expert software was used to analyze the experimental design's outcomes. The amounts of the drug and stabilizer, among other chosen independent factors, had an effect on the entrapment efficiency and average particle size seen in the responses. The results of the measurements of the responses are given in Table 4.

The data suggested a general trend of average particle size getting reduced with the increase in stabilizer concentration in the nicotinamide microsponges. Stabilizers are typically amphiphilic molecules, possessing both hydrophilic and hydrophobic moieties. During microsphere formation, the stabilizer molecules can adsorb over the surface of the nascent particles, forming a steric barrier.^[18] This steric barrier hinders the aggregation of drug molecules and polymer chains on the particle surface, thereby inhibiting uncontrolled particle growth.^[19] As the stabilizer concentration increases, the surface coverage by the stabilizer molecules also increases, leading to a steric hindrance effect and a greater reduction in average particle size.^[20] Stabilizers can interact with the dispersion medium, reducing interfacial tension and preventing particle aggregation. By improving the dispersion of drug and polymer particles, stabilizers can minimize inter-particle interactions and potential aggregation during the microsphere formation process. This contributes to the formation of smaller and more uniform particles, especially at higher stabilizer concentrations.^[21] As per the literature, stabilizers can react with certain functional groups on the drug or polymer, influencing their conformation and aggregation behavior. As stabilizer concentration increases, these interactions might influence particle growth, resulting in the noted reduction in average particle size.^[22]

The data suggested that stabilizer concentration has a minimal or inconsistent impact on the entrapment efficiency of nicotinamide within the microsponges in this particular study. While there was a small improvement in the entrapment efficiency is observed as the stabilizer concentration increased in some batches (B1-B3 and B7-B9), the overall change is relatively small and might not be statistically significant.^[18] Stabilizers can enhance the dispersion of drug and polymer particles, potentially leading to better mixing and interaction during microsphere formation. This could theoretically contribute to slightly higher entrapment efficiency by facilitating the encapsulation of a greater proportion

of the drug molecules within the polymer matrix.^[23] It was difficult to conclude with certainty, given the data at hand, that the stabilizer concentration significantly and consistently affected the nicotinamide entrapment efficiency in these microsponges.

A better number of drug molecules are available to take part in the early phases of particle production as the drug amount in the microsponges increases. Drug molecules have the potential to function as nucleation sites, encouraging the polymer chains surrounding them to aggregate. In contrast to formulations with lower drug loadings, this results in the development of bigger primary particles.^[24] Furthermore, at the later phases of microsphere production, interactions between the drug molecules themselves may contribute to further particle growth. As the dosage of the medicine increases, this cumulative effect causes the average particle size to grow overall. There is a limited quantity of possible binding sites for the medication molecules in the polymer. These binding sites get increasingly saturated when the drug concentration rises, but the amount of polymer stays the same. Due to this saturation effect, a sizable amount of the additional medication is unable to be efficiently encapsulated within the polymer matrix.^[25] The dispersion of these untrapped drug molecules throughout the formulation can reduce the overall entrapment efficiency.

Optimization of the Formulation Using 3² Factorial Design

The three-level two factor design was statistically analyzed and the details are displayed in Table 5. Both independent factors were shown to have a substantial impact (p -value < 0.05) on the dependent variables. With a high determination coefficient, F value, and fit, every regression model produced a satisfactory result. Since the R^2 for both replies was greater than 0.9, meaning that the model could justify a variation of more than 90% in the response, the model's efficacy of fit was validated.

Effect of Amount of Drug and Amount of Stabilizer on Entrapment Efficiency

The positive coefficient (2.02) for the amount of stabilizer (X_1) suggested that increasing the stabilizer concentration enhanced entrapment efficiency, possibly by improving the structural integrity of the microsphere matrix and facilitating drug entrapment. Conversely, the negative coefficient (-1.99) associated with the quantity of drug (X_2)

Table 5: Statistical analysis of 3² factorial design

Dependent variables		X_1	X_2	X_{12}	X_{11}	X_{22}	$F_{calculated}$	R^2
Entrapment efficiency (Y_1)	p -value	0.0001	0.0001	0.2639	0.7353	0.0203	253.26	0.9976
	Coefficient	2.02	-1.99	-0.1350	0.0517	-0.6283		
Average particle size (Y_2)	p -value	0.0001	0.0001	0.2456	0.9777	0.0374	531.12	0.9989
	Coefficient	-4.53	12.23	-0.4475	-0.0133	1.57		

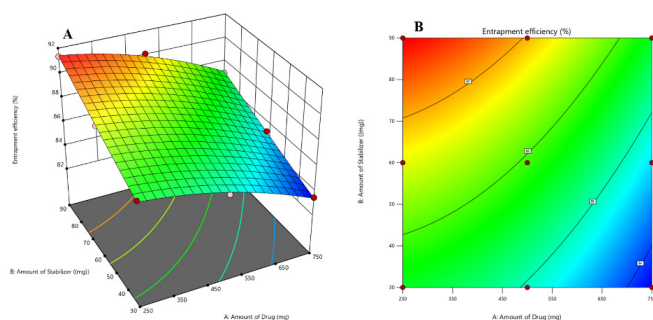


Fig. 1: A. 3D response surface plot; B. Contour plot of effect of the amount of drug and amount of stabilizer on entrapment efficiency

indicated that increasing the amount caused a decrease in entrapment efficiency, suggesting a potential saturation effect where higher drug concentrations exceeded the capacity of the microsp sponge matrix for encapsulation as per Fig. 1. Also, the interaction term coefficient (X_1X_2) suggested a synergistic effect between the amount of stabilizer and drug on entrapment efficiency, with the combined presence of optimal drug and stabilizer concentrations maximizing entrapment efficiency. Additionally, the quadratic terms (X_{11} and X_{22}) indicated nonlinear relationships between the independent variables and entrapment efficiency, highlighting the complex interplay of factors influencing drug encapsulation within the microsp sponge formulation.

During the microsp sponge preparation process, more stable emulsion droplets formed at higher stabilizer concentrations. As pore-forming agents, the stabilizer molecules modify the microsponges' structure and promote effective drug entrapment. Because of the improved stabilization of the droplets during emulsification, increasing the concentration of the stabilizer can result in smaller particle sizes. Smaller final particle sizes may arise from a more uniform droplet size distribution caused by the increased stabilizer content. Higher concentrations of the stabilizer molecules can create a denser layer around the droplets, which inhibits coalescence and encourages homogeneous particle formation.^[26]

Effect of Amount of Drug and Amount of Stabilizer on Average Particle Size

The negative coefficient (-4.53) for the amount of stabilizer (X_1) indicated that improving stabilizer concentration caused a reduced average particle size, possibly by promoting tighter packing of polymer chains and minimizing particle aggregation during microsp sponge formation. In contrast, a positive coefficient (12.23) of drug amount (X_2) suggested that increasing drug concentration led to increased average particle size, potentially because of the incorporation of drug molecules within the microsp sponge matrix, leading to larger particle sizes as shown in Fig. 2. The presence of interaction term suggested that the combined effects of the drug and concentration of

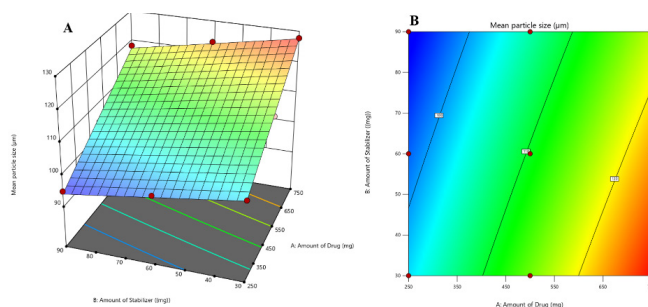


Fig. 2: A. 3D response surface plot and B. Contour plot for effect of the amount of drug and amount of stabilizer on average particle size

stabilizer on average particle size would probably not be purely additive, indicating potential interactions between the independent variables. Moreover, the coefficients of quadratic terms (X_{11} and X_{22}) suggested nonlinear relationships between the independent variables and average particle size, highlighting intricate nature of factors affecting particle size distribution in microsp sponge formulations.

A larger ratio of drug to polymer indicated a higher concentration of drug molecules in comparison to the polymer matrix. During the preparation phase, more effective microsp sponge nucleation and development would occur due to this higher concentration of drug molecules. Because there are more drug molecules accessible to bind with the polymer and start the generation of smaller-sized particles, smaller microsp sponge particles end up forming. On the other hand, larger microsp sponge particles form when the drug: polymer ratio is lower because fewer drug molecules are accessible to take part in the nucleation and growth process. The viscosity of the solution employed in the manufacture of the microsp sponge can be impacted by the increased drug:polymer ratio. Viscosity that is higher can encourage the emulsification process to produce smaller droplets, which in turn produce smaller microsp sponge particles.^[27]

To create the microsponges with predetermined restrictions, optimization studies were conducted. Using Design Expert 13 software, the desirability function was applied based on the equations derived from the statistical analysis of 3^2 factorial designs. The restrictions were designed to obtain at least 89% of the Y_1 responses while maintaining the Y_2 within the 100 to 105 μm range. The software generated two solutions as displayed in Table 6, together with the anticipated values of the responses and desirability as well. The levels of each factor are shown, too. The desirability rating of 1 was the same for both solutions. The first solution was selected for confirmation because it required a little less amount of drug.

A final formulation of nicotinamide microsponges, labeled as batch D1, was prepared based on the levels determined by the desirability function. Table 7 shows that the evaluation parameters closely matched the theoretical



Table 6: Solutions provided by Design Expert 13 software

S. No.	Drug (mg)	Stabilizer (mg)	Entrapment efficiency (%)	Average particle size (μm)	Desirability
1	302.874	59.715	89.018	100.748	1.000
2	310.017	59.972	89.007	100.992	1.000

Table 7: The values of optimized batch for experimental and observed responses

S. No.	Parameters	Predicted	Observed	%Difference
1	Entrapment efficiency (%)	89.018	88.41	0.68
2	Average particle size (μm)	100.748	103.33	2.57

Table 8: Flow properties of design batches

Batch	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
B1	0.28 \pm 0.02	0.34 \pm 0.01	17.65 \pm 2.94	1.21 \pm 0.08	32.14 \pm 1.87
B2	0.30 \pm 0.01	0.36 \pm 0.02	16.67 \pm 1.78	1.20 \pm 0.06	30.82 \pm 1.54
B3	0.32 \pm 0.03	0.38 \pm 0.01	15.79 \pm 2.31	1.19 \pm 0.07	29.50 \pm 1.28
B4	0.24 \pm 0.01	0.30 \pm 0.02	20.00 \pm 3.14	1.25 \pm 0.10	34.28 \pm 2.06
B5	0.26 \pm 0.02	0.32 \pm 0.01	18.75 \pm 2.63	1.23 \pm 0.08	32.91 \pm 1.97
B6	0.28 \pm 0.03	0.34 \pm 0.02	17.65 \pm 2.41	1.21 \pm 0.07	31.54 \pm 1.82
B7	0.22 \pm 0.01	0.28 \pm 0.02	21.43 \pm 3.42	1.27 \pm 0.11	35.71 \pm 2.14
B8	0.24 \pm 0.02	0.30 \pm 0.01	20.00 \pm 2.87	1.25 \pm 0.09	34.18 \pm 2.03
B9	0.26 \pm 0.03	0.32 \pm 0.02	18.75 \pm 2.71	1.23 \pm 0.08	32.74 \pm 1.94

and practical values of the observed responses, validating the generated mathematical model. The optimized batch was then further assessed for additional evaluation parameters.

Observing the data across the nine batches (B1-B9), nuanced disparities emerge as per Table 8. Bulk densities ranged from 0.22 to 0.32 g/cm³, indicative of the mass of material per unit volume, with a tendency towards lower densities in B7 and B8. Tapped densities, representing the compactness post-tapping, exhibit similar trends, with values fluctuating between 0.28 and 0.38 g/cm³. Notably, batches B4 and B7 demonstrated relatively lower tapped densities, indicating a propensity for greater compaction upon tapping. Carr's index, a measure of flowability, showcases variations from 15.79 to 21.43%, portraying differences in the ability of the microsponges to flow freely. Lower Carr's index values signify better flow properties, highlighting the favorable flowability of batches B3 and B5. Hausner's ratio, indicative of interparticle friction and packing properties, ranges from 1.19 to 1.27, with lower values indicative of improved flowability and packing characteristics. Moreover, the angle of repose, an indicator of particle cohesion and flowability, spans from 29.50 to 35.71°, with lower angles signifying enhanced flow properties. Notably, batches B7 and B4 exhibit higher angles of repose, implying relatively poorer flow properties.^[28]

***In-vitro* Dissolution Study**

The information gathered from the release studies displayed unique drug-release profiles for every batch, demonstrating variances in the kinetics of drug release impacted by formulation elements. The prompt breakdown of the surface drug molecules is responsible for the burst release shown during the first time points (0.5–1 hour). Then, there was a sustained release pattern, which indicated that drug molecules were gradually diffusing out of the microsphere matrix.^[2] Batch B2 exhibited the highest drug release among all batches at various time points, suggesting optimized formulation parameters leading to enhanced drug release kinetics. Conversely, Batch B7 demonstrated relatively laggy release kinetics than the other batches, which could be because of formulation factors *viz.* the type of stabilizer used and its concentration. Observed drug release profiles (Fig. 3) align with previous research on microsphere-based drug delivery systems. It has been in the prior knowledge that factors such as polymer type, drug loading, and particle size influence drug release kinetics from microsphere formulations. Additionally, the presence of porosity within microsponges facilitated the diffusion of drug molecules, contributing to sustained drug release for a long period.^[29] The sustained drug release observed here was admissible for achieving prolonged therapeutic effects and minimizing the frequency of drug administration.

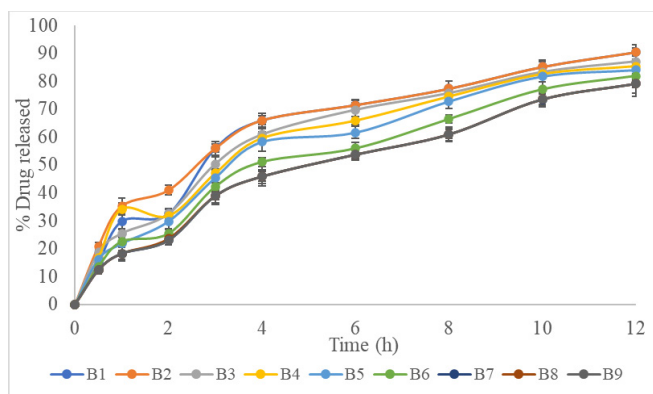


Fig. 3: *In-vitro* dissolution studies of design batches of nicotinamide microsponges

Moreover, the controlled release of nicotinamide from microsponges could be beneficial for the treatment of acne. Reduced stabilizer concentration results in smaller pores, which may restrict drug molecule accommodation and cause a slower and lower release of the drug. Greater drug incorporation into the microsphere matrix was indicated by a higher drug:polymer ratio. Because of this, the drug's concentration gradient within the matrix is larger, which causes the drug to quickly diffuse out of the microsponges and cause an enhanced initial burst release.^[30] Nevertheless, the polymer matrix swells and erodes when the medication is released. A denser and more compact structure results from a higher drug:polymer ratio because more drug is trapped within the polymer matrix. Because of its denser matrix, the drug molecules are unable to diffuse as widely within the polymer network, which inhibits additional drug release.^[31] Furthermore, the physical characteristics of the polymer matrix, such as porosity and tortuosity, may be impacted by the increased drug loading. These modifications may

Table 9: Evaluation parameters of optimized formulation

Name of evaluation parameter	Result
Production yield (%)	78.43 ± 1.63
Angle of repose (°)	29.57 ± 1.12
Carr's index	15.87 ± 1.34
Hausner's ratio	1.18 ± 0.08
Drug content (%)	91.25 ± 1.54

also affect the drug's diffusion kinetics, which may have an effect on the drug's overall release profile.^[32]

Evaluation Parameters of Optimized Batch

The evaluation parameter results of the prepared optimized batch are as per Table 9.

With a production yield of 78.43%, the manufacturing process demonstrates efficiency and reproducibility. The angle of repose indicates favorable flow properties crucial for pharmaceutical applications. Carr's index suggests moderate compressibility, while Hausner's Ratio reflects good flowability and minimal interparticle friction, as shown in Table 9. The high drug content of 91.25% reflected the precise drug loading. These results affirmed the effectiveness of the chosen formulation parameters and manufacturing process in achieving desired product attributes, positioning the optimized microsphere batch as a promising candidate for pharmaceutical drug delivery applications.

SEM of Optimized Batch

The SEM images of the microsponges revealed a uniform and spherical morphology. The microsponges having the mean particle size ranging from 20 to 50 µm were observed as per Fig. 4, indicating successful microsphere formation with appropriate size for drug delivery applications.^[33] The surface of the microsphere contains the pores, which

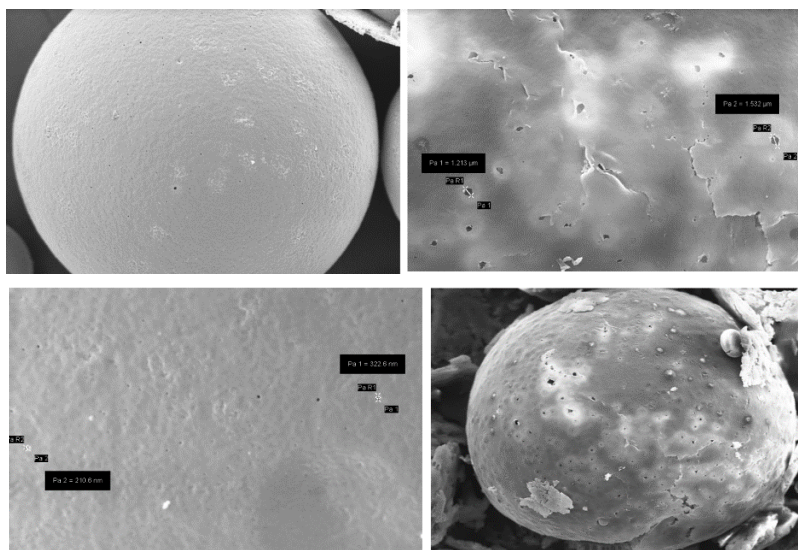


Fig. 4: Scanning electron microscopy of an optimized batch of nicotinamide microsphere



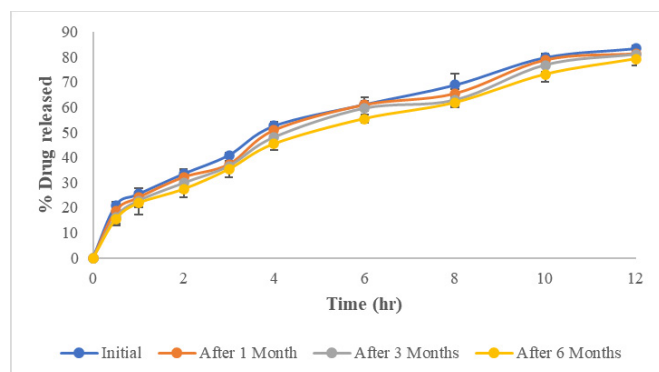


Fig. 5: Accelerated stability studies of optimized batch of microsponge

gives the sponginess of the surface, which will play a major role in the nicotinamide diffusion rates. The surface pores were found less than 2 μm in size.

Accelerated Stability Study of Optimized Batch

The initial drug release profile displays the baseline behavior of the microsponges and acts as a point of reference. The data clearly showed that at different time intervals, the initial drug release percentages varied from 20.85 to 83.40%, and the related standard deviations demonstrated the heterogeneity within the samples. Significant alterations in the drug release profiles were noted when subjected to accelerated aging circumstances (Fig. 5). All batches showed a decrease in drug release after a month, which could be the result of changes to the microsponge structure or interactions between the drug and the polymer.^[30] At three and six months, more declines in the drug release percentages could be observed, depicting the continuation of this tendency. The reduced drug release might probably be because of the degradation of drug molecules or microsponge matrix as time passes, which would lead to a slower release rate. Furthermore, the variability in drug release across various batches is highlighted by the observed standard deviations at each time point, highlighting the significance of strong formulation procedures to guarantee consistency and repeatability in drug delivery systems.^[24]

CONCLUSION

In this study, the development and evaluation of nicotinamide microsponges were successfully conducted, presenting a promising platform for the controlled and targeted delivery of nicotinamide for topical acne treatment. Quasi-emulsion solvent diffusion method was implemented to formulate the microsponges. The effects of processing variables (stirring speed, time, and internal phase volume) and stabilizer concentration on particle size, entrapment efficiency, and production yield were examined in this work. Processing variables and stabilizer concentration significantly impacted all the response parameters. The optimized formulation achieved a high

entrapment efficiency (88.41%) and a suitable particle size range (20–50 μm) for topical delivery. Prolonged effects may be possible, as evidenced by *in-vitro* drug release studies that demonstrated sustained release. These results are indicative of the fact that nicotinamide microsponges possess characteristics desirable for a topical drug delivery system. Their sustained release properties could potentially enhance therapeutic efficacy and patient compliance in acne treatment. Additional clinical studies are needed to examine the effectiveness of this innovative delivery system for topical acne treatment.

FUTURE PROSPECTS

This research work was focused on the development of nicotinamide-based microsponges. The future prospects of this work incorporate the formulation and optimization of clindamycin phosphate based microsponges and subsequent creation of a topical dosage form using these microsponges of both the drugs. A suitable proportion of the microsponges will be incorporated in this topical dosage form that will be useful for the treatment of Acne vulgaris. This final formulation is expected to be a gel or an emulgel, which will incorporate microsponges prepared in current work along with the microsponges of clindamycin phosphate. In conclusion, the future prospects of this work would be useful to provide the scope for the further development of a combination-based formulation able to produce a prolonged effect on acne vulgaris.

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