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Formulation and Development of Cyclosporine Microsponges Loaded Topical Drug Delivery System by Using Quality by Design

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ABSTRACT

Objective:

The Presented research work was aimed to formulate microsponges loaded topical gel of poorly water-soluble drug Cyclosporin A with purpose of increasing residence time into skin, to avoid systemic side effects, to reduce particle size, increase surface area with increasing permeation of drug, to reduce dose and dose frequency & increases better in-vitro release/diffusion performance than conventional dosage forms.

Experimental Work:

Preformulation studies, FTIR, DSC was carried out for identification of drug & to check interaction between drug & excipients. Microsponges dare prepared by Qausi emulsion diffusion method & this microsponges incorporated into gel using polyethylene glycol, triethanolamine, water, methyl paraben, propylparaben in different concentrations. 3^2 full factorial design employeded to study the effect of independent variables, Prepared formulation is evaluated for their physical parameters Viscosity, pH, Spreadability, In-vitro release kinetic, Ex-vivo permeation study, Skin irritation study, stability analysis. The release kinetic models are used to determine the diffusion pattern of the drug from the microsponges loaded gel.

Results & Discussion

The primary identification of drug showed that the drug is pure. IR spectra of Cyclosporin A revealed that function group of cyclosporin A present in the sample shows their stretching in the standard range. Thus, present sample was confirmed as Apremilast with high purity grade. DSC study showed that drug is compatible with the polymers. The results of 3^2 full factorial design shown that the Drug: polymer & Stirring Speed significantly affected on dependent variables. From whole experimental work, we get results that formulation We get results of various evaluation of optimized Batch like pH was 6.93±0.024, Spreadability was 10.39±0.85, viscosity was 9260±0.76, % Drug content was 92.25 ±0.24. In-vitro diffusion study, Ex-vivo permeation study and In-vitro release kinetic study shows good result of optimized batch. Skin irritation study results shows that there was no irritation of skin. Stability study of optimized batch shows good result there were no degradation of gel.

Conclusion

Microsponge containing Cyclosporine A will be ready by a semi emulsion dispersion technique utilizing Eudragit RS100 utilizing QbD approach. All the were oppressed for % yield, % Entrapment productivity, % drug content, examining electron microscopy, FTIR ghostly investigations, and Ex vivo drug discharge studies,

The microsponges which gave better physical, morphological and % embodiment in both of the polymers were chosen for joining into the Topical gel definitions. Different Topical gel plans with Cyclosporine A in free structure and in microsponges conveyance framework were figured out and the in-vitro discharge studies were completed.

Keywords: Microsponges, cyclosporin A, Qausi emulsion diffusion method, 3^2 factorial designs.

I. INTRODUCTION

Microsponge containing Cyclosporine A will be ready by a semi emulsion dispersion technique utilizing Eudragit RS100 utilizing QbD approach. All the were oppressed for % yield, % Entrapment productivity, % drug content, examining electron microscopy, FTIR ghostly investigations, and Ex vivo drug discharge studies,

The IR otherworldly investigation recommended similarity between the medication and definition added substance. The medication exists in unique structure and accessible for the organic activity.

The disintegration boundaries were contemplated by involving disintegration programming PCP DISSO V.3 for microsponges details which demonstrated expansion in drug focus, drug discharge was diminished.

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By thinking about every one of the aftereffects of Check Point Analysis the Microsponges details and further continue for effective gel definitions and Characterization of same. It shows that the arrival of medication from Microsponges consolidated into the Topical gel, follow Higuchi (framework) dispersion model. No progressions found after security investigation for a time of 1 months.

From the review it very well may be reasoned that it is feasible to plan an effective polymeric Microsponges definition for Cyclosporine A might build viability and patient consistence which are of prime significance. Nonetheless, Ex vivo tests are fundamental to lay out the genuine helpfulness of these Microsponges.

II. MATERIALS & METHODOLOGY

Materials

cyclosporin A was a gift sample from Balaji Pharmaceuticals, Surat. Eudragit RS100, Ethyl Cellulose, Eudragit RL 100 were obtained from Sulab, Vadodara, India. Ethanol, Methanol, Acetone, Dichloromethanewere obtained from Chem Think Lab, Ankleshwar, India. Polyvinyl Alcohol, Tween 80 were obtained from Chem Dyes Co.,Rajkot, India. Carbopol 934pwas obtained from ACS Chemicals, Ahmedabad, India.

Methodology

Gelling Agent was soaked in water for 2 h and then dispersed by agitation at approximately 600 rpm with the aid of magnetic stirrer to get a smooth dispersion. The dispersion was allowed to stand for 15 min to expel entrained air. To it the aqueous solution of triethanolamine (2% v/v) was added with slow agitation for adjusting pH to 6.5–7.5. At this stage permeation enhancers and microsponges containing drug were incorporated into the gel base. Prepared gels were packed in wide mouth glass jar covered with screw capped plastic lid after covering the mouth with aluminum foil and were kept in dark and cool place until use.

Physical evaluation:
It will be evaluate Organoleptic property, Occlusiveness and wash ability of gel.

Measurement of pH of Gel:
The pH will be checked by a digital pH meter of formulated gel.

Viscosity study of Gel:
50 gm of arranged gel will be kept in 50 mL beaker and shaft Groove will dipped at specific RPM in Brookfield Viscometer. This was completed multiple times and recorded observation will considered as mean of viscosity.

Spreadability of Gel:
An accurately weighed quantity of 1 g of gel will be pushed among two slides and left as such for about 5 minutes. Diameters of speed circles was measure in cm and were taken as comparative values for spreadability when no further spreading. The readings attained are mean of three determinations.

Homogeneity and Grittiness
The consistency of prepared gel will be determined by pressing between the thumb and the index finger. Minor quantity gel is wiped on skin of back of hand to check the homogeneity and grittiness.

Drug Content:
1 gm of each gel formulation will be determined in 20 mL of alcohol in volumetric flask with 30 min mixing. At long last, it was diluted and separated. Further dilution was made up to 10 mL alcohol and again 1 mL was removed from above and diluted to 10 mL alcohol. The absorbance was estimated at 215 nm in UV.

In-vitro diffusion Studies
In-vitro dissemination study will be performed utilizing Design glass cylinder (open at the two ends). Weighed 1 gm of gel was moved in 20 mL Phosphate buffer in 250 mL volumetric flask with mixing for 30 mins. The volume were made up to 100 mL and filter. 1 mL of above solution was diluted to 10 mL with Phosphate buffer and further 1 mL of the above solution were diluted to 10 mL with Phosphate buffer. The absorbance of the solution was estimated spectrophotometrically at 407 nm.

Flux and Permeability co-efficient:
The Flux (mgcm-2hr-1) of Cyclosporine A will be determined from the incline of the plot of the cumulative amount of Cyclosporine A permeated per cm^2 of skin at at steady state against

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the time using linear regression analysis. The steady state permeability co-efficient (Kp) of the drug through rat epidermis was calculated by using the following equation.

$$Kp = J/ C$$

Where, J = the flux

C =the concentration of Cyclosporine A in the gel.

III. RESULTS & DISCUSSION

PreliminarySelectionofDrug:PolymerRatio

SelectionofDrug:PolymerRatio

Batch	Drug:PolymerRatio	VolumeofInnerPhase(ml)	VolumeOfOuter(ml)	SurfactantConc.(mg)	StirringSpeed(R.P.M.)	StirringTime(Mins)
1	1:1	20	30	100	1500	75
2	**1:2**	**20**	**30**	**100**	**1500**	**75**
3	1:3	20	30	100	1500	75
4	1:4	20	30	100	1500	75
5	1:1	20	30	100	1500	75
6	1:2	20	30	100	1500	75
7	1:3	20	30	100	1500	75
8	1:4	20	30	100	1500	75

Results of Effect of Drug: Polymer Ratio on Batch

EffectofDrug:PolymerRatio onBatch 1-8

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Batch	Yield(%) (Mean±S.D.) (n= 3)	Loading Efficiency (%)(Mean±S.D.) (n= 3)	DrugContent (%) (Mean ± S.D.)(n= 3)
1	83.33±1.3	90.6±1.2	88.6±1.35
2	**94±0.9**	**95.2±1.05**	**94.7±1.04**
3	92.5±1.2	94.3±1.15	92.8±0.84
4	91.66±0.85	92.1±0.9	92.3±0.73
5	76.73±1.2	84.7±1.1	89.4±0.5
6	88.5±1.35	87.2±1.25	93.9±1.2
7	86.7±1.15	88.9±1.15	92.6±1.29
8	83.66±1.05	92.7±1.03	91.7±1.12

Effect of Drug: Polymer Ratio:
Theminimumconcentrationhadfoundtobe1:2ofdrug: polymerrationbecauseatthisconcentration,themicros pongesshowedgoodphysicalcharacteristiclikeproper shape, size, porosity, particle size distribution and did not collapse even after removalfromthesolventandsubsequentdrying.TheLo adingefficiencyand%yieldgradually improved with an increase in Drug: Polymer ratio. Hence, Batch 2(EU)hasbeenselectedasoptimizedbatch.

SelectionofInnerPhaseVolume(ml)
Selection ofInnerPhaseVolume(ml)

Batch	Drug:PolymerRatio	VolumeofInnerPhase (ml)	VolumeOf Outer(ml)	SurfactantConc.(mg)	StirringSpeed(R.P.M.)	StirringTime(Mins)
9	1:2	10	30	100	1500	75

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10	**1:2**	**20**	**30**	**100**	**1500**	**75**
11	1:2	30	30	100	1500	75

Result of Effect of Inner Phase Volume Batches
Effect ofInnerPhaseVolumeBatches

Batch	**Yield (%)(Mean ± S.D.)(n= 3)**	**LoadingEfficiency (%)(Mean±S.D.) (n= 3)**	**DrugContent(%) (Mean±S.D.) (n= 3)**
9	91.8±1.2	95.8±1.15	89.3±1.3
10	**94.4±0.5**	**97.2±0.9**	**94.9±1.15**
11	92.1±1.35	96.4±1.2	91.4±1.05

EffectofInternalPhaseVolume:
Whentheamountofinnerphasewasgraduallyincreasing,%loadingefficiency anddrugcontentincreased.Hence, Batch 10 havebeenselectedasoptimizedbatch.

Selection ofSurfactant Conc.(mg):
SelectionofSurfactantConc.(mg)

Batch	**Drug:PolymerRatio**	**VolumeofInnerPhase (ml)**	**VolumeOf Outer(ml)**	**SurfactantConc.(mg)**	**StirringSpeed(R.P.M.)**	**StirringTime(Mins)**
12	**1:2**	**20**	**30**	**100**	**1500**	**75**
13	1:2	20	30	200	1500	75
14	1:2	20	30	300	1500	75

ResultsofEffects ofSurfactantConc.onBatch
EffectsofSurfactantConc.onBatches12-14

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Batch	Yield (%)(Mean ± S.D.)(n= 3)	LoadingEfficiency (%)(Mean±S.D.) (n= 3)	Drug Content(%) (Mean±S.D.) (n= 3)
12	**93.3±1.26**	**96.1±1.15**	**95.9±1.26**
13	91.9±2.14	90.6±1.46	93.7±1.56
14	91.5±1.46	91.8±1.42	92.5±1.54

Effect of surfactant conc. (PVA):
Microsponges did not form in the absence of surfactant. When concentration of PVAwas higher it affects the drug content and % yield. Increase the PVA concentrationthat time decrease in drug content, % yield & loading efficiency. Hence, Batch 12havebeenselectedasoptimizedbatch.

SelectionofStirring Speed(RPM)
Selection ofStirring Speed(RPM)

Batch	Drug:PolymerRatio	Volume ofInnerPhase (ml)	VolumeOf Outer(ml)	SurfactantConc.(mg)	StirringSpeed(R.P.M.)	StirringTime(Mins)
15	1:2	20	30	100	500	75
16	1:2	20	30	100	1000	75
17	**1:2**	**20**	**30**	**100**	**1500**	**75**

ResultsofEffectsofStirring SpeedonBatch
EffectsofStirring SpeedonBatches

Batch	Yield (%)(Mean ± S.D.)(n= 3)	LoadingEfficiency (%)(Mean±S.D.) (n= 3)	Drug Content(%) (Mean±S.D.) (n= 3)
15	91.6±1.2	90.9±1.15	93.4±0.73

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16	92.8±1.08	93.4±1.03	93.9±1.2
17	**93.5±0.85**	**97.7±0.5**	**95.3±1.29**

Effectofstirringspeed:
It was observed that increasing the stirring speed from 500, 1000 and 1500 RPMincreased the % yield, drug content and loading efficiency. Hence, Batch17 havebeenselectedasoptimizedbatch.

SelectionofStirringTime(Min)
SelectionofStirring Time(Min)

Batch	Drug:PolymerRatio	VolumeofInnerPhase (ml)	VolumeOfOuter(ml)	SurfactantConc.(mg)	StirringSpeed(R.P.M.)	StirringTime (Mins)
18	1:2	20	30	100	1500	60
19	**1:2**	**20**	**30**	**100**	**1500**	**75**
20	1:2	20	30	100	1500	90

ResultsofEffectsofStirringTimeon Batch
EffectsofStirringTime onBatches

Batch	Yield (%)(Mean ± S.D.)(n= 3)	LoadingEfficiency (%)(Mean±S.D.) (n= 3)	Drug Content(%) (Mean±S.D.) (n= 3)
18	92.1±1.3	96.8±1.14	95.4±0.8
19	**94.2±1.05**	**97.2±1.35**	**96.3±1.15**
20	91.5±0.74	94.5±1.25	93.1±1.2

Effects of Stirring Time:
It was observed that gradually increasing the stirring time from 60, 75 and 90 Minsincreased the % yield, drug content and loading efficiency. Hence, Batch 19 havebeenselectedasoptimizedbatch.

RiskAssessmentofCriticalQualityAttributesfrom PreliminarytrialBatches toDevelopQbDApproach:
The critical quality attributes are categorized in high, medium and low risk parametersbased on knowledge space to check influence of formulation and process parameters.Usually, high risk parameters are considered important for Design of Experiments asthey are havingmore effect than others and need tobein accepted multivariateranges. The Critical parameters and critical quality attributes (CQAs) for selection ofoptimumformulationareshownintable.

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Riskassessment toidentifyvariableaffectingDrugproduct quality

DrugProduct CQAs	Drug:Polymer Ratio	StirringSpeed
Yield(%)	Medium	Medium
%DrugContent	High	Low
LoadingEfficiency (%)	Medium	Medium
%Cumulative Drug release	High	Medium

Development of Cyclosporine A loaded microsponge by using 3^2 factorial design approach

3^2 factorialDesignBatches

Independentvariables			
Independent variables	Low(-1)	Medium(0)	High(+1)
Drug: polymer(X_1)	1:1	1:2	1:3
Stirringspeed (RPM) X_2	500	1000	1500
Dependentvariables			
Y_1- Yield (%)			
Y_2-%Drug Content			
Y_3-%CumulativeDrugreleasein Hours			

Compositions of factorial batches in coded form

Composition offactorialdesign batchesincodedform

3^2=Batches		
Batches	Drug:polymer(X_1)	Stirring Speed(RPM) (X_2)
1	-1	-1
2	-1	0
3	-1	+1
4	0	-1
5	0	0
6	0	+1

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7	+1	-1
8	+1	0
9	+1	+1

Compositions of factorial batches in Decoded form
CompositionsoffactorialbatchesinDecodedform

3^2= Batches		
Batches	**Drug:polymer(X1)**	**Stirring Speed(RPM) (X2)**
1	1:1	500
2	1:1	1000
3	1:1	1500
4	1:2	500
5	1:2	1000
6	1:2	1500
7	1:3	500
8	1:3	1000
9	1:3	1500

CharacterizationofBatches
CharacterizationofBatches

Batch	**Yield (%)(Mean ± S.D.)(n= 3)**	**Drug Content(%) (Mean± S.D.) (n= 3)**	**% CDR inHours (Mean ± S.D.)(n= 3)**
1	91.6±1.2	92.4±0.73	85.22±1.22
2	92.8±1.08	93.65±1.2	86.05±1.25
3	93.5±0.85	93.9±1.03	87.21±1.11
4	93.4±1.04	94.2±1.5	89.07±1.89

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5	94.7±1.1	94.7±0.5	89.41±1.36
6	95±0.9	95.7±1.04	91.17±1.74
7	92.66±1.15	94.5±1.35	90.86±1.69
8	91.3±0.5	94±0.9	90.52±1.21
9	89.6±1.29	93.7±1.3	89.79±1.70

% Cumulative Drug Release Study
%CumulativeDrugReleaseprofile

Time	**Batch 1 (Mean ±S.D.) (n= 3)**	**Batch 2 (Mean ±S.D.) (n= 3)**	**Batch 3 (Mean ±S.D.) (n= 3)**	**Batch 4 (Mean ±S.D.) (n= 3)**	**Batch 5 (Mean ±S.D.) (n= 3)**
0	0	0	0	0	0
1	26.60±1.65	24.64±1.73	26.36±1.53	27.49±1.06	27.83±1.36
2	33.88±1.54	35.25±1.35	36.85±1.23	37.27±1.54	38.16±1.52
3	45.86±1.25	46.33±1.69	46.73±1.92	47.90±1.63	48.34±1.92
4	52.80±1.91	54.06±1.56	54.46±1.68	54.79±1.97	55.28±1.63
5	57.85±1.54	59.91±1.87	60.02±1.72	60.63±1.55	61.33±1.80
6	68.75±1.47	69.50±1.90	72.18±1.30	74.82±1.84	75.49±1.32
7	79.01±1.05	81.95±1.11	83.62±1.64	84.29±1.26	85.09±1.79
8	88.17±1.74	90.86±1.69	92.52±1.21	91.79±1.70	92.17±1.74

%CumulativeDrugReleaseprofile

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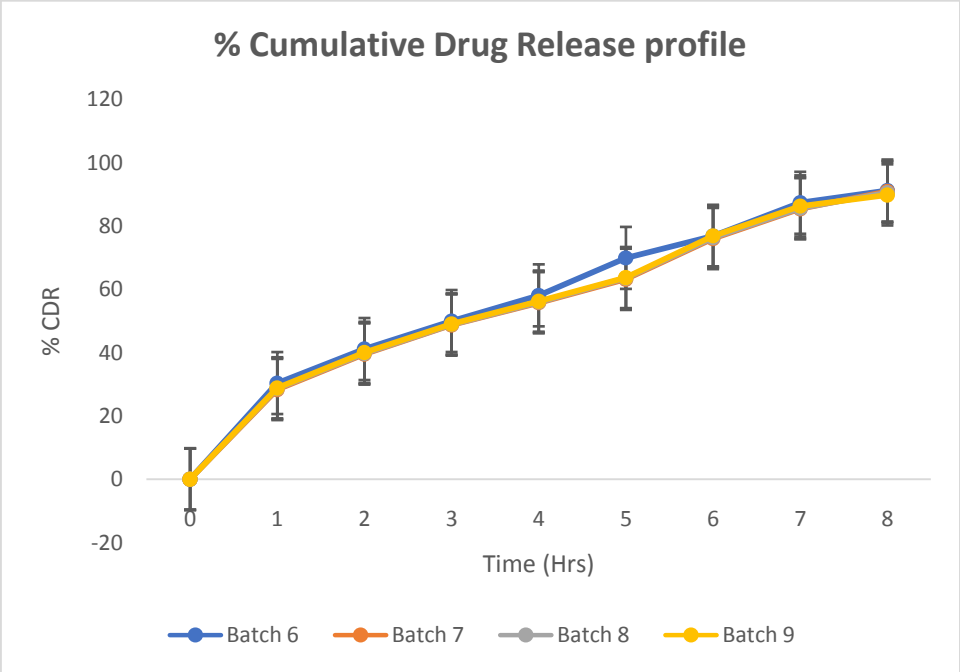
Time	Batch 6 (Mean±S.D.) (n= 3)	Batch 7 (Mean±S.D.) (n= 3)	Batch 8 (Mean±S.D.) (n= 3)	Batch 9 (Mean±S.D.) (n= 3)
0	0	0	0	0
1	30.36±1.25	28.33±1.72	28.62±1.78	28.85±1.31
2	41.11±1.64	39.54±1.45	39.78±1.09	40.06±1.39
3	49.96±1.78	48.69±1.22	48.90±1.59	49.01±1.90
4	58.06±1.32	55.73±1.68	55.96±1.57	56.23±1.22
5	69.89±1.20	63.13±1.49	63.52±1.60	63.68±1.89
6	76.85±1.67	76.01±1.63	76.36±1.32	76.88±1.48
7	87.29±1.79	85.41±1.11	85.67±1.73	86.30±1.67
8	91.17±1.74	90.86±1.69	90.52±1.21	89.79±1.70



%CumulativeDrugReleaseprofile

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IV. STATISTIC ALANALYSIS

Design expert version 10 was used for statistical analysis and to produced first orderpolynomial equations. From preliminary results, 3^2 full factorial design was utilized inwhichtwofactorswasevaluated,separatelyatthreelevelsandpossibleninecombinations were formulated. Three level factorial studies were carried outusingtwodifferentvariables.Infirstfactorialdesign ,Drug:PolymerRatio(X1)andStirring Speed (X2) was taken as independent variables while %Yield (Y1), %DrugContent(Y2)and%CumulativeDrugRelease(Y3)wasselectedasdependentvariablesforbothfactorialdesigns.

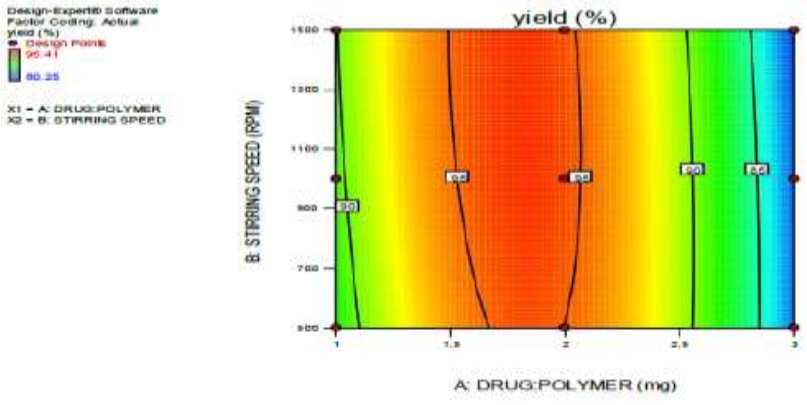
Effecton%Yield(Y1)surfaceresponsestudy:

Negative value of a indicates decrease in % Yield. Positive value of coefficient Bindicates increase in %Yield. It indicateslinearity of surface response and contourplotas showinfigure.Fullmodeswasfoundsignificantfortwo independent variables and detailed ANOVA, Response surface counter plot and 3Dplots areas follows:

Yield=+95.32-3.99*A+0.12*B-0.62*AB-9.93*A^2-0.22*B^2

Table 5. 1 ANOVATABLEforResponsesurfaceY1

Analysisofvariancetable[Partialsumofsquares-TypeIII]						
	Sumof		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob >F**	
Model	294.45	5	58.89	50.07	0.0043	significant
A-DRUG: POLYMER	95.52	1	95.52	81.22	0.0029	
B-STIRRING	0.089	1	0.089	0.076	0.8013	
SPEED						
AB	1.53	1	1.53	1.30	0.3375	
A^2	197.21	1	197.52	167.68	0.0010	
B^2	0.10	1	0.10	0.086	0.7883	
Residual	3.53	3	1.18			
CorTotal	297.97	8				



ResponsesurfaceplotDRUG:POLYMER(mg)andStirringSpeed(RPM)on%Yield(Y1)

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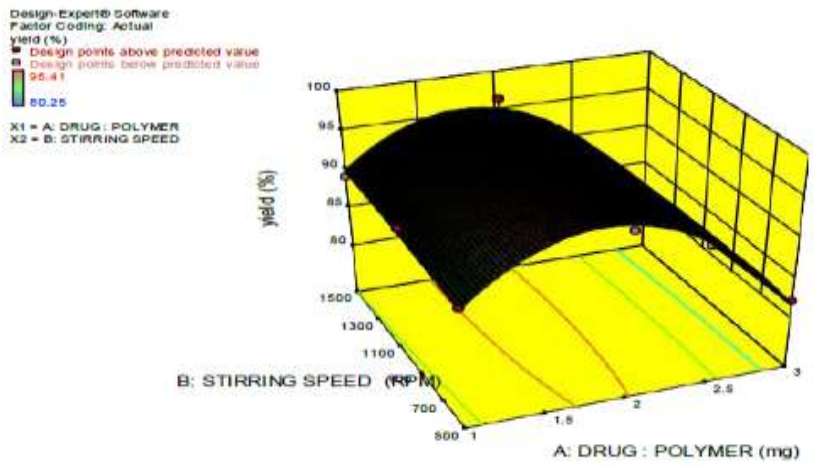

3Dsurfaceplot DRUG:POLYMER(mg)andStirringSpeed(RPM)on%Yield(Y1)

Effect on % Drug Content (Y2) Surface response study:

Positive value for coefficient of B Stirring Speed in equation indicates increase in %DrugContent. Positivevalue of coefficientof A indicates in %Drug Content. Itindicateslinearityofsurfaceresponseandcounter plot.

Drugcontent=+96.42-3.77*A+0.31*B-0.68*AB-9.91*A^2-0.038*B^2

ANOVATABLEforResponsesurfaceY2

Analysisofvariancetable [Partialsumofsquares-TypeIII]						
	Sumof		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	283.96	5	58.89	50.47	0.0043	significant
A- DRUG: POLYMER	85.20	1	95.52	75.41	0.0032	
B-STIRRING SPEED	0.57	1	0.089	0.51	0.5279	
AB	1.84	1	1.53	1.63	0.2914	
A^2	196.35	1	197.52	174.48	0.0009	
B^2	2.939E-003	1	2.939E-003	2.612E-003	0.9625	
Residual	3.83	3	1.13			

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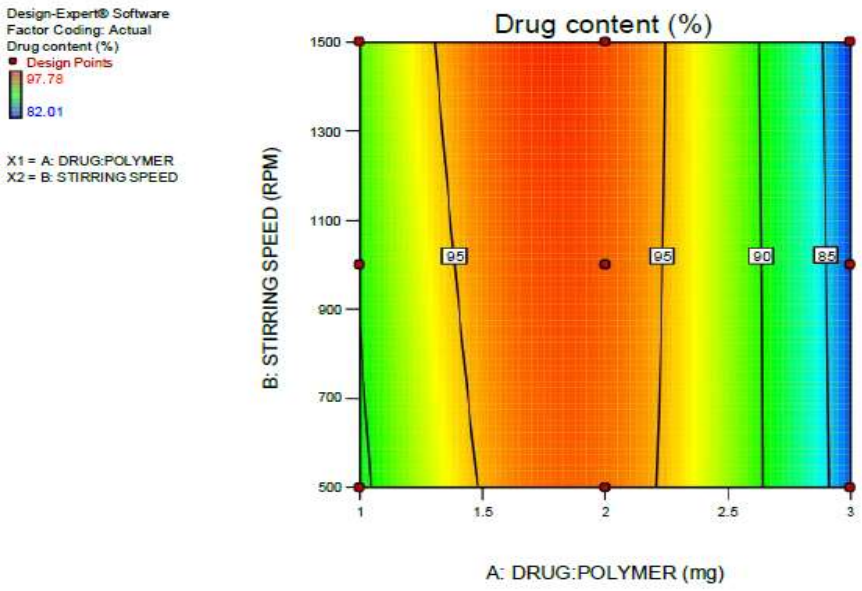
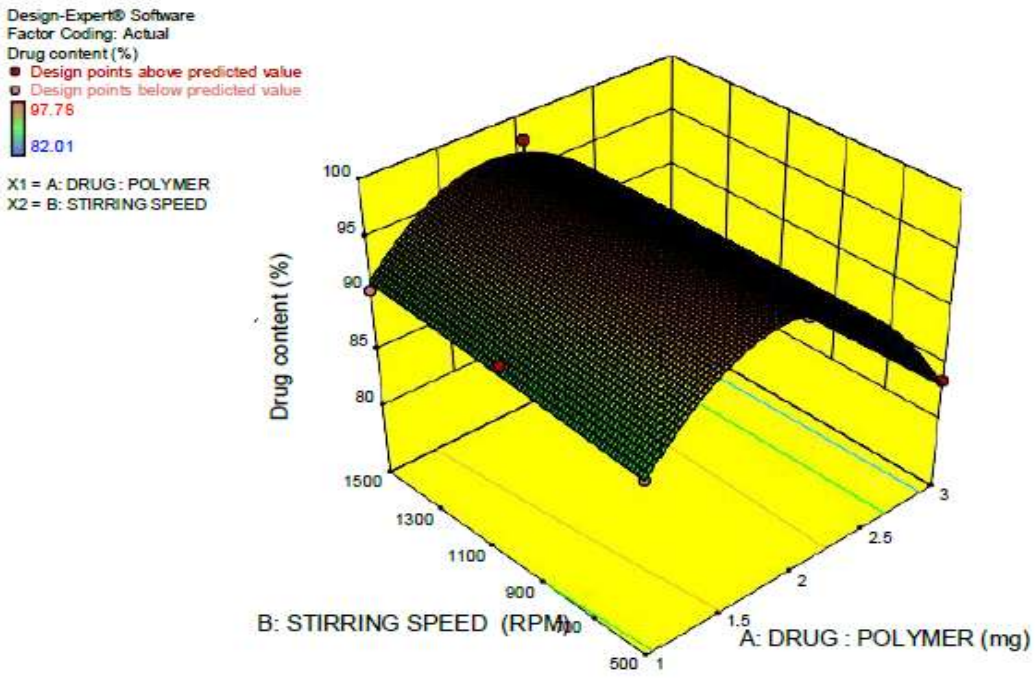
CorTotal	287.34	8				



Responsesurfaceplot DRUG:POLYMER(mg)andStirringSpeed(RPM) on%DrugContent(Y2)



3Dsurfaceplot DRUG:POLYMER(mg)andStirringSpeed(RPM) on%DrugContent(Y2)

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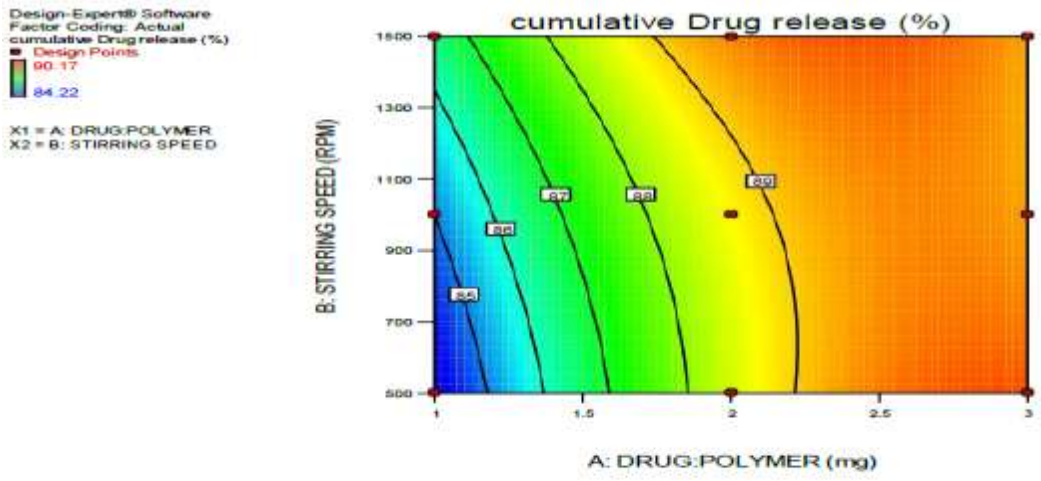
Effect on % Cumulative Drug release (Y3) Surface response study:
PositivevalueforcoefficientofBStirringSpeedinequation indicatesincreasein %CDR.PositivevalueofcoefficientofAindicatesin% CDR.Itindicateslinearityofsurface responseandcounterplot.
%CDR=+88.73+2.12*A+0.50*B-0.77*AB-1.61*A^2+0.23*B^2

ANOVATABLEforResponsesurfaceY3

Analysisofvariancetable[Partialsumofsquares-TypeIII]						
	Sumof		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob >F**	
Model	35.98	5	7.20	18.40	0.0185	significant
A-DRUG: POLYMER	26.84	1	26.84	68.62	0.0037	
B-STIRRING SPEED	1.52	1	1.52	3.89	0.1432	
AB	2.34	1	2.34	5.99	0.0920	
A^2	5.17	1	5.17	13.23	0.0358	
B^2	0.10	1	0.10	0.26	0.6436	
Residual	1.17	3	0.39			
CorTotal	37.15	8				



ResponsesurfaceplotDRUG:POLYMER(mg)andStirringSpeed(RPM)on%CumulativeDrugRelease

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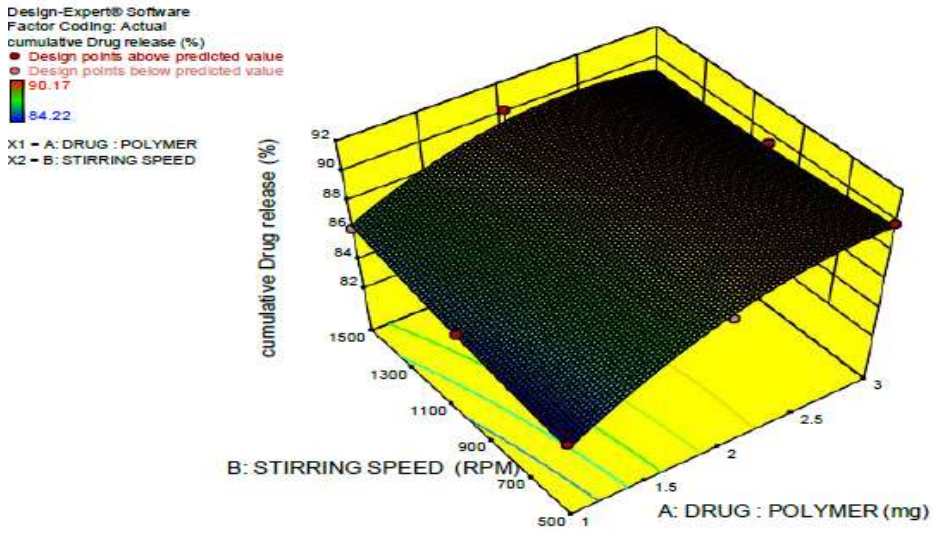
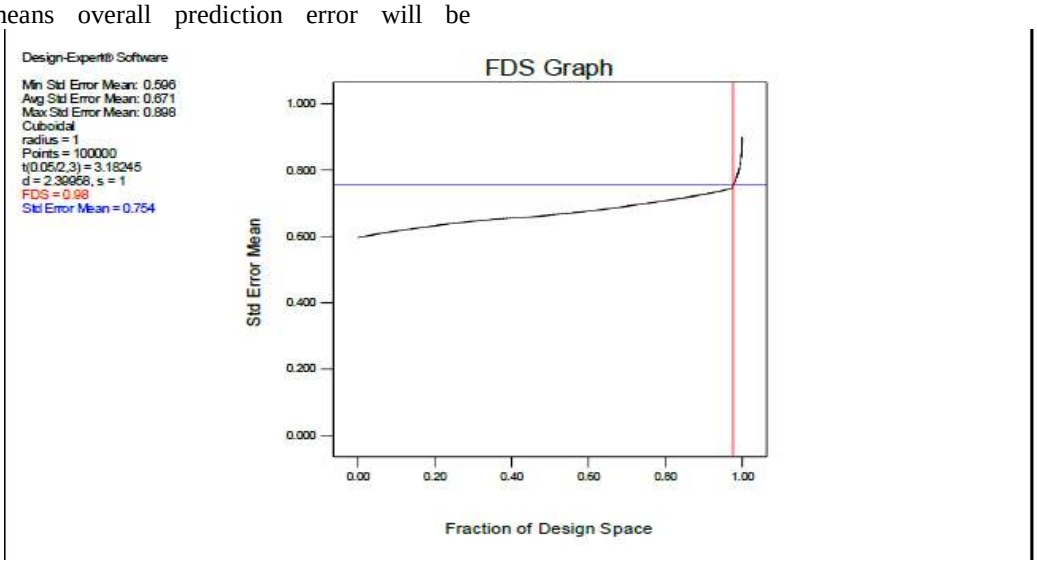


3D surface plot DRUG: POLYMER (mg) and Stirring Speed (RPM)on %CumulativeDrugRelease(Y3)

Establishing design space and control strategy

FDS curve shows what percentage fraction of design spacehas a given predictionerror orlower.A good design willhave aflatterand curve than a poor design asshown in figure 5.30. Flatter means overall prediction error will be constant. Lowermeans overall prediction error will be smaller. FDS should be least 0.8 or 80% forexploration, and 100% for robustness testing. FDS was 0.98 or 98% which indicatingrobust standard error of prediction related to prediction interval around a predictionresponse atagivenpairoffactorlevel.



FDSGraph

Validation:

Frompolynomialequationgeneratedforresponse,intensivegridandintegratedexaminewasperformedoverexperimentfieldusingdesignExpertsoftware 10.Duringindependentvariablecharacterizationstudy ,impactof parameterDRUG:POLYMER (mg)and Stirring Speed (RPM)were assessed. Criteria consideration ofresponse%Yield(Y1),%DrugContentand%CumulativeDrugrelease(Y2)isbetween 1-8 hrs and 84-90%respectively. Design space shown in figure 5.31 and 5.32also called as overly plot which is

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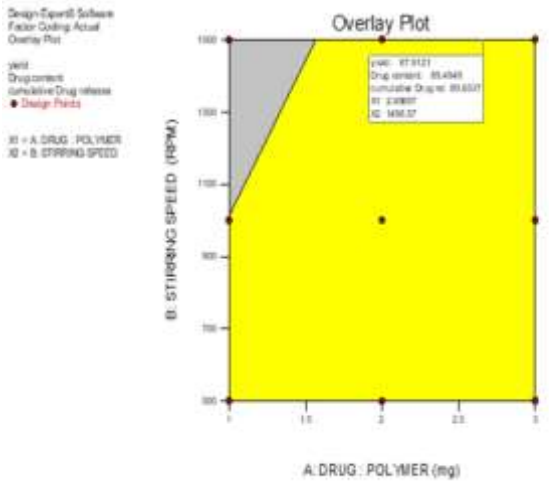
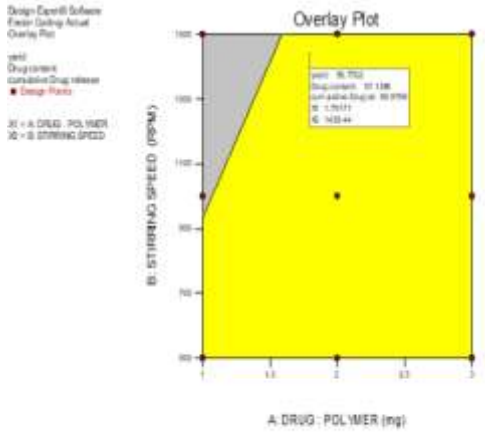
shaded region with yellow color indicates thatregionofsuccessfuloperatingranges.





OverlayPlot

Check point analysis of validation batches:

Batch 10 & 11 formulation was made for check point analysis and predictandexperimentalvalues compared.

ValidationofBatch:Predicted Response

Batch	**Drug:Polymer ratio(X1)**	**StirringSpeed(X2)**	**% Yield(Y1)**	**% Drugcontent(Y2)**	**% CumulativeDrugrelease(Y3)**
10	1:2.6	1498	87.91	89.49	89.65
11	1:1.7	1438	95.77	97.13	88.13

ValidationofBatch: ActualResponse

Batch	**Drug: Polymer ratio(X1)**	**StirringSpeed (X2)**	**% Yield(Y1)**	**% Drugcontent (Y2)**	**% CumulativeDrugrelease (Y3)**
10	1:2.6	1496	86.05	88.65	88.70
11	**1:1.7**	**1436**	**95.84**	**97.85**	**89.28**

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%Cumulativedrugreleaseprofile:
%CumulativedrugreleaseprofileofMicrosponges

Time	Batch 10 (Mean±S.D.) (n=3)	Batch 11 (Mean±S.D.) (n=3)
0	0	0
1	29.54±1.38	33.84±1.45
2	38.61±1.97	41.16±1.67
3	46.77±1.77	48.92±1.83
4	59.13±0.86	62.09±1.34
5	68.35±1.43	70.61±1.62
6	74.12±1.73	77.33±1.18
7	84.26±1.14	85.97±0.90
8	89.70±1.49	90.28±0.97

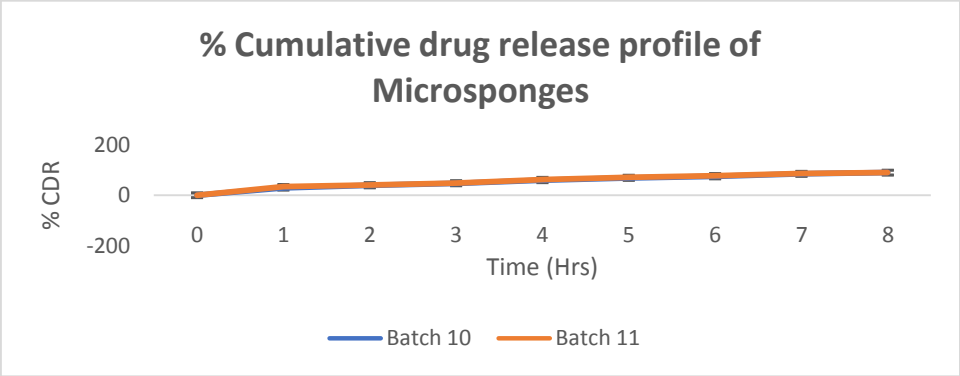

Figure 5. 1 Releaseprofile

Formulation of final optimized batch 11
Formulation of final optimized batch

Ingredients	Batch 11
Drug:Polymerratio [Cyclosporine A:EudragitRS100]	1:1.7
VolumeofInnerphase(ml) [methanol: DCM]	20
VolumeofOuterphase(ml)[water]	30
Surfactant [PVA] Conc.(mg)	100
StirringSpeed(R.P.M)	1438
StirringTime(min)	75

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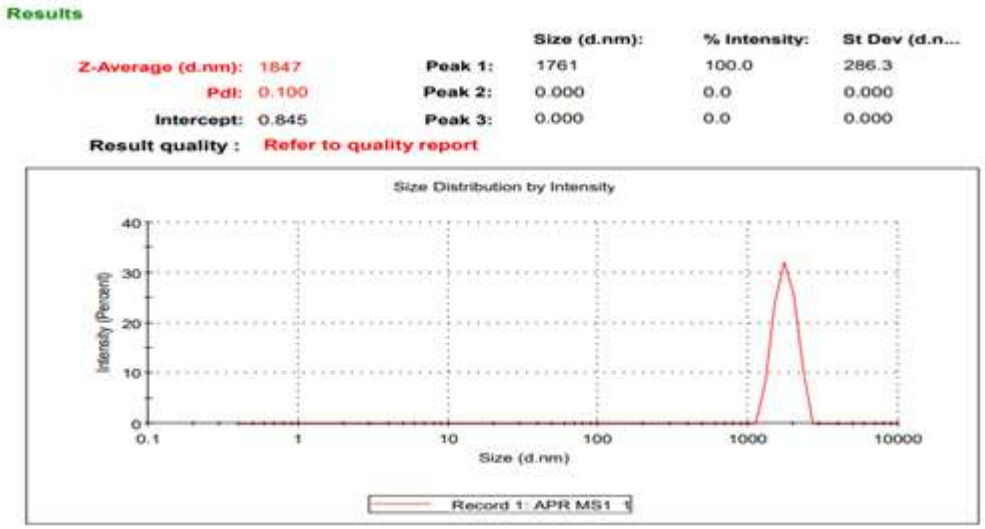
SelectionofOptimizedformulation

11 was selected as validated optimized batch and further consider for loadinginto gel which was having of %yield 94.84%, Drug content 96.85% & %CDR 89.28%withdesirabilityfactorof1.

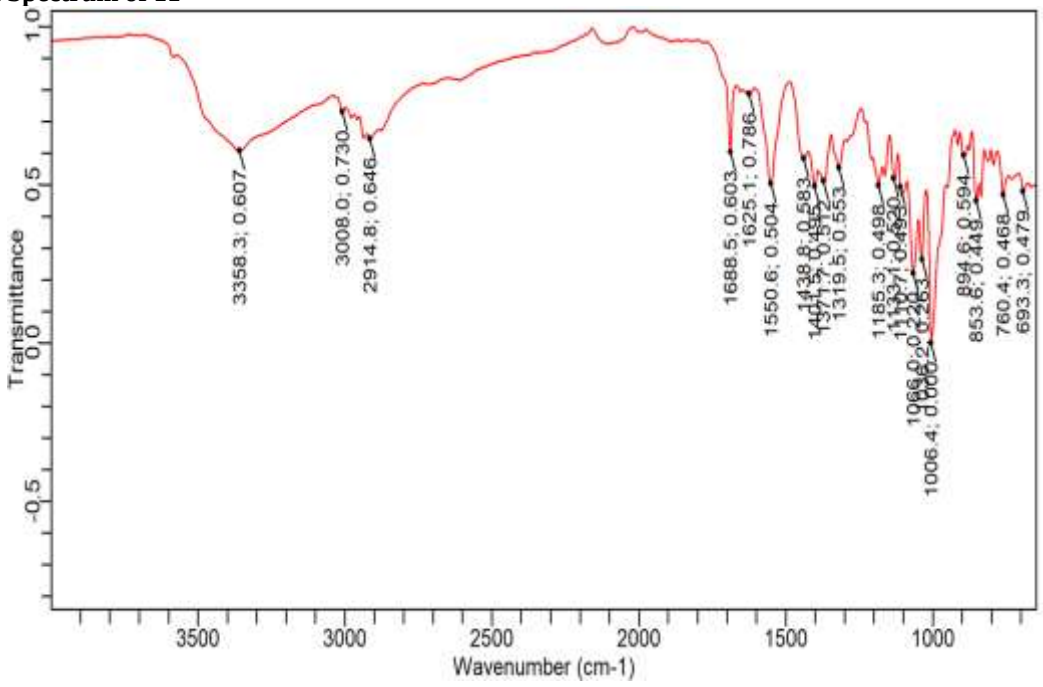
AnalysisofOptimizedformulation

Particle size analysis of Optimized batch 11



ParticlesizeofOptimized batch 11

FTIR Spectrum of 11



FTIRSpectrumofOptimized batch11

Scanningelectronmicroscopy(SEM)ofOptimized batch 11

From SEM studies it was found that sample had porous and spherical nature. Drugloaded Microsponge showed that Microsponge containing drug was bulging. Thisshowed that Drug had been incorporated inside the Microsponges. Microsponges ofERS100was

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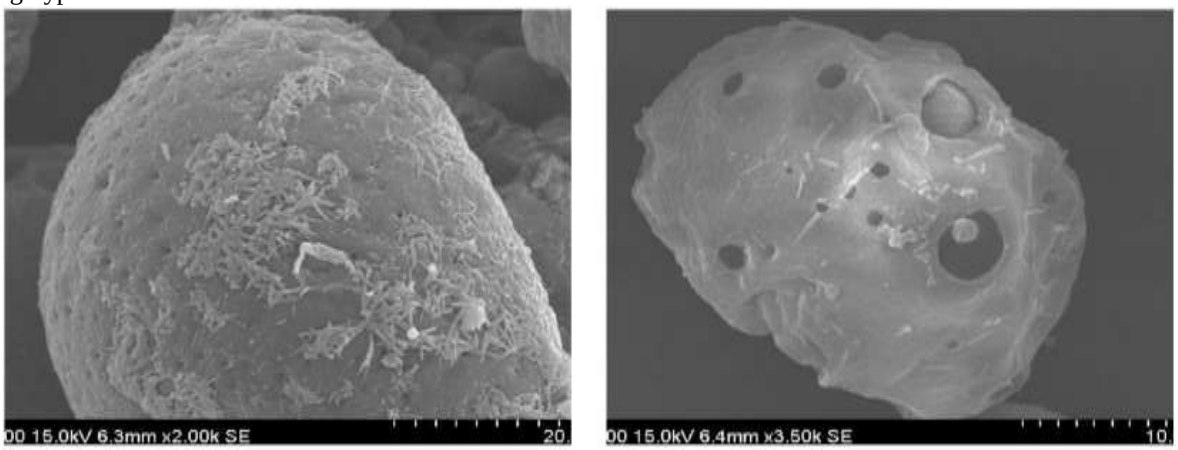
highlyporous.



SEMofoptimized MicrospongeBatch11

Dose Calculation of Cyclosporine A Microsponges for topical gel

As per taken patent reference Cyclosporine ATopical Formulation Contain 0.5% ofCyclosporine Adrug.

0.5% Cyclosporine Atopical=0.5/100
=0.005gm

1gmCyclosporine Acontain=1000mg
0.005gmCyclosporine Acontain=(?)
0.005*1000/1=5mgCyclosporine Arequiredin1gmofgel.
1gmgelrequired5mgdrugSo,20gmrequired= (?)
20*5/1=100mgCyclosporine Arequiredin20gmofgel.

PreparationandcharacterizationofCyclosporine A Microspongesloadedgel[38]

Gel forming polymer was soaked in water for 2 hours and then dispersed by agitationapproximately 600 rpm with the aid of magnetic stirrer to geta smooth dispersion.The dispersion was allowed to stand for 15 min to expel entrained air. To this aqueous slnof triethanolamine (2% v/v) was added with slow agitation. At this stageMicrosponges and permeation enhancers were incorporated in to the prepared base assolution.

Preliminarytrialbatches

Ingredient	**CG1**	**CG2**	**CG3**
HPMC (gm)	1	**1.5**	2
Polyethyleneglycol(gm)	5	**5**	5
Methylparaben(gm)	0.1	**0.1**	0.1
Propylparaben (gm)	0.05	**0.05**	0.05
Triethanolamine(ml)	0.25	**0.25**	0.25
Water(ml)	100	**100**	100

Evaluation of HPMC gel base
Evaluation HPMC gel base

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Batchcode	Colour	Odour	pH (mean ± S.D.)(n=3)	Viscosityspindleno:62(mean± S.D.)(n=3)	Spreadability(gm.cm/sec)(mean±S.D.)(n=3)
CG1	Colorless	Odourless	6.82±0.024	8084±0.68	10.42±1.27
CG2	**Colorless**	**Odourless**	**6.93±0.024**	**9260±0.76**	**10.39±0.85**
CG3	Colorless	Odourless	6.88±0.018	9422±0.62	9.56±1.90

FormulationofCyclosporine Amicrospongeloadedtopicalgel
FormulationofCyclosporine Amicrospongeloadedtopicalgel

Ingredients	OptimizedGel
Batch 11 (mg)	100
HPMC (gm)	1.5
Polyethyleneglycol(gm)	5
Methylparaben (gm)	0.1
Propylparaben(gm)	0.05
Triethanolamine(ml)	0.25
Water(ml)	100

Characterization of Cyclosporine A microsponge loaded topical gel
CharacterizationofOptimizedCAMSG

Parameter	OptimizedCAMSG
Dose	100mg
Strength	20gm
Clarity	Clear
Odour	odourless
pH (mean±S.D.)(n=3)	6.93±0.024
Spreadability(mean±S.D.)(n=3)	10.39±0.85
Viscosity(mean ±S.D.)(n=3)	9260±0.76
%Drugcontent(mean±S.D.)(n=3)	92.25±0.24

From these data we have found that Cyclosporine Amicrosponge topical gel preparedfrom Eudragit RS 100 having greater drug content and Spreadability mostly CAMSGcontainingAPR-ER100Microsponge.Tableshowsdatafordrugcontent ,Spreadability,clarity,pH ofvariousCyclosporine ATopicalGel.

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In-vitroDiffusionstudies

Table 5. 2 DataofIn-Vitro DiffusionStudies

Time	%CDR (Mean±S.D.) (n=3)
0	0
1	32.15±1.36
2	40.80±1.79
3	48.50±1.32
4	60.80±1.80
5	70.42±1.63
6	77.15±1.92
7	86.96±1.52
8	93.42±1.68

J-flux&permeabilityCo-efficient

Table 5. 3 J-flux&permeabilityCo-efficient

Time(hrs)	FluxJ(mg/cm^2/hr)	Permeabilityco-efficient(Kp)
0	0	0
1	0.163772124	0.002183628
2	0.045670354	0.000608938
3	0.039723451	0.000529646
4	0.072477876	0.000966372
5	0.218156028	0.002908747
6	0.236312057	0.003150827
7	0.254751773	0.00339669
8	0.133333333	0.001777778

In-vitroReleaseKineticstudy

Table 5. 4 DataofIn-vitroreleasekineticstudy

Model	Parameter	OptimizedCAMSG

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ZeroOrder	R2	0.9378
	Slop	10.126
	Intercept	15.297
Firstorder	R2	0.977
	Slop	-0.1145
	Intercept	2.0107
Higuchi model	R2	0.9912
	Slop	0.0312
	Intercept	0.0688
HixonCrowell	R2	0.9883
	Slop	0.2872
	Intercept	0.1144
Korsmeyer	R2	0.9742
Peppas	Slop	0.5124
	Intercept	1.479

By plotting values forKorsmeyer peppas model,near straightlines with parallelpositive slopes were obtained indicating that, best fit model for formulations wasKorsmeyermodel.

Stabilityanalysis

Table 5. 5 DataofStabilityanalysis

Parameter	**OptimizedCyclosporine AMicrospongesloadedGel**			
	Roomtemperature			
	0day	**10days**	**20days**	**30days**
Clarity	clear	Clear	clear	Clear
Odour	odourless	Odourless	odourless	odourless
pH	6.93±0.024	6.90±0.018	6.92±0.024	6.90±0.019
Spreadability	10.39±0.85	10.39±0.76	10.38±0.71	10.36±0.73
Viscosity	9260±0.76	9257±0.75	9258±0.72	9260±0.79
%Drugcontent	92.25±0.24	91.25±0.21	92.24±0.25	92.24±0.23

V. CONCLUSION

Microsponge containing Cyclosporine A will be ready by a semi emulsion dispersion technique utilizing Eudragit RS100 utilizing QbD approach. All the were oppressed for % yield, % Entrapment productivity, % drug content,

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examining electron microscopy, FTIR ghostly investigations, and Ex vivo drug discharge studies,

The IR otherworldly investigation recommended similarity between the medication and definition added substance. The medication exists in unique structure and accessible for the organic activity.

The disintegration boundaries were contemplated by involving disintegration programming PCP DISSO V.3 for microsponges details which demonstrated expansion in drug focus, drug discharge was diminished.

The microsponges which gave better physical, morphological and % embodiment in both of the polymers were chosen for joining into the Topical gel definitions. Different Topical gel plans with Cyclosporine A in free structure and in microsponges conveyance framework were figured out and the in-vitro discharge studies were completed.

By thinking about every one of the aftereffects of Check Point Analysis the Microsponges details and further continue for effective gel definitions and Characterization of same. It shows that the arrival of medication from Microsponges consolidated into the Topical gel, follow Higuchi (framework) dispersion model. No progressions found after security investigation for a time of 1 months.

From the review it very well may be reasoned that it is feasible to plan an effective polymeric Microsponges definition for Cyclosporine A might build viability and patient consistence which are of prime significance. Nonetheless, Ex vivo tests are fundamental to lay out the genuine helpfulness of these Microsponges.

Expected Outcomes:

Cyclosporine A stacked Microsponges based skin drug conveyance framework might be decrease incidental effects with decrease of portion by conveying drug at dermal site. The medication delivery can alter and warehouse drug inside the scalp through diminishing transdermal entrance into circulatory framework by MDS innovation. Subsequently, this examination work might be helpful to form Cyclosporine A Microsponges utilizing QbD approach which can be maximize viability decrease endlessly portion recurrence and henceforth increment patient Compliance.

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