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ORIGINAL RESEARCH

Quality by Design (QbD) Approach for Optimization of Microemulsion based Topical Gel

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ABSTRACT

The objective of the study was to develop a microemulsion based topical gel formulation of Aceclofenac, an oral NSAID with known major complications like dyspepsia, ulcer and bleeding. Topical route overcomes the above complications and provides the additional advantage of site specific delivery. Aceclofenac being BCS class II drug pose the formulation problem because of lower aqueous solubility. Thus development of microemulsion based gel will be of greater benefit as oil phase will aid in drug solubilisation and its smaller size will facilitate higher permeation. The components of the formulation include Labrafac Lipophile WL1349, Cremophor EL and Transcutol P as oil phase, surfactant and cosurfactant, respectively. The effect of oil to surfactant/co-surfactant ratio and carbopol 940 on drug release and viscosity profile of the formulation was studied by 3^2 factorial design. Dynamic light scattering demonstrate a well defined spherical shape and uniform size (<90 nm) with narrow poly-dispersity index (0.234) and a zeta potential -7.02 mV. The *in vitro* drug release from the optimized batch containing oil to surfactant/co-surfactant ratio (1:9) and 1.015 %w/w Carbopol 940 was found to be 73.85±2.07% at 180 min. The *in-vitro* drug release profile of the optimized formulation was compared with marketed product showing greater drug release with similarity factor (f2) of 34.486 %. The results revealed that the developed microemulsion gel has great potential for topical delivery of Aceclofenac.

Keywords: Microemulsion, Topical gel, Aceclofenac, Factorial design, Quality by design.

1. Introduction:

Aceclofenac, 2-[2-[2-[(2,6-dichlorophenyl)amino]phenyl] acetyl]oxyacetic acid, is a new generation nonsteroidal anti-inflammatory drug possessing anti-inflammatory and analgesic property. It is indicated for the management of arthritis, dental pain, spondylitis, post-operative pain and gonalgia. Oral administration of Aceclofenac (ACE) is commonly reported to cause gastrointestinal ulcers and bleeding on chronic use which may further result in anaemia (1). ACE being BCS Class II drug has very low solubility in biological fluids leading to poor bioavailability after oral administration.

Topical drug delivery offers several advantages like eliminating first pass metabolism, non-invasiveness and increased patient compliances. However, the major problem with topical delivery is stratum corneum which behaves as a natural barrier against diffusion of drug through underlying tissue. Several novel drug delivery technologies such as iontophoresis (2), nanoparticles (3), liposomes (4), chemical

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penetration enhancer (5), ethosomes (6) overcome this challenge.

Microemulsions (ME) are isotropic, thermodynamically stable transparent or translucent systems composed of oil, water and surfactant, often in combination with a co-surfactant. Their size generally ranges from 10-200 nm which provides advantage of ease of penetration through skin (7). ME are reported to improve adherence with skin surface, filling even wrinkles and microscopic gaps enhancing the vehicle skin drug transfer. Their topical formulations are reported to enhance the cutaneous absorption of both lipophilic and hydrophilic API's (8). Moreover, surfactants and co-surfactants possess lipophilicity that improves permeation rate and solubilisation of drug in oil phase.

However microemulsion the low viscosity of ME pose problem of applicability to skin, decreasing the patient compliance (9). Alternative approach like microemulsion based topical gel has been utilized to overcome these problems. Moreover, microemulsion based gel limits the absorption of drug in systemic circulation and provides higher drug accumulation in the skin for efficient action (10).

The traditional experimentation based on trial and error experiments are cumbersome, time-consuming and expensive as it often requires a large number of samples. Quality by Design approach provides the best potential solutions by providing formulation and process understanding. It provides comparison between predicted responses and observed experimental responses. This helps in the identification of the independent factors with significant impact and their interaction effect on the desired responses (11,12). The core importance of designing experiments is to ensure that the results can be obtained with utilization of minimum time, resources and effort.

Thus the aim of the present study was to develop microemulsion based gel of ACE for topical delivery by QbD approach. The objectives to attain this aim were formation of pseudo-ternary phase diagram, identification of crucial formulation variables and its effect on dependent variables with aid of Design of experiment (DOE) and obtain a suitable design space. 3^2 full factorial design was used to explore the effect of ratio of oil to surfactant/cosurfactant mixture (Smix), and concentration of gelling agent on the response dependent variable drug release and viscosity of formulation. Finally, optimized formulation was compared with the marketed product. This work exemplifies the use of DOE approach for microemulsion based gel of Aceclofenac.

2. Materials and Methods

2.1. Materials

Following were the kind gift samples provided by companies. Aceclofenac BP (Schion Pharmaceuticals, Indore, India); LabrafacLipophile WL, Maisine 35-1, Gelucire 44/14, Capryol 90, Transcutol P (Gattefosse, Mumbai, India), Cremophor EL (BASF, Mumbai, India), Carbopol 940 (Corel PharmaCheml, Ahmedabad). Isopropyl myristate (IPM), Polyethyleneglycol 400 (PEG 400), Propylene glycol, Tween 20 and Tween 80 were purchased from S.D. Fine Chemicals, Mumbai, India. All other reagents used were of analytical grade.

2.2. Methods

2.2.1. Solubility studies

The solubility of ACE was determined by adding excess amount of drug into 1 ml of oil/surfactant/co-surfactant in the vial, and placed in an isothermal shaker at 25 °C for 24 h at 100 rpm. Solutions were centrifugedusing centrifuge (Remi, India) at 10,000 rpm for 15 min. The supernatant was diluted with methanol and filtered through 0.2 µm membrane filter (HiMedia, India) and analysed using UV-Visible spectrophotometer (Shimadzu 1700) at 274 nm.

2.2.2. Pseudo-ternary phase diagrams

The weight ratio of surfactant to co-surfactant (Km) varied as 2:1, 3:1 and 4:1. For each pseudo-ternary phase diagram at a specific surfactant/co-surfactant weight ratio, the oily mixtures containing oil, surfactant and co-surfactant were prepared with the weight ratio of oil to the surfactant/co-surfactant mixture at 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 (w/w). Water was added drop by drop to each oily mixture under proper magnetic stirring (500rpm) at 37°C until the mixture became turbid. The points at which mixture became turbid were plotted on to the phase diagram.

2.2.3. Preparation of formulation

Drug loaded microemulsion systems were prepared by dissolving ACE in oil and Smix followed by the addition of water drop by drop with constant stirring at ambient temperature. Later the microemulsions were allowed to equilibrate with gentle magnetic stirring followed by ultrasonication. Carbopol 940 was dissolved in deionized water. The microemulsion was then added to this system to obtain final formulation. The resulting solution was equilibrated with gentle magnetic stirring and then ultrasonicated producing transparent and homogenous MEG.

Formulation were prepared by varying oil to Smix ratio and concentration of Carbopol 940 using 3^2 full factorial design as shown in Table 1.

Table 1: Microemulsion based Topical Gel of Aceclofenac as per 3^2 full factorial design

Formulation (%)	Batch code								
	MEG1	MEG2	MEG3	MEG4	MEG5	MEG6	MEG7	MEG8	MEG9
Aceclofenac	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Labrafac Lipophilen WL 1349	4.45	9.09	20.54	4.45	9.09	20.54	4.45	9.09	20.54
Cremophor EL/Transcutol P	39.18	39.59	47.04	39.18	39.59	47.04	39.18	39.59	47.04
Water	56.36	51.31	32.41	56.36	51.31	32.41	56.36	51.31	32.41
Carbopol 940	1	1	1	1.5	1.5	1.5	2	2	2

2.3. Characterization of formulation

2.3.1. Droplet size and Zeta potential measurement:

The particle size distribution of the oil droplets in the ME were analyzed using a dynamic light-scattering particle size analyser, Malvern Zetasizer Nano-ZS (Malvern Instruments, UK). All measurements were carried out at 173° at 25°C using disposable polystyrene cells and disposable plain folded capillary cells after proper dilutions.

2.3.2. Viscosity measurements

Viscosity was measured using a Rheometer (Anton Par, USA) fitted with a CP-52 spindle at 100 rpm shear rate at 25 ±1°C.

2.3.3. In vitro drug release

In vitro drug release study of Aceclofenac was conducted using Franz diffusion cell. The 1.0 gm of the prepared sample equivalent to 15 mg of ACE was placed in contact with the dialysis membrane (cellulose acetate, molecular weight 12 kDa) of the donor compartment. The receptor cell contained 65 ml of phosphate buffer (PBS) pH 7.4 were stirred using a magnetic stirrer at 100 rpm and maintained at 37±0.5°C by an outer jacket. 5 ml sample was periodically withdrawn from the receptor compartment, replaced immediately with an equal volume of fresh dissolution medium at the same temperature; in this way sink conditions were maintained during the test. The sample withdrawn was filtered, diluted appropriately and measured in UV–VIS spectrophotometer at 274 nm.

2.4 Design of Experiments

DOE is used exploring the quadratic response surface and for creating a polynomial model using Design-Expert software (Trial Version7.0.2, Stat-Ease Inc., MN). Full factorial design was employed to statistically optimize the independent variables: concentration of oil to Smix ratio (X_1) and concentration of carbopol 940 (X_2) and evaluate the main effects, interaction effects and quadratic effects of these formulation ingredients on dependent variables *viz in vitro* drug release (Y_1) and viscosity(Y_2).

$$Y= \beta_o + \beta_1 X_1 + \beta_2 X_2 + \beta_1 X_1^2 + \beta_2 X_2^2 + \beta_{12} X_1 X_2 + \varepsilon \quad (1)$$

Table 2 shows the coded and uncoded independent variables. Consequently the values were determined in order to evaluate the effect of each response. To test whether the term were statistically significant in the regression model, t-tests were performed using a 95% (α= 0.05) confidence level. The t-test analysis shows that the parameters are highly significant.

Table 2: Variables in factorial design

Independent variables	Level used, actual (coded)		
	Low (-1)	Medium (0)	High (+1)
Independent variable			
X_1 = Oil to Surfactant/ cosurfactant ratio	1:9	2:8	3:7
X_2 = Concentration of Carbopol 940 (% w/v)	1	1.5	2
Dependent variables			
Y_1 = *In vitro* drug release			
Y_2 = Viscosity (cps)			

3. Result and discussion:

3.1. Solubility study

Molecularly dissolved state of drug is responsible for the therapeutic activity. ACE being BCS class II compound

possess least aqueous solubility. Unlike gastric fluid, topical formulation has less medium for drug dissolution (13). ACE is having Log P around 3.65 showing more affinity to oil phase. Thus investigating solubility of drug in oil phase of microemulsion is the important parameter shown in Table 3. Among different oils, Labrafac Lipophile WL1349 showed the maximum solubility of 10.57 mg/ml. Thus this was selected for further studies.

Table 3: Solubility profile of Aceclofenac

Ingredients	Solubility (mg/ml)	Ingredients	Solubility (mg/ml)
		Oils	
Captex 200	3.10±0.40	Isopropyl Myristate	4.21±0.74
Labrafil M 1944CS	5.54±0.20	Lauroglycol FCC	5.36±1.04
Oleic acid	6.77±0.44	Nikkol BB-5	8.01±2.89
Olive oil	7.64±0.22	Capmul MCM	9.7±2.36
		Labrafac Lipophile WL1349	10.57±0.62
		Surfactants (1%w/v)	
Maisine 35-1	9.95±0.42	Capryol 90	198.56±2.36
Tween 80	41.7±1.31	Tween 20	255.2±1.82
Acconon MC8-2	60.80±2.03	Gelucire 44/14	288.68±2.02
Brij O10	70.86±1.01	Cremophor EL	315.68±3.02
		Co-Surfactants	
Plurol oleique CC 497 CG		10.31±1.50	
Propylene glycol		12.27±1.97	
PEG 400		202.32±3.30	
Transcutol-P		450.65±2.29	

Safety is the primary parameter to be well thought-out in selection of the surfactant. Non-ionic surfactants are reported to be less toxic than ionic surfactants (14). O/W microemulsions are more patient friendly as they are less greasy and ease of removal by water. To reduce the amount of surfactant in microemulsion particular balance of low and high HLB surfactants is necessary. High HLB surfactant will reduce interfacial tension between oil and water while low HLB molecule will act as cosurfactant to provide plasticity to interfacial membrane (15). Lesser the HLB of the molecule, higher will be the surface activity (16). Cremophor EL having HLB 15 showed highest solubility of 315.68 mg/ml. As a result Cremophor EL was used as surfactant for the formulations. Solubility in different cosurfactants were studied and Transcutol P showed good solubility of ACE so was further evaluated for their emulsification property by Pseudo-ternary phase diagrams. Awariet et al. has reported the importance of the excipients as the permeation enhancer in nanoemulsion for topical delivery (17).

3.2. Selection of composition for ME

Pseudo-ternary phase diagrams (Figure 1) were constructed to determine the concentration range of components that can emulsify spontaneously to form o/w microemulsion (18). Pseudo ternary phase diagrams of LabrafacLipophile WL 1349 and Cremophor EL with Transcutol P in different Km ratio 4:1, 3:1, 2:1 were studied. Phase diagram depicts greater area of microemulsion at 3:1 ratio. This is may be due to appropriate packing of surfactant and cosurfactant molecules at this concentration to adequately decrease the interfacial tension resulting single phase system. The isotropic monophase microemulsion system can be obtained when the surfactant concentration reaches appropriate concentration to stabilize the oil (19). Garti et al. showed the effect of alcohols and polyols in destabilisation of the liquid crystalline phase and extend the isotropic region to higher surfactant concentrations (20).

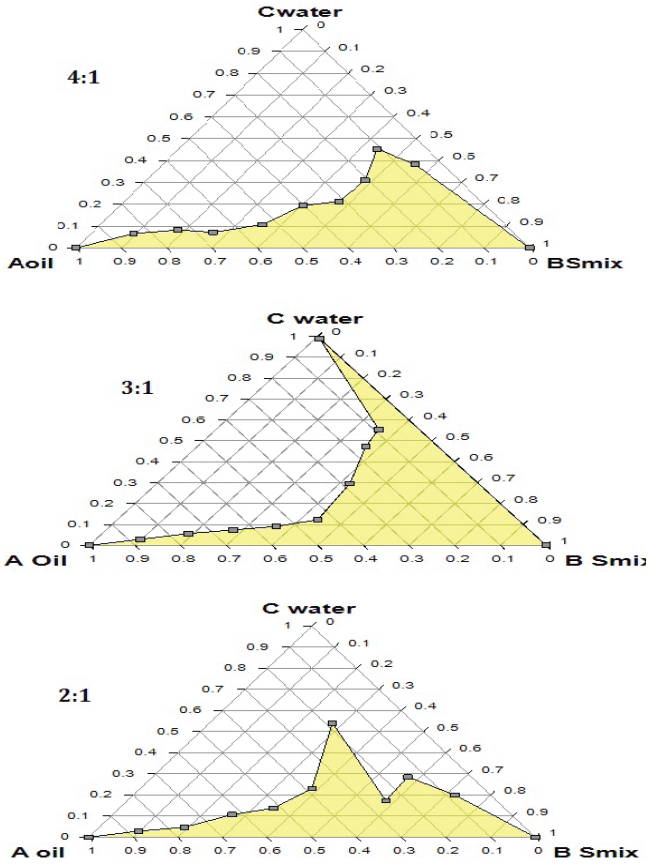

Figure 1: Pseudo-ternary phase diagrams of systems composed of oil, water and Smix. Shaded region shows area of microemulsion.

3.3. Droplet size and zeta potential

The mean droplet size and polydispersity index (PDI) were calculated from intensity, volume and bimodal distribution assuming spherical particles. The optimized batch MEG10 was evaluated for droplet size showing Zavg of 90 nm (Figure 2). Small droplet sizes are prerequisite for drug delivery as the oil droplets tend to fuse with the skin thus providing a channel for drug delivery. PDI is a measure of particle homogenicity and it varies from 0.0 to 1.0. The closer to zero the PDI value the more homogenous are the particles. Formulations showed their PDI in between 0.234 that indicates acceptable homogenicity (21). Zeta potential of the formulation was found between -7.02 to -0.044 mV in the 100 times diluted. This microemulsion consists of non-ionic surfactant/co-surfactant as a result show relatively neutral charge. Dennis et al described the nanometer dimension of microemulsion droplets results in better system for uptake of bupivacaine compared to the intralipid macroemulsion (22).

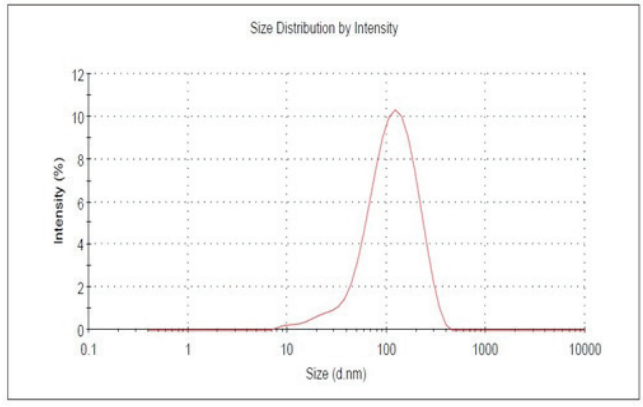

Figure 2: Droplet size of optimized microemulsion batch (MEG_{10})

3.4 Formulation optimization

A two-factor, three-level 3^2 full factorial experimental design was employed to optimize the formulation variables as the response surface methodology requires nine experiments (23). The contour plots and 3D response surface plots were obtained using Design Expert software are shown in Figure 3a & 3b and data transformation and responses are shown in Table 4. Based on the results of pseudo-ternary phase diagrams, Smix i.e Cremophor EL to Transcutol P ratio was fixed to 3:1. The oil phase to Smix ratio was used as one of the independent variable and viscosity of gelling agent as another independent variable and their effect on independent variables were studied.

Table 4: Observed responses in factorial design for MEG of Aceclofenac

Formulation code	Independent variables		Dependent variables	
	X_1	X_2	Y_1	Y_2
MEG1	-1	-1	75.28±1.85	4832±14.52
MEG2	0	-1	71.45±0.98	4893±26.84
MEG3	+1	-1	69.37±2.05	4927±13.25
MEG4	-1	0	71.50±1.65	6547±23.81
MEG5	0	0	65.66±1.78	6608±15.63
MEG6	+1	0	63.99±1.54	6687±26.86
MEG7	-1	+1	67.14±1.15	8755±16.85
MEG8	0	+1	61.64±1.78	8819±15.54
MEG9	+1	+1	55.66±1.55	8878±17.53

Note: X_1 = Oil to Surfactant/cosurfactant ratio, X_2 = Concentration of Carbopol 940 (% w/v), Y_1 = *In vitro* drug release, Y_2 = Viscosity (cps)

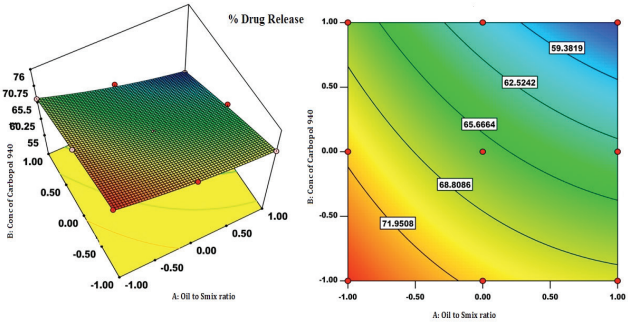

Figure 3a: Effect of oil to S_{mix} ratio and carbopol 940 on in vitro drug release

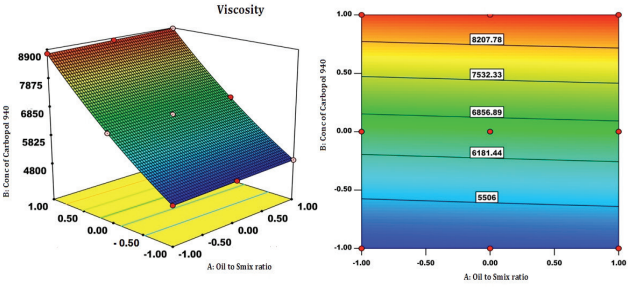

Figure 3b: Effect of oil to S_{mix} ratio and carbopol 940 on viscosity

The responses, % DR (Y_1) and Viscosity (Y_2) was found to be in range from 55.66 to 75.28% (Figure 5 a) and 4832 to 8878 cps respectively. The in vitro drug release was found to be inversely related viscosity. The response models were calculated with Design expert software by applying coded values of factor levels in order estimate quantitative effects of the different combination of factors and factor levels on drug release and viscosity. The model described could be represented by full model equations:

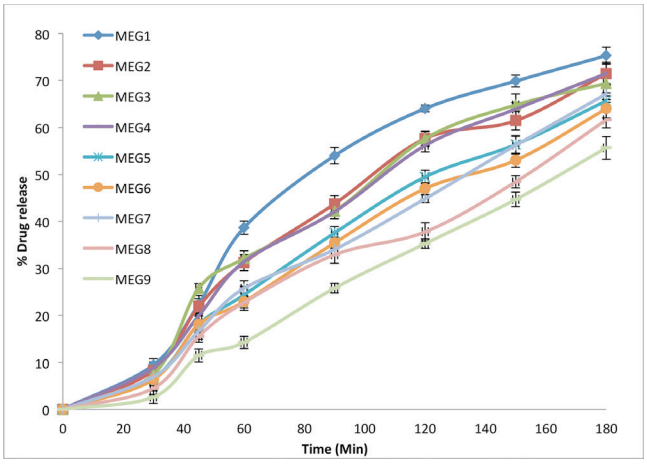

Figure 5 (a): In vitro drug release of MEG formulations.

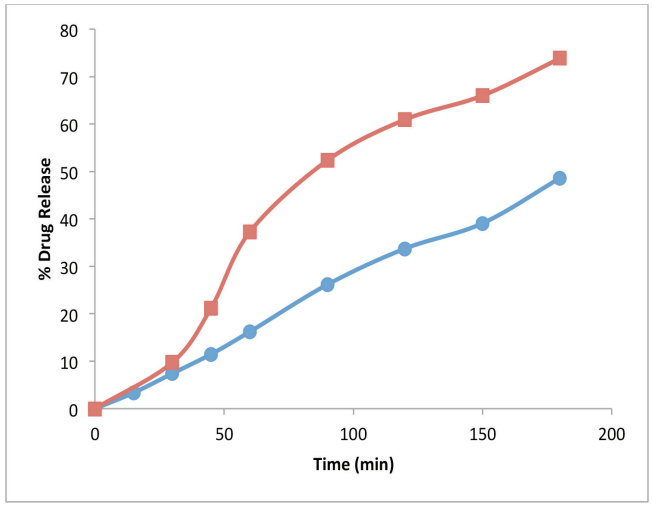

Figure 5 (b): In vitro drug release of (0) optimized batch and (0) marketed product.

$$Y_1 = 66.44556 - 4.15X_1 - 5.27667X_2 - 1.3925X_1X_2 + 0.906667X_1^2 - 0.29333X_2^2 \quad (2)$$

$$Y_2 = 6615.556 + 59.666X_1 + 1966.667X_2 + 7X_1X_2 - 2.X_1^2 - 0.29333X_2^2 \quad (3)$$

For responses reduced mathematical model was evolved omitting the insignificant terms ($p>0.05$) by adopting multiple regression analysis (24). The polynomial terms X_1^2 and X_2^2 for response Y_1 and the polynomial term X_1^2 and interaction term X_1X_2 for response Y_2 were found insignificant as P value was more than 0.05. Thus reduced model equations having significant effect on response variable were:

$$Y_1 = 66.44556 - 4.15X_1 - 5.27667X_2 - 1.3925X_1X_2 \quad (4)$$

$$Y_2 = 6615.556 + 59.666X_1 + 1966.667X_2 - 0.29333\,X_2^2 \quad (5)$$

The responses of all the formulations prepared were simultaneously fit to first order, second order and quadratic models using Design Expert 7.0.2. It was observed that the best fit model was quadratic model and ANOVA details are given in Table 5a & 5b. Coefficients with one factor represent the effect of that particular factor on responses while the coefficients with more than one factor and those with second order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign in front of the terms indicates positive effect while negative sign indicates negative effect upon the responses (25,26).

From the equation of the reduced model as shown, it can

Table 5a: ANOVA table for *In* vitro drug release model

Source	Sum of squares	Df	Mean square	F value	p-value Prob > F	Remarks
Model	279.97	5	55.99	73.97	0.0024	Significant
A	103.33	1	103.33	136.61	0.0013	Significant
B	167.06	1	167.06	220.69	0.0007	Significant
AB	7.76	1	7.76	10.25	0.0493	Significant
A^2	1.64	1	1.64	2.17	0.2370	NS
B^2	0.17	1	0.17	0.23	0.6661	NS
Residual	2.27	3	0.76			

Table 5b: ANOVA table for Viscosity model

Source	Sum of squares	Df	Mean square	F value	p-value Prob > F	Remarks
Model	23340000	5	4668000	28631.85	0.0001	Significant
A	21360.67	1	21360.67	131.02	0.0014	Significant
B	23210000	1	23210000	142300	0.0001	Significant
AB	196	1	196	1.20	0.3530	NS
A^2	10.89	1	10.89	0.067	0.8128	NS
B^2	112000	1	112000	687.10	0.0001	Significant
Residual	489.11	3	163.04			

be concluded that X_1 and X_2, both had negative effect on the release of drug from the microemulsion based topical gel. As the X_1 (oil to surfactant/co-surfactant ratio) and X_2 (concentration of Carbopol 940) were increases, the % release of the drug decreases. As the X_1 and X_2 increases, the viscosity of microemulsion based topical gel increases. Increasing the oil concentration leads to reduced partitioning in aqueous phase thus limiting the drug release. While increasing the concentration of Carbopol 940 results in increased viscosity (27). This results in increasing the barrier for the diffusion of drug molecules.

The data generated by experimental design were utilized for drawing contour plots to find the factors that affect the responses. The slope or curvature in a variable shows that response is sensitive to change in that variable whereas relatively flat line shows insensitivity or less dependency to that factor. For response Y_1, variable X_1 and X_2 shows curvature indicating decrease in drug release with increase in concentration of oil and viscosity.

For response Y_2, flat lines to X-axis indicate the lesser effect of oil/Smix on the viscosity. Lines perpendicular to Y-axis shows that concentration of carbopol 940 is most important for determining the viscosity.

3.5. Data analysis

The value of R^2 of Eq. (2) and (4) was found to be 0.9919 and 0.9999, indicating good fit. In order to investigate the significance and fitness of the model, an ANOVA also shows the effects of individual parameters and interaction of variables on the microemulsion topical gel. ANOVA results are presented in Table 5. The high value of adjusted R^2 signifies a good explanation of the variability by the selected mode. The standard error of the regression is the estimated standard deviation associated with the regression coefficient estimate. The model F-value for *In* vitro drug release factor and viscosity factor was found to be 73.97 and 28631.85 respectively implies that model is significant. The p-value (or Prob>F) is the probability of achieving the F-value. The values less than 0.05 indicate statistically significant difference between the means.

3.6. Validation of response surface methodology

Check-point formulation MEG_{10} (Figure 4) was prepared for the validation of the QbD method and comparison of their predicted responses with those observed ones. Optimization of microemulsion based gel was done to find the level of variable $X_1$and X_2, which gives Y_1maximum drug release in range of 65-80% and Y_2having sufficient viscosity for spreading on skin in range of 4000-5000 cps. The model predicted Y_1 and Y_2 in required range at X_1 and X_2 values of 1:9 and 1.015% respectively. The predicted value of responses Y_1 and Y_2 were 74.506% and 4882.577 cps. The check point batch form the design space was prepared by the overlay of both the contour plots. The actual values of Y_1 and Y_2 were found to be 73.85 ± 2.6 % and 4843.42 ±5.95cps, which was in close conformity to the predicted values. As MEG_1 batch showed maximum drug release compared to other batches resulting in faster onset of action so it was selected as optimized batch.

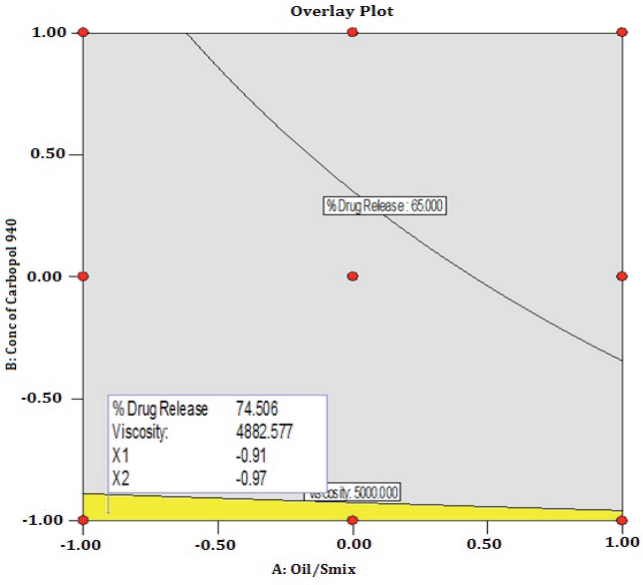

Figure 4: Check point formulation batch (MEG_{10})

3.7. Comparison with marketed product:

The difference factors (f1) and the similarity factors (f2) were calculated to compare dissolution profiles. The difference factor, f1, was determined with Eq. (6) and the similarity factor, f2 is by Eq. (7). The values of f1 between0 and 15 and f2 between 50 and 100 suggest that two dissolution profiles are similar (28). The optimized formulation was compared with the marketed gel product for drug release profile (Figure 5 b) and similarity and dissimilarity factors were calculated.

$$f_1 = \left\{ \frac{\left\{ \sum_{t=1}^{n} |Rt - Tt| \right\}}{\sum_{t=1}^{n} Rt} \right\} \times 100 \quad (6)$$

Dissimilarity factor (f1) = 56.84141

$$f2 = 50 \times \log\left[\left\{ 1 + \frac{1}{n} \sum_{r=1}^{n} wt(Rt - Tt) \right\}^{-0.5} \times 100 \right] \quad (7)$$

Similarity factor (f2) = 34.486

where n is the number of dissolution sample times, Rt and Tt are the percent drug dissolved at each time point for the test and reference products, respectively.

The comparison of the release profiles of formulated and marketed preparation shows, the f1 value to be greater than 15 and the f2 value smaller than 50, which clearly indicates that the release profiles of drug from the formulated dosage form was different than release profile of the marketed product. The formulated dosage form has faster onset of action compared to marketed preparation. The initial slow permeation through skin may be due to various sequential steps. First is the drug release from gel matrix followed by permeation through skin and finally deposition of drug in skin layers. Deposition in skin resulted in the flux development which provides faster drug release (29). The smaller droplet size of microemulsion further facilitates the enhanced permeation compared to the simple gel system.

4. Conclusion:

Keeping in view the above-mentioned results, it could be concluded that the proposed quadratic models obtained by applying regression analysis to the 3^2 full factorial experimental designs were significant and reliable for prediction of percent drug release and viscosity. The percent drug release and viscosity were strongly affected by the two independent variables selected for this study oil to Smix ratio and concentration of Carbopol 940 which had a nonlinear relationship and mutually dependent influence on both responses. Thus experimental design aids in the optimisation of the formulation variable.Formulated microemulsion based topical gel of Aceclofenac played an important role in increasing the solubility and permeability of Aceclofenac as well as in increasing the retention time of the dosage form topically, which ultimately increases the patient compliance.

Declaration of interest

The authors report no conflicts of interest for this study.

Mikroemülsiyon esaslı topikal jel optimizasyonu için tasarımla kalite (QbD) yaklaşımı

ÖZ

Bu çalışmanın amacı oral bir NSAID olan Aseklofenak'ın dispepsi, ülser ve kanama gibi önemli komplikasyonlarına karşı mikroemülsiyon esaslı topikal bir formülasyonunu geliştirmektir. Topikal yol yukarda sayılan komplikasyonları giderir ve ilave olarak bölgeye özgü taşıma sağlar. Biyofarmasötik sınıflandırma sistemine (BCS) göre sınıf-II olarak tanımlanan Aseklofenak, sudaki çözünürlüğünün düşük olması nedeniyle formülasyon problemleri ortaya koyar. Bu nedenle mikroemülsiyon esaslı jel, yağlı fazın çözünürlüğü arttırması ve daha küçük boyutun da daha yüksek geçirgenliğe yardımcı olması faydalarını bir araya getirir. Formülasyon bileşenleri yağ fazı olarak sırasıyla Labrafac Lipophile® WL1349, Cremophor® EL ve Transcutol® P'yi ve sürfaktan ile ve yardımcı sürfaktanı içerir. Yağ fazının sürfaktan / yardımcı sürfaktana oranı ve Carbopol® 940'ın formülasyondan ilaç serbestleşmesi ve viskozite profili üzerine etkisi 3^2 faktöriyel tasarımla çalışılmıştır. Dinamik ışık saçılımı tekniği, mikroemülsiyonun iyi tanımlanmış küresel şekile, tekdüze boyuta (90 nm), dar poli-dispersite indeksine (0.234) ve -7,02 mV'luk bir zeta potansiyeline sahip olduğunu göstermiştir. Yağ sürfaktan/yardımcı sürfaktan oranı (1:9) olan ve %1,015 a/a Carbopol® 940 içeren optimize seriden *in vitro* ilaç serbestleşmesi 180. dakikada %73,85 ±2,07 olarak bulunmuştur. Optimize edilmiş formülasyonun ilaç serbestleşme profili daha yüksek ilaç serbestleşmesi gösteren pazar ürünüyle karşılaştırılmış ve benzerlik faktörü (f_2) % 34,486 olarak bulunmuştur. Sonuçlar Aseklofenak'ın topikal yoldan taşınması için geliştirilen mikroemülsiyon esaslı jelin yüksek potansiyele sahip oluğunu ortaya koymaktadır.

Anahtar kelimeler: Mikroemülsiyon, Topikal jel, Aseklofenak, Faktöriyel tasarım, tasarımla kalite.

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