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Formulation and characterization of acyclovir based topical microemulsions by QBD approach

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ABSTRACT

Objective: The proposed study is focussed at developing acyclovir microemulsions for topical drug delivery systems. QbD was applied for better understanding of the process and to generate design space, using quality target product profile, critical quality attributes, and risk assessment. The aim of the experiment is to prepare a safe, efficacious, stable and patient compliant microemulsion dosage form of Acyclovir. **Materials and methods**: Pre-formulation studies were carried out which helped in developing a suitable dosage form. UV, FTIR and DSC studies were done for pre-formulation and post-formulation evaluations. QbD was applied to generate design space, using QTPP, CQA, and risk assessment. Microemulsions of acyclovir were developed by using 3^2 factorial designs. Pseudo terneary phase diagrams were constructed to screen various surfactants and co-surfactants for the preparation of microemulsions. Two independent variables Oil Concentration (X_1) and S_{mix} Concentration (X_2) at three levels low, medium and high were selected and response surface plots were generated. The microemulsions were prepared by plotting pseudo terneary phase diagrams. Various characterizations that were carried out include % transmittance, Viscosity and % drug release. Statistical analyses of batches and surface response studies were done to understand the effect of various independent variables on the dependent variables. **Results and Discussions**: The λ_{max} was confirmed at 251 nm by UV spectroscopy. The melting point was determined experimentally to be 246^0C which confirms the drug to be Acyclovir. FTIR and DSC studies confirmed that the drug is Acyclovir. **Conclusion**: The study indicates that microemulsions of Acyclovir by QbD approach were successfully developed.

Keywords: Microemulsion, Acyclovir, DoE, QbD

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INTRODUCTION

Acyclovir is a potent, specific antiviral drug which is active against herpes simplex viruses' types I and II and varicella zoster virus[1]. Acyclovir is available as various dosage forms in the market which includes capsules, creams, ointments, tablets and suspension. Idea of microemulsions was first presented by Hoar and Schulman in 1940s. It is an arrangement of water, oil and surfactant, which is optically isotropic and thermodynamically stable fluid that have low consistency or interfacial film comprising of surfactant/co-surfactant[2]. It is vehicle for enhancing drug delivery, optimization of dose and bioavailability of drugs[3]. It is well-established that medium chain unsaturated fats impact tight intersections of epithelial cells, and long chain unsaturated fats allow lipoprotein amalgamation and consequential lymphatic absorption. Lately, various investigations have suggested that microemulsion [o/w or w/o] can possibly promote bioavailability of medications by means of topical routes.

Quality by design (QbD) is an efficient way to bring quality into both product and process. QbD can be achieved by constructive planning of all the previous data that is accessible. Although it is based on certain amount of risks, it gives results that reduces the risk of end product failure and increases the chances of regulatory acceptance[4]. ICH Q8, ICH Q9 and ICH Q10 do explain the principles of QbD in the best way. They provide guidelines on science and risk based assessment, life cycle of product and various approaches in its development. It is also well known fact that there can be a great deal of unpredictability in scale up of a product from research and development, although the reason for failure is

not generally understood. QbD is an approach to be applied in all stages of drug discovery, production and delivery[5-6].

MATERIALS AND METHODS

Materials

The drug Acyclovir was obtained as gift sample from Aurobindo Pharma, Hyderabad. All other chemicals that were used in the experiment were of the analytical grade.

Methods

Pre-formulation studies

Determination of melting point of Acyclovir:

Melting point of Acyclovir was determined by open capillary method.

Determination of wavelength maxima (λ_{max}) of Acyclovir:

Determination of wavelength maxima (λ_{max}) was done for Acyclovir.

Preparation of calibration curve for Acyclovir:

The calibration curve of Acyclovir was plotted by taking 0.1N HCl as the solvent.

Identification of Acyclovir by FT-IR Spectroscopy:

FTIR study was carried for Acyclovir.

Identification of Acyclovir by DSC Study:

The thermograph of Acyclovir was obtained by DSC.

Screening for components of microemulsion

Most important criterion for screening of component for microemulsion formulation is solubility of the drug in oils, surfactants and co-surfactants. Solubility of Acyclovir in various oils, surfactants and co-surfactants was determined by dissolving excess amount of drug in 2 mL of each selected oils, surfactants and co-surfactants in 5 mL capacity stoppered vials separately and mixed using vortex mixer. Equilibrated samples were removed and centrifuged; the supernatant liquid was taken and filtered through 0.45 µm membrane filter. Concentration of Acyclovir was determined in each component by double beam UV-VIS spectrophotometer at λ_{max}251 nm after appropriate dilution.

Construction of pseudo ternary phase diagram

Pseudoternary phase diagram were constructed using water titration method at ambient temperature (25°C). Surfactant and co-surfactant were in different volume ratios and titrated with water by drop wise under gentle agitation. Proper ratio of one excipient to another in microemulsion formulation was analysed and pseudoternary plot is constructed.

Optimization of oils, surfactants and co-surfactants:

From pseudoternary phase diagrams showing maximum microemulsion region, number of microemulsion with different formula were selected covering entire range of microemulsion occurrence in phase diagram. For each phase diagram constructed, different formulation was selected from microemulsion region so that drug could be incorporated in oil phase on following bases. (a) Oil concentration should be such that it solubilizes drug (single dose) completely depending on solubility of drug in oil. (b) Minimum concentration of S_{mix} used for that amount of oil was taken. (c) For convenience purpose, about 1 mL was selected as microemulsion formulation, so that it can increase or decreased as per requirement in proportions. Beauty of this system is scale up of proportions is easy, as system is thermodynamically stable.

Formulation and development of Acyclovir microemulsion using Design of experiments [DoE] approach:

A design space can signify formulation and process understanding viz. attributes which are related to drug substance, materials, equipment and finished product quality. For this purpose, risk assessment was done based on understanding process and formulation related parameters on microemulsion quality. Preliminary studies and later Design of Experimentation (DoE) was carried out for high risk parameters. Based on effect of critical quality attributes of target product profile, we proposed design space for obtaining robust formulation. Characterization of microemulsion is done for various parameters like effect of globule size, viscosity, %transmittance, %drug release.

Characterization of acyclovir loaded microemulsion

Droplet size analysis:

Droplet size analysis of microemulsion was measured by diffusion method using light-scattering particle size analyser.

Zeta potential:

Zeta potential is measured by instrument known as Zetasizer. It is used to measure charge on surface of droplet in microemulsion.

pH:

pH of formulation is measured by pH meter.

Viscosity determination:

Viscosity of microemulsion is measure by using Brookfield-type rotary viscometer at different shear rates.

In-vitro drug release studies

Drug release kinetics are studied using modified method glass cup with cross-sectional area of 1.5 cm^2 will fill with 0.2ml of microemulsion, covered with cellophane membrane, sealed with rubber band and adhesive tape, and inverted under surface of 30 ml of phosphate buffer pH in USP XXIII Type I Dissolution Test Apparatus with speed of 30 rpm. Aliquots are withdrawn at specified time intervals and immediately replaced with fresh dissolution medium to maintain sink condition. Drug content in withdrawn samples will be determined spectrophotometrically at 251 nm.

Risk Assessment to identify CQAs affecting drug product quality:

Risk assessments was done to select formulation and process variable which may affect product quality for CQAs by process characterization that defines satisfactory changes in material and process parameters. As a final point, this can result in quality assurance by process design space to understand and develop control strategy. Critical quality attributes were categorized into high, medium and low risk parameters based on knowledge space. Usually high-risk parameters are considered important for Design of Experiments as they are having more effect than others and need to be in accepting multivariate ranges.

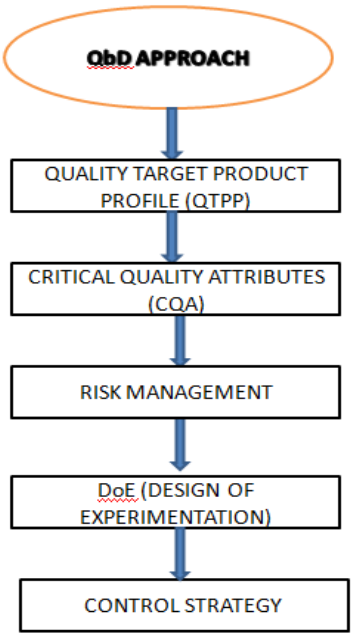

Figure 1 QbD approach

Table 1 Independent and dependent variables

Independent variables – X	Dependent Variables – Y
Oil Concentration (%) S_{mix} Concentration (%)	% Transmittance Viscosity % Drug release

Effect of different independent variables (Oil concentration and S_{mix} Concentration) were checked by evaluating % Transmittance, viscosity and % drug release of Acyclovir microemulsion formulated in preliminary trial batches. Based on that characterization, CQAs were selected which have greater effect on microemulsion formulations.

Design of Experimentation (DoE) of Acyclovir microemulsion by using QbD approach:

A design space can signify formulation and process variables that affects attributes which are related to drug substance, materials, equipments and finished product quality. For this purpose, risk assessment was done based on understanding of process and formulation related parameters on microemulsion quality. Preliminary studies and later Design of Experimentation (DoE) was carried out for high risk parameters. Based on effect of critical quality attributes of target product profile, design space for obtaining robust formulation was proposed.

RESULTS AND DISCUSSIONS

Pre-formulation studies

Determination of melting point of Acyclovir:

The melting point of Acyclovir was found to be 246^{0}C.

Determination of wavelength maxima (λ_{max}) of Acyclovir:

The wavelength maxima (λ_{max}) of Acyclovir were found to be 251 nm.

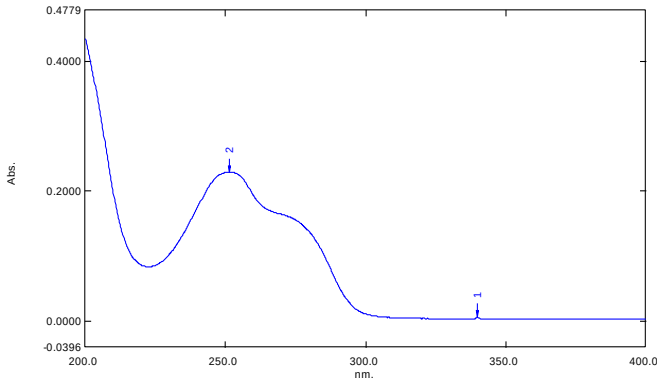

Figure 2 Wavelengthmax (λ_{max}) of Acyclovir

Preparation of calibration curve for Acyclovir:

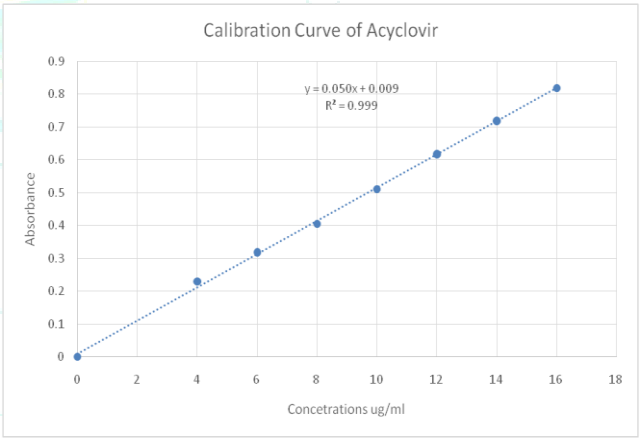

Figure 3 Calibration curve for Acyclovir

Identification of Acyclovir by FT-IR Spectroscopy:

The recorded IR spectrum of Acyclovir is

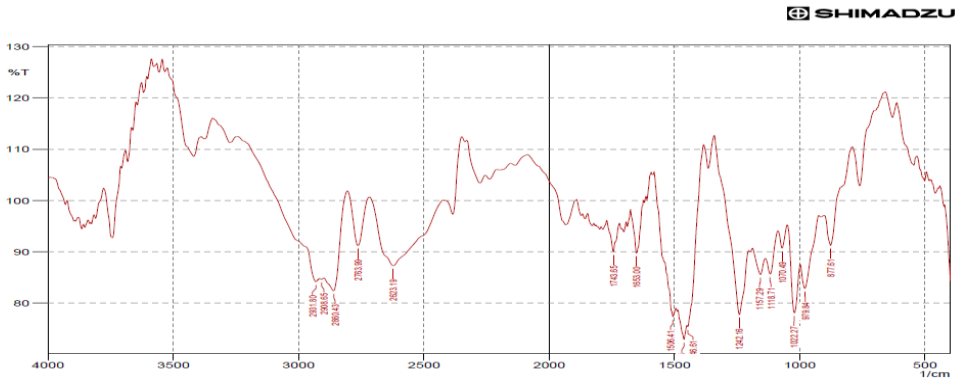

Figure 4: FTIR spectrum of Acyclovir

Table 2: FT-IR peaks of Acyclovir

Type of Vibration	Standard Wave number(cm^{-1})	Observed Wave number(cm^{-1})
C=C Stretching of Aromatic	1600-1475	1465.90
N-H Stretching of 1˚ amine	3500-3300	3417.88
N-O Stretching of N - Oxide	1300-1200	1222.87
C-H Stretching of Piperidines	2850-3000	2937.59
C-N Stretching of C-NH2	860-766	761.88

Identification of Acyclovir by DSC Study:

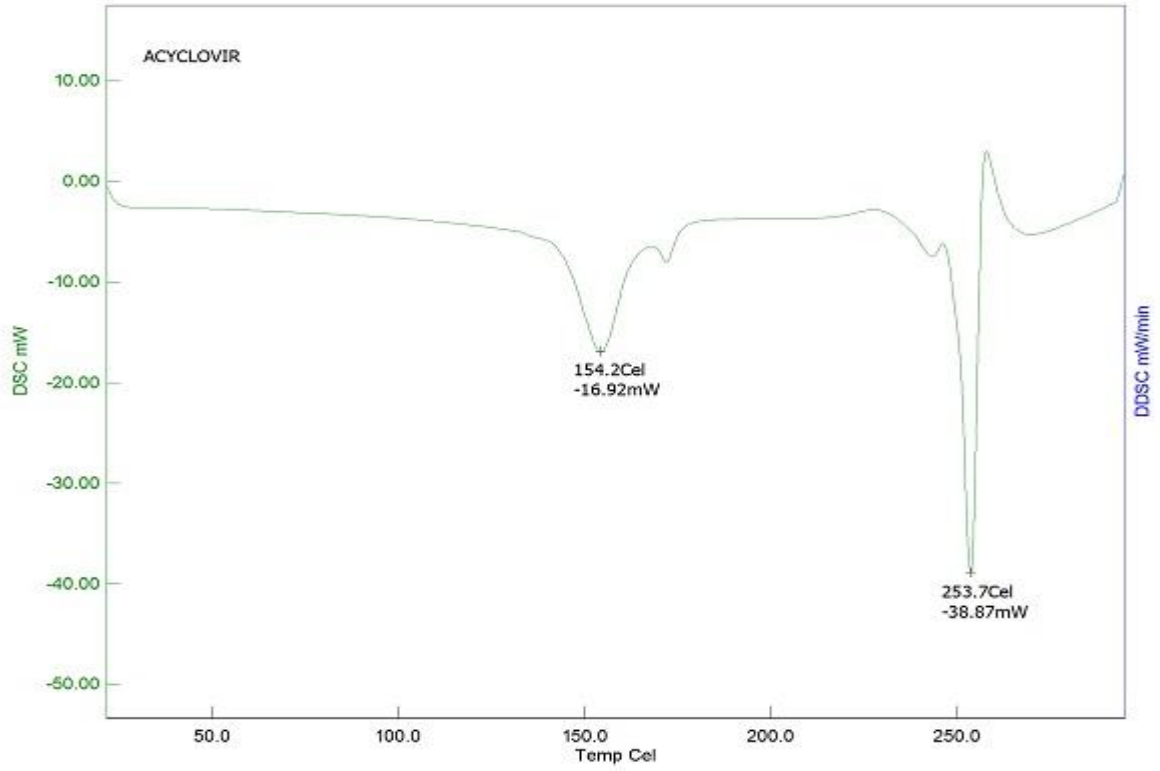

Figure 5: DSC thermograph

Construction of pseudo ternary phase diagram

Pseudo ternary phase diagrams are constructed to identify microemulsion region and suitable composition of oil, surfactant, co-surfactant for formulation of microemulsion. From pseudoternary diagram it was found that system containing of Captex 200 as oily phase, Tween 20 as surfactant and PEG 400 as co-surfactant showed good microemulsifying property at S_{mix} ratio 4:1.it was observed that by increasing oil content, system show appearance of coarse emulsion. It was observed that by increasing co-surfactant in S_{mix} ratio system show decreasing property of spontaneous microemulsion formation. Hence from this observation it is clear that surfactant play key role in formation of microemulsion.

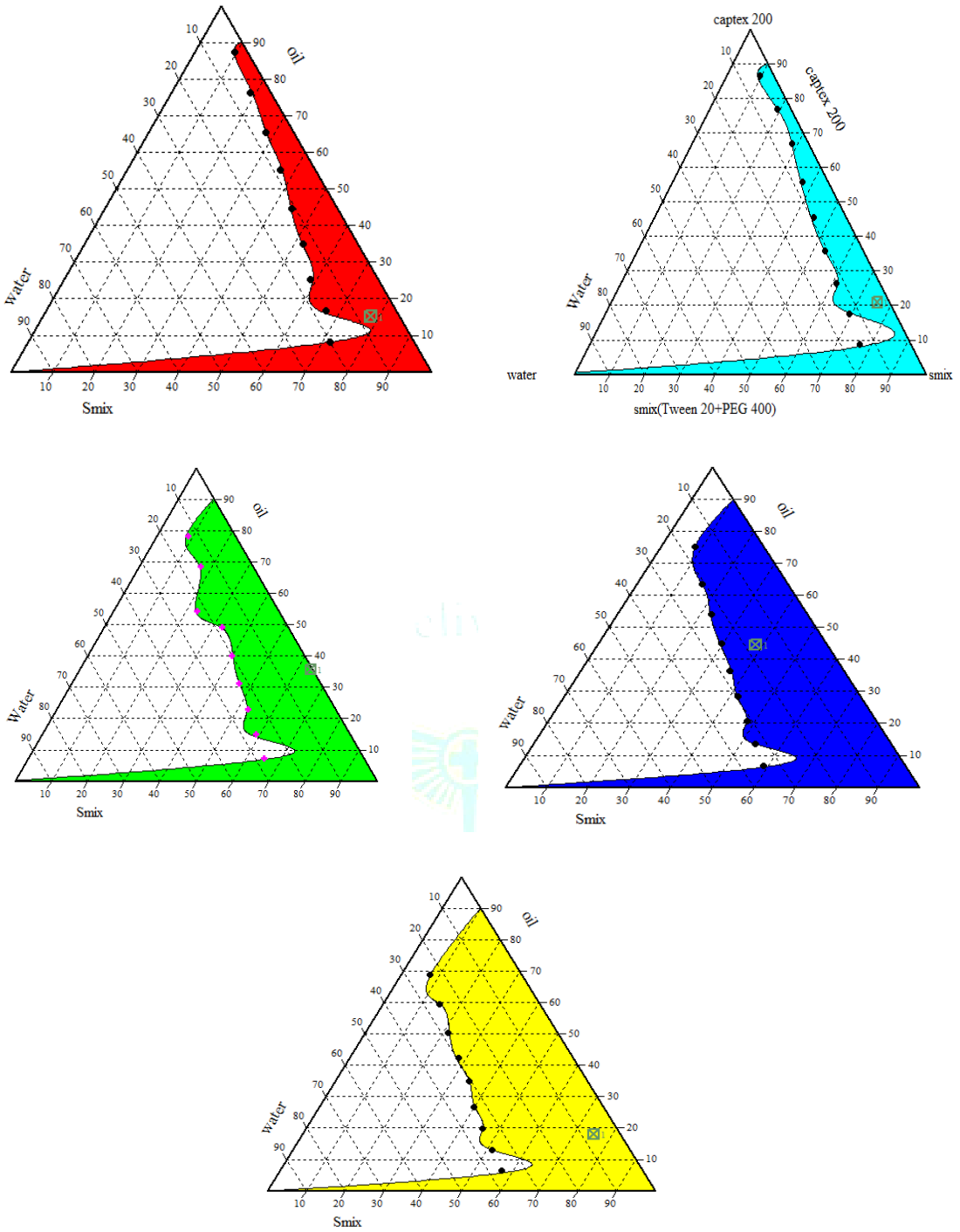

Figure 6: Pseudo ternary phase diagram

3^2 Factorial Design for Acyclovir microemulsions

Various batches of Acyclovir microemulsion were designed by DoE using QbD approach according to 3^2 factorial designs which are as shown in Table 3.

Table 3: 3^2 Factorial Designs

Independent variable of formulation			
Independent variable	**Low (-1)**	**Medium (0)**	**High (1)**
Oil Concentration (%) (X_1)	5%	10%	15%
S_{mix} Concentration (%) (X_2)	50%	55%	60%
Dependent variable			
Y_1= % Transmittance			
Y_2 = Viscosity			
Y_3 = % Drug release			

Compositions of Factorial Batches in Coded Form

Various batches of Acyclovir microemulsions with Eudragit RS 100 were prepared according to 3^2 factorial designs which are as shown in Table 4.:

Table 4: Compositions of Factorial Batches in Coded Form

Acyclovir Microemulsion 3^2 = 9 batches		
Batch No	Variable level in coded from	
	Oil Concentration (X1)	S_{mix} Concentration (X2)
ACME1	-1	-1
ACME2	0	-1
ACME3	+1	-1
ACME 4	-1	0
ACME 5	0	0
ACME 6	+1	0
ACME 7	-1	+1
ACME 8	0	+1
ACME 9	+1	+1

Formulation Design by 3^2 Factorial Design

Table 5: Formulation Design by 3^2 Factorial Designs

ACYCLOVIR Microemulsion 3^2 = 9 batches				
Batch No	Actual Value			
	Oil Concentration (X1)	S_{mix} Concentration (X2)	Oil Concentration (%) (X1)	S_{mix} Concentration (%) (X2)
ACME1	-1	-1	5	50
ACME2	0	-1	10	50
ACME3	+1	-1	15	50
ACME4	-1	0	5	55
ACME5	0	0	10	55
ACME6	+1	0	15	55
ACME7	-1	+1	5	60
ACME8	0	+1	10	60
ACME9	+1	+1	15	60

Characterization of Acyclovir microemulsions batches ACME1-ACME9:

Table 6: Characterization of batches ACME1-ACME9

Batch No.	% Transmittance (Y1)	Viscosity (Y2)	% Drug release (Y3)
ACME1	98.5	138	23.05
ACME2	98.6	135	26.41
ACME3	99.8	133	28.32
ACME 4	98.2	144	7.51
ACME 5	98.3	142	19.42
ACME 6	99.5	139	22.4
ACME 7	89.2	156	10.6
ACME 8	95.1	152	12.54
ACME 9	96.3	148	15.14

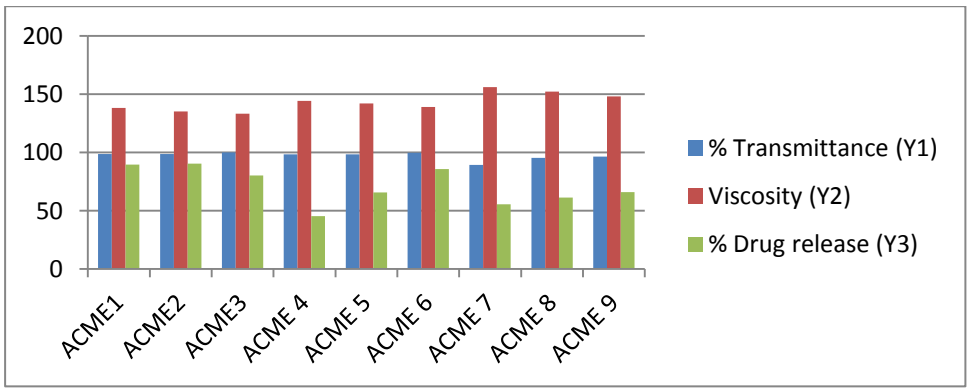

Figure 7: Characterization of Batches **ACME1-ACME9**

Statistical analysis of batches ACME1-ACME9

In factorial design, **amount of Oil Concentration (X1)** and **S_{mix} Concentration (X2)** were taken as independent variables while **% Transmittance (Y1), % Viscosity (Y2) and % Drug Release (Y3)** were selected as dependent variables for both factorial designs.

Effect on % Transmittance (Y1) - Surface Response Study

% Transmittance (Y1) =97.36-3.58* X1+1.38*X2

Negative value of coefficient of X1 indicates decrease in response of Y1 i.e. % Transmittance. Positive value of coefficient X2, S_{mix} concentration indicates increase in % Transmittance.

Effect on Viscosity (Y2) - Surface Response Study

Viscosity (Y2) =144.0+8.33* X1-3.00* X2

Positive value of coefficient of X1 indicates increase in response of Y2 i.e. %viscosity. Negative value of coefficient X2, Smix Concentration indicates decrease in viscosity.

Effect on %Drug Release (Y3) - Surface Response Study

Drug Release Release (Y3) =18.38-6.51*X1+2.55* X2

Negative value of coefficient of X1 indicates decrease in response of Y2 i.e. % Drug release. Positive value of coefficient X2, S_{mix} Concentration indicates increase in %Drug Release.

CONCLUSION

The focus of the current study was to develop topical microemulsion drug delivery system of acyclovir using QbD approach. Pre-formulation studies were carried out which helped in developing a suitable dosage form. UV, FTIR and DSC studies were done for pre-formulation and post-formulation evaluations. QbD was applied to generate design space, using QTPP, CQA, and risk assessment. Microemulsions of acyclovir were developed by using 3^2 factorial designs. Pseudo terneary phase diagrams were constructed to screen various surfactants and co-surfactants for the preparation of microemulsions. Two independent variables Oil Concentration (X_1) and S_{mix} Concentration (X_2) at three levels low, medium and high were selected and response surface plots were generated. The microemulsions were prepared by plotting pseudo terneary phase diagrams. Various characterizations that were carried out include % transmittance, Viscosity and % drug release. Statistical analyses of batches and surface response studies were done to understand the effect of various independent variables on the dependent variables. Lastly it was concluded that microemulsions of Acyclovir using QbD approach were successfully developed.

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