ORIGINAL RESEARCH

Ibuprofen Nanoemulsion as a Promising Drug Delivery Strategy

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ABSTRACT

Phenyl propionic acid derivative drug Ibuprofen was selected for the study's model medication. It is hypothesized that nanoemulsion might be a useful medication delivery method for enhancing oral absorption. According to the findings, the nanoemulsion formulation greatly enhanced the drug's anti-inflammatory capabilities when compared to the Ibuprofen solution. Ibuprofen's solubility and oral bioavailability are enhanced using nanoemulsion technology. To evaluate and pinpoint nanoemulsion area's are made of glycerol, olive oil, and various sucrose esters, a pseudo ternary phase diagram was created (co-surfactant). Following the discovery of such a nanoemulsion zone, a colloidal system was created to serve as an ibuprofen carrier system. Droplet size, polydispersity index, zeta potential, and morphological measurements were made to determine the characteristics of the chosen nanoemulsion (NE) area.

Keywords: Ibuprofen, Oil-in-Water emulsion, Olive oil, Pseudo ternary phase diagram, Silicone nanoemulsion.

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INTRODUCTION

The use of nanotechnology in the pharmaceutical industry has unquestionably increased during the past several years. Thermodynamically stable systems with a certain ratio of oils, water and surfactants or cosurfactants are known as nanoemulsions.[1] Lipophilic medication are maintained in the outermost layers of the skin when administered topically. Topical administration of NEs utilizing various ways improves the amount of an active component, whether it is administered locally or systemically. Nanoemulsions (NEs) provide the trapping of a greater amount of medication compared to customary topical formulations (*e.g.,* creams, ointments, lotions, and gels). NEs pharmaceuticals, distributed in oil droplet phase, can enhance the solubility of insufficiently water-soluble medications.[2] Different NE compositions increase the drug's ability to pass past the skin's diffusional barrier.[3]

Nonsteroidal anti-inflammatory drugs (NSAIDs); Ketoprofen, ibuprofen, indomethacin, aceclofenac, and celecoxib are having manufactured in nanoemulsion forms to improve skin permeations.[4]

Ibuprofen (phenyl propionic acid derivative) is widely used to treat osteoarthritis, rheumatoid arthritis, and other problems connected to these diseases. This molecule has been selected as the study's model. This is due to the low gastrointestinal absorption and solubility of ibuprofen when taken orally. Thus, it is hypothesized that nanoemulsion might be a useful medication delivery method for enhancing oral absorption. Ibuprofen is now offered for sale in the form of pills, gel, and oral solutions.[5]

According to the findings, the nanoemulsion formulation greatly enhanced the drug's anti-inflammatory capabilities when compared to Ibuprofen solution.

In research, the effectiveness of nanoemulsion in enhancing oral bioavailability and solubility of Ibuprofen was examined. To evaluate and pinpoint a nanoemulsion area made of glycerol, olive oil and various sucrose esters, a pseudo ternary phase diagram was created (co-surfactant).[6,7] Following the discovery of such a nanoemulsion zone, a colloidal system was created to serve as an ibuprofen carrier system. Droplet size, polydispersity index, zeta potential, and morphological measurements were made to assess the characteristics of the chosen nanoemulsion (NE) area. Additionally, *in-vitro* research was done to determine whether or not an ibuprofen-loaded nanoemulsion may improve the drug's oral bioavailability after delivery.

MATERIALS AND METHODS

All other compounds, including Ibuprofen, sodium chloride, Pluronic 17 R4, were analytical quality and utilised as directed.

Preparation of Nanoemulsion

Oil (olive acid), a surfactant (Pluronic 17 R4), a percentage of NaCl content, and filtered water were utilized in the preparation process by titration (continuous phase). In a nutshell, oil phase combined with Smix, or oil:Smix (0-3:3-0), were taken

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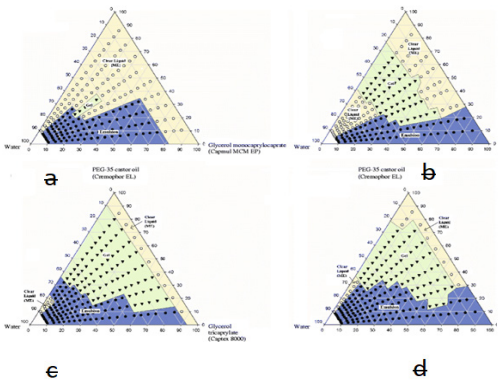


Figure 1: Phase diagrams

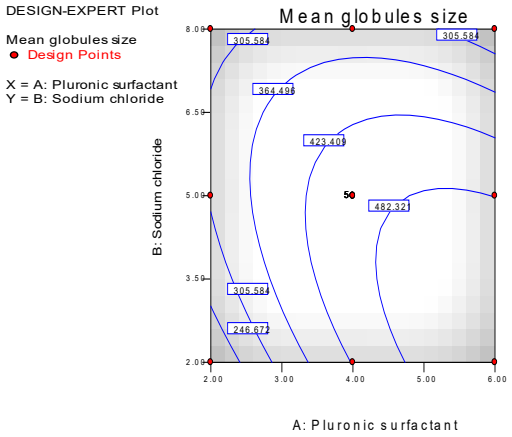
in a variety of ratios (1-9:9-1), titrated with purified H_2O, and introduced drop-wise to the internal phase while being constantly stirred. To assess the transparent nanoemulsion, pseudo-ternary-phase diagrams were created (Table 1).[8]

Construction of Phase Diagrams

In separate 100 mL volumetric flasks, the following lipid/surfactant mixtures (4 g each) were made: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1. Then, 5% w/w H_2O was added to each flask at regular periods.

Experimental Design for Optimization

This statistical experimental investigation was conducted using Design Expert. For formulation optimization, the 32 (three level-two factor) response surface approach was used to identify impact of different independent variables on responses. The percent Pluronic 17 R4 concentration (X_1) and percent



(a)

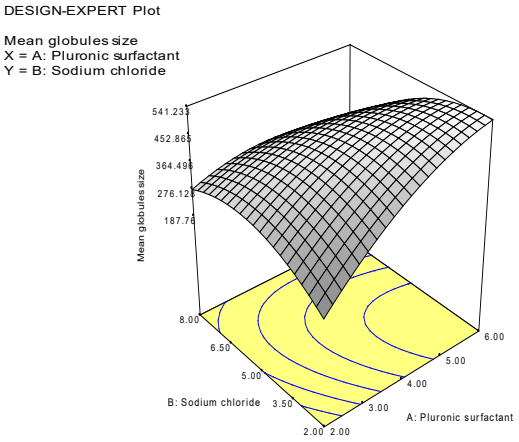


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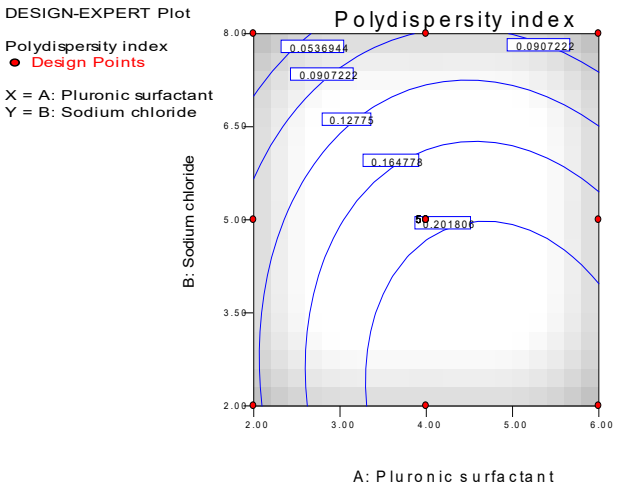
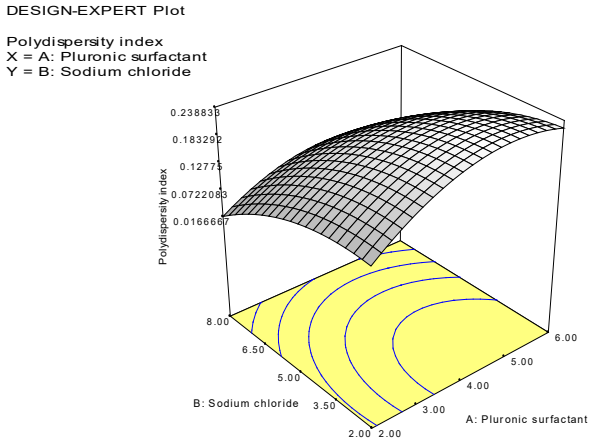
Figure 2: Mean globules size (a) 2D and (b) 3D graph



(a)



(b)

Figure 3: (a) 2D, (b) 3D graph for mean polydispersity index

Table 1: Nanoemulsion formulation batches

Batch	*Pluronic 17 R4 surfactant (%)*	*Nacl (%)*	*Mean globules size (nm)*	*Polydispersity index*
1	4	5	312	0.184
2	6	8	225.8	0.015
3	6	2	544	0.21
4	4	2	380	0.195
5	2	8	275	0.031
6	6	5	515	0.238
7	4	8	369	0.124
8	4	5	412	0.194
9	2	5	268	0.044
10	4	5	533.5	0.211
11	4	5	526	0.199
12	4	5	517	0.187
13	2	2	230	0.166

Table 2: Regression analysis for responses Y_1 and Y_2

Source	*Sum of squares*	*DF*	*Mean square*	*F Value*	*Prob > F*	*Remarks*
Response Y_1						
Mean	2006501	1	2006501			
Linear	57118.15	2	28559.07	2.282667	0.1525	
2FI	32978.56	1	32978.56	3.221466	0.1063	
Quadratic	45169.79	2	22584.9	3.36626	0.0946	Suggested
Cubic	9636.173	2	4818.087	0.645368	0.5632	
Response Y_2						
Mean	0.307077	1	0.307077			
Linear	0.035014	2	0.017507	5.255078	0.0276	
2FI	0.0009	1	0.0009	0.249887	0.6291	
Quadratic	0.018211	2	0.009106	4.48764	0.0557	Suggested

Table 3: ANOVA of models for Y_1 and Y_2

Source	*Std. deviation*	*R-squared*	*Adjusted R-squared*	*Predicted R-squared*	*PRESS*	*Remark*
Response Y_1						
Linear	111.8538	0.313438	0.176126	-0.37154	249937.7	
2FI	101.1787	0.49441	0.32588	-0.65218	301077.6	
Quadratic	81.90968	0.742281	0.558196	0.159208	153218.2	Suggested
Cubic	86.40393	0.79516	0.508384	0.629773	67466.73	
Response Y_2						
Linear	0.057719	0.512437	0.414924	-0.02035	0.069719	
2FI	0.060014	0.525608	0.367478	-1.1576	0.147426	
Quadratic	0.045045	0.792132	0.643656	-1.05796	0.140618	Suggested
Cubic	0.009571	0.993297	0.983913	0.990213	0.000669	

Sodium chloride concentration (X_2), which were altered at 3 levels (1, 0, +1), were chosen as independent variables for this investigation. Dependent factors were chosen globules size (nm) and polydispersity index. Table 1 contains the statistical design that the program displays for dependent and independent variables.[9] Following equation was used to represent how independent (X_1, X_2) affected dependent variables (Y_1, Y_2):

$$Y = \beta_0 + \beta_1 x_1 + \beta_1 x_1 + \beta_3 x_1 x_2 + \beta_4 x_1^2 + \beta_5 x_2^2$$

Where,

Y is response, $\beta 0$ is intercept and $\beta 1$–$\beta 5$ is regression

coefficients. individual effects. is interaction effect and, are the quadratic effects. Using one-way ANOVA, the significance of model was assessed at $p < 0.05$.[10]

Characterizations

Diffusion Study

Ibuprofen *in-vitro* from nanoformulations was investigated in the manner described below. The *in-vitro* skin diffusion investigations employed a technique comparable to membrane release research.

Partition Coefficient

At 37°C, the nanoemulsion was estimated in octanol/water. Graduated tubes were stocked with octanol and 50 mL water each. Ibuprofen nanoemulsion in the amount of 30 mg equivalent weight was then added to each flask, and the solutions were mechanically shaken for 24 hours.

Zeta Potential

Malvern Zetasizer Nano ZS was used to examined, size distribution & droplet size of ibuprofen nanoemulsion (Malvern Instruments, Worcestershire, UK).

RESULTS AND DISCUSSION

Phase Diagrams with Individual Lipids

Same surfactant, pluronic olive acid, was used to construct all phase diagrams since the primary objective of this work was to investigate a number of medium chain glycerides applicable to the development of dosage forms. Since lipids and surfactants were nonionic in nature ans prior study suggested that change in pH had no effect on phase diagrams, distilled H_2O was chosen as an aqueous medium. According to a preliminary test, using 0.01 M HCl as a dilution medium instead of water had no influence on the phase diagram. Diagrams of lipid/surfactant/water phases of 4 medium chain lipids Figure 1.

Partition coefficient

The Ibuprofen nanoemulsion sample's estimated partition coefficient at 37°C was 3.35, which was quite similar to the 3.2 value that was previously reported.

Zeta potential

In this work, the prospective short and long-term stability of nano-formulations were related using zeta-potential values. According to the literature, a 20 mV or more zeta potential indicates short stability, whereas a value of 30 mV or more is considered stable. The spectrum considered to contain stable emulsions encompasses all of the ibuprofen nanoemulsion's zeta-potentials.

Optimization

With the least amount of experimental runs possible, the influence of independent (X_1, X_2) on dependent variables (Y_1, Y_2) was determined using a 3^2-response surface approach. Counter plots in 2D Figures 2a, 3a and 3d Figure 2b, 3b were built to examine the impact of same independent factors. Globules size (nm) and the polydispersity index were chosen as the dependent variables for this investigation, where as percent Pluronic concentration (X_1) and NaCl concentration (X_2) were selected as independent factors. All 13 experimental runs at three levels produced globules with sizes between 225.8 and 544 nm and polydispersity indices between 0.015 and 0.238, which are listed in Table 1. Polynomial equations and counterplots are developed to research the mathematical relationship between the dependent and independent variables (Table 2). Correlation coefficient (R^2) values of 0.742281 for the quadratic model of Y_1 response and 0.792132 for the linear model of Y_2 response indicate a satisfactory match (Table 3). The following equations were found for the Globules Size (Y_1) and Polydispersity Index (Y_2) response.

$$Y_1=+458.33+85.30\ X_1-47.37X_2-62.42\ X_1^2-79.42\ X_2^2-90.8\ X_1\ X_2 \ldots (2)$$

$$Y_2= +0.20+0.037\ X_1-0.067\ X_2-0.054\ X_1^2-0.035\ X_2^2-0.015X_1\ X_2 \ldots (3)$$

Positive and negative values in the equations above describe synergistic and antagonistic effects. ANOVA of model for the Y_1 and Y_2 responses is displayed in Table 3. For EE () factor, quadratic equation predicts that affected by independent variables like. According to equations (2 and 3), a positive value has a positive/synergistic impact. Conversely, negative number has the opposite impact on the reaction.[11] Additionally, at $p < 0.05$, these independent effects on globule size and polydispersity index were significant. Both the quadratic and linear models' p-values were under 0.05. At F values of 3.36 and 4.48 and $p < 0.05$, both models were significant. Diagnostic case statistics including actual, anticipated, and residual values for various response factors.

CONCLUSION

Ibuprofen may have a greater oral bioavailability if nanoemulsion is used. To select the area of the nanoemulsion that is most suited for drug administration, an optimal concentration of oil, surfactant, and the co-surfactant combination was created using a pseudo ternary phase diagram. We discovered that mixing glycerol, SE L-1695, and olive oil created a significant nanoemulsion zone that may be used for drug delivery. Additionally, an *in vitro* evaluation found that oral bioavailability of nanoemulsion ibuprofen was 2.2 times greater than that of the control formulation. This research demonstrates how a stable nanoemulsion of ibuprofen was created to offer a higher oral bioavailability through careful excipient selection.

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