Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(12):926-937

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Design and development of hydrogel based microemulsion of valacyclovir hydrochloride

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ABSTRACT

The purpose of this investigation was to develop a Hydrogel Based Microemulsion of Valacyclovir hydrochloride for Topical Drug carrier system for Herpis Simplex, Chicken-Pox and Cold sores with aim to get maximum bioavailability and better patient compliance. On the basis of solubility in various oils, surfactants and co-surfactant, Iso Propyl Myristate, Span 20 and DMSO selected as the components of micro-emulsion system.Pseudo-ternary phase diagrams were constructed to identify the micro-emulsion region and a suitable mixture of surfactant and co-surfactant was identified to formulate the micro-emulsion. Water titration method is used for the construction of phase diagrams. The prepared micro-emulsions were evaluated for drug content, zeta potential, viscosity, Refractive index, globule size, p^H, Drug release etc. SEM studies were also carried out of the prepared micro-emulsions.Micro-emulsions have lower viscosity and are difficult to apply on skin so for the ease of application they are tried to be gelled with 1% w/w Carbopol 934 is used as gelling agent. Optimized micro-emulsion selected on the basis of drug release study and prepared hydrogel based micro-emulsion further evaluated for homogenicity, p^H, grittiness, Drug content and Stability studies. In vitro Drug release of prepared microemulsions was observed to follow Zero order kinetics. ME5 formulation is seleced as best formulation on the basis of drug release in 8 hr 96.38% and Zeta potential -48±0.041 mv. Optimized ME5 formulation converted into hydrogel which showed drug release in 12 hr 94.85±0.202 % and and found to be stable for 3 month.

Key words: Valacyclovir Hydrochloride, Solubility, Phase Diagram, Zeta potential.

INTRODUCTION

Topical drug delivery systems is widely used drug delivery system. This system existed from ancient time to treat disorders. Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Semi-solid formulations in all their diversity dominate the system for topical delivery [1].

A micro-emulsion is a system of water, oil, and amphi-philic compounds (surfactant and co-surfactant) which is a transparent, single optically isotropic, and thermodynamically stable liquid [2]. Micro-emulsions are readily distinguished from normal emulsions by their transparency, their low viscosity, and more fundamentally their thermodynamic stability and ability to form spontaneously[3].Micro-emulsions provides various benifits over

traditional creams, gels, and solutions as topical drug delivery. Micro-emlsion based Hydrogel system will be able to maintain therapeutic concentration at the site of action with greater bioavailability [4].

Valacyclovir Hydrochloride is a pro-drug and synthetic purine nucleoside analogue with inhibitory activity against herpes simplex virus types 1(HSV-1), 2(HSV-2),varicella-zoster virus (VZV),Epstein-Barr virus(EBV), and cytomegalovirus (CMV). Valacyclovir Hydrochloride is almost completely converted to acyclovir and L-valine. The inhibitory activity of Valacyclovir Hydrochloride is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV[5]. Topical microemulsion based hydrogel of Valacyclovir Hydrochloride for the treatment of cutaneous infections have several advantages over oral and intravenous administration, including targeting of drug to the specific sites of infection, higher tissue drug levels, reduced side effects, lower treatment costs, and better patient compliance and convenience[6].

The present Research work have carried out for the design and characterise hydrogel based microemulsion of valacyclovir hydrochloride for topical administration,better patient compilance and maximum bioavailability**.**

EXPERIMENTAL SECTION

Material : Valacyclovir Hydrochloride was obtained as gift sample from Lupin Research Park, Pune, India. Iso Propyl Myristate, DMSO, Span 20, Carbopol 934 purchased from Central Drug House,New Delhi. All other chemicals and solvents were used of Analytical grade.

Solubility Studies Of Valacyclovir Hydrochloride : The solubility of the Valacyclovir Hydrochloride was determined by adding excess amount of drug in the different solvent and The solubility of Valacyclovir Hydrochloride in various oily phase (Iso propyl myristate, Oleic acid, Olive oil , Castor oil, Peeperment oil) and mixture of oils, Surfactants (Tween 80, Tween 20, Span 20) and cosurfactants (Ethanol, and Di Methyl Sulfoxide) was determined by dissolving excess amount of Valacyclovir Hydrochloride in 2 ml of each of selected oils, Surfactants and Cosurfactants in 5 ml capacity stoppered vials separately and mixed by continuously stirred for 72 hrs. equilibrium solubility was determined by taking supernatant and analyzing it on UV spectrophotometer.

Selection of Oil, Surfactant, and Cosurfactant

On the Basis of Solubility study IPM, Span20, and DMSO were selected as Oil phase, Surfactant and Cosurfactant respectively. Composition given in the table-I

Construction of Pseudo Ternary Phase Diagrams

To investigate the microemulsion region, pseudoternary phase diagrams were constructed by using CHEMIX SCHOOL (3.60, Arne Stendnes). The pseudo-ternary phase diagrams of oil, surfactant, cosurfactant, and water were constructed using water titration method to obtain the components and their concentration ranges that can results in large existence area of microemulsion. Surfactant was blended with cosurfactant in fixed weight ratios (1:1, 1:2, 1:3, and 1:4). Aliquots of each surfactant and cosurfactant mixture (S_{mix}) were then mixed with oil at room temperature. Then each mixture was visually observed for transparency.

Table I:Composition of ME Formulations

Formulation Code	%Valacyclovir Hydrochloride	% Oil (w/w)	% S_{Mix}1:3(w/w)	%Water(%w/w)
ME1	0.1	20	40	40
ME2	0.1	20	45	35
ME3	0.1	20	50	30
ME4	0.1	15	40	45
ME5	0.1	15	45	40
ME6	0.1	15	50	35
ME7	0.1	10	40	50
ME8	0.1	10	45	45
ME9	0.1	10	50	40

Preparation of Microemulsion Formulations

After identification of the microemulsion regions in the phase diagram, the microemulsion formulations were selected for S_{mix} (1:3) at desired component ratios. The preparation of selected microemulsion was simply performed

by adding the weighed components together and well mixed using magnetic stirrer at ambient temperature. Homogenous and stable microemulsions were formed spontaneously.

EVALUATION PARAMETERS

The prepared ME formulations were evaluated for Phase Behavior Study, Drug content, Zeta potential,Shape and Surface morphology, Droplet size and PDI, Viscosity, $p^{H,}$ Refrective index, *In-vitro* drug release study.

A. Phase Behavior Studies

Phase behavior studies are essential for the study of surfactant system determined by using phase diagram that provide information on the boundaries of the different phases as a function of composition variables and temperatures, and, more important, structural organization can be also inferred.

B. Drug content:

Preparation of Standard solution:

50 mg of Valacyclovir was accurately weighed and dissolved in 50 ml of methanol to get a concentration of 1 mg/ml. The stock solution was suitably diluted to get a concentration of 100 mg/ml.

Assay procedure

Into a series of 125 ml separating funnels containing aliquots of standard drug solution (0.5-2.5 ml) and 1.0 ml of buffer solution and 1.0 ml of wool fast blue solution were added. The total volume of aqueous phase in each separating funnel was adjusted to 15 ml with distilled water and 5.0 ml of chloroform was added. The contents were shaken for 2 min. the two phases were allowed to separate and the absorbance of the separated organic layer were measured at 585 nm against a reagent blank prepared under identical conditions. The amount of valacyclovir present in the sample was measured from calibration curve.

C. Zeta Potential Measurement:

The surface charge on microscopic particles produces a difference in electrical potential in mv between the surface of each particle and bulk of the suspending liquid. This difference is called zeta potential. Zeta meter measures the effect of electrostatic charge, this is basic force which causes electrical repulsion between adjacent particles. Net result attraction or repulsion depends upon the relative magnitudes of both forces. Zeta potential affects the Stability of Microemulsion.

D. Determination of Shape and surface morphology

The scanning electron microscope creates the magnified image by using electrons instead of light waves.

E. Droplet Size and Polydispersity index Determination

Size of droplet is measured by photon correlation spectroscopy (PSC) with Zetasizer. All measurements are carried out at scattering angle of 90° and 25°C temperatures. Experiments were performed in triplicate for each sample, and results were presented as average ± standard deviation.

F.Viscosity Measurements

The Rheological property of the microemulsion was evaluated by Brookfield viscometer using a CPE 42 spindle at 5 rpm at 28°C. Experiments were performed in triplicate for each sample, and results were presented as average ± standard deviation.

G. p^{H}:

The pH was determined using pH meter (Digital p^{H} Meter). pH is an imp. Parameter for topical formulation.

H. Refractive Index

Refractive index indicates the transparency of formulation. The refractive index of the system is measured by Abde refractometer by placing drop of solution on slide and it compare with water (1.333)**.** Datas were generated in triplicate.

I. *In Vitro* Drug Release Study Study

The release study was carried out by using Cellophane membrane. The experimental unit consists of a donor and receptor compartment. Donor compartment consists of a boiling tube which was cut open at one end and tied with

membrane at the other end into which 5mg drug equivalent formulation quantity was taken for release study. Receptor compartment consists of a 250 ml beaker which was filled with 250 mL release medium (pH 7.4 phosphate buffer) and the temperature of it was maintained at 37±0.5°C. At 1,2,3,4,6,8 hour time points, 1 mL samples were withdrawn from receiver compartment and replenished with the same volume of release medium. The collected samples were suitably diluted and analyzed for drug content by reading the absorbance at 254 nm against blank (pH 7.4 phosphate buffer) in UV-Visible spectrophotometer (UV method).

J. Dispersion Stability Studies:
The formulations having no phase separations were taken for the heating and cooling cycle (freeze thaw cycle). Six cycles between the temperatures 4°C (refrigerator) and 45°C in a hot air oven with storage at each temperature for not less than 48 h were done. The formulations which were stable at these temperatures were selected for further studies, The optimized microemulsion formulation was stored at 4°C, room temperature and 45°C for 3 months and samples were evaluated for physicochemical parameters like p^H, % drug release, Viscosity and drug content at 1 month interval[7-9].

Formulation of Optimized Microemulsion into Microemulsion Gel:
On the basis of *in vitro* drug release studies, Drug content the optimized microemulsion formulation which showed the highest drug release profile, and drug content was selected and formulated into gel by the use of 1% w/w Carbopol 934 which shows better consistency[10], weighed amount of Carbopol 934 was soaked in the microemulsion, stirred to dispersed Carbopol 934 in the microemulsion and left over night to obtained a gel of desirable viscosity with high thickening capability and compatibility with the microemulsion.

EVALUATION PARAMETERS FOR MICROEMULSION BASED HYDROGEL
The prepared microemulsion based hydrogel was inspected for homogeneity, grittiness, viscosity, spreadability, pH, drug content, *in-vitro* drug release and stability studies.

1. **Homogeneity:** Developed MBH was tested for homogeneity by visual inspection after the gel have been set in the container. It was tested for their appearance and presence of any aggregates.
2. **Grittiness:** Microemulsion Based Hydrogel formulation were evaluated microscopically for the presence of particles.
3. **Viscosity:** The measurement of viscosity of the MBH was done with a Brookfield viscometer. The gels were rotated at 100 rpm using spindle no. F96. At each speed, the corresponding dial reading was noted.
4. **pH measurement:** The pH of MBH was measured, using Digital pH meter and datas are generated in triplicate.
5. **Spreadability:** The spreadability of the MBH was determined by measuring the spreading diameter of 1g of gel between two horizontal plate (20 cm x 20 cm) after one min. The standard weight applied on the upper plate was 125 gm.
6. **Drug content:** To ensure uniform distribution of drug in gel formulation, it was sampled from the different locations in the mixer and assayed for the drug content. Drug content of the gel was determined by dissolving an accurately weighed quantity of gel (about 1 gm) in about 100 ml of phosphate buffer pH 7.4. These solutions were quantitatively transferred to volumetric flasks and appropriate dilutions were made with the same buffer solution. The resulting solutions were then filtered from membrane filters (0.45 mm size) before subjecting the solution to spectrophotometric analysis at 254 nm. Drug content was determined from the standard curve of Valacyclovir Hydrochloride.
7. ***In-vitro* drug release studies:** The drug Release studies for MBH was carried out as described previously for ME.

Analysis Of Release Data In order to determine the release model which describes the pattern of drug release across cellulose membrane, the release data were analyzed with the following mathematical models: zero order kinetic; first order kinetic, Higuchi and Korsmeyer-Peppas.

Zero-order kinetics: $F = K_0 t$
First-order kinetics: $\ln(1-F) = -K_1 t$
Higuchi model: $F = K_H t^{1/2}$
Korsmeyer-Peppas model: $F = K_p t^n$

Where
F=Fraction of drug released in time t

K_0 = zero order release constant,
K_1 = First-order release constant,
K_H= Higuchi dissolution constant
K_p = Korsmeyer-Peppas release rate constant and n = Diffusion exponent.

8. **Stability study**

The stability studies for MBH was carried out. MBH kept in glass containers and undisturbed, in the chamber. The analytical condition was 40 ±2°C temperature and 75±5% RH. Then interval of 1,2 and 3 month the samples were withdrawn for pH, viscosity and drug content determination.

RESULTS AND DISCUSSION

A. Solubility determination:

On the basis of solubility study in various oils, surfactants and cosurfactant Valacyclovir Hydrochloride was found to be freely soluble in Water, Soluble in DMSO, Iso Propyl Myristate and Span 20 and Tween 20, Sparingly soluble in Oleic acid, Insoluble in Ethanol.Results are given in the Table II.

Table II: Results Of Solubility Determination

Medium used	Solubility(mg/100ml)
Water	170±0.21 mg/ml
DMSO	14±0.15mg/ml
Ethanol	<1 mg/ml
Span 20	30± 0.24mg/ml
Iso propyl Myristate	13.5±0.15mg/ml
Tween 20	16±0.14 mg/ml
Oleic acid	3.2±0.17 mg/ml
Castor oil+ olive oil	4.1±0.15mg/ml
Eucalyptus oil	2.2±0.14mg/ml
Tween 20	7.2±0.58mg/ml
IPA	1.2±0.23 mg/ml

Construction of Pseudo Ternary Phase Diagrams

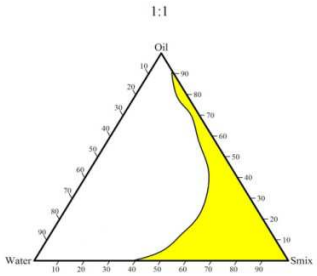

Figure 1(A):Pseudo ternary phase diagram for 1:1 S_{mix}

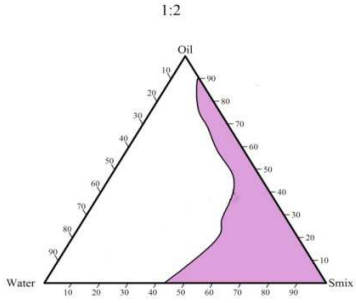

Figure 1(B):Pseudo ternary phase diagram for 1:2 S_{mix}

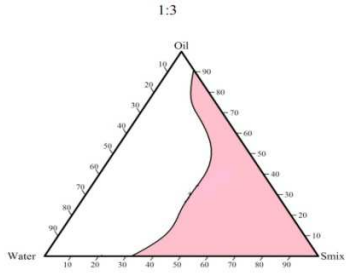

Figure 1 (C) :Pseudo ternary phase diagram for 1:3 S_{mix}

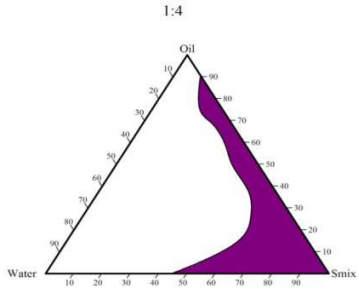

Figure 1 (D):Pseudo ternary phase diagram for 1:4 S_{mix}

A. Phase Behaviour Study:

Phase studies were carried out to find the area of microemulsion existence and to investigate the effect of different surfactant/cosurfactant weight ratios on the extent of stable microemulsion region.From the pseudoternary phase diagrams for microemulsion along with the ratios of surfactant and cosurfactant(Span20: DMSO), as 1:1, 2:1, 3:1, and 4:1 the phase diagram at 3:1 (s/co-s) weight ratio had obtained the highest area of emulsification and so it was selected for Batch formulation.

B. Drug Content:

The percentage drug content was evaluated in formulations of Valacyclovir HCl o/w microemulsion. The drug present in Valacyclovir HCl microemulsion was determined and shown in Table III .Formulations was found to be in the range of 98.22±0.051to 99.89±0.052.

C. Zeta Potential Measurement:

The surface charge (zeta potential) of the microemulsion was believed to play a role in its bioavailability. Zeta potential is an important parameter for prediction of stability. Because of the presence of fatty acids in the structure of the excipients used, generally the surface charge of the droplet is negative. Zeta Potential of all formulated o/w microemulsions shown in Table IV were in the range of -25±0.012 to -48±0.041 mV, which indicates moderate to good stability.

D. Determination of Shape and surface morphology:

Scanning electron photomicrographs of formulation shows Particles of optimized formulation were smooth, oval and discrete.

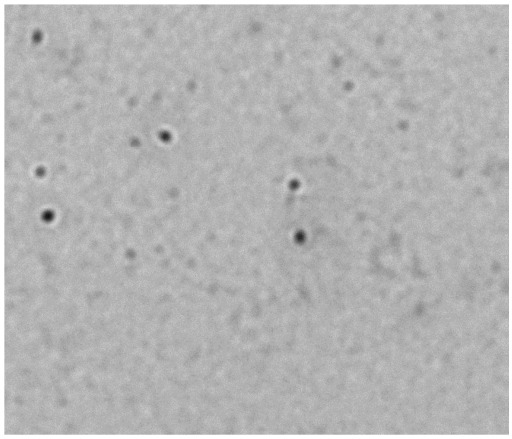

Figure 2: SEM Image for Microemulsion Formulation

E. Droplet size determination :

The average globule size shown in Table III of the optimized formulation was determined by photon correlation spectroscopy with in-built Zetasizer; The Results were found to be in the range of 156±0.365 to 388±0.052.

F.Viscosity:

The viscosity values of all samples were low and found to be in the range of 53±0.017 to 60±0.001 . All samples exhibited Newtonian flow behaviour, as expected from microemulsions. Results shown in Table IV.

G. P^H :

The pH value for theValacyclovir HCl Microemulsion formulations were recorded on digital pH meter shown in Table III and found to be in the range of 6.213±0.045 to 6.721±0.0007. It is suitable for topical as well as transdermal application because the pH of skin in the range of 5.5 to 7.0.

H. Refrective index:

Refrective index for the formulations were determined by the help of Abde Refrectometeer and results were shown in Table IV, found to be in the range of 1.40±0.021 to 1.44±0.001.

Table III: Evaluation Parameter of the Various Formulations Of Microemulsion

Formulation	Drug Content (%)	P^H Values	Mean Diameter (nm)	P.D.I.
ME1	98.63±0.15	6.615±0.021	220±0.002	0.44±0.016
ME2	98.75±0.005	6.470±0.032	186±0.025	0.310±0.012
ME3	98.36±0.023	6.213±0.045	178±0.052	0.305±0.097
ME4	98.23±0.049	6.695±0.049	238±0.125	0.230±0.015
ME5	99.89±0.052	6.721±0.007	156±0.365	0.114±0.031
ME6	98.22±0.051	6.325±0.091	288±0.457	0.320±0.010
ME7	98.54±0.052	6.535±0.063	192±0.012	0.249±0.090
ME8	99.29±0.14	6.321±0.157	164±0.014	0.158±0.014
ME9	98.14±0.56	6.524±0.142	182±0.006	0.251±0.085

Table IV: Evaluation Parameter of the Various Formulations Of Microemulsion

Formulation	Zeta Potential (mV)	Viscosity (cp)	Refractive Index
ME1	-25±0.012	60±0.001	1.44±0.001
ME2	-29±0.126	57±0.011	1.42±0.012
ME3	-38±0.014	54±0.02	1.43±0.012
ME4	-32±0.058	58±0.013	1.41±0.005
ME5	-48±0.041	55±0.002	1.40±0.021
ME6	-30±0.712	56±0.015	1.43±0.001
ME7	-29±0.285	53±0.017	1.43±0.005
ME8	-33±0.125	62±0.052	1.41±0.018
ME9	-43±0.002	78±0.14	1.43±0.024

I. In Vitro Drug Release Study:

It was observed that maximum drug delivery from the microemulsion achieved in 8 hr. The % drug release after 8 hour for the formulations ME1- ME9 shown in Table V and varied from 83.01% to 96.38% . ME5 formulation containing show highest drug release 96.38%.

Table V: *In-Vitro* Drug Release Datas of Various ME Formulations

Formulation Code	% Drug Release					
	0.5 hour	1 hour	2 hour	4 hour	6 hour	8hour
ME1	12.85	32.21	51.58	70.96	82.45	92.15
ME2	14.68	43.65	55.32	71.56	79.63	83.01
ME3	13.80	43.80	59.59	75.17	84.65	93.71
ME4	14.63	48.18	54.08	65.10	76.09	89.47
ME5	17.25	45.63	56.03	71.34	81.59	96.38
ME6	12.32	38.21	56.56	79.67	84.23	89.13
ME7	15.60	41.05	54.40	89.65	92.50	94.06
ME8	16.21	38.15	57.19	68.21	79.61	94.24
ME9	13.25	33.84	58.21	70.14	82.21	95.61

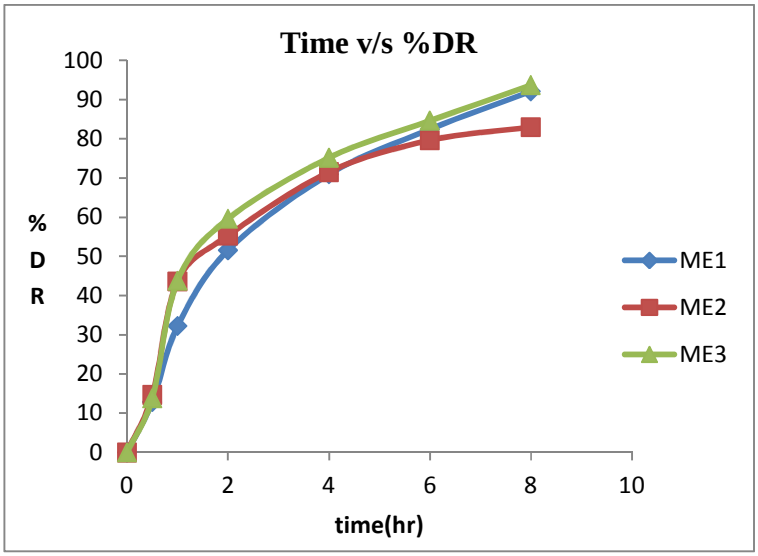

Figure 3(A): Drug releaseCurve For ME1 –ME3

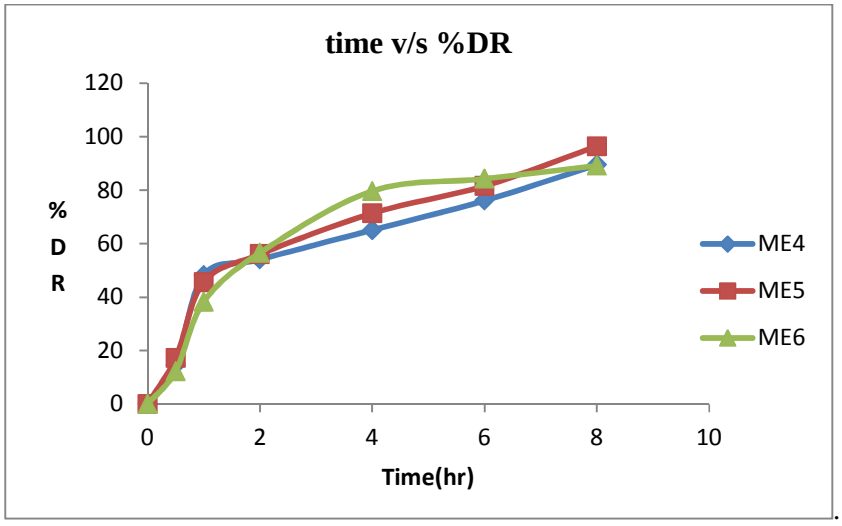

Figure 3(B): Drug Release Curve For ME4 –ME6

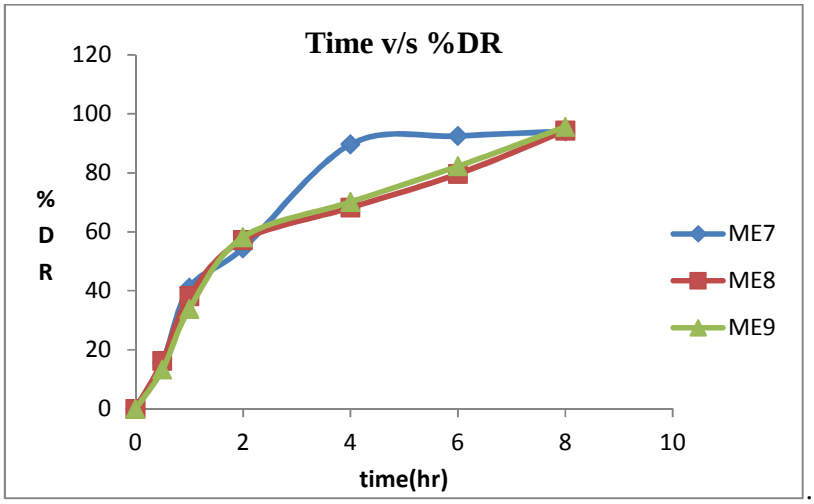

Figure 3(C): Drug ReleaseCurve For ME7 –ME9

J. Stability Studies:

On the basis of Drug content, % drug release studies ME5 formulation showed highest results with 99.89±0.052% drug content, 96.38% drug release with the p^H value 6.72±0.052 and viscosity 55±0.002 cp. Thus ME5 selected for further stability studies. No visual changes was observed after stability studies.All the results shown in Table VI.

Table VI: Stability Studies

Parameter	Initial	After 1 Month	After 3 Month
P^H	6.72±0.052	6.66±0.12	6.51±0.14
% D.R.	96.38%	96.12%	94.12%
Drug Content	99.89±0.052%	98.21±0.021	94±0.015
Viscosity	55±0.002 cp	54±0..34	52±0.014

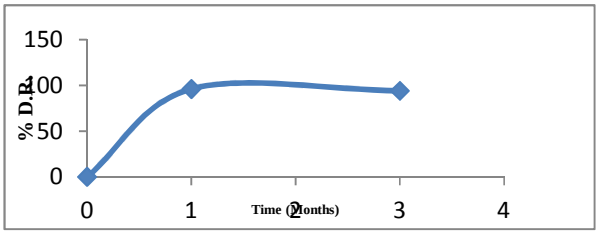

Figure 4: Stability studies for optimized microemulsion

EVALUATION PARAMETERS FOR MICROEMULSION BASED HYDROGEL

The prepared microemulsion based hydrogel was evaluated for homogeneity, grittiness, viscosity, spreadability, pH, drug content, *in-vitro* drug release and stability studies results are shown in table:

1. **Homogeneity:** The prepared MBH showed a smooth and Homogenous appearance.
2. **Grittiness:** MBH formulations was evaluated microscopically for the presence of particles and no appreciable particulate matter was seen under light microscope.
3. **Viscosity:** Viscosity is an important physical property of topical formulations, which affects the rate of drug release. An increase in the viscosity vehicles would cause a more rigid structure with a consequent decrease of the rate of drug release.The viscosity of MBH is 112±0.145
4. **pH Measurement:**The pH of microemulsion gel was found in the range of 6.9±0.15, which are considered acceptable to avoid the risk of irritation after topical application.
5. **Spreadability:** Spreadability denotes the extent of area to which the readily spreads on application to the skin or the affected part. The efficacy of the formulation or the bio-availability efficiency of the gel also depends on the spreadability value. The higher the value of spreadability of the gel the higher is the absorption area or higher is the

bio-available efficiency of the formulation. The spreadability is important for uniform and ease of application of topical preparation from patient compliance point of view. It was found in the range of 3.5±0.08 cm for different formulations which indicated good spreadability. MBH was easily spreadable, with acceptable adhesion and fair mechanical properties.

6. Drug content : Drug content uniformity of the formulation is shown in Table . The percentage drug content of MBHwas found to be 98.02±0.09% . All the results shown in Table VII.

Table VII: Evaluation Parameters of MBH

S. No.	Parameter	Results
1	Homogenity	Smooth and Homogenous
2	Grittiness	No Grittiness
3	Viscosity	112±0.145cp
4	p^H	6.9±0.15
5	Spreadibility	3.5±0.08cm
6	Drug Content	98.02±0.09%

7. *In-vitro* Drug Release: *In-vitro* drug release studies were carried out using Modified Franz diffusion cells.The study was performed for 12 hrs, and cumulative drug release was calculated at different time intervals shown in Table VIII .The *in-vitro* drug release profiles for the formulations were tabulated in Table VIII. The MBH showed 94.85±0.202 drug release in 12 hr.

Table VIII: *In -Vitro* Drug Release For MBH

Time (hr)	% Drug Release
0.5	12.36±0.157
1	29.91±0.099
2	52.46±0.432
4	82.56±0.317
6	91.50±0.172
8	91.82±0.236
12	94.85±0.202

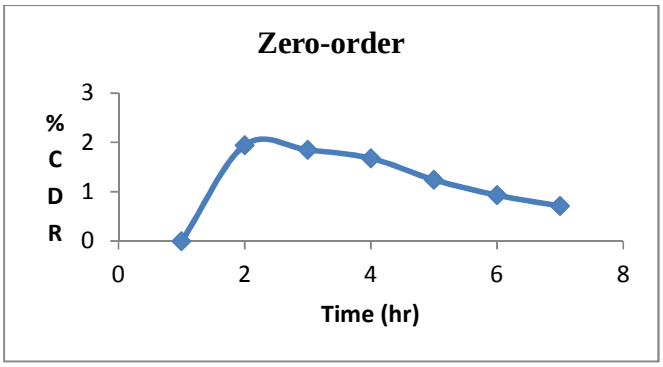

Figure 5:Zero order plot for MBH

Table IX: Results of kinetic model fitted for microemulsion-based hydrogel

Diffusion model	R^2 value
Zero order plot	0.9979
First order plot	0.8458
Higuchi plot	0.9377
Korsmeyer peppas plot	0.9951

8. Stability Studies:

The accelerated stability studies were carried out acc.to ICH guidelines at 40°C and 75% RH for 1,2 and 3 months. The MBH were evaluated before and after one month for change in drug content, p^H, and viscosity. Results shown in Table X.

Table X: Stability Studies for MBH

Parameter	Initial	After 1 Month	After 3 Month
P^H	6.9±0.015	6.76±0.12	6.61±0.14
Drug Content	98.02±0.09%	97.21±0.021%	97±0.015%
Viscosity	112±0.145 cp	110±0..34 cp	98±0.014 cp

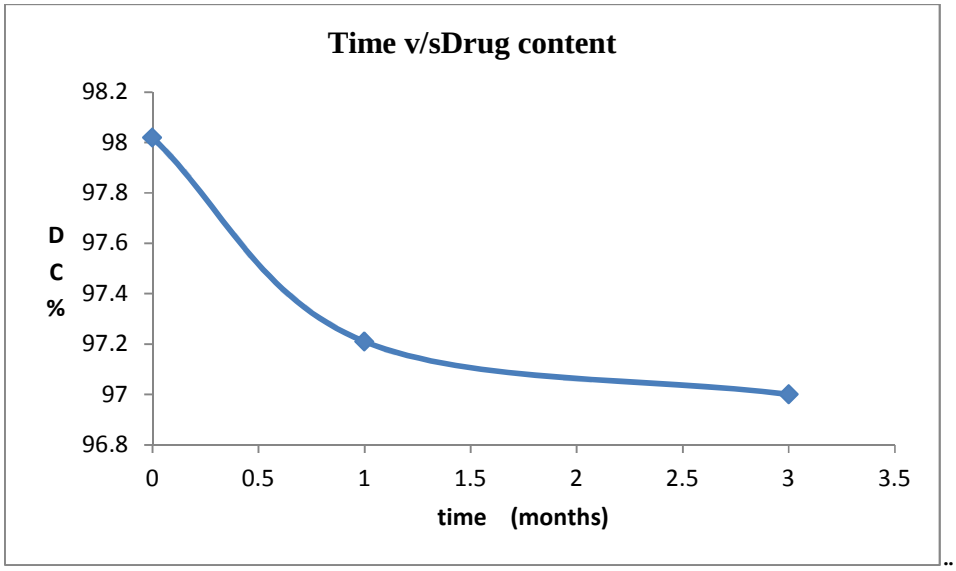

Figure 6: Stability study for MBH

CONCLUSION

In the present study a satisfactory attempt was made to formulate a Hydrogel based Micro-emulsion of Valacyclovir hydrochloride for topical delivery.

Valacyclovir Hydrochloride found to be soluble in IPM, DMSO & Span 20 and used as oil phase,Co-surfactant and Surfactant respectively.Valacyclovir Hydrochloride Microemulsion formulated using water titration method.The prepared formulations exhibit all the desirable attributes of microemulsion and were also found to be stable for 3 months.On the basis of Drug Release and Zeta potential optimized ME converted into gel with the help of gelling agent Carbopol 934 and evaluated for various physico-chemical parameters and stability studies.

From the results of the present research work it can be concluded that Hydrogel based Microemulsion of valacyclovir Hydrochloride provide a basis for successful design of topical delivery of Valacyclovir Hydrochloride.

Future Prospectus
Further detailed investigations in terms of clinical studies need to be carried out for the formation of a clinically effective hydro-gel based micro-emulsion of Valacyclovir hydrochloride. The research work can be further continued to perform *in-vivo* studies to establish *in-vitro* & *in-vivo* correlation.

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