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Research article on Microemulsion An Innovative Approach To Drug Delivery

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ABSTRACT

Objective:

Aim of present studies to reduce the particle size, increase the surface area withincrease permeation of drug and modify release of drug at specific site hence dose anddose frequency may be decreased, thereby obtaining greater therapeuticefficacy.

Experimental Work:

Present study has been involved to prepare microemulsion of a poorly water-solubledrug, Etodolac.Before the formulation of Etodolac microemulsion,perform the preformulation study. Find out maximum solubility of Bifonazole in oils, surfactants and co-surfactants was evaluated to identify potential excipients. Themicroemulsion area were selected through the construction of the pseudo ternary phasediagrams by phase titration method.

Results & Discussion:

A 3^2 full factorial design was applied to examinethe combined effect of two formulation variables, each at 3 levels and thepossible 9 combinations of Etodolac ME were prepared. Optimized ME was preparedand incorporated into gelling agent added as gel matrix to convert microemulsion intomicroemulgel.Microemulsion and microemulgel evaluated by %transmittance,viscosity, pH, Density, conductivity, TEM, particle size, Zeta potential, surfacetension, refractive index, In-vitro diffusion study. Physical appearance, viscosity,spreadability, extrudability measurement,syneresis measurement,comparison withmarketed product,antifungal activity and accelerated stability studies. From FTIR andDSC study found there is no interaction between drug and excipient. On the bases ofpseudo ternary phase diagram has been found that the system consisting of capryol 90, tween 80 and PEG 400 showed good emulsifying property at Smix ratio 4:1.Microemulsion formulation F10 was optimized on the basis of %Transmittance,viscosity, %cumulative drug release. On the basis of physical examinationviscosity, pH and spreadability result Diffusion Study, Sensitivity Study on animaland Kinetic Model Study of gel.Gel formulation was optimized batch thatcontains 1% carbopol as gelling agent.These above results indicate itraconazoleloaded microemulgel drug delivery system may be promising vehicle for topicaldelivery of Etodolac.

Key words: Etodolac, Microemulsion, Microemulgel

INTRODUCTION

Hoar and Schulman were the first to introduce micro-emulsion in 1943. Micro-emulsions are isotropic liquid combinations of oil, water, and surfactant, often in combination with a co-surfactant that are transparent, thermodynamically stable, and isotropic.

"A micro-emulsion may be a system comprising oil, water, and an amphiphile that may be a single optically identical and thermodynamically stable liquid solution," according to one of the best definitions of micro emulsions.

Micro emulsions have been extensively researched as a way to improve the bioavailability of poorly soluble medicines. In such circumstances, they provide a cost-effective solution. Micro emulsions have a low surface tension and a small droplet size, resulting in excellent absorption and penetration.

Micro emulsions are thermodynamically stable isotropic and transparent systems made up of oil, water, and a surfactant, usually in combination with a co-surfactant. The size of the droplets might range from 10 to 200 nanometers.

Single-chain and double-chain surfactants can be used to create micro emulsions. Co-surfactants are essential because single chain surfactants do not sufficiently reduce the oil-water interfacial tension. By penetrating into the surfactant layer, co-surfactant accumulates significantly at the interface layer, improving the fluidity of the interfacial film. The inclusion of co-surfactants gives the interfacial film the flexibility it needs to take on the various curvatures required to create a micro emulsion in a variety of

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compositions. If a single surfactant film is needed, the surfactant's lipophilic chains must be short enough or contain fluidizing groups (e.g. unsaturated bonds). Co-surfactants with short to medium chain length alcohols (C3-C8) are often used to lower interfacial tension and promote interface fluidity. A co-functions surfactant's include increasing interface fluidity, destroying liquid crystalline or gel structure that would hinder the development of a micro emulsion, and adjusting the HLB value and spontaneous curvature of the interface by changing the surfactant partitioning characteristic.

Materials & Methodology

Materials

Etodolac was received as a gift sample from Torrent Pharmaceutical Ltd., Ahmedabad. Labrasol , PG were received as a gift sample from Laboratory Sulab Reagent, Vadodara. Sodium alginate was received as a gift sample from Colorcon Pt. Ltd., Goa.

Methodology

Method of Preparation ETODOLAC Microemulgel

Sodium alginate will be carefully weighed and dissolved in 100 mL of water for 2 hours of soaking with 600 RPM agitation, followed by the addition of a penetration enhancer to the formed gel to avoid drying. Slow agitation and continuous stirring will be used to introduce the Triethanolamine. In the gel, Etodolac Loaded Microemulsion will be added.

Physicalevaluation

It will be carried out to assess the gel's organoleptic properties, occlusiveness, andwashability.

MeasurementofpH

AdigitalpHmeterwillbeused to assessthepHoftheprepared gel.

Viscositystudy

The produced gel will be stored in a 50 mL appropriate beaker,and the spindleGroove will be dipped in a Brookfield Viscometer at a set RPM. This will be repeatedthreetimes,withthemeancomputedfromthe collectedobservations.

Spreadabilitystudy

1 g of gel will be precisely weighed and put between two slides, where it remained foraround 5 minutes. When no more spreading will be seen, the diameters of speedcircleswillbemeasuredincmand used ascomparison valuesfor Spreadability.

Homogeneityandgrittiness

By squeezing the produced gel between the thumb and index finger, the consistencywill be assessed.A little amountof gel will be applied to the back of the hand tocheckforhomogeneityandgrittiness.

Drugcontent

In a volumetric flask, 1 gm of each gel formulation will be dissolved in 20 mL ofalcohol after 30 minutes of stirring. It will be then diluted and filtered. A furtherdilution to 10 mL alcohol will be prepared, and 1 mL will be removed from the aboveand diluted to 10 mL alcohol once more. In ultraviolet light, the absorbance will bemeasuredat277nm.

KineticsofDrugRelease

In order to investigate the mechanism of drug release from microemulgel of differentratios, the release data obtained from dissolution studies will be fitted to variouskinetic equations.

The kinetics models used will be aZero orderequation,(**$Q_t=Q_0–K_0t$**)First order equation, (**$\ln Q_t= \ln Q_0 - Kt$**)Higuchi'sequation(**$Q_t=Kht^{1/2}$**)

Thefollowingplotswillbemade,

Q_tVs.t(Zeroorderkineticmodel),

$(Q_0 - Q_t)$ Vs. t (First-order kinetic model)And **$Q_t$vs.$t^{1/2}$**(HiguchiModel),

Where,

Q_t isthepercentofdrug released at timet,

Q_0istheinitialamountofdrugpresentinthemicrospheresand

K_0, K and K_h are the constant of the equations of Zero order, First order and Higuchirespectively.

StabilitystudiesofMicroemulgel as per ICH guidelines

Stability tests revealed that the quality of a medicine or dosage form can be influencedby changes in temperature, humidity, and light over time. It will be carried out for onemonth at room temperature for the chosen formulation. On the 0th, 15th, and 30thdays,sampleswillbetakenand examinedforphysicalappearanceand drug content.

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RESULTS & DISCUSSION

Screening of oils, surfactants and co-surfactants:

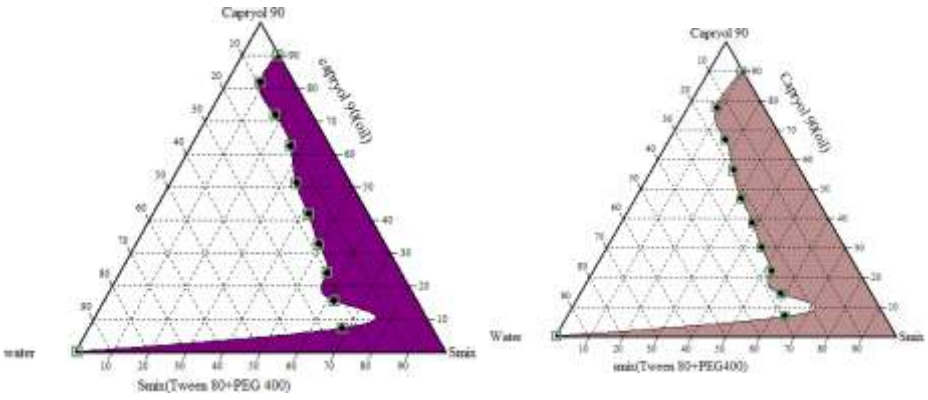
SolubilityofEtodolacinvariousoils,surfactantsandco-surfactants

Excipients	Solubility (mg/ml)(n=3)	SD
Oils		
Isopropyl myristate	0.171	0.22
Captex200	0.651	0.42
Capryol90	5.02	1.26
CapmulMCM	1.75	1.24
CastorOil	1.13	1.10
Sunfloweroil	**21.62**	**1.91**
Surfactants		
Labrasol	**25.01**	**0.24**
Tween80	12.14	0.01
Tween20	1.47	1.71
Cosurfactants		
PEG400	1.1	0.22
PropyleneGlycol	**2.073**	**1.91**

Selection of Surfactants and co-surfactants.

Sr no	Excipients	%Transmittance	No.offlaskinversion
1	Tween80	88.2	14
2	Tween20	87	17
3	Labrasol	98	3
4	PEG400	86.4	8
5	PG	98.1	4

Construction of pseudo ternary phase diagram by optimizing Oil Surfactant: Co-surfactant Ratio.



A **B**

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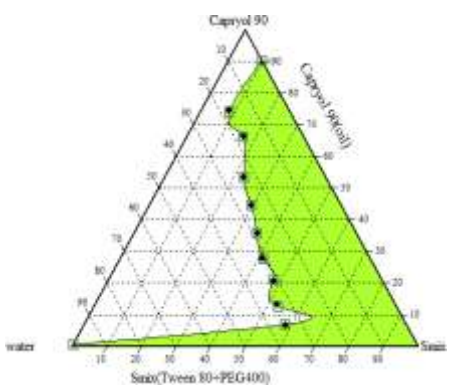

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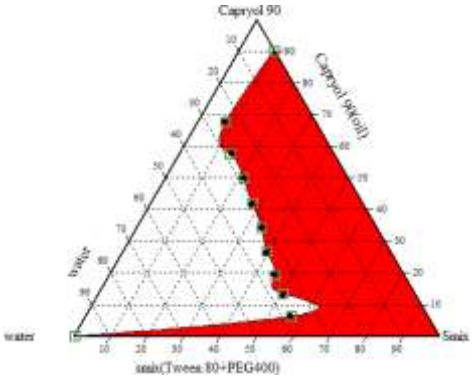

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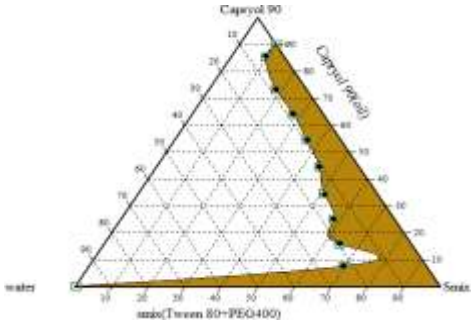

E

Pseudo ternary phase diagramwithout drug by using Sunflower oil phase and Labrasol /PG as the S/Cos rept(A=Smix1:1,B=Smix2:1,C=Smix3:1,D=Smix4:1,E= Smix1:2)

Pseudo ternaryDiagramWithout Drug

Srno.	Surfactant:Co-Surfactant	Oil(%w/w)	Smix(%w/w)	Water(%w/w)	%Transmittance
1	1:1	7.58	68.18	24.24	95%
		15.50	62.02	22.48	94.3%
		24	56	20	93.7%
		32.79	49.18	18.03	92.5%
		42.02	42.02	15.96	91%
		51.28	34.19	14.53	77.6%
		62.50	26.79	10.71	65.2%
		72.07	18.02	9.91	53.1%
		81.82	9.09	9.09	45.4%

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2	**2:1**	7.09	63.83	29.08	96.5%
		14.71	58.82	26.47	95.7%
		22.39	52.24	25.37	93.8%
		30.30	45.45	24.25	92.4%
		38.46	38.46	23.08	90.1%
		46.88	31.25	21.87	89.2%
		56.45	24.19	19.36	73%
		66.67	16.67	16.66	65.4%
		77.59	8.62	13.79	58.3%
3	**3:1**	6.49	58.44	35.07	98.2%
		13.16	52.63	34.21	98%
		20.55	47.95	31.5	95.7%
		27.59	41.38	31.03	91.4%
		35.71	35.71	28.58	91.2%
		44.44	29.63	25.93	90%
		53.44	22.90	23.66	77.1%
		66.12	16.53	17.35	69.7%
		74.38	8.26	17.36	62%
4	**4:1**	6.25	56.25	37.5	99.8%
		12.74	50.96	36.3	98.9%
		19.35	45.16	35.49	97.1%
		26.32	39.47	34.21	92.4%
		34.25	31.25	34.5	91.8%
		41.67	27.78	30.55	90.3%
		50	21.43	28.57	82%
		57.55	14.39	28.06	79.5%
		67.67	7.52	24.81	73.1%
5		7.75	69.77	22.48	91.1%
		16.13	64.52	19.35	87%

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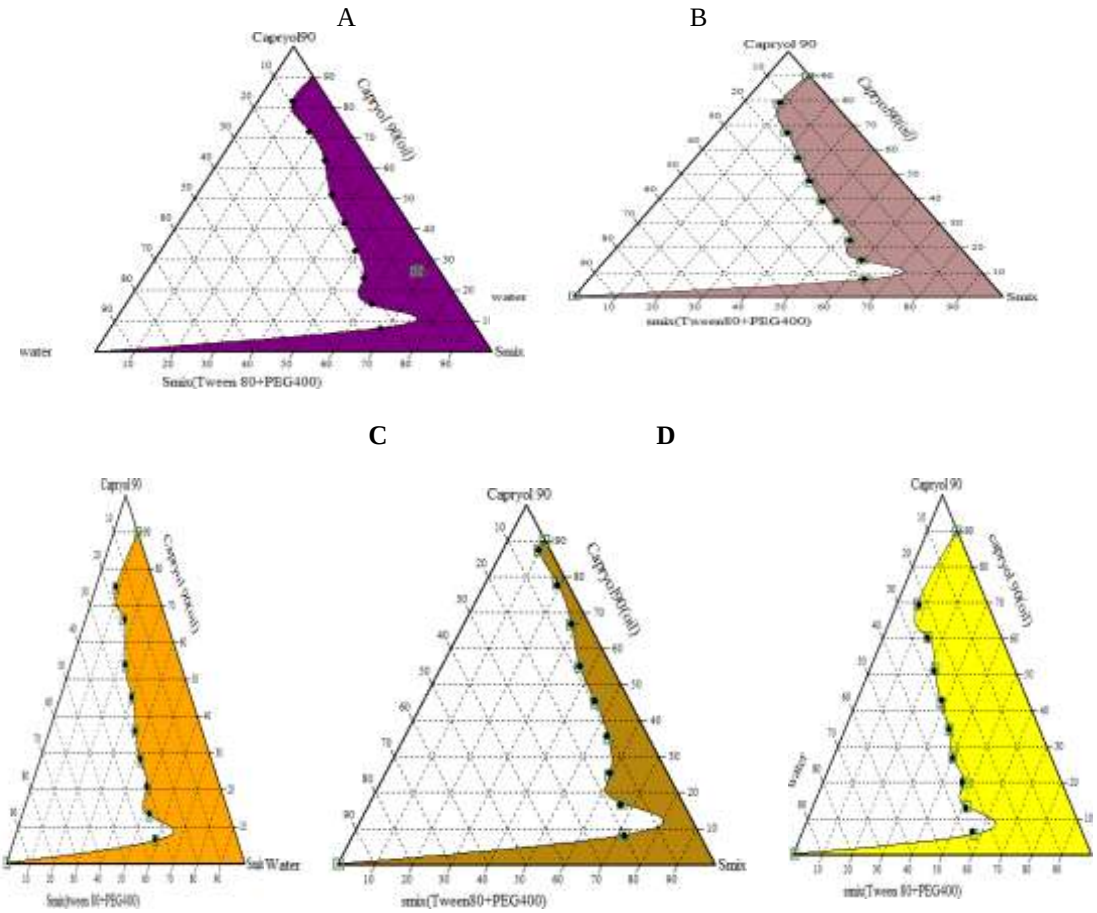
	1:2	25.0	58.33	16.67	83.4%
		34.19	51.28	14.53	80.7%
		44.64	44.64	10.72	74.5%
		54.55	36.36	9.09	65.3%
		64.22	27.52	8.26	52.2%
		73.39	18.35	8.26	48%
		85.71	9.52	4.77	35%

Pseudoternaryphasediagramareconstructed toidentifythemicroemulsionregionandselectsuitable compositionofoil, surfactantandcosurfactantfor formulation of microemulsion. From pseudo ternary diagramhas been foundthatthesystemconsistingofcapryol90asanoilyp hase, tween80assurfactant and PEG 400 as co-surfactant showed good emulsifying property atSmix ratio 4:1. It was observed that by increasing oil content system showappearance of coarse emulsion.it was also observed that by increasing co-surfactant in Smix ratio the system show decreasing property of spontaneousmicroemulsion formation. Hence from the observation it is clear that surfactantplaykeyroleinformationofmicroemulsion inproperrangespontaneously.



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E

Pseudoternary phase diagramwith drug using Sunflower oil phase and Labrasol /PG as the S/Cos rept((A=Smix1:1,B= Smix2:1,C=Smix3:1,D=Smix4:1,E= Smix1:2)

1:1 2:1

3:1 **4:1**

Pseudo ternaryDiagramwithDrug

Sr no.	Surfactant: Cosurfactant	Oil(%w/w)	Smix(%w/w)	Water(%w/w)	%Transmittance
1	1:1	7.69	69.23	23.08	93.1%
		15.75	62.99	21.26	92.7%
		24.59	57.38	18.03	90.9%
		33.33	50	16.67	87.5%
		42.74	42.74	14.52	82%
		52.63	35.09	12.28	72.6%
		63.06	27.03	9.91	61%
		72.73	18.18	9.09	52.8%
		82.57	9.17	8.26	43%
2	2:1	7.14	64.29	28.57	95%
		14.93	59.70	25.37	93.5%

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		22.73	53.03	24.24	91.2%
		30.77	46.15	23.08	89.8%
		38.76	38.76	22.48	87%
		47.24	31.50	21.26	85.6%
		56.45	24.19	19.36	70%
		66.67	16.67	16.66	63.7%
		78.95	8.77	12.28	60%
3	3:1	6.58	59.21	34.21	97.3%
		13.33	53.33	45.34	96%
		20.83	48.61	30.56	93.8%
		28.17	42.25	29.58	91%
		35.97	35.97	28.06	88.4%
		45.11	30.08	24.81	87.7%
		53.85	23.08	23.07	74.3%
		66.12	16.53	17.35	65%
		75	8.33	16.67	61%
4	4;1	6.33	56.96	36.71	98.2%
		12.90	51.61	35.49	97.6%
		20	46.67	33.33	95%
		26.85	40.27	32.88	92%
		34.97	34.97	30.06	89.7%
		42.86	28.57	28.57	90.1%
		51.09	21.90	27.01	80.7%
		60.15	15.04	24.81	72.5%
		69.23	7.69	23.08	68%
5	1:2	8	72	20	88.5%
		16.97	66.67	16.36	82%
		25.42	59.32	15.26	78%
		35.71	53.57	10.72	77.5%
		45.45	45.45	9.1	70%
		55.05	36.70	8.25	65.1%
		66.67	28.57	4.76	50.3%
		77.67	19.42	2.91	47%

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		87.38	9.71	2.91	34.4%

Preliminary Trial Batches:
Thepreliminarybatcheswastakenafterscreeningandconstructionofpseudo ternary phase diagram to optimize various types and levels of variablesforDoEstudy.

PreliminaryTrialBatchesBasedonPseudo ternaryPhaseDiagram

Batchcode	**Compositionofmicroemulsion**					
	Oil (%w/w)	**Smix (%w/w)**	**Water (%w/w)**	**Oil(ml)**	**Smix(ml)**	**Water(ml)**
ETD1	6.33	56.96	36.71	0.63	5.69	3.67
ETD2	12.90	51.61	35.49	1.29	5.16	3.54
ETD3	20	46.67	33.33	2	4.66	3.33

CharacterizationOfbatchETD1-ETD3

Batchcode	**Viscosity(cps)**	**%Transmittance**	**%CDR**		
			Time(hr)		
			1	2	3
ETD1	144	99	12.22	16.59	31.62
ETD2	150	98.5	8.67	13.52	20.02
ETD3	155	96.3	6.52	13.07	18.17

Low concentration of oil and high concentration of Smix gives faster drug release due tosmaller globule size. As concentration of oil increase, raise in droplet size because of thatdecreases thedrug release.

Risk assessment to identify variables affecting drug product quality:
RiskassessmentswasdonetoselectformulationandprocessvariablewhichmayaffectproductqualityforcQAsbyprocesscharacterizationthatdefinessatisfactorychangesinmaterialandprocessparameters.Finally,thisc ouldresultin quality assuranceby Process Design Space tounderstand and developcontrolstrategy.Thecriticalqualityattributes willbecategorizedintohighseverityandlowseverityparametersbasedonknowledgespace.Usuallyhigh riskparametersareconsideredimportantforDesignofExperimentsastheyarehaving more effect than others and need to be in accepting multivariate ranges.The effect of different variables was checked by %Drug release, %TransmittanceandViscositycharacterizationofMicroemulsionformulatedinPreliminarytrialbatches.Based onthatcharacterization,CQAswasselectedwhichaffecthighlyonMicroemulsionFormulation.

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3^2FactorialDesign

Independentvariablesofformulations			
Independentvariables	Low(-1)	Medium(0)	High(1)
Oilconcentration (%) (X_1)	5%	10%	15%
Smixconcentration (%) (X_2)	50%	55%	60%
Dependentvariables			
Y_1=%Transmittance			
Y_2= viscosity			
Y_3=%Drugrelease			

Compositions of Factorial Batches in Coded Form

VariousbatchesofEtodolacMicroemulsionwithSunflower oil phase and Labrasol /PGwaspreparedaccordingto**3^2**factorialdesignswhichare asfollow:

CompositionsofFactorialBatchesinCoded Form

ETDMicroemulsion3^2=9Batches		
BatchNo	**Variablelevelin coded form**	
	Oil Concentration(X1)	**Smix Concentration(X2)**
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

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CompositionsofFactorialBatchesin ActualForm

BatchNo	ETDMicroemulsion3^2=9Batches			
	Actualvalue			
	OilConcentration(%) (X1)	SmixConcentration(%) (X2)	Amount ofOil(ml) (X1)	Amount ofSmix(ml) (X2)
F1	5	50	0.5	5
F2	5	55	0.5	5.5
F3	5	60	0.5	6
F4	10	50	1	5
F5	10	55	1	5.5
F6	10	60	1	6
F7	15	50	1.5	5
F8	15	55	1.5	5.5
F9	15	60	1.5	6

Characterization OfbatchesfromF1toF9

Batches	%Transmittance(Y1)	Viscosity(Y2) (cps)	%CDR (Y3)(%)
F1	98.4	147	26.31
F2	98.6	141	29.67
F3	98.8	138	32.32
F4	98.0	153	11.83
F5	98.3	151	15.84
F6	98.4	148	20.62
F7	95.1	165	9.65
F8	96.4	160	12.95
F9	96.8	157	18.96

Effect on %Transmittance(Y1) - Surface Response Study:

The Negative value for coefficient of X1 indicates decrease in response of Y1 i.e.% transmittance. Positive value of coefficient X2, Smix concentration indicates increase in %transmittance. It indicates linearity of surface response and contour plot as shown in figure. Full model was significant and detailed ANOVA,

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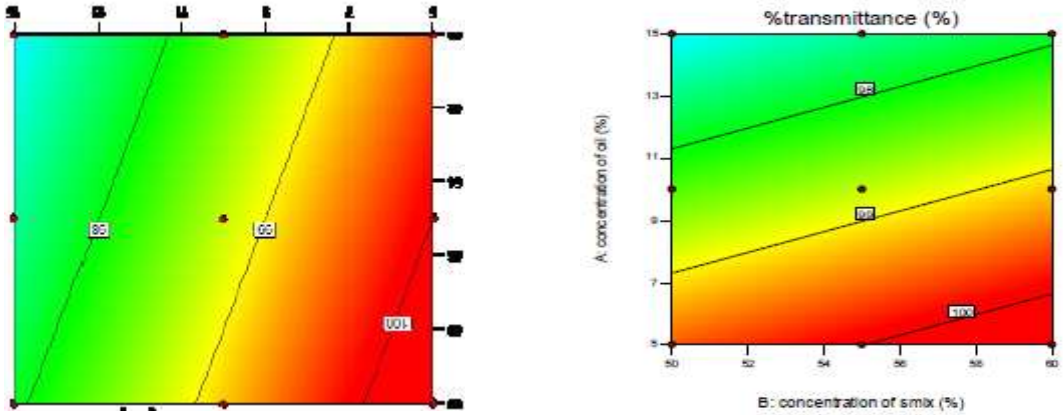
Response Surface Counter Plot and 3 D plots are as follows:

%transmittance= +97.63-1.14* X1+0.31* X2

ANOVATableforResponseY1

ANOVAforResponseSurfaceLinearmodel						
Analysisof variancetable[Partialsumof squares-TypeIII]						
	Sumof		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob>F**	
Model	9.31	2	4.10	12.68	0.0046	significant
A-concentrationofoil	8.27	1	8.27	23.72	0.0014	
B-concentrationofsmix	1.03	1	1.03	1.65	0.1367	
Residual	1.16	6	0.27			
CorTotal	11.57	8				



Response Surface Plot: (a)Concentration of oil(%) and (b)concentrationofSmixon%Transmittance (Y1)

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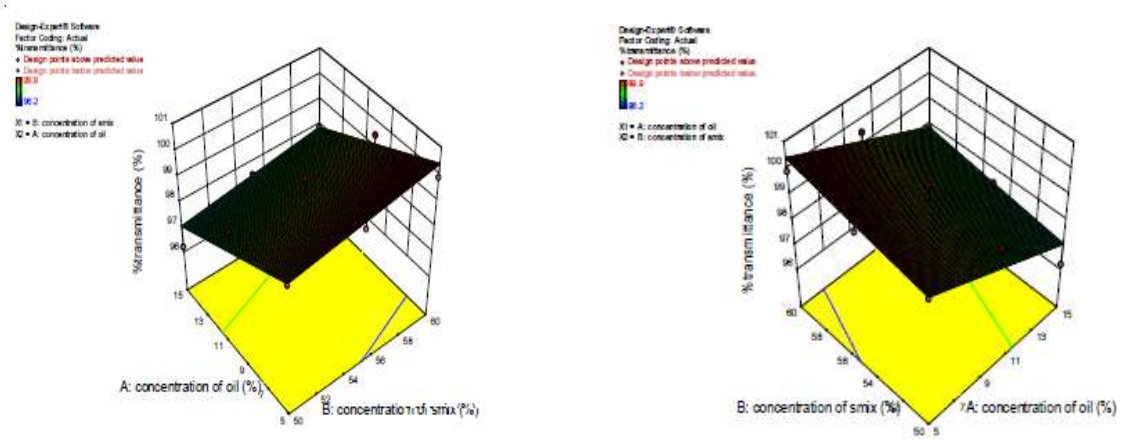

3D Surface Plot: (a) Concentration of oil(b) concentration of Smixon%Transmittance(Y1)

Effect on viscosity (Y2) - Surface Response Study:

ThepositivevalueforcoefficientofX1oilconcentrationindicatesincreaseinresponse of Y2 i.e. Viscosity.Negative value of coefficient X2, concentration of Smixindicates decrease in response of Y2 i.e viscosity. It indicates linearity of surfaceresponseandcontourplotasshowninfigure.Full lmodelwassignificant and detailed ANOVA, Response Surface Counter Plot and 3 D plots areasfollows:

Viscosity=+142.22+8.44* X1-2.56*X2

ANOVATableforResponseY2

ANOVAforResponseSurfaceLinearmodel						
Analysisof variancetable[Partialsumof squares-TypeIII]						
	Sumof		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob>F**	
Model	502.22	2	201.56	228.45	<0.0001	Significant
A-concentrationofoil	511.56	1	511.56	404.95	<0.0001	
B-concentrationofsmix	79.56	1	79.56	63.95	0.0002	
Residual	6.45	6	1.15			
CorTotal	510.78	8				

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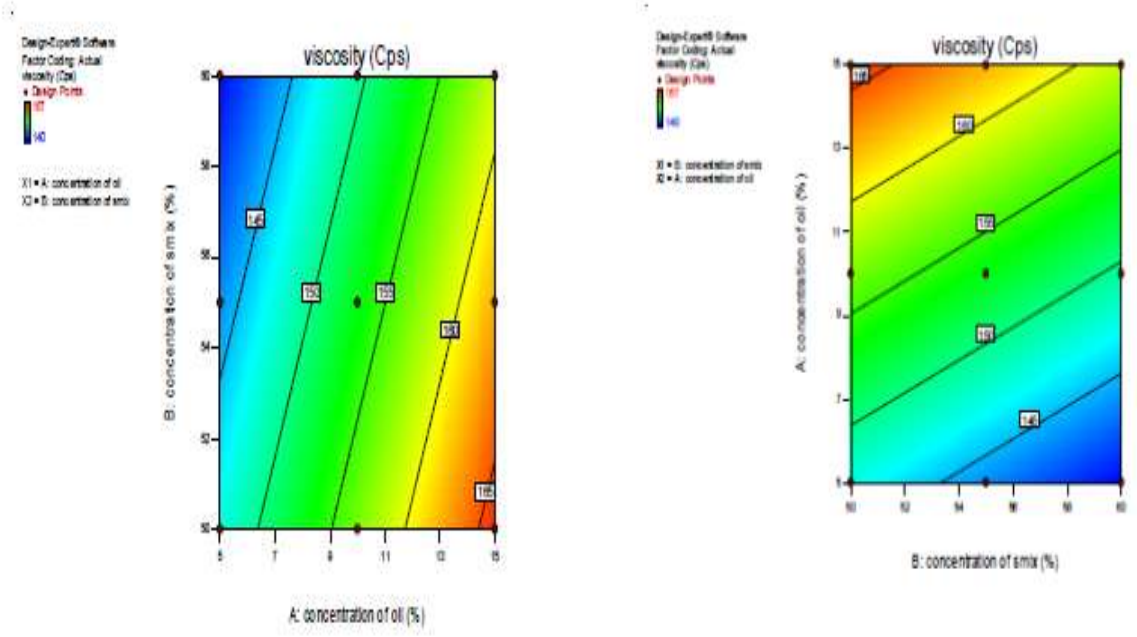
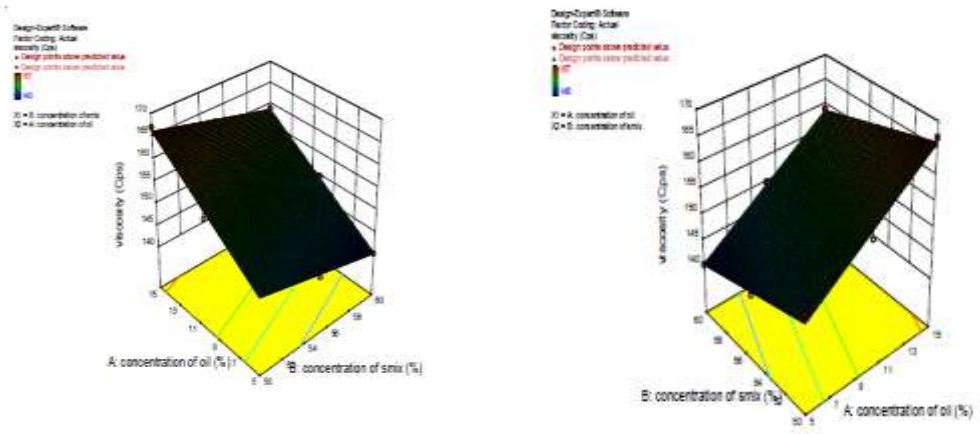


ResponseSurfacePlot(a)Oilconcentrationand(b)SmixconcentrationonViscosity(Y2)



3DSurfacePlot:(a)OilConcentrationand(b)Smix concentrationon Viscosity(Y2)

Effect on %CDR(Y3) - Surface Response Study: ThenegativevalueforthecoefficientofX1indicatesdecreaseinresponseofY3i.e. %CDR .The positivevalue of coefficient of X2concentration indicates increase inresponse of Y3 i.e. %CDR. Itindicates the linearity of the surface response andcontour plot as shown in figure. Full model was significant and detailed ANOVA,Response Surface CounterPlotand3D plotsare asfollows:

%CDR=+18.68-7.79*X1+4.02*X2

ANOVATableforResponseY3

ANOVAforResponseSurfaceLinearmodel						
Analysisof variancetable[Partialsumof squares-TypeIII]						
	Sumof		**Mean**	**F**	**p-value**	

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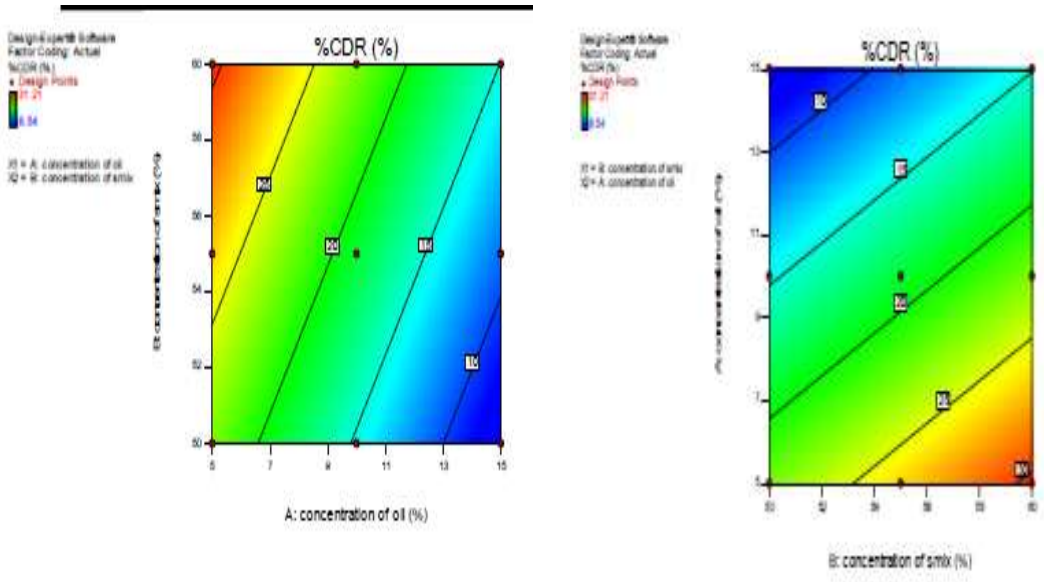
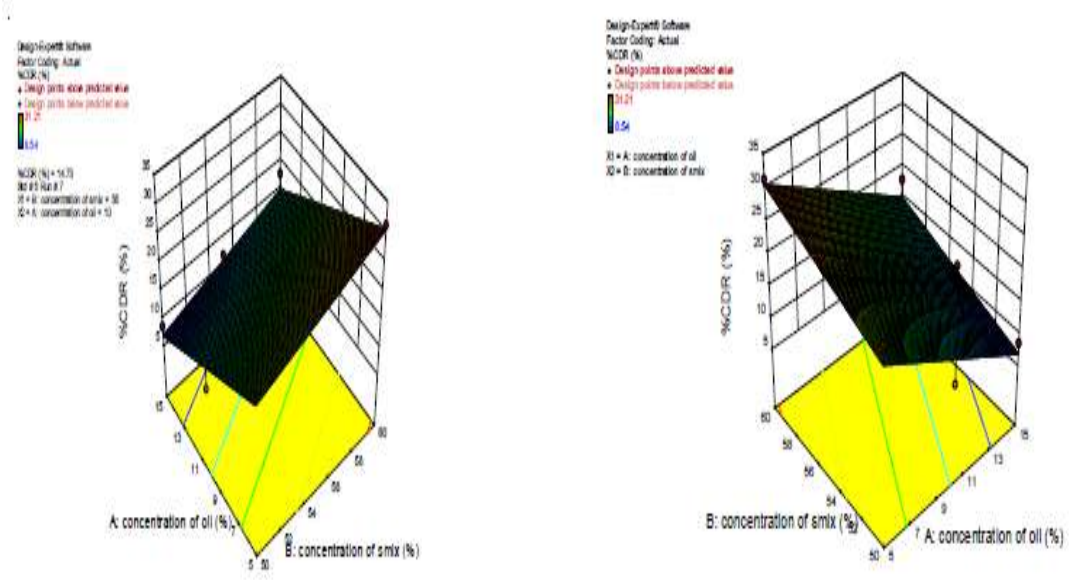
Source	Squares	df	Square	Value	Prob>F	
Model	459.88	2	229.38	19.93	0.0019	Significant
A-concentrationofoil	353.09	1	353.10	32.95	0.0011	
B-concentrationofsmix	95.77	1	95.77	7.79	0.0240	
Residual	65.98	6	10.00			
CorTotal	516.96	8				



Response Surface Plot: (a) Oil Concentration, (b) Smixconcentrationon%CDR(Y3)



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3D Surface Plot: (a) OilConcentration and (b) SmixConcentrationOn%CDR(Y3)

ValidationofBatchesF10&F11: PredictedResponse

BatchNo	OilConcentration(%) (X1)	Smixconcentration(%) (X2)	%Transmittance(Y1) (%)	Viscosity(cps) (Y2)	%CDR (Y3)
F10	6.03	55.9	99.81	144.9	25.65%
F11	6.7	51.12	99.24	149.80	20.70%

ValidationBatchesF10&F11:ActualResponse

Batch No	Oil Concentration (%) (X1)	Smix concentration (%) (X2)	%Transmittance (Y1) (%)	Viscosity(cps) (Y2)	%CDR (Y3)
F10	6.03	55.9	98.6	145.7	24.57%
F11	6.7	51.12	97.1	149.53	20.14%

CompositionFormulaofMicroemulsion

Ingredients	Concentration (%)	Actualvalue for10ml microemulsion
Oil	6.03%	0.6
Smix	55.9%	5.59
Water	49.87%	4.9

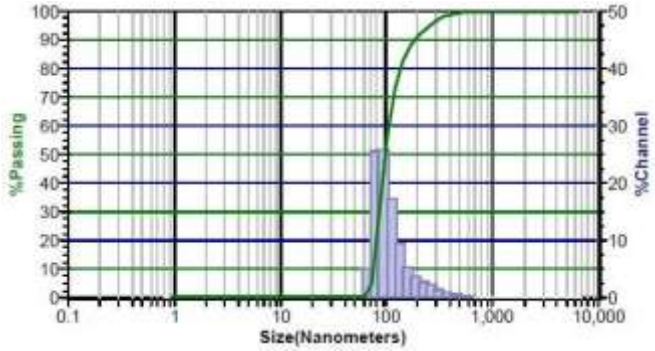
Selection of optimized formulation

F10 was selected as validated optimized batch and further considered for formulating into gel which was having %transmittance 98.6%, viscosity 145.7, and %CDR24.57%.

5.5 Analysis of Optimized Formulation of Etodolac microemulsion.

Zeta potential and globule size analysis.

Zeta potentialofoptimized batch



Particle Sie Analysis

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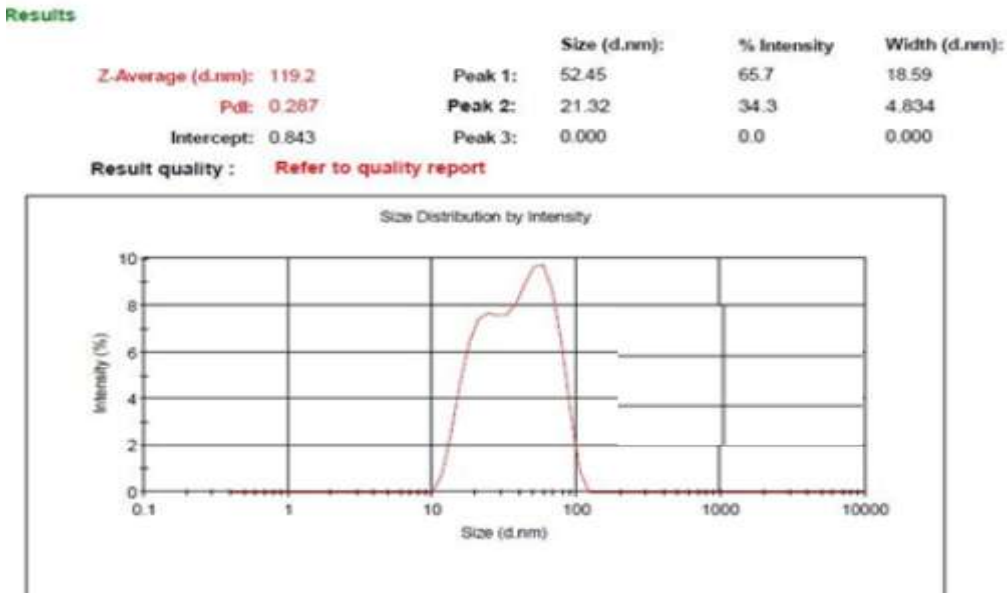

Particlesizeanalysis

pH,DensityandConductivityofoptimizedmicroemulsion(F10)

Parameters	**Result (Mean±S.D)(n=3)**
pH	6.24±0.04
Density(gm/ml)	1.01±0.02 gm/ml
Conductivity(µs)	50.5±0.04µs

Dilution Test of Optimized Batch (F10).
DilutionTest ofmicroemulsion

Dilution	**Observation**
10	Notfoundphaseseparation
50	Notfoundphaseseparation
100	Notfoundphaseseparation

The prepared microemulsion formulation was diluted in 1:10, 1:50 and 1:100 ratiowith distill water the system doesn'tshow any sign of separation andfound tobe clear.Soits confirmthatpreparedmicroemulsionis o/wtype.

Refractive Index of Optimized Batch (F10).
Refractive index of optimize formulation found to be 1.33±0.12 (Mean±S.D=3).Itprovesthat formulationwasstableand desiredforpresentworkand objective.

Determination of Surface Tension of Optimized Formulation(F10).
Developed formulation have found 55.01± 0.02 (dynes/cm)surface tension, because ofthe present of highly fluid interfacial film of surfactant and co surfactant. Which reducethesurfacetensionandinterfacialtensionbetwe

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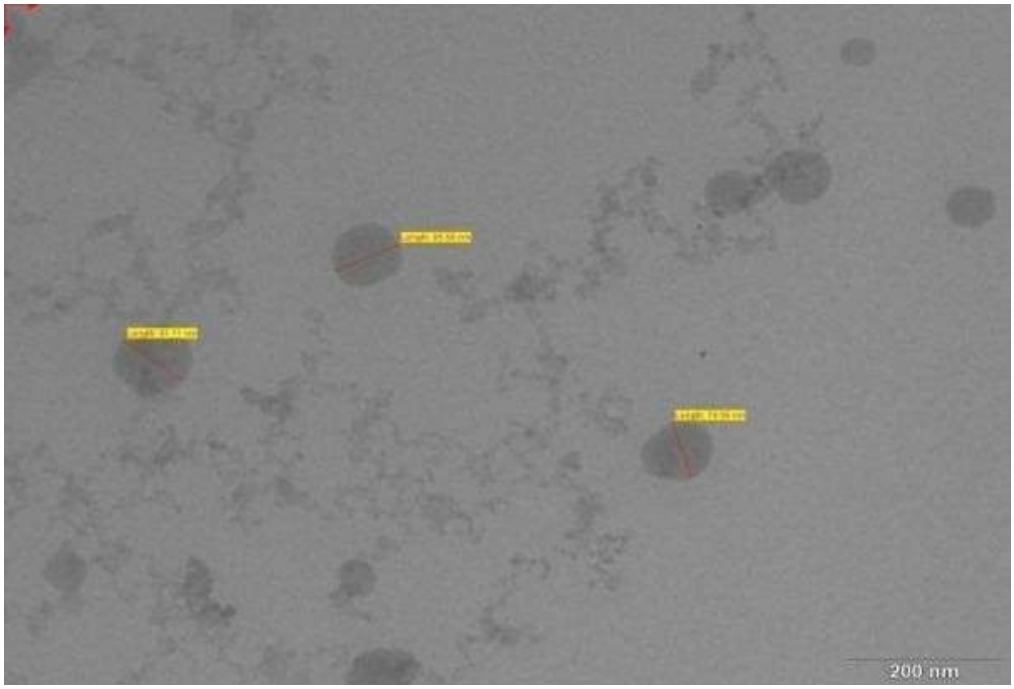
endropletsofoutermorethemicroemulsioniscalledther modynamicallystableandformsspontaneously. Adecreaseinsurfacetensionisexpectedtoimproveflui dpenetrationbycapillaryflow.
These include occura very low surface tension at the oil–water interface,and thepenetrationandrelationofoilmoleculeswiththeinte rfacialsurfactantfilm. Surfactant– oil miscibility can thus give initial indication on the possibility ofmicroemulsionformationwiththis system.

Transmission electron microscopy (TEM) study Of Optimized Batch (F10).



TEMstudyofmicroemulsion

Determination of drug content of Microemulsion Formulations.

Drug content of the optimized formulation was found to be 95.13±0.03%. According toresultindicate that the drug is distributed almost uniformly throughout the formulationandtherewasnoloss of druginformulation. From theresultalsoconsiderthatformulationhavebetterdrug loadingcapacityandessentialdoseofdrugwasobtainab leforthepharma logicalaction.

In –vitrodiffusion studyofoptimized batch(F10)

Time(hr)	**%CDR ofoptimizedmicroemulsion (Mean±S.D.) (n=3)**
0	0
1	6.38±1.46
2	16.48±1.22
3	26.72±1.64

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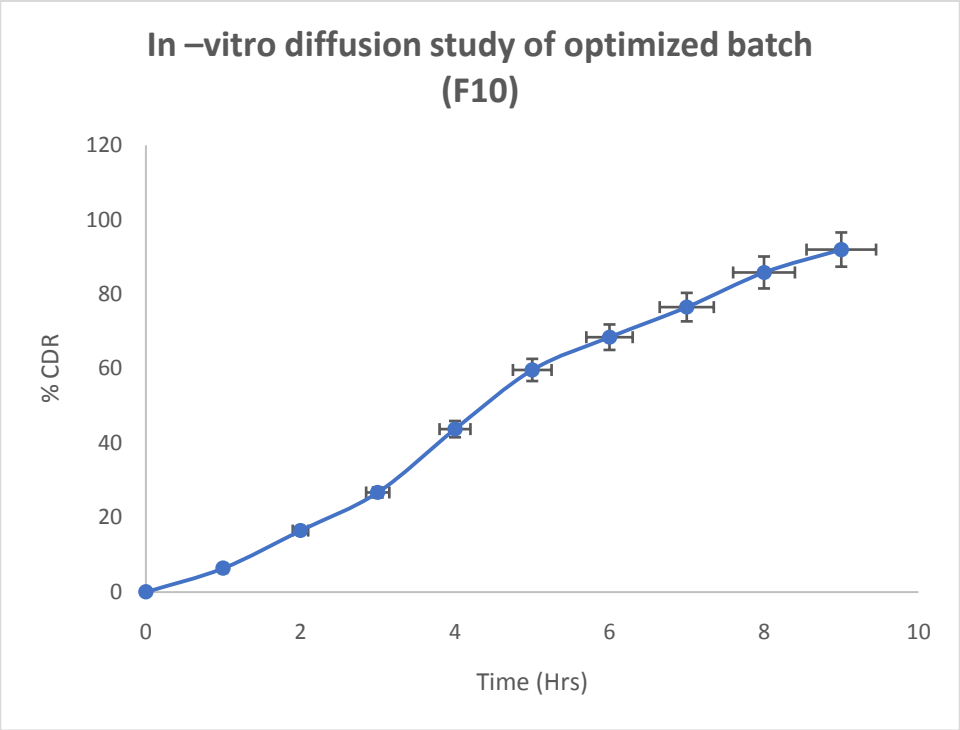
4	43.73±1.00
5	59.62±2.23
6	68.42±1.56
7	76.50±1.22
8	85.80±1.12
9	91.95±0.45



In –vitrodiffusion studyofoptimized batch(F10)

Thermodynamicstabilitystudy

Batch	**Heating-coolingcycle**	**Centrifugation**	**Freezthawcycle**
F10	Passed	Passed	Passed

Dose calculation for loading drug containing microemulsion in to topical gel.

Dosecalculation loading ETDMEinto topicalgel

- MarketedEtodolacformulationcontain1%w/wEtodolacdrug.
- ✓ Hence1%w/wmeans1gm ETDpresentin100 gmpreparation
- ✓ In100gmEtodolac formulation=1gm (1000mg) Etodolac present

So,for20gmEtodolacmicroemulgel=(?) Etodolacrequired

$=\frac{20*1}{100}$

=0.2gm(200mg)ITZrequire

- So,In20gmEtodolacmicroemulgelformulationrequired200 mgEtodolac drug

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FormulationofTopicalGeltrialBatchesatdifferent concentrationofSodium alginate

Ingredients	**G1**	**G2**	**G3**	**G4**
Sodium alginate (%w/v)	**1**	1.5	2	2.5
Propyleneglycol(mL)	**5**	5	5	5
Methylparaben	**0.1**	0.1	0.1	0.1
Propylparaben	**0.05**	0.05	0.05	0.05
Triethanolamine(mL)	**0.25**	0.25	0.25	0.25
Water(mL)	**100**	100	100	100

Result ofEvaluationofgel

Batchcode	**Colour**	**Odour**	**pH (Mean ±S.D.)(n= 3)**	**ViscositySpindleno:61 (Mean ±S.D.)(n=3)**	**Spreadability(gm.cm/sec) (Mean ±S.D.)(n=3)**
G1	**Colorless**	**Odourless**	**6.5± 0.01**	**9241± 45**	**11.46±0.77**
G2	Colorless	Odourless	6.3±0.04	9324± 50	11.34±1.11
G3	Colorless	Odourless	6.4±0.06	12239± 29	9.6±1.23
G4	Colorless	Odourless	6.4±0.01	14498± 56	9.56±1.61

G1*Formulationwastakenasoptimizedformulation
G1 shows good Spreadability and viscosity. Therefore, it was taken as optimizedformulaforfurtherformulationofpromising differentMicroemulgel

Optimization of Topical gel
Allpreparedtopicalgelsusingdifferentconcentrationof Sodium alginatepolymerswere characterizedbyviscosity,pH andspreadabilitytesting.

On the basis ofviscosity, pH and spreadability result, formulationCG1 shows goodSpreadabilityandviscosity.Thatcontains1%carbopol934asgellingagent.Therefore, it was taken as optimized formula for further formulation of promisingalternative Microemulgel. Optimized **F10** Microemulsion Formulation was incorporatedintooptimizedgelCG1Formulationtoprepare EtodolacMicroemulgel.

FormulaforEtodolacmicroemulgel

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Sr.no	Ingredients	Quantity
1	Oil	0.6ml
2	Smix	5.59ml
3	Water	4.9 ml
4	Drug (Etodolac)	200mg
5	1% Sodium alginate Gel	10gm

Characterization of Microemulgel
Physical evaluation
PhysicalEvaluation ofOptimizedBatch

Properties	Observation
Colour	Pale yellow
Odour	Odourless
Texture	Smooth
Feelonapplication	Coolingsensation
Consistency	Good
Homogeneity	Verygood
Grittiness	Notfound
pH	6.4±0.07
Conductivity	47.3±0.04

Viscosity ofETDMicroemulgel

Srno	Speed(rpm)	Viscosity(cps) (Mean ± S.D.)(n=3)
1	10	12,250±0.002
2	30	11,110±0.022
3	50	10,091±0.002
4	100	9360±0.045

Themeasurementofviscosityofthepreparedgelwasdonewithа Brookfieldviscometeratdifferentrpmbyusingspindleno61.

ExtrudabilityStudyandswellingindexofmicroemulgel

Parameters	Observation (Mean±S.D.) (n=3)

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Spreadability	22±0.86gm.cm/sec
Extrudabilitystudy	16.5 ±0.7gm/cm
Swelling index	49.5±0.01%

Syneresis Measurement And Drug Content of Microemulgel

Parameters	**Observation(Mean ± S.D.)(n=3)**
Syneresismeasurement	nosyneresisfound
Drugcontent (%)	97.29± 0.7

DrugReleasedataofformulations

Time(hr)	**%CDROf Pure DrugGel(Mean± S.D.) (n=3) (%)**	**%CDRofOptimizedETDMicroemulgel (Mean ± S.D.)(n=3) (%)**	**%CDRofOptimizedETDmicroemulsion (Mean ± S.D.)(n=3) (%)**
0	0	0	0
1	6.71±1.32	8.34±0.23	6.38±1.56
2	15.58±1.17	18.56±1.56	16.48±1.11
3	20.81±0.22	26.02±1.44	26.72±1.64
4	28.54±1.21	35.79±2.21	43.73±1.0
5	42.26±2.22	45.55±1.78	59.62±2.23
6	57.54±1.11	57.24±1.90	68.42±1.56
7	65.68±1.45	68.95±1.88	76.50±1.22
8	70.17±2.91	76.96±1.46	85.80±1.12
9	76.76±1.14	83.50±1.67	91.95±0.45

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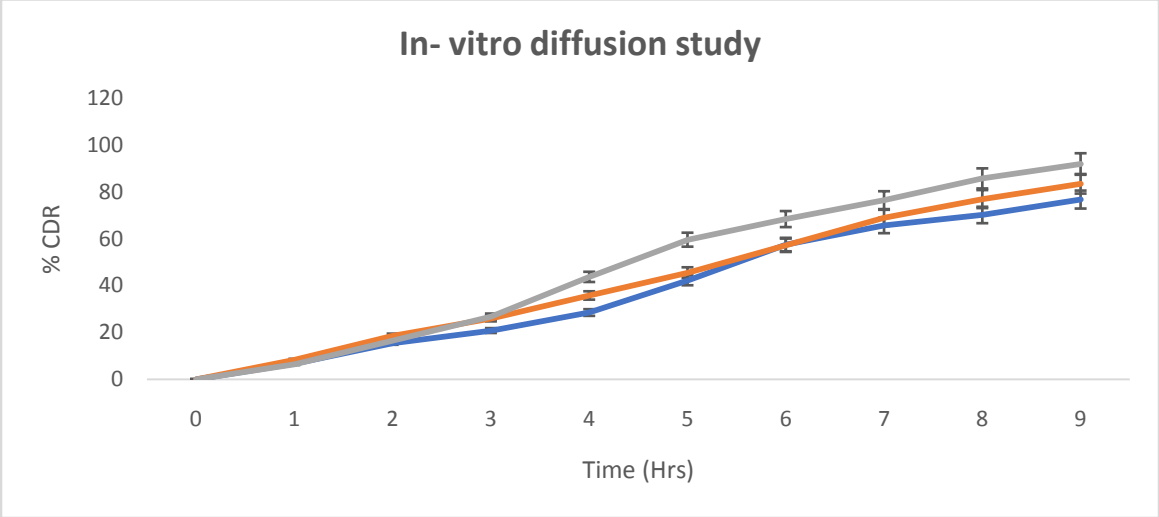

Figure 5. 1 In- vitrodiffusion study

Release Kinetic study of Etodolac microemulsion andmicroemulgel

Model	Parameter	Optimized ETDmicroemulsion	Optimized ETD Microemulgel (ITZCG1)
ZeroOrder	R2	0.98	0.991
	Slope	11.98	9.307
	Intercept	-5.293	-1.341
FirstOrder	R2	0.94	0.968
	Slope	-0.083	-0.058
	Intercept	2.06	2.024
HiguchiModel	R2	0.991	0.996
	Slope	3.53	3.53
	Intercept	9.021	9.021
HixonCrowell	R2	0.957	0.981
	Slope	3.53	0.182

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	Intercept	-0.159	-0.061
Kors-meyerPeppas	**R2**	0.92	0.943
	Slope	79.12	61.42
	Intercept	-1.62	1.505

J-flux & Permeability Co-efficient

J-Flux& PermeabilityCo-EfficientOfOptimized Batch

Time(hr)	**FluxJ(mg/cm^2/hr)**	**Permeabilityco-efficient(Kp)**
0	0.0000	0
1	0.1823	0.000912
2	0.0685	0.000343
3	0.0209	0.000105
4	0.1417	0.000709
5	1.4140	0.00707
6	0.4331	0.002166
7	0.2866	0.001433
8	0.5414	0.002707
9	0.2301	0.001151

Stability Analysis.

Stability Analysis of optimized batch at Room Temperature for 1Months

PARAMETER	**OptimizedEtodolac(ITZ)microemulgel**			
	RoomTemperature			
	0Day	10Day	20Day	30Day
Clarity	Opaque	Opaque	Opaque	Opaque
Odour	Odourless	Odourless	Odourless	Odourless
pH	6.4	6.45	6.47	6.5
Spreadability	22 gm.cm/sec	21.10 gm.cm/sec	22.18 gm.cm/sec	22.11 gm.cm/sec
Viscosity(cps)	9360	9370	9370	9380

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%Drug content	97.29%	97.00%	96.78%	96.76%

CONCLUSION

Micro emulsion is one of the methods that might be used to make liquid/semi-solidformulations of poorly water-soluble medicines.Hydrophobic medications can bemade more soluble by using a micro emulsion. Micro emulsion, unlike emulsion, isthermodynamically stable, allowing for a longer shelf life. It's also optically clear andmacroscopically homogenous. Furthermore, because considerable energy input is notrequired for production, micro emulsion is simple to prepare and scale-up, making itcost-effective.

Expectedoutcome

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID)used to treatmild tomoderatepain,andhelpstorelievesymptomsof arthritis(eg,osteoarthritisandrheumatoidarthritis),including inflammation,swelling,stiffness,andjointpain.Etodolac has negative effects when used orally like Belching, bloody or black, tarrystools, body aches or pain, chest pain, cloudy urine, cough or hoarseness, especially athigh dosages. As a result, topical therapy may be advantageous in avoiding systemicadverse effects. It may also minimise the amount of Etodolac needed compared tocommerciallyavailable Etodolactopicalformulations(emulsionbased).

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