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Development, Optimization & Evaluation Of Solid Lipid Nanoparticles Of Celecoxib

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ABSTRACT
Celecoxib belongs to the category of nonsteroidal anti-inflammatory drug having poor oral bioavailability caused by the first-pass metabolism. Work in present to improve the oral bioavailability of celecoxib by incorporating into SLNs. Several celecoxib loaded formulation of SLNs were formulated using lipid by a method known as solvent emulsification-diffusion method and optimization is done by central composite drug design. The physical compatibility study of drug excipients was done by FTIR. Optimizes celecoxib loaded-SLNs have particle size in range of 314 nm with entrapment efficiency varying in between 79% was developed. The comparision between the data of ex-vivo release and marketed formulation was done. It showed an important difference observed between marketed formulation and optimized formulation. The data of optimized formulation released and was subjected to many release kinetic model, the model known as Higuchi kinetic was found to be best fitted with R^2=0.955. The result obtained shows that the SLNs are potential lipid carrier for the improvement of celecoxib by the minimization of the first pass metabolism.

Keywords: *SLN, FTIR,Non-steroidal Anti-Inflammatory, Emulsification-Diffusion.*

1. INTRODUCTION

1.1 ORALDRUGDELIVERY

The most simple, convinient and economical route for drug delivery is oral route. The most prefrential route of administration and researchers are finding ways to incorporate various technologies in oral formulations **(Gupta et al. 2009).**

The most preferedroute is oral drug delivery as it provides the large active surface area than other delivery system for the various drug administrations **(Kushal et al. 2013).** The recent development and advancement in technology of oral medication have helped the pharmaceutical industry in the improvement of dosage form **(Zaman et al. 2016).** Many unique features are presently being efficiently utilized for increasing the most great outcomes with fewer disadvantages. NDDS (Novel drug delivery system) is imperative. This system has remedial efficiency, little predominance of toxicity and better stability profile **(Moodley et al. 2012).**

1.1.1 Gastrointestinaltract (GIT)

GIT comprises of a void muscular tube beginning from the oral cavity, where food entersintothe mouth, and ends with anus where food is discharged, in between comprises of the pharynx, throat, abdomen, and intestines to the rectum **(Saunders et al. 2006).**

1.1.2UPPERGIT

Esophagus,Stomach,andduodenum

The esophagus is a tube composed of muscles and approximately250mm in length and 20mm in diameter.It reaches out from the pharynx to the abdomen after passing through an opening inthe sromach**(Drake et al. 2005).** The esophagus functions as a vehicle medium between compartments **(Barron et al. 2010).**

Ajshapedexpandedbagiscalledabdomenwhichisfoundsimplyleftofthemidlinebetween the small intestine and esophagus.

The internal surface of the abdomen is composed of longitudinal folding called rugae which enables the stomach to enlarge when nourishment enters. The functions of the stomach incorporate capacityofnourishment, mechanical breakdown, absorptionanddigestion **(Cohenet al. 2005).**

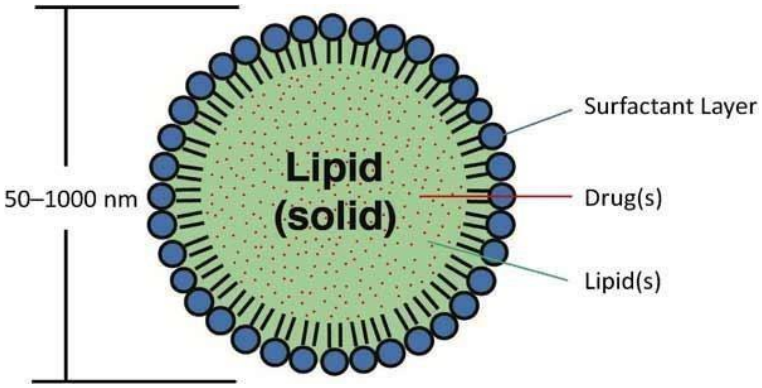
Theduodenumliesinthemiddleoftheupperandlowertracts.Theduodenumispartitionedinto four segments in particular bulb, descending, horizontal, and ascending **(Farlex et al. 2011).**

1..1.3 LOWERGIT

SmallIntestine

The principle capacity of the small digestive system is to assimilate proteins, lipids, andnutrients. It is around 6m long, reaching out from the pyloric sphincter of the abdomen to the ileocaecal valve isolating the ileum from the caecum.

1.2 SOLIDLIPIDNANOPARTICLES



In the quicklydeveloping field ofnanotechnology, SLNs areat the cutting edge with a numerous prospective applications in the medication conveyance, research, clinical medicine just as inother varied sciences. Because of their extraordinary size-dependent properties, nanoparticles recommendthepossibilityto createnewtherapeutics **(Kishoreetal. 2016).** The medicationscan be integrated into

the nanocarriers. This capacity provide another model in medication conveyance and can be utilized for secondary and tertiary levels of targeting drugs. therefore, great promise for achieving the objective of site-explicit and controlled medication conveyanceis holded by SLNs and hence wide researchers are attracted **(Reddy et al. 2014).**

1.3 METHODOFPREPARATION OFSLNs

1.1.3 High-pressurehomogenization

1.1.3.1 Hothomogenization

1.1.3 .2 Coldhomogenization

1.3.4 Ultrasonication/high-speedhomogenization

1.3.2.1 Probeultrasonication

1.3.2.2 Bathultrasonication

1.3.5 Solventemulsification-evaporationmethod

1.3.6 Solventemulsification-diffusionmethod

1.3.7 Supercriticalfluidtechnique

1.3.8 Microemulsion-basedtechnique

1.3.9 Precipitationtechnique

1.3.10 Film-ultrasounddispersiontechnique

1.3.11 Doubleemulsionmethod

1.3.12 SolventInjectionTechnique

1.3.13 MembraneContactor method

2. OBJECTIVEOFPROPOSEDRESEARCH WORK

TheobjectiveofpresentresearchworkisFormulation,optimization,andevaluationofsolidlipid nanoparticles of Celecoxib.

1. TheSLNsofcelecoxibisprepared bytheSolvent emulsification-diffusiontechnique.
2. TheoptimizationoftheSLNformulationisdonebyusingCentralCompositeDesign.

3. Ex-vivoreleasecharacterizatio

2.1 PLANOFWORK

2.1.1 Literaturesurvey

2.1.2 PROCUREMENTOFDRUGANDEXCIPIENTS

2.1.3 PreformulationStudies

a) Identificationofdrug
b) Assay
c) Solubilityprofile
d) MeltingPoint
e) Partitioncoefficient
f) Drug-Excipientinteraction

2.1.4 PREPARATIONOFTHEFORMULATION

g) Selectionoflipid andsurfactant(Onbasisofsolubilitystudies)
h) Determinationoftheconcentrationrangeof Lipid,surfactant,and solvent.
i) PreparationofformulationsbySolventemulsification-diffusiontechnique
j) Optimizationbydesignexpertsoftware.

2.1.5 CharacterizationofdrugloadedSolidlipidnanoparticles

k) Morphology
l) Particlesize
m) Zetapotential
n) Polydispersityindex
o) Drugentrapment efficiency
p) Drugloading

2.1.6 Ex-vivostudies

2.1.7 INvivostudies(PawEdemamethod)

2.1.8 Stabilitystudies

2.1.9 Resultanddiscussion

2.1.10 Summaryandconclusion

3. RESULTANDDISCUSSION

3.1 ORGANOLEPTICPROPERTIES

3.1.1 PhysicalAppearance Colour : White Physical state:Solid

3.1.2 Melting Point

ThemeltingpointofCelecoxibwasobservedintherangeof157-159°Cwhichwassimilartothe pure reference drug.

3.2 ANALYTICALSTUDIES

3.2.1 UltraVioletAbsorption Maxima

3.2.2 DeterminationofAbsorptionmaxima(λmax)ofCelecoxib

TheAbsorption maxima (λmax) ofCelecoxibwereobserved tobe252 nm.

3.2.3 FTIRSpectroscopy

The FTIR spectraofthe celecoxib (Fig6.1) which is similar to the standard ofcelecoxib. The spectrumofCelecoxibshowedthe followingfunctionalgroupattheir frequencymentioned in table 6.1.

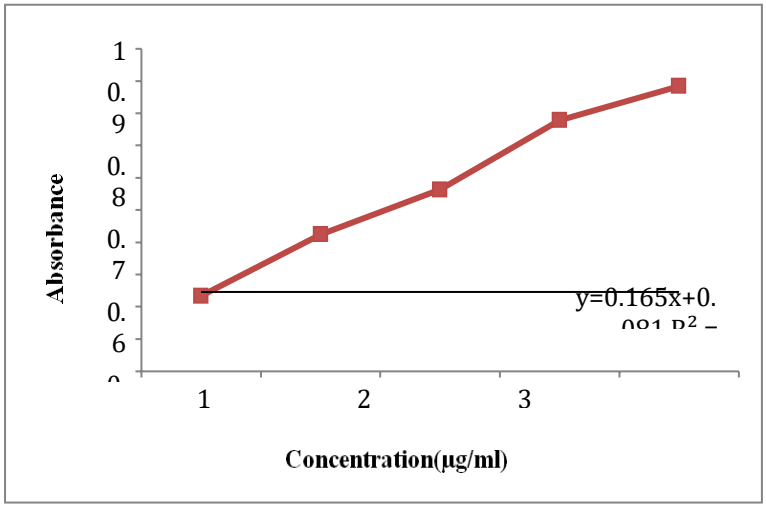


Fig.6.1IRspectraofCelecoxib

Table6.1IRspectrumvalueofCelecoxib

ObservedPeak(cm^{-1})	GroupFrequency(cm^{-1}) Reference	Functionalgroup
1022.09, 1361.5	1150-1350	S = O stretching (sulfonamidegroup)
1550.49	1550-1600	N–Hstretching
3316.96,3390.24,3513.67	3300–3500	NH2stretching

3.3 PARTITIONCOEFFICIENT

The partition coefficient of the drug was observed to be 3.5.It conforms to the standard this showed the lipophilic nature of the drug.

3.4 QUANTITATIVE ESTIMATION OF DRUG

3.4.1 UV Spectrophotometry

3.4.1.1 Preparation of calibration curve of Celecoxib in methanol

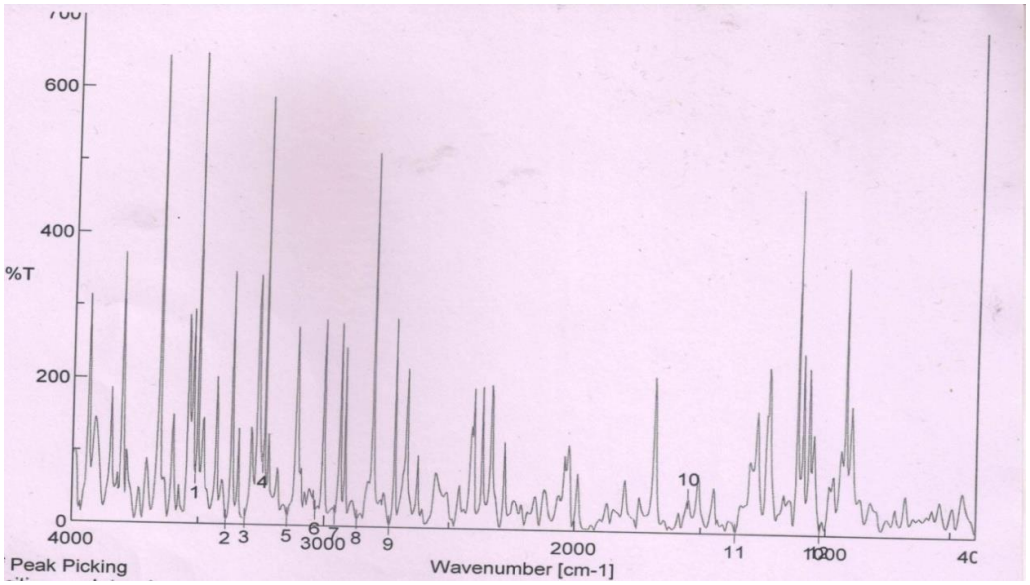


Fig.6.6Calibrationcurveofcelecoxibinmethanol

Table6.3Calibrationcurveofcelecoxibin methanol

Concentration(µg/ml)	Absorbance(nm)	Statistical Parameters
10	0.234	**Correlationcoefficient: R^2= 0.991**
20	0.425	**Equationofline: y= 0.165x+ 0.081**
30	0.564	
40	0.779	
50	0.884	

The calibration curve was prepared in between10-50(µg/ml).In this range,it demonstrated the linearity with r^2 = 0.991.

3.5 FORMULATION DEVELOPMENT

Method of preparation of SLNs

3.5.1 Screening of lipid

The lipid was chosen based on solubility. Asaresul to fall the polymers,palmiticacid was selected due to the highest solubility.

Table6.5 The solubility of different polymers with Drug

SerialNo.	Polymer	Lipid (mg)	Solubledrug(mg)
1	GMS	200	65
2	Palmiticacid	200	78
3	Stearicacid	200	42

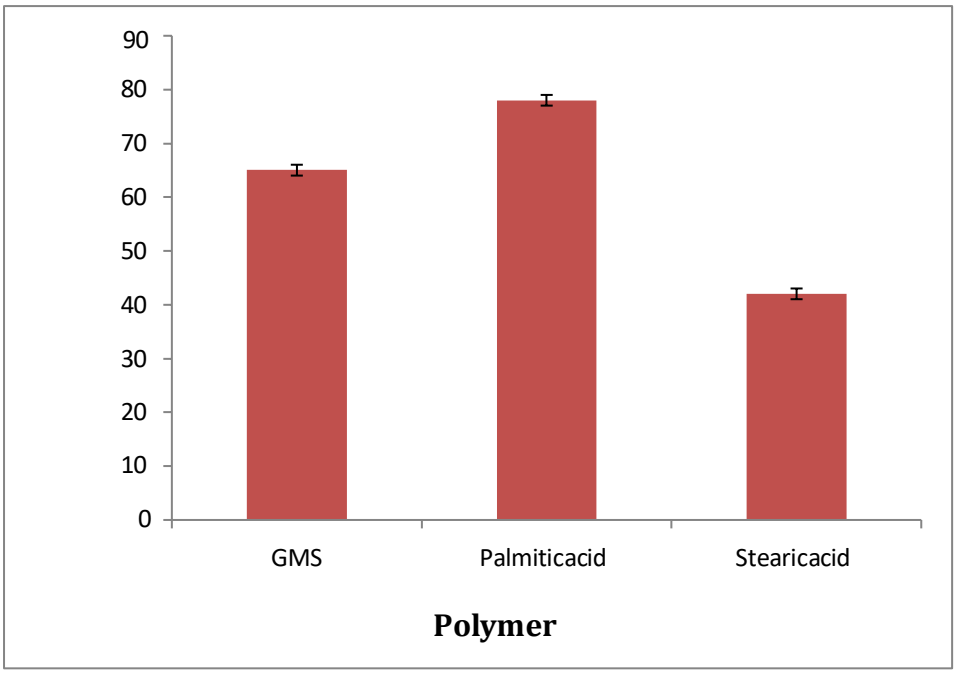


Fig.6.8The solubility of different polymers with Drug

3.5.2 Selection of surfactant

Different concentration of surfactant was included in the formulation and formulation was optimized based on particle size.

Drug(mg)	Lipid (mg)	Surfactant concentration (%)	Particlesize (nm)
100	100	1.0	409
100	100	1.5	366
100	100	2.0	314
100	100	2.5	340
100	100	3.0	472

Selection of drug lipid ratio

The drug lipid ratio was selected baesd on entrapment efficiency.A saresul to fall the formulation 1:1 was selected due to the highest entrapment efficiency.

Table6.7 Optimizationofthedruglipidconcentration intheformulation

Druglipidratio	Entrapmentefficiency(%)
1:1	79
1:2	66
1:3	54

3.5.3 Selection of solvent

The solvent was selected based on solubility. A saresul to fall the solvents, methanol and chloroform was selected due to the highest solubility.

Table6.8Solubility studies of Celecoxib in organic solvents

Solvents(10ml)	Solubility of Celecoxib(mg/ml)
Acetone	5.93
Ethanol	16.89
Chloroform	11.31
Methanol	34.49

Table6.9 Solubility studies of Lipidin organic solvents

Solvents(10ml)	Solubility of Palmitic acid (mg/ml)
Chloroform	670
Methanol	420
Ethanol	330
Acetone	110

3.6 PREPARATION OF SOLID LIPID NANOPARTICLES

3.6.1 Optimization by central composite design(CCD)

Based on mention trials the following mention concentration of variables like a drug lipid ratio, surfactant was selected to optimize while the concentration of other ingredients like stirring speed, the temperature was kept constant. Central composite experimental design (Design Expert Version 11- trial version) was utilized to evaluate the effect of the above mention variables (independent) on various evaluative parameters (dependent variables).

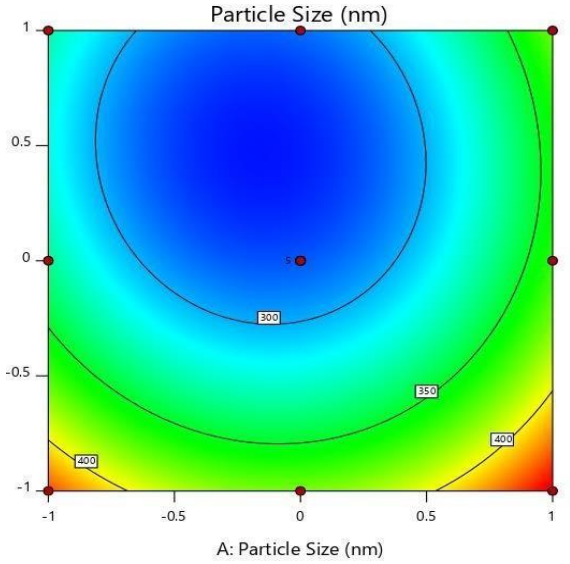
Table6.11Observed responses for13 runs of SLN according to Central composite design

Formulation code	Drugto lipid ratio	Surfactant (%)	Particlesize(nm)		Entrapmentefficiency (%)	
			Actual value	Predicted value	Actual value	Predicted value
SLN1	0	0	270	285.03	49	47.97
SLN2	0	1	302	288.75	66	59.25
SLN3	-1	0	366	331.08	65	63.92
SLN4	0	0	272	285.03	45	47.97
SLN5	0	0	270	285.03	49	47.97
SLN6	0	-1	405	377.08	40	43.92
SLN7	0	0	280	285.03	47	47.97
SLN8	1	-1	442	448.79	57	55.21
SLN9	1	0	370	363.75	54	52.25
SLN10	-1	-1	409	430.13	55	52.87
SLN11	1	1	375	374.46	53	56.54
SLN12	0	0	292	285.03	47	47.97
SLN13	-1	1	314	327.79	79	82.21

Final Equation in Terms of Coded Factors

$Y1=+285.03+16.33\ A-44.17B+7.00\ AB+62.38A^2+47.88B^2$

The condition as far as coded elements can be utilized to make expectations about the reactionfor given dimensions of each factor. As a matter of course, the high levels of the factors arecoded as +1 and the low level are coded as - 1. The coded equation is helpful for distinguishing the general effect of the elements by looking at the factor coefficients.



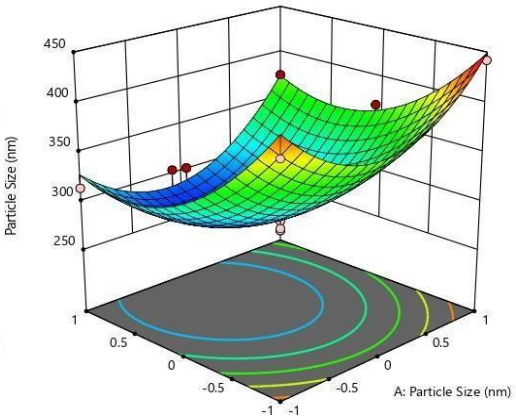


Fig.6.13Contour plot showing particle size **Fig.6.14 3-D surface response plot showing particle size**

Table6.15 Model summary for response Y2

P-values under 0.0500 demonstrate model terms are critical. In this situation A, B, AB, A^2 are noteworthy model terms. Values greater than 0.1000 show the model terms are not critical. If there are numerous unimportant model terms, model decrease may improve your model.

The **Lack of Fit F-value** of 11.58 suggests the Lack of Fit is critical. There is just a 1.93% chance that a Lack of Fit F-value this huge could happen because of noise. Significant lack of fit is bad - we need the model to fit.

Table6.17CoefficientsinTermsofCodedFactors

Factor	**Coefficient Estimate**	**Df**	**Standard Error**	**95% CI Low**	**95% CI High**	**VIF**
Intercept	47.97	1	1.63	44.10	51.83	
A-Particle Size	-5.83	1	1.61	-9.63	-2.03	1.0000
B-Entrapment Efficiency	7.67	1	1.61	3.87	11.47	1.0000
AB	-7.00	1	1.97	-11.65	-2.35	1.0000
A^2	10.12	1	2.37	4.52	15.72	1.17
B^2	3.62	1	2.37	-1.98	9.22	1.17

FinalEquationinTermsofCodedFactors

$Y2=+47.97-5.83A+7.67B-7.00AB+10.12\ A^2+3.62B^2$

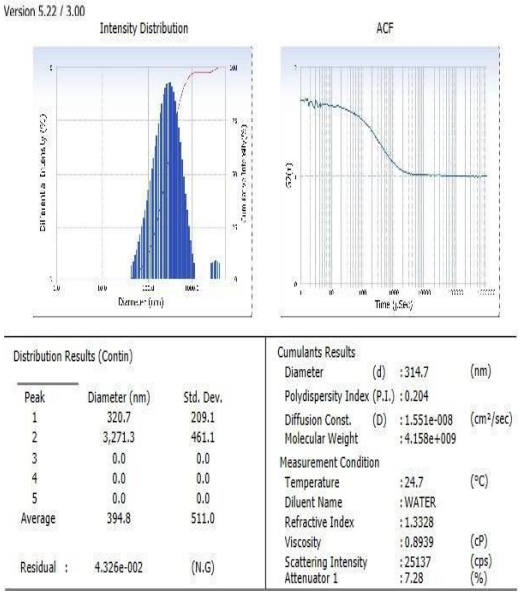
The condition as far as coded elements can be utilized to make expectations aboutthe reaction for given dimensions of each factor. As a matter of course, the high levels of the factors arecoded as +1 and the low level are coded as - 1. The coded equation is helpful for distinguishing the general effect of the elements by looking at the factor coefficients.

3.7 CHARACTERIZATION OF SOLID LIPID NANOPARTICLES

3.7.1 Particle size and zeta potential

The particle size of the optimized formulation (SLN13)was found to be 314.7 nm

Fig.6.18Zetapotentialofoptimizedformulation



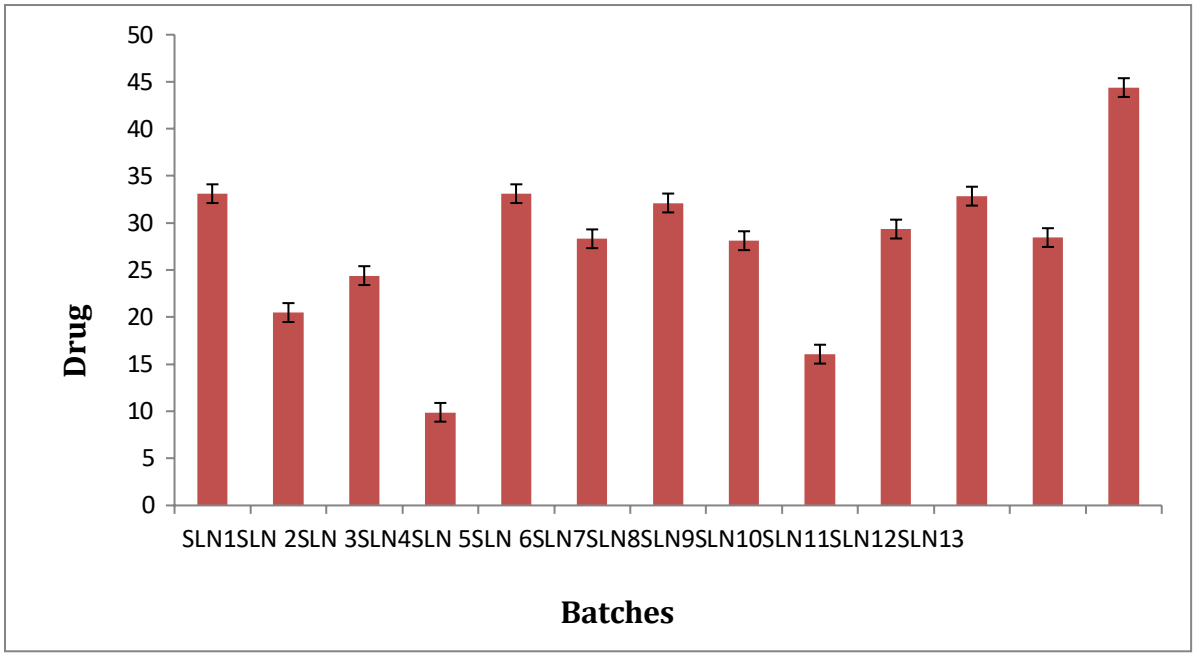
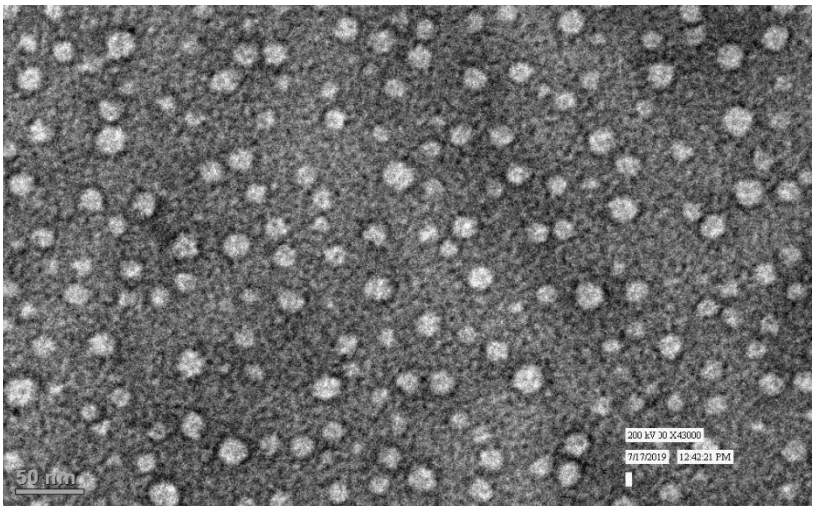


Fig.6.19EntrapmentefficiencyofSLNformulations

3.7.2 Transmission Electron Microscope(TEM)



The characterization of optimized formulation was done by using TEM which indicated well dispersed particles that are more or less spherical. The size of these particles ranges from 50-100 nm which confirms their nanoparticles.

3.8 Ex-vivo release through rat skin (permeation studies) atpH7.4Experiment

3.8.1 Preparation of Rat Skin

Male Wistar rats were relinquished with delayed ether anesthesia and the abdominal skin ofeach rat was excised. Hairs on the skin of animal were expelled with a hair remover (Veet) and the skin was washed with physiological saline (pH 7.4), subcutaneous tissues were surgically removed and dermis side was cleaned with isopropyl alcohol to expel lingering following fat.The skin was washed with distilled water, enclosed by aluminum foil and put away in a deep freezer at -20°C till further use **(Bhaskar et al. 2009).**

The full-thicknessabdomenskin fromratswas utilized for allthe penetrationtests.Thethickness of each skin was comparative. The skins were clamped between the donor and the receptor assembly of vertical Franz diffusion cell with an effective diffusion area of 3.14 cm 2 and a cell volume of 15 ml **(Lai et al. 2007, Shakeel et al. 2008).**

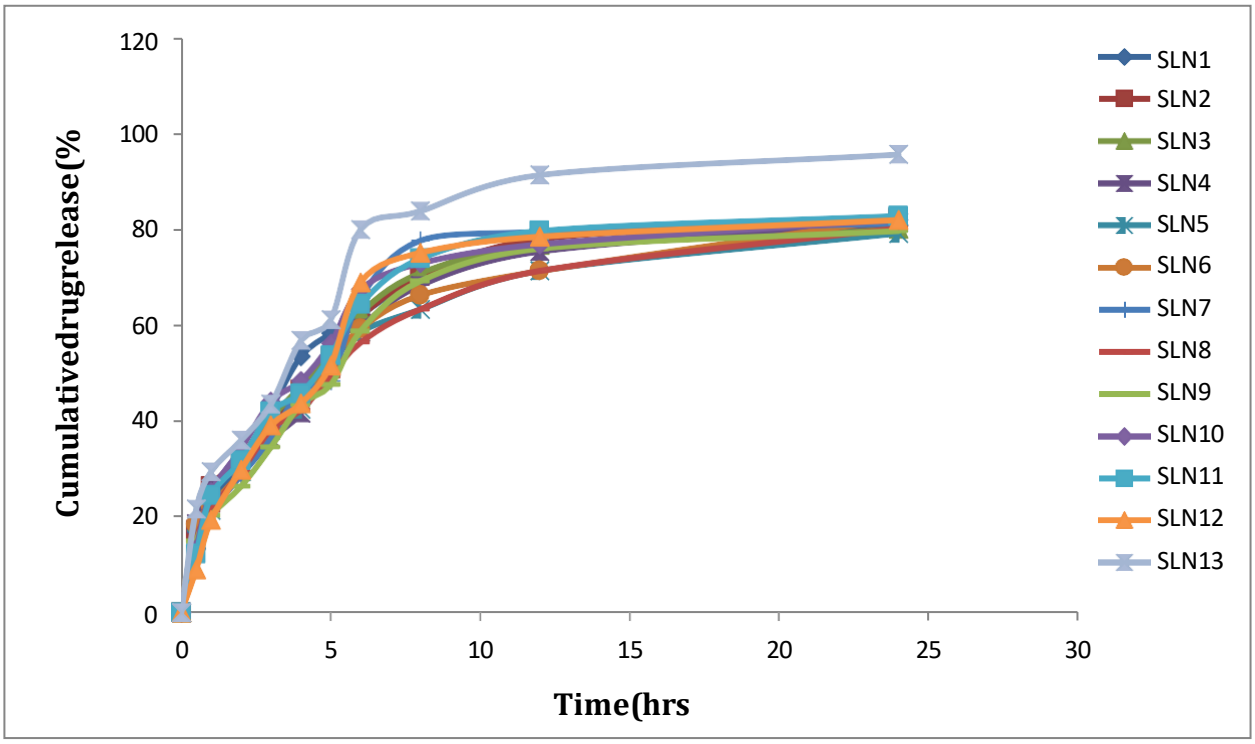


Fig.6.22Ex-vivo release of various SLN formulations

Table6.19 Ex-vivo drug release study of optimized formulation

Time (hrs)	Square rootof time	Log t	Cum.drug release%	LogCum. drug release%	Cum.drug remaining %	LogCum. drug remaining %
0	0	0	0	0	0	0
0.5	0.71	0	19.35	1.286	80.65	1.906
1	1	0	27.31	1.436	72.69	1.861
2	1.41	0.301	35.22	1.546	64.78	1.811
3	1.73	0.47	42.38	1.627	57.62	1.760
4	2	0.602	51.72	1.713	48.28	1.683
5	2.23	0.698	62.25	1.794	37.75	1.576
6	2.45	0.778	71.51	1.854	28.49	1.454
8	2.65	0.903	82.35	1.915	17.65	1.246
12	3.464	1.079	87.45	1941	12.55	1.098
24	4.89	1.38	92.29	1.965	7.71	0.88

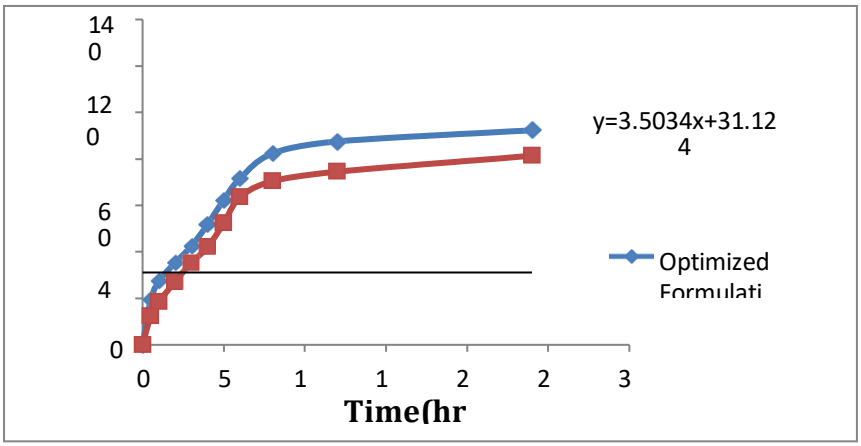
3.8.2 Release kinetics study

It has been appeared on account of lypophilic matrices, swelling and disintegration of polymer happens all the while, and them two add to the general medication discharge rate. It is all around reported that medication discharge from lypophilic matrices demonstrate a normal time- dependent profile(i.e.,diminishedmedicationdischargewithtime becauseofincreaseddiffusion path length). This inherent limitation prompts first-order release kinetics **(Bourne et al. 2002).**

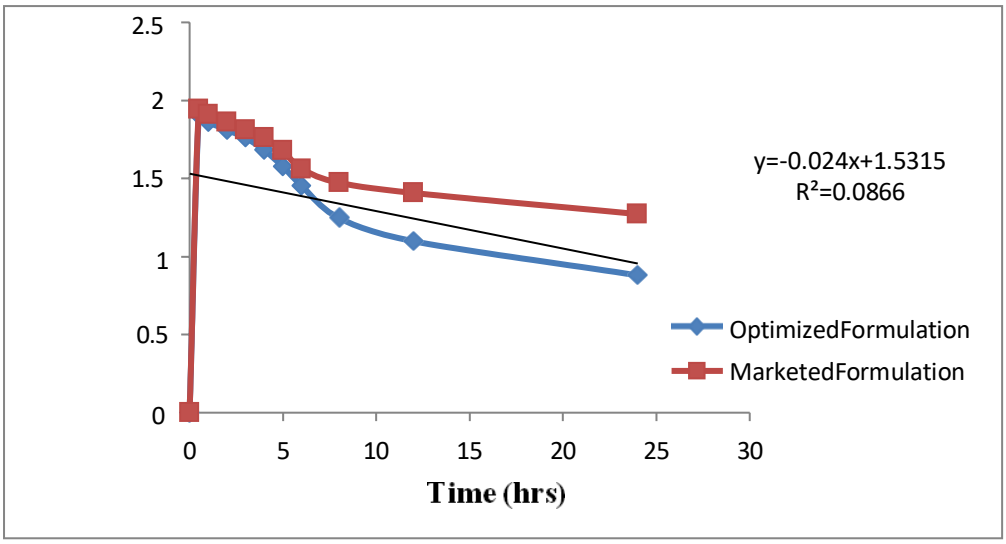
In the present investigation, the formulation (SLN) was designed for the sustained release of Celecoxib, which was evaluated by ex-vivo medication release **(Korsmeyer et al. 1983).** To study the release kinetics of medication, the results of the ex-vivo medication release study were plotted with different kinetic models like zero order (eq. 1) (cumulative drug released v/s time), first order (eq. 2) (log cumulative drug remaining v/s time), Higuchi's kinetics (eq. 3) (cumulative drug release v/s square root of time) and Kosermeyer and Peppas equation (eq. 4) (log cumulative release v/s log time).

C= K0t

WhereK0=zeroorderrateconstant,t=time.



Release kinetics of zero order



Release kinetics of first order

IN-VIVO DRUG RELEASE

Male Wistar rats were utilized for this study. The rats were obtained from the Central animal house facility I.T.S College of Pharmacy Muradnagar, Ghaziabad, U.P. (INDIA).

The wistar rats weighed from 200-250 g toward the beginning of the study and were exclusively housed in stainless steel cages. The temp of the experimental animal room was 20°C (±4°C) and the relative humidity was 50% (±15%). The light conditions were controlled to give 12 hours fake light (8 a.m. - 8 p.m.) every day. For encouraging, conventional laboratory diets were utilized with an unlimited supply of drinking water.

3.8.3 Anti-inflammatoryactivity

3.8.3.1 Carrageenaninducedpawedemamethod

This technique was utilized to study the in vivo performance of the prepared drug delivery system. Anti-inflammatory activity was controlled by estimating changes in the volume of inflamed paw, created by infusion of carageenan (0.1 ml of 1% w/v) utilizing plethysmometer (MCORP, India).

Male Wistar rats was chosen for the investigation. Male Wistar rats were weighed and marks were made on the right paw simply behind tibia-tarsal intersection on each animal. Accordingly, every time the paw was dipped in the plethysmograph up to the fixed mark to guarantee steady pawvolume. Wistarrats wereseparatedinto fourgroupsincorporatingonecontrolled groupwith each group including 6 animals. The paw volume was notes at 0, 0.5, 1, 2, 4, 8 and 24 h **(Bhaskar et al. 2009).**

The formulations SLN-13, standard (marketed), and pure API were offered orally to Wistar rats of separate groups, except the animals of controlled group. The controlled group animals were infused with saline (0.9% NaCl) containing no medication. After 0.5 h of orally administered of SLN-13, standard (marketed), and pure API formulations, 0.1 ml of1% w/v carragenan (in 0.9% normal saline) wasinfusedin the sub planter region of the rightpaw of rats. The initial reading of paw just after injection and subsequent paw volumes was estimated up to 24 h. The percent inhibition of edema was calculated using the following formula:

$$\%\text{inhibitionofedema}=\frac{\text{Vcontrol-V treated}}{\text{Vcontrol}}\times 100$$

Table6.22Observationtable forcarrageenaninducedpawvolume

	Pawvolumeafterdrugadministration (mm)

Group	0.5hr	1hr	2hr	4hr	8hr	24hr
Control	Avg.±SD 6±0.70	Avg.±SD 7±0.56	Avg.±SD 7±0.68	Avg.±SD 6±0.94	Avg.±SD 5±0.82	Avg.±SD 3±0.44
Standard (Marketed)	5±0.59	5±0.65	4±0.89	3±0.29	3±0.55	2±0.42
PureAPI	5±0.75	5±0.69	4±0.87	3±0.65	3±0.55	2±0.62
SLN-13	5±0.51	4±0.78	3±0.66	2±0.78	2±0.42	1±0.32

Table6.23Percentage inhibition of paw volume

Formulation	Time(hrs)					
	0.5	1	2	4	8	24
Standard (marketed)	16.66	28.57	42.85	50	40	33.33
PureAPI	16.66	28.57	42.85	50	40	33.33
SLN-13	16.66	42.85	57.4	66.66	60	50

4. CONCLUSION

The Celecoxib sample was identified and characterized. The purity of celecoxib was found to be 99.71% and the melting point of the celecoxib was observed to be 157-159°C by capillary rise method. Identification confirmed by UV-Visible spectroscopy. The lamda max was observed to be 252 nm which was concordant with the given value. The solubility of the celecoxib was resolved in aqueous and non aqueous solvent and it founds that the drug is freely soluble in methanol and partially soluble in ethanol. The partition coefficientof the drug was observed to be 3.5, which indicates the lipophillic nature of the drug; it favours better entrapment and decreased drugleakage fromthe formulation. In present research the SLNs have been effectively developed (Solvent emulsification-diffusion technique) and evaluated and optimized by CCD. The particle size, PDI, zeta potential and entrapment efficiency of optimized formulation was observed to be 312 nm, 0.204, -18.73 and 79% respectively. The % drug release after 24 h was observed to be 92.29%. The data of ex-vivo release was compared with marketed formulation (CapsulZycel), is difference observed between optimized formulation and marketed formulation (81.29%). The release data of optimized formulation was subjected to various release kinetics model, the higuchi kinetic model was observed to be best fitted with R^2=0.955. Pharmacokinetic study was performed on albino wistar rats. The pharmacokinetic parameters demonstrated huge distinction between optimized formulation and marketed formulation.

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