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Original Article

3^2 Factorial Design of O/W Nanoemulsions of Cholecalciferol Using Box–Behnken Model for Plaque Psoriasis

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ABSTRACT

Aim: The aim of the study was to design O/W Nanoemulsion using Cholecalciferol in different ratios of surfactants with Box-Behnken design model using Design Expert version 12. Response surface methodology, Box-Behnken was most suited followed by 3 independent variables (A, B, C) and 9 different responses with 17 different batches. Various responses like pH, % drug content drug entrapment and % *in vitro* drug release at different time intervals comparable with independent variables with % predicted errors calculated with SD±5 values. **Materials and Methods:** Cholecalciferol used as model drug, SPAN 20, SPAN 80 used as surfactant and Soybean oil used as oil phase for making Nanoemulsion preparation for plaque psoriasis treatment prepared by probe sonication method. **Results:** The VIF values were 1.0-1.03 and Ri^2 range between 0.00-0.0058 means correlated with each-others were in range, showed statistically correct and chances of error is minimum shown in Table 1. The predicted pH 7.79±0.38, Drug entrapment 92.68±4.67 and % Drug content was found to be 92.5±6.08 while experimental values were 7.20±0.11, 95.32±0.76, 93.29±1.15%. The predicted values of *in vitro* drug release were 5.54±1.57, 13.98±2.19, 25.96±4.40, 47.14±3.18, 68.17±6.02, 80.36±4.39% while experimental values were 8.50±0.50, 16.54±2.30, 29.54±2.27, 42.20±1.10, 68.54±1.27, 79.64±2.35% at 10, 30,60,90,120,210 min respectively see Table 2. The *p* values was <0.0001. **Conclusion:** The model showed *F*-values were in the range 0.28-5.08 showed non-significant while *p*-values was 0.028 showed significant values followed quadratic model. This showed that the model is best suitable for optimization.

Keywords: Optimization, Nanoemulsion, Box-Behnken design, Psoriasis, 3^2 factorial designs.

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INTRODUCTION

In Psoriasis skin cell has matured and ultimately flakes off. The Life cycle of human skin completed within 28 to 44 days and move from bottom layer of the epidermis to the horny layer stratum corneum, but many factors like stress, trauma, inflammation or diseased condition of psoriasis the cell cycle completed on 3-4 days and forms scaly silver patch which shaded rapidly. A skin cycle is too fast in psoriasis patient as compared to normal healthy person.[1] It affects life of children and young people and spare bad life with disease condition. Skin disorders affect many people globally, psoriasis is one of them which affect life of people emotionally, psychologically and sociologically bad. In some research studies showed that Niosomal gel produced an enhanced *ex vivo* permeation up to 30 hr.[2] Various drug delivery systems including use of topical corticosteroids, Vitamin D analogues, Phototherapy, Photochemotherapy, systemic therapy with methotrexate, cyclosporin, and combination therapies used in psoriasis. Anti-interleukin-12 agents have been successfully used for the treatment of psoriatic adults found in literature.[3,4] A skin cycle affected by several factors such as age, hormones, skin condition/health and stress. Psoriasis is a common cause, exist for long time, causing inflammation process occurs in skin and join in most of the patient.[5] Psoriasis is a non-communicable skin disease, with no clear cause or cure.[6] Psoriasis has great effects on life, combination therapy is needed.[7] It is a common, chronic inflammatory skin condition that affects 2-3% of the US population and represents a large psycho-social burden for patients.[8]

Box-Behnken technique is mainly used here to map the optimisation of Nanoemulsion.[9] Multiple responses are discussed, including the desirability function, which was proposed by Derringer and Suich in 1980.[10] The model not only analysed factors but also responses like *in vitro* drug release which was important parameter.[11,12] Psoriasis is common skin disorders occurs in 0.44% world population. It's autoimmune disorder when immune cells get activated by signalling mechanism and various triggers like environment, genetic, stress, depression and infections. The cytokines storm in body and destructs own

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immune cells and beginning of psoriasis seen in lower and upper extremities. Cholecalciferol is a drug depletes keratinocyte layer produced during psoriasis and stop trigger mechanism during autoimmune reaction. Calcipotriol and calcitriol also show similar receptor binding.[13-15] Many drugs Like capsaicin (CAP)-containing Liposomes, Niosomes and Emulsomes in providing the topical delivery but Cholecalciferol is a choice of drug.[16] The Nanoemulsion of Cholecalciferol used for topical drug delivery, it was thermodynamically stable formulation.[17,18] The advantage of emulsion is mend for mostly water insoluble drug. The oil phase dissolves the drug and water phase help in hydration. Emulsion is best suited but have various problems like cracking, phase separation and inversion when wrongly combination of oil: surfactant: water taken. Selection of suitable combination must for emulsion formulation so that optimization is essential.[19] Using Design expert software with ANOVA model and Box-Behnken model made suitable tools for optimization. It maps the optimal composition range for excipients. It will give predicted values compared with experimental values made suitable model. This model save time and help in selection of oil, water and drug made statistical error free.

MATERIALS AND METHODS

Chemicals

All chemicals were used as analytical grade for study. Span 20, Span 80, Soybean oil, Cholecalciferol purchased from Sigma Aldrich >98% HPLC grade with CAS no. C9756.[19-26]

Drugs and optimization model

Box-Behnken model was used for optimization of pharmaceutical novel dosage form using Design Expert software version 12 Stat ease with ANOVA model. The variables which would significantly affect the performance of desired final product behavior were considered as independent variable and the parameters to be employed for performance evaluation of the final product were selected as dependent or response variable. The A, B and C had high and low values.

Formulation development

For the preparation of O/W type Cholecalciferol Nanoemulsions, probe sonication method was most suited. About 17 Formulations were prepared by mixing of defined ratio of soyabean oil, surfactant mixture with drug prepared oil phase A and water phase B maintained at 75°C then poured B into A dropwise with high stirring 4000 rpm to prepared microemulsion. Then this microemulsion processed with nano emulsion using probe sonicator in the range of 200-800 nm. Prepared Nanoemulsion stored at 15-25°C in suitable container referred in Table 2.

Characterisation[22,23]

pH

The pH meter was calibrated at three points 4, 7, 9.2 with standard buffers, then formulations F1 to F17 taken in beaker and observed pH individually.

Drug content

1 mL of the nano-emulsion formulation dissolve in 10 mL of methanol than placed in ultra-sonicator for 30 min. After 30 min centrifuge the sample 10 min and supernatant was collected and analysed using UV-spectrophotometer at 267 nm against methanol as blank.[23]

Drug Entrapment (DE)

The entrapment is used to calculate how much amount of drug reside in nano globules using formula. DE= (Initial drug-free drug)/total quantity of drug in nano formulation X100

% *In vitro* drug release

This study done using Franz diffusion cell. About 1 mL formulation loaded in donor chamber and added saline phosphate buffer kept in receptor chamber at 37°C separated by selective semi-permeable membrane. The drug release rate observed every 30 min interval till 150 min. The saline phosphate buffer pH 6.8 stimulated to skin. 2 mL sample withdrawn, analysed

Table 1: For predicted and experimental values.

Sl. No.	Responses	Predicted value	Observed value	% Predicted error values
1	pH	7.79±0.38	7.20±0.11	8.19
2	Drug Content	92.5±6.08	95.32±0.76	2.95
3	Drug Entrapment	92.68±4.67	93.29±1.15	0.65
4	*In vitro* Drug Release at 10 min	5.54±1.57	8.50±0.50	34.82
5	*In vitro* Drug Release at 30 min	13.98±2.19	16.54±2.30	15.48
6	*In vitro* Drug Release at 60 min	25.96±4.40	29.54±2.27	12.12
7	*In vitro* Drug Release at 90 min	47.14±3.18	42.20±1.10	11.71
8	*In vitro* Drug Release Rate at 120 min	68.17±6.02	68.54±1.27	0.54
9	*In vitro* Drug Release Rate at 210 min	80.36±4.39	79.64±2.35	0.90

Table 2: For independent variables and responses.

Independent variables	Low	High
Quantity of oil (gm)	1	6
Quantity of surfactant and water (ratio)	1	9
Quantity of drug (mg)	100	300
Response		
pH	6.46±0.40	8.87±0.40
Drug content	80±5.02	98±5.02
Drug Entrapment	78±4.70	97.5±4.70
In vitro drug release at 10 min (µg/mL)	3.2±1.60	10.4±1.60
In vitro drug release at 30 min (µg/mL)	10.4±2.20	19.5±2.20
In vitro drug release at 60 min (µg/mL)	19.5±4.41	38±4.41
In vitro drug release at 90 min (µg/mL)	40±3.19	52.5±3.19
In vitro drug release at 120 min (µg/mL)	55.6±6.02	77.8±6.02
In vitro drug release at 210 min (µg/mL)	69.5±4.39	91.2±4.39

spectrophotometrically and same amount of saline phosphate buffer was added for sink condition.[22]

For optimization independent variables quantity of oil A, quantity of surfactant and water B, quantity of drug C with 9 responses (pH, Drug content, Entrapment efficiency and % *In vitro* drug concentration at 0, 10, 30, 60, 90, 120, 210 min. All values fit in Box-Behnken model total 17 combination were made showed in Table 3.

The standard error values observed in the range of 0.3536 to 0.5000. Low values were best for model. The VIF value was 1.0. and observed R^2 values were 0.0-0.0058.

Response surface curve between concentration of oil % (A), ratio of surfactant and water (B), and standard error of design.

The above graph showed the minimum standard error 0.437, 0.584 and maximum up to 1.167 observed which was optimum for model refereed above Figure 1. This above curve seems to be mathematically parabola in which at higher concentration of ratio of surfactant and water errors seems to be 0.800 and when concentration of oil and surfactant low the value was 0.40. At high concentration of oil, the value of standard error of design is 0.800.

ANOVA for Mean model

In this, independent variables A and B compared with R1 to R9. Various responses studies compared and *p*-value and *F*-Value were calculated. *p* value less than 0.0218 indicate model terms are significant. Values greater than 0.1000 indicate the model terms are not significant. The lack of Fit *F*-value ranges in 0.143 to 5.08 implied the lack of fit is not significant relative to the pure error. Non-significant lack of fit is good showed in Table 4.

Also, contour 3D plots made between quantity of drug, quantity of oil and surfactants and various responses shown in Figures 2 and 3.

In Figure 4 predicted values of all responses calculated that was compared with experimental values for better optimization. The comparison between predicted and experimental value of optimized formulation along with all responses given in below Table 1.

The above study Box-Behnken Design is used for optimization for pharmaceutical formulations like Nanoemulsion. There are 3 independent variables like quantity of oil A, quantity of surfactant and water B and quantity of drug C and 2 levels high and low. 3^2 designs compared on 9 responses namely pH, percentage drug content, drug entrapment, *In vitro* drug release at different time interval like 10, 30, 60, 90, 120 and 210 min studied.[3,9,11,27,28]

RESULTS

During the experimentation it was found that predicted value of % drug content was 92.5±6.08 while experimental value observed was 95.32±0.76, drug entrapment was 92.68±4.67, % *in vitro* drug release was 5.54±1.57, 13.98±2.19, 25.96±4.40, 47.14±3.18, 68.17±6.02, 80.36±4.39% while experimental values were 8.50±0.50, 16.54±2.30, 29.54±2.27, 42.20±1.10, 68.54±1.27, 79.64±2.35% in 10, 30, 60, 90, 120, 210 min also % predicted errors calculated were shown in Table 1.

DISCUSSION

O/W Nanoemulsion of Cholecalciferol using various combination of oil, surfactants: water using Box-Behnken design model and ANOVA study prepared by probe sonication method. Response surface methodology followed by 3 independent variables (A, B, C) and 9 different responses with 17 different batches. Cholecalciferol used as model drug for Nanoemulsion preparation for psoriasis treatment. The predicted pH 7.79±0.38 simulated with skin pH

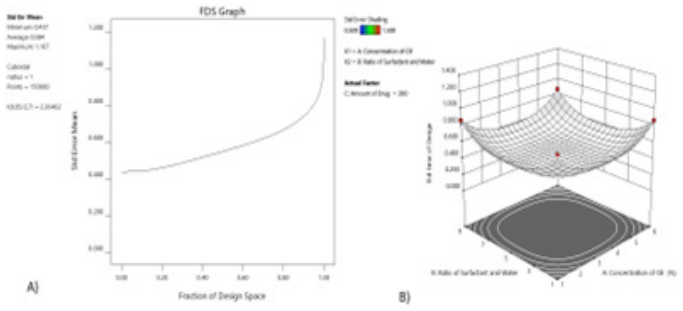

Figure 1: (a) A graph between Standard Error Mean and Fraction of Design Space, (b) Response surface curve between concentration of oil % (A), ratio of surfactant and water (B), and standard error of design.

Table 3: Optimization of various combination of oil: surfactant water and drug.

Run	A	B	C	R1	R2	R3	R4	R5	R6	R7	R8	R9
1	3.5	9	300	7.14	96	95	5.4	10.5	25.2	45	66	80.4
2	3.5	5	200	7.95	96.5	96	4.2	12.3	25.5	43	76	80
3	3.5	1	100	6.92	90	89	3.6	11.25	26	42	65	78
4	6	5	100	6.87	92	91	5.2	12.4	21	40	63	80.1
5	3.5	5	200	7.53	80	78	4.8	11.4	20.2	48	55.6	76.5
6	6	5	300	6.46	80.2	88	6.7	11.3	19.5	49.6	61.3	69.5
7	3.5	1	300	6.47	94.5	94	7.3	12.3	22.5	48.6	59.7	77.6
8	1	1	200	6.46	93	92	4.2	10.4	23	51	74	85.4
9	3.5	9	100	6.5	95.6	95	3.6	12.5	24	51.3	76	79
10	3.5	5	200	8.06	95	93	6	16.5	25.3	51.4	75	76.6
11	6	9	200	6.65	94	96	5.3	14.3	25.4	52.5	69.5	83.5
12	1	5	300	6.84	96.5	94	3.2	12.1	25.6	52.3	65	79.5
13	3.5	5	200	8.00	96	97	5.4	13.2	26.3	44.6	74	89.2
14	1	9	200	8.87	98	97.5	10.4	19.5	35.7	50.6	77.8	91.2
15	1	5	100	6.91	96	95.4	6.2	15.3	31.4	45.3	67	70.32
16	3.5	5	200	7.42	95	94.6	6.3	16.5	32.5	44.3	68.4	79.5
17	6	1	200	6.98	92	90.2	6.4	16.5	38	42	65.7	79.6

Table 4: Comparation of *p*-Values and *F*-Values with various responses.

Responses	Sum of square	df value	Mean square	*F*-value	*p*-value	Inference
Response 1: pH						
Model	6.76	9	0.7507	5.08	0.009	Significant follow quadratic model
Lack of fit	0.6841	3	0.2280	2.60	0.1893	Not significant
Response 2: Drug Content						
Lack of Fit	131.34	9	14.59	0.2963	0.27	Not significant
Response 3: Drug Entrapment						
Lack of Fit	105.39	12	8.78	0.10	<0.0001	Significant
Response 4: % *in vitro* drug release at 10 min						
Lack of Fit	21.84	6	3.64	4.93	0.04	Significant
Response 5: % *in vitro* drug release at 30 min						
Lack of Fit	28.26	3	9.42	1.95	0.03	Significant
Response 6: % *in vitro* drug release at 60 min						
Lack of Fit	59.35	3	19.78	1.03	0.02	Significant
Response 7: *In vitro* drug release at 90 min						
Lack of Fit	72.99	3	24.33	2.39	0.07	Not significant
Response 8: *In vitro* drug release at 120 min						
Lack of Fit	196.44	3	65.48	1.81	0.19	Not significant
Response 9: *In vitro* drug release at 240 min						
Lack of Fit	27.13	3	69.61	0.3348	0.02	Significant

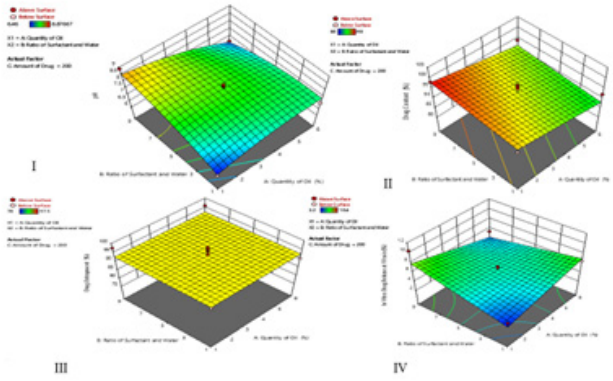

Figure 2: (I) 3D plot showed the effect of quantity of oil and ratio of surfactant: water against pH, (II) Effect of A and B against % drug content.[11] (III) Effect of B and A against drug entrapment.[11] (IV) Effects of independent variables A and B against *in vitro* drug release at 10 min.[11].

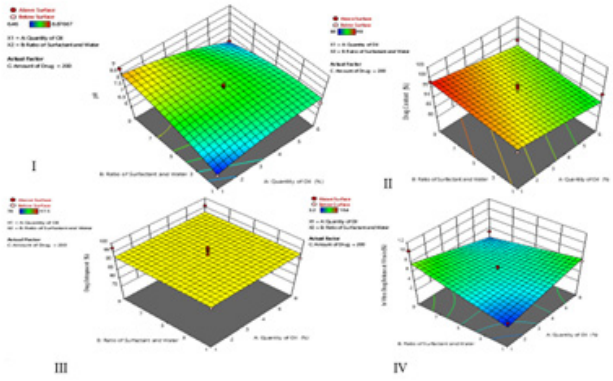

Figure 3: (V) Plot for the effect of concentration of A and B with % *in-vitro* drug release at 30 min.[11] (VI) Plot for *in vitro* drug release at 60 min with A and B variables.[11] (VII) 3-D plot of % *in vitro* drug release at 90 min.[11] (VIII) 3-D plot of % *in vitro* drug release at 120 min.[11] (IX) 3-D plot of % *in vitro* drug release at 240 min.[5,11]

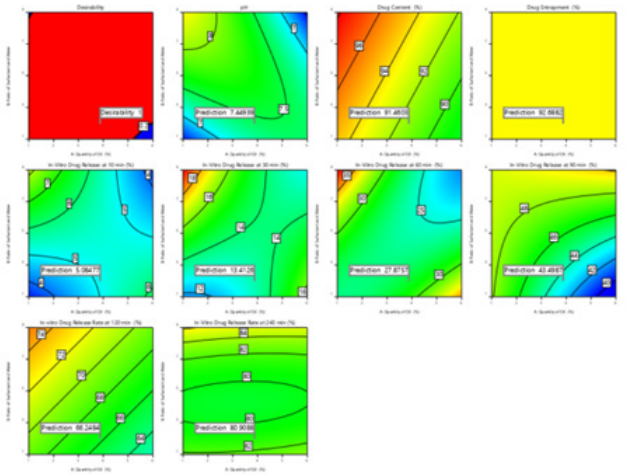

Figure 4: Predicted values of all responses.

while high Drug entrapment 92.68±4.67 and % Drug content was found to be 92.5±6.08 while experimental value was 7.20±0.11, 95.32±0.76, the predicted values of % *in vitro* drug release was 5.54±1.57, 13.98±2.19, 25.96±4.40, 47.14±3.18, 68.17±6.02, 80.36±4.39% at 10, 30, 60, 90, 120, 210 min while experimental values were 8.50±0.50, 16.54±2.30, 29.54±2.27, 42.20±1.10, 68.54±1.27, 79.64±2.35%. In Figure 3, 3D plot between A, B against independent variables showed that increased concentration of A, B high drug content and % drug entrapment achieved showed curve graph means followed quadratic equation. In Figure 4 green colour images showed optimum predicted values compared with experimental values. In RSM, the predicted values compared with experimental value and studied ANOVA model found that lack of fit is not significant and *p* values was <0.0001 showed the model is best suited followed by quadradic equation.

CONCLUSION

For the preparation of O/W Nanoemulsion of Cholecalciferol various levels like quantity of oil, surfactants and water are independent variables while pH, % entrapment efficacy, % drug content and % *in vitro* drug release at different time were dependent variables. O/W nanoemulsion of Cholecalciferol used as model drug for Nanoemulsion preparation for psoriasis treatment. The predicted pH 7.79±0.38 simulated with skin pH while high Drug entrapment 92.68±4.67 and % Drug content was found to be 92.5±6.08 while experimental value was 7.20±0.11, 95.32±0.76, the predicted values of % *in-vitro* drug release was 5.54±1.57, 13.98±2.19, 25.96±4.40, 47.14±3.18, 68.17±6.02, 80.36±4.39% at 10, 30, 60, 90, 120, 210 min while experimental values were 8.50±0.50, 16.54±2.30, 29.54±2.27, 42.20±1.10, 68.54±1.27, 79.64±2.35% with SD±5. In RSM, the predicted values compared with experimental value and studied Anova model found that lack of fit is not significant showed the model is best suited followed by quadradic equation.

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CONFLICT OF INTEREST

The author claims no potential conflicts of interest concerning the research, authorship and publication of this article.

ABBREVIATIONS

CAS: Chemical Abstracts Service; **%:** Percentage; **Min:** Minutes; **M.P.:** Madhya Pradesh; **3-D:** Third Dimension; **µg:** Microgram; **mL:** Millilitre; **>:** Less than; **°C:** Degree Celsius; **UV:** Ultra violet; **O/W:** Oil in Water type; **nm:** Nano-meter; **VIF:** Variance Inflation Factor, **FAC:** Factorial, **RS:** Responses, **RSM:** Response Surface Methadology.

SUMMARY

O/W Nanoemulsion of Cholecalciferol using soybean oil, surfactants: water using Box-Behnken design model prepared by probe sonication method. 3^2 factorial designs followed by 3 independent variables (A, B, C) and 9 different responses with 17 different batches. Various responses like pH, % drug entrapment, % drug content and % *in vitro* drug release at different time with independent variables studied. Cholecalciferol used as model drug for Nanoemulsion preparation for psoriasis treatment. The predicted pH 7.79, Drug entrapment 92.6882% and Drug content was found to be 91.46% while experimental value was 95.32, % *in vitro* drug release was 5.084, 13.412, 27.875, 43.498, 66.248, 80.908% at 10, 30, 60, 90, 120, 210 min while experimental values were 8.50, 16.54, 29.54, 42.20, 68.54, 79.64%. The predicted values compared with experimental value and studied ANOVA model found that lack of fit is not significant showed the model is optimised and best suited followed by quadradic equation.

AUTHOR CONTRIBUTION

Dr. Mukesh Chandra Sharma conceptualization, supervision review and editing the article. Mr. Mukul Sharma conceptualization, methodology, data curation, writing the original draft and editing the article.

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