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CURCUMIN-LOADED SOLID LIPID NANOPARTICLES: A NOVEL APPROACH FOR IMPROVING ANTI-DIABETIC ACTIVITY AND BIOAVAILABILITY

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Abstract:

Background*: Curcumin is effective in the treatment of diabetes mellitus. But they have low aqueous solubility and poor bioavailability. Solid lipid nanoparticles (SLN) could be used to enhance their effectiveness as they increase the bioavailability of lipophilic compounds and protect the drug from gastrointestinal degradation. The main objective of the present study was to prepare solid lipid nanoparticles of curcumin to improve their pharmacokinetics and antidiabetic activities in streptozotocin induced-diabetic rats.*

Results & Discussion*: The actual values of the particle size, %EE, and PDI were found to be in close agreement with the predicted values obtained for the optimized Cur-SLN. TEM results confirmed the monodispersion and spherical shape of the particles and DSC results confirmed the change of drug from crystalline to amorphous form in the optimized Cur-SLN. The formulations showed burst release of the drug followed by sustained release. The results of pharmacokinetic study showed the enhancement of bioavailability in the optimized formulations of curcumin than compared to the plain drug suspension. The improvement in the body weight with a marked reduction in the fasting blood glucose level was observed for optimized Cur- SLN than compared to their plain drug suspension.*

Conclusion: *Curcumin loaded SLN were successfully prepared and showed remarkable effectiveness in the management of diabetes mellitus.*

Key words: Curcumin, solid lipid nanoparticles , pharmacokinetics ,diabetes mellitus.

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INTRODUCTION:

Nanoparticles (NPs) are colloidal particles in which the active ingredients are dissolved, entrapped in and/or is adsorbed or attached on to the particle(1) and Solid lipid nanoparticles (SLNs) as colloidal carrier systems combine the advantages of traditional systems but avoid some of their major disadvantages. These colloidal systems have many important advantages, such as biocompatibility, good tolerability, and ease of scale-up.(2) Recently phytotherapeutics were prepared in nano size to improve pharmacokinetic and pharmacodynamics characteristics (3) Curcumin, a phenolic compound from the plant Curcuma Longa as a traditional spice have many pharmacological activities including: anti-diabetic, anti-inflammatory, anti-cancer, anti-oxidant, antibacterial, anti-HIV and anti-aging activity and hepato protective activity as well as cardiovascular benefits.(4) It has been well documented that curcumin possesses a wide variety of important pharmacological activities including anticancer,antimicrobial,anti-inflammatory, anti-amyloid, antioxidant, and neuroprotective effects.(5,6) Traditionally, turmeric has been used for several aliments and especially it is widely consumed for dietary and medicinal purposes in Southeast Asia, the China, and India.(7)curcumin is poorly water soluble drug with low bioavailability. Use of lipid systems in lipophilic substances increases solubility and bioavailability of poorly soluble drugs. The aim of this study was to prepare curcumin loaded Solid Lipid Nanoparticles (SLNs) with high loading efficiency, small particle size and prolonged release profile with enhanced antibacterial efficacy.

AIM AND OBJECTIVES

AIM

The present study aims to develop a solid lipid nanoparticle-based oral delivery system for curcumin, with a focus on its potential application in the management of diabetes mellitus.

RESEARCH OBJECTIVES:

1. Develop and validate a UV-Visible spectrophotometric method for curcumin quantification.
2. Investigate curcumin's lipid solubility and develop curcumin-loaded SLN using central composite design.
3. Characterize the optimized SLN formulation and evaluate its stability, pharmacokinetics, and pharmacodynamics in diabetic rats.

MATERIALS AND METHODS :

Experimental Methods: Pre-formulation studies of curcumin

Pre-formulation involves applying biopharmaceutical principles to understand a drug's physicochemical properties, which is crucial for designing an effective drug delivery system. Before developing a dosage form, it's essential to determine the drug's physical and chemical properties, such as its solubility, stability, and compatibility with excipients. By evaluating these parameters, researchers can gather critical information to inform the formulation development process.

Physicochemical characterization:

Appearance

A physical examination of curcumin was done.

Melting Point

The melting point of curcumin was determined using differential scanning calorimeter (DSC) and by melting point apparatus.

Solubility

The solubility of curcumin was evaluated in various media using the shake flask method. The study assessed apparent solubility in simulated intestinal fluid (SIF) at pH 6.8 and 7.4, and simulated gastric fluid (SGF) at pH 1.2. Excess curcumin was mixed with each solvent and shaken at 37°C for 48 hours. After filtration and dilution, the solutions were analyzed spectrophotometrically to determine curcumin's solubility profile according to USP criteria. The results were used to calculate the parts of solvent required to dissolve one part of solute, determining the drug's solubility level in each solvent.

FTIR Analysis of Curcumin

The identity of curcumin was confirmed using Fourier Transform Infrared (FTIR) spectroscopy. The analysis was performed using a KBr pellet system, and the spectrum was recorded in the range of 4000-650 cm-1. The characteristic peaks corresponding to various functional groups were identified and compared with reference values to verify the authenticity of the curcumin sample.

Differential scanning calorimetric study

DSC (DSC Q20 V24.11 Build 124) was used for thermal analysis to confirm the drug's authenticity. A small amount (2-5mg) of the drug sample was sealed in the aluminum pan and heated in temperature range (0-250ºC) at the heating rate of 10ºC per minute in the presence of a nitrogen atmosphere.

Preparation of curcumin loaded solid lipid nanoparticles using experimental design

Optimization of formulation variables

The central composite design (CCD) was selected for the optimization of formulation variables. Based on experiments conducted and literature review ; the drug, lipid, and surfactant concentration were chosen as formulation independent variable at three levels(+1, 0, and -1) as shown in table 4.2, and experiments were

conducted to obtain the more acceptable particle size and maximum % entrapment efficiency. The sonication frequency and stabilizer concentration (1%) were kept fixed. The trial version of design expert 12.0 software was used for statistical analysis by ANOVA.

Table 1: Factors used in experimental design of curcumin

Factor	Name	Units	Level		
			High (+1)	Medium (0)	Low(-1)
A	Drug Concentration	%	1	0.75	0.5
B	Lipid Concentration	%	8	6.5	0.5
C	Surfactant Concentration	%	2.5	1.75	1

The SLN were prepared by previously published method with slight modification. In this technique, the lipid phase consisted of glyceryl monostearate and curcumin, and the aqueous phase consisted of non-ionic surfactant (tween 80), both were heated separately at 70ºC. The aqueous phase was poured slowly in the lipid phase using a high-speed mechanical stirrer while maintaining the temperature at 70ºC. The stirring was continued for 30 minutes at 70ºC. The droplet size of the prepared emulsion was reduced by sonication using probe sonicator at 40% amplitude for 8 minutes . But on increasing amplitude and time beyond a limit, particle size increases due to particle aggregation. The formed SLN were stored at 4ºC immediately after sonication.

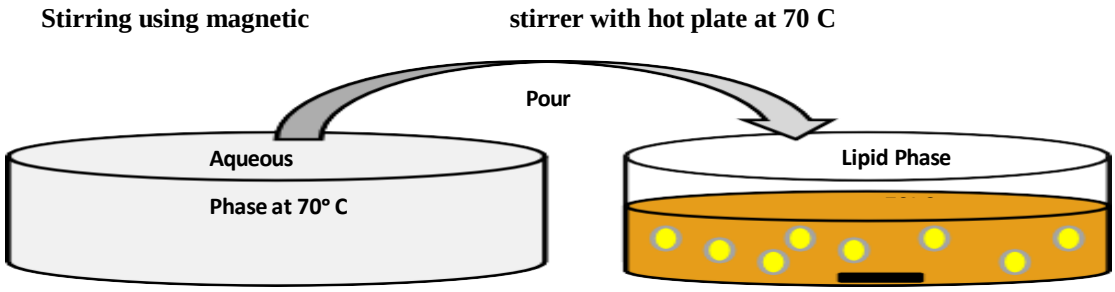
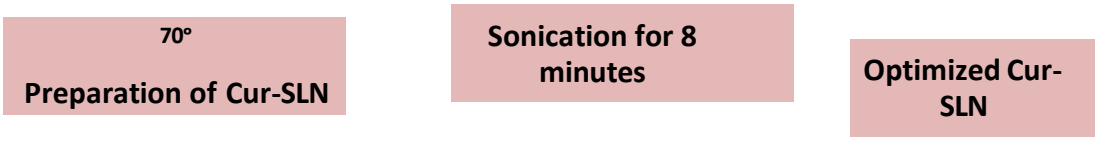


Figure 2: Preparation of curcumin loaded SLN



Characterization of Cur-SLN Particle size, PDI, and Zeta potential

Particle size, polydispersity index, and zeta potential of all the formulations were determined using the Malvern Zeta Sizer, Malvern, UK, after diluting the samples with double distilled water.

Drug content

Drug content was determined by diluting 0.1 ml of SLN with 10 ml of methanol. The mixture was sonicated for 2 minutes and filtered using a syringe filter (0.45 µm). The solution was analyzed spectrophotometrically at 421 nm. Drug content was calculated using the formula:

$$Drug\ Content == \frac{Amount\ o\int\ drug\ obtained}{Total\ drug\ added} \times 100$$

The melting point of curcumin was found at 177.5±0.325ºC when observed in triplicate and at 177.57ºC using a differential scanning calorimeter.The curcumin is yellow coloured and crystalline in nature.

SOLUBILITY PROFILE OF CURCUMIN

Curcumin's solubility was evaluated in various media, with results showing

- ✓ Practically insoluble in water and Simulated Gastric Fluid (SGF, pH 1.2)
- ✓ Very slightly soluble in Simulated Intestinal Fluid (SIF, pH 6.8 and 7.4)

These findings indicate curcumin's limited solubility across different pH conditions.

Fourier Transformation Infrared study

The FTIR spectrum of curcumin is shown in figure .The absorption bands were obtained with characteristic peaks in the range of 4000-650 cm^{-1}. The characteristics peaks of all the functional groups were present in the spectrum of curcumin and found in correlation with the reference value, which confirms the authenticity of the drugs.

Table 2 : FTIR interpretation of curcumin

IR absorption bands (cm^{-1})	Reference Value	Interpretation
3503.30	3505	OH stretching of phenol group
1624.75	1625	C=O, C=C streching
1557.90	1600	C=C stretching of
		aromatic
1152.80	1150	C–O–C asymmetrical stretching
1273.20	1273	CH in plane bending of C=CH, aromatic C–O stretching
719 .88	713	C stretching

PREPARATION AND CHARACTERIZATION OF CURCUMIN LOADED SOLID LIPID NANOPARTICLES USING EXPERIMENTAL DESIGN

Formulation variables were optimized using central composite design. Three independent factors were selected; drug concentration, lipid concentration, and surfactant concentration at three levels (low, medium, and high). All the formulations were successfully prepared using emulsification, followed by the sonication method.

STATISTICAL ANALYSIS OF EXPERIMENTAL DATA

Particle Size And % Entrapment Efficiency

The particle size and % entrapment efficiency obtained for all the formulations are shown in table 3.

Table 3: Values obtained for particle size and % entrapment efficiency by conducting experimental runs (Cur-SLN)

Formulation Run	code	Particle Size (nm), Response Y_1	% Entrapment efficiency*, Response Y_2
1	F1	230.8	68.1±0.975
2	F2	118	56.9±1.282
3	F3	145	82.3±0.969
4	F4	238.8	93.5±0.827
5	F5	145.1	82.4±1.164
6	F6	95.21	68.4±0.993
7	F7	129.9	65±1.179
8	F8	362.7	85.1±0.938
9	F9	289.1	89.3±0.941
10	F10	145.7	82.4±1.172

Run	Formulation code	Particle Size (nm), Response Y_1	% Entrapment efficiency*, Response Y_2
11	F11	135.3	82.1±1.206
12	F12	322.6	93.7±0.893
13	F13	103.9	84±1.211
14	F14	145	82±1.308
15	F15	146.4	55.9±1.276
16	F16	239.7	65.2c0.985
17	F17	371.8	95.7±0.929
18	F18	130.7	61.8±0.958

*values are expressed as Mean±S.D.

The particle size ranged from 95.21 nm to 371.8 nm. A quadratic model was suggested by the Sequential Model Sum of Squares, which was significant (F-value = 58.56, $p < 0.0001$). The significant model terms were A, B, C, BC, A^2, B^2, and C^2 ($p < 0.05$). The R^2 value was 0.9850, indicating a strong fit. The predicted R^2 was in reasonable agreement with the adjusted R^2. The signal-to-noise ratio was 25.408, indicating adequate precision. The lack of fit was marginally insignificant, validating the model's adequacy.

DRUG ENTRAPMENT EFFICIENCY ANALYSIS

The % entrapment efficiency ranged from 55.9% to 95.7%. A quadratic model was fitted to the data, which was significant (F-value = 30.82, $p < 0.05$). The significant model terms were A, B, C, A^2, and C^2. The model's R^2 value was 0.9404, and the predicted R^2 (0.7871) was in reasonable agreement with the adjusted R^2. The signal-to-noise ratio was 19.140, indicating adequate precision. The lack of fit was insignificant, confirming the model's validity.

The equation for % entrapment efficiency (Y2) was:

$$Y2 = 82.19 - 3.81A + 12.87B + 3.29C - 2.17A^2 - 2.35C^2$$

The response surface plots showed the effects of independent variables on % entrapment efficiency. Key findings:

- Increasing drug concentration decreased % entrapment efficiency.
- Increasing lipid amount (B) positively affected % entrapment efficiency.
- Increasing surfactant concentration increased % entrapment efficiency.
- Optimal conditions for maximum entrapment (95.7%) were 9.022% lipid, 1.75% surfactant, and 0.75% drug.

ZETA POTENTIAL AND PDI

The zeta potential was observed between -17.3 to -25.2, representing the formulations' stability. The optimized batch's zeta potential is shown in. PDI was found to be decreased by increasing the surfactant concentration. In contrast, an increase in the drug and lipid concentration increase the PDI.

Table 4 : Zeta potential and PDI of all the formulations (Cur-SLN)

Formulation	PDI	Zeta potential (mV)
F1	0.071	-17.3
F2	0.168	-21.1
F3	0.072	-17.9
F4	0.071	-23.9
F5	0.072	-17.6
F6	0.282	-14.8
F7	0.325	-22.1
F8	0.167	-25.2
F9	0.077	-24.4
F10	0.073	-17.9
F11	0.069	-17.4
F12	0.247	-21.0
F13	0.180	-18.2
F14	0.265	-17.6
F15	0.170	-22.4
F16	0.308	-23.5
F17	0.179	-16.2
F18	0.064	-23.7

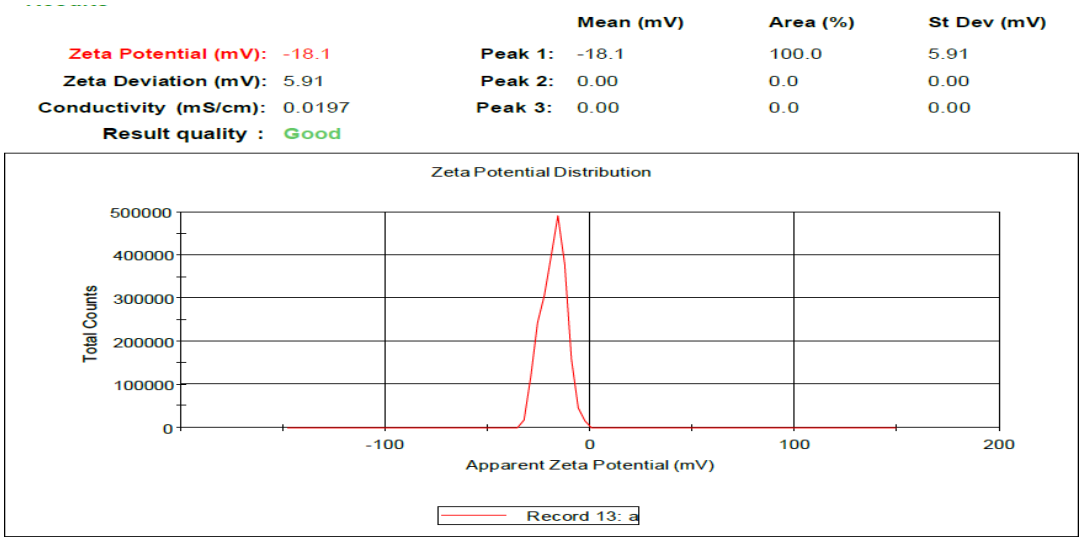


Figure 3 : Zeta potential of optimized Cur-SL

CHARACTERIZATION OF OPTIMIZED FORMULATION

In-vitro release study

The drug release study was conducted over 24 hrs. The plain drug suspension released 79.81% of the drug in 24 hrs. In contrast, 20 % burst release of the drug was observed in the first 2 hrs from the optimized formulation, followed by the sustained release of up to 65.78% in 24 hrs (figure 4).

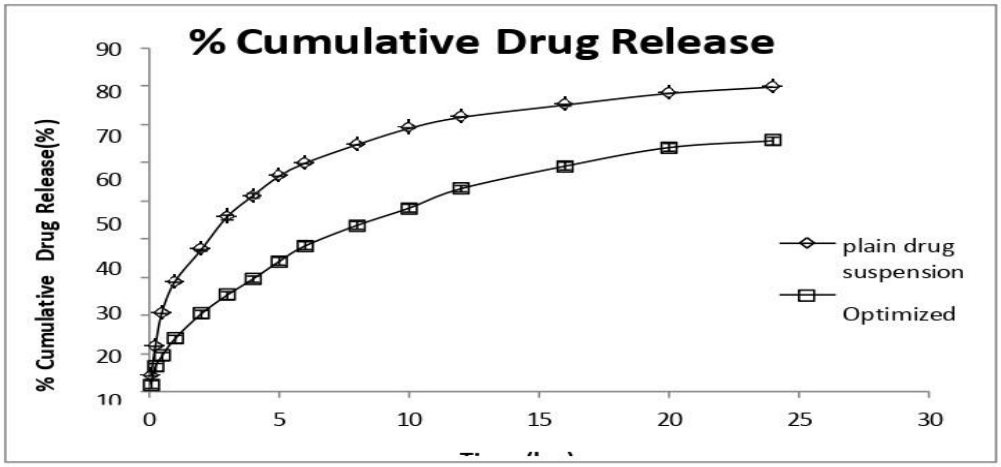


Figure 4: In-vitro release of free drug and optimized Cur-SLN

DRUG RELEASE KINETICS

In the release kinetics study, the *in-vitro* drug release data was fitted into Zero-order First-order Higuchi kinetics and Korsmeyer- peppas model. The maximum value of the correlation coefficient (R^2=0.9895) was observed in the Higuchi model, which shows that the optimized batch's release kinetics followed the Higuchi model.

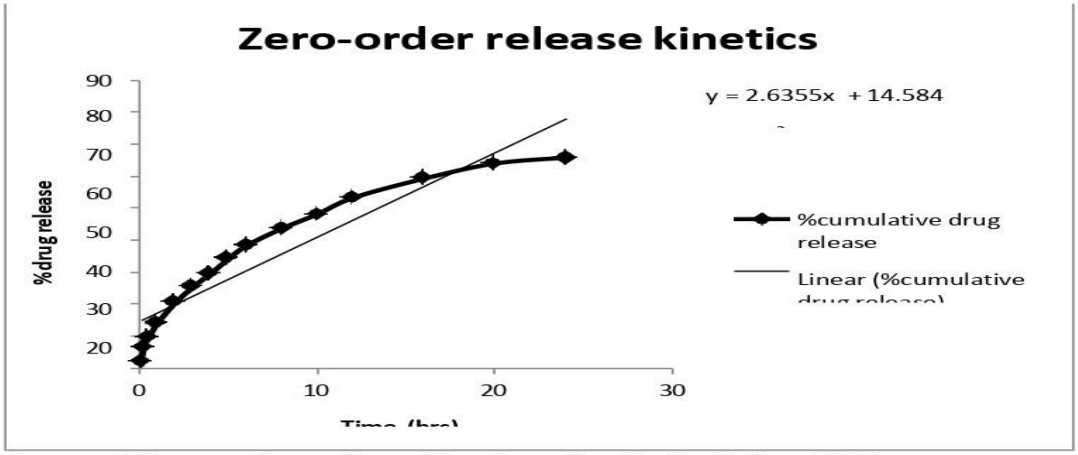


Figure :5 Zero-order release kinetics of optimized Cur-SLN

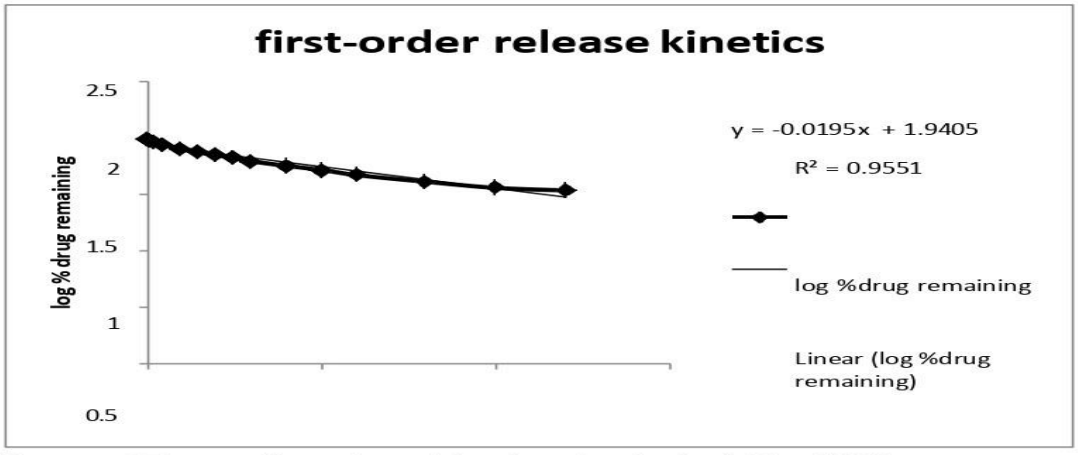


Figure : 6 First-order release kinetics of optimized Cur-SLN

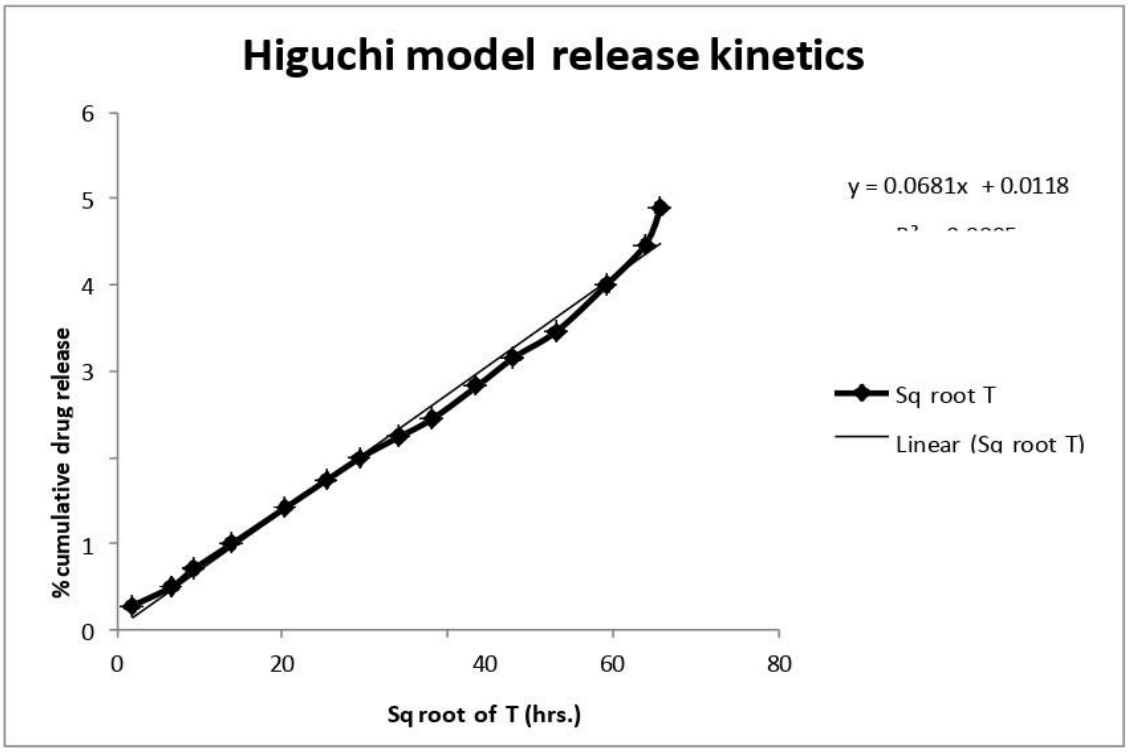


Figure : 7 Higuchi model release kinetics of optimized Cur-SLN

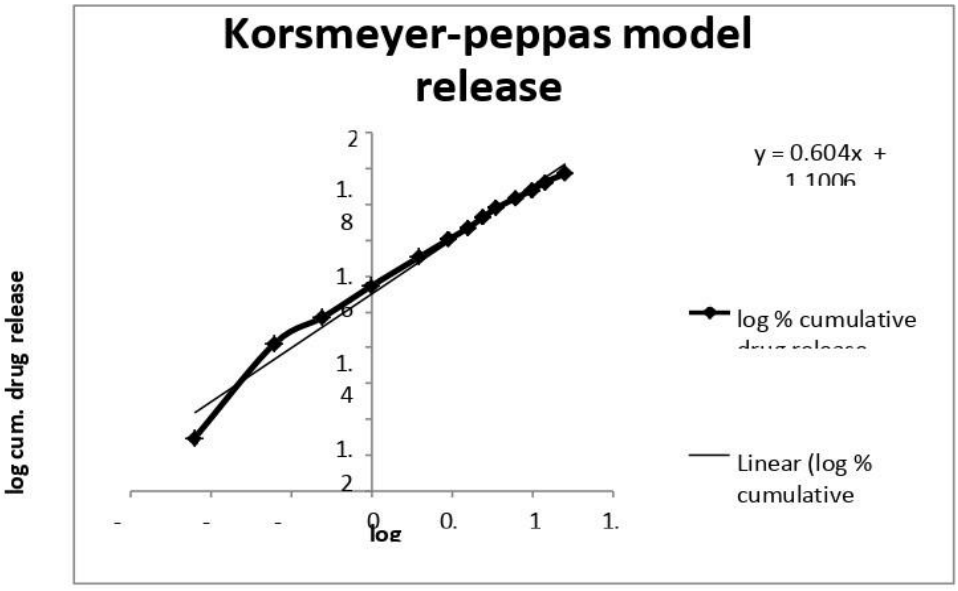


Figure :8 Korsmeyer-peppas model release kinetics of optimized Cur-SLN

CHARACTERIZATION OF OPTIMIZED FORMULATION IN-VITRO RELEASE STUDY

The plain drug suspension shows 85.50 % release in 24 hrs. Burst release of 27 % drug was observed in the first 2 hrs from the optimized formulation followed by the sustained release of 71.04% up to 24 hrs .

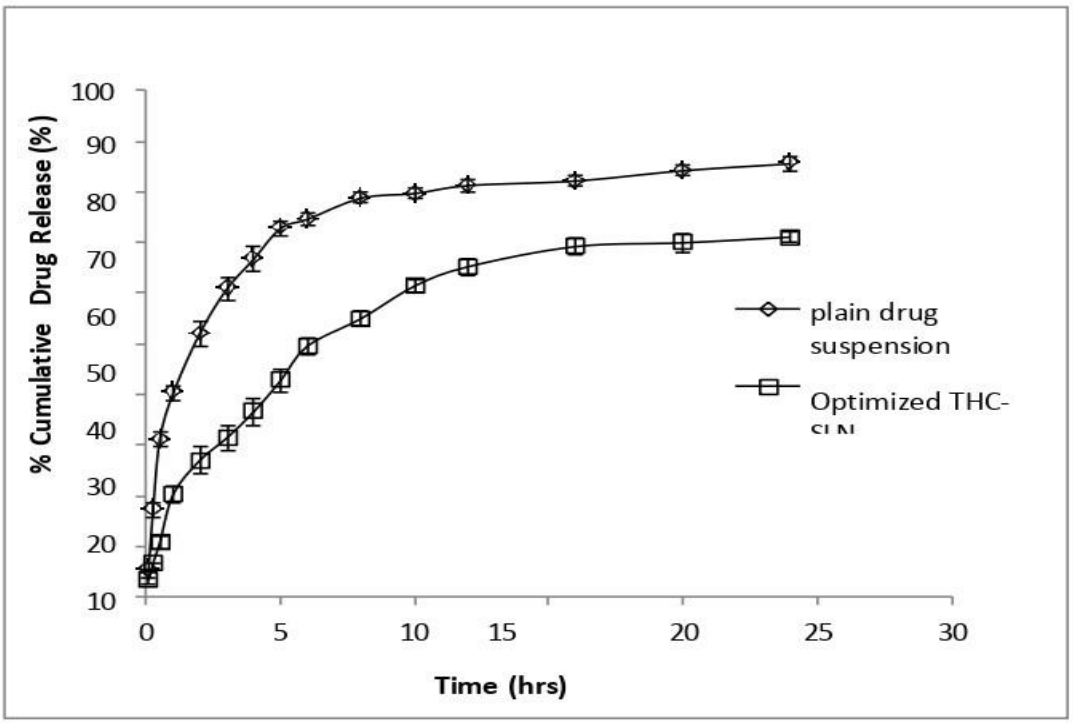


Figure : 9 In-vitro release of free drug and optimized batch

DRUG RELEASE KINETICS

In the release kinetics study, the in-vitro drug release data were fitted into zero-order first-order order higuchi kinetics order and korsmeyer-peppas model order The highest value of the correlation coefficient (R2=0.9883) was observed for the korsmeyer-peppas model, so the drug release kinetics of optimized batch followed the Korsmeyer-peppas model.

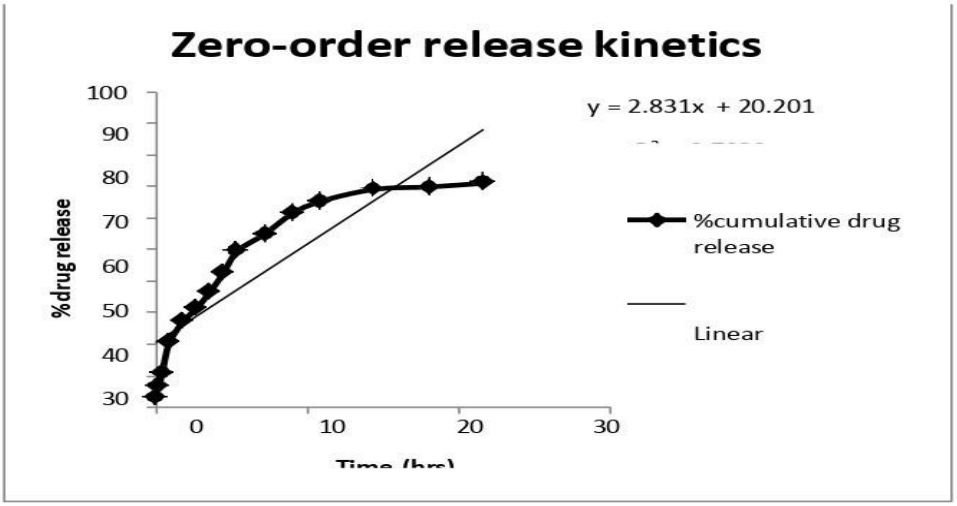


Figure : 10 Zero-order release kinetics of optimized THC-SLN

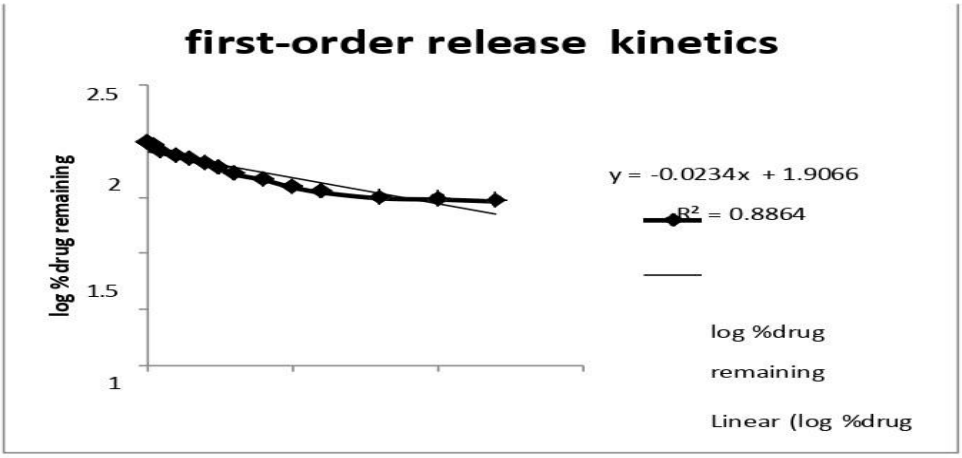


Figure :11 First-order release kinetics of optimized THC-SLN

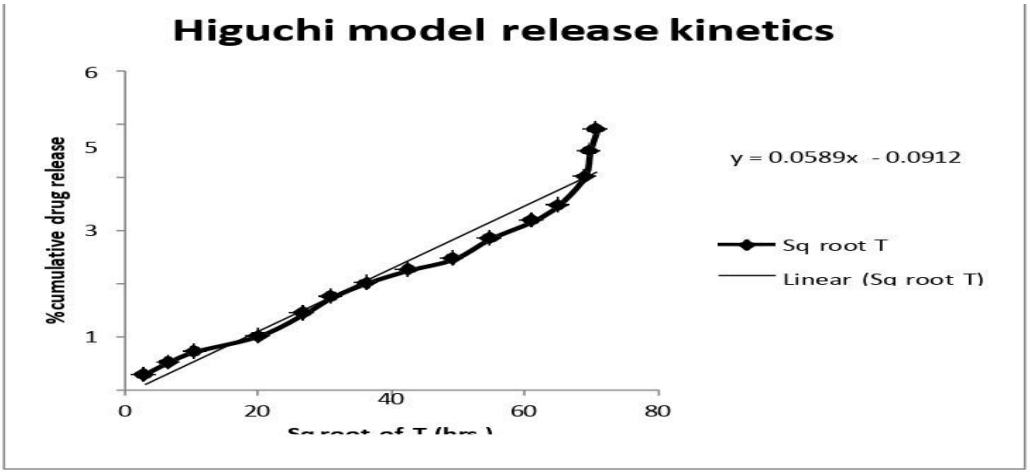


Figure :12 Higuchi model release kinetics of optimized THC-SLN

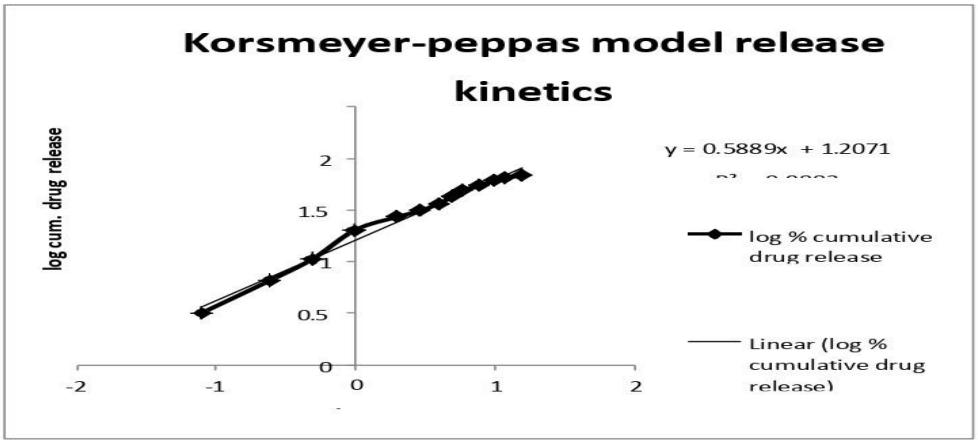


Figure: 13 Korsmeyer-peppas release kinetics of optimized THC-S

Pharmacokinetic studies

The comparative pharmacokinetics of the optimized Cur-SLN and plain drug suspension after oral administration is shown in figure 14. Various pharmacokinetics parameters such as C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, K_{el}, $t_{1/2}$, V_d, and Cl were calculated using plasma concentration versus time profile; . A significant was observed in the t_{max} and half-life of optimized Cur- SLN compared to a plain drug suspension. The clearance and volume of distribution (V_d) of the optimized formulation were lower than plain drug suspension with an extremely significant p-value. C_{max} and $AUC_{(0-24)}$ obtained using plasma drug concentration/time curve of optimized Cur-SLN were found to be 5.21 and 7.34 fold higher ($p < 0.01$) than the plain drug suspension. The relative bioavailability (F) of optimized Cur-SLN was found 734 %.

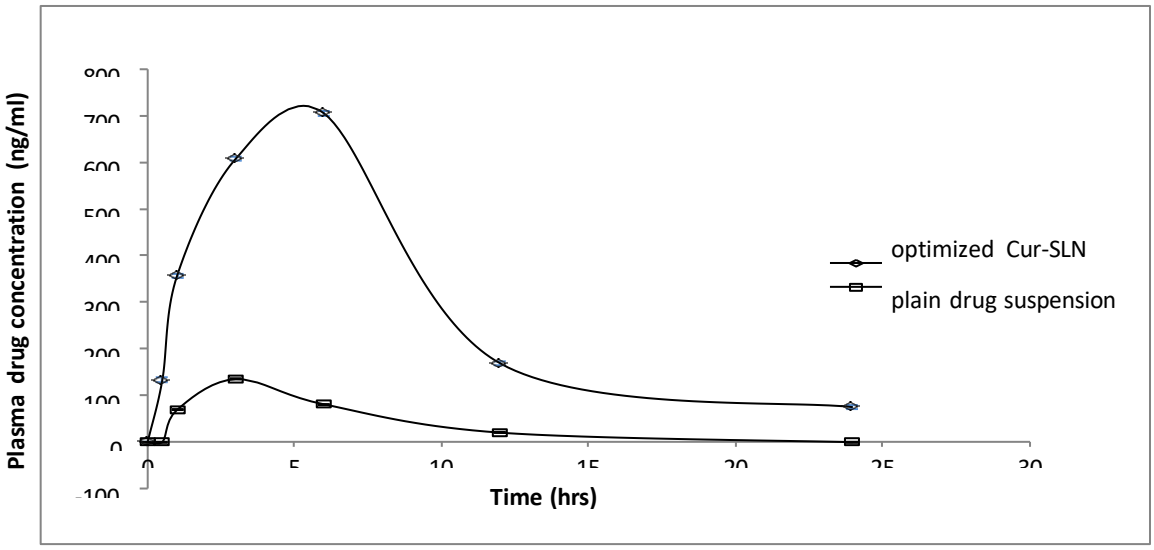


figure : 14 Comparative pharmacokinetics study of plain drug suspension and optimized Cur-SL

Table 5: Comparative results of pharmacokinetics parameters of optimized Cur-SLN and plain drug suspension

Pharmacokinetic parameter	Optimized Cur-SLN*	Plain drug suspension*
C_{max})(ng/ml)	704.43±49.98***	135.35±24.17
$AUC_{(0-t)}$(ng/ml*h)	7165.70±313.25***	975.606±119.18
$AUC_{(0-inf)}$(ng/ml*h)	8376.123±392.3***	1155.055±168.83
t_{max}(hrs)	6±0.00	3±0.00
$K_{el}(h^{-1})$	0.06196±0.003	0.115±0.001
$t_{1/2}$(hrs)	11.18±1.91**	6.01±1.33
V_d (L)	245.24±18.77***	748.96±44.89
Cl (L/h)	15.19±3.15***	86.22±6.54
F	734%	-

*values are expressed as Mean±S.D. Unpaired T-test, and ***p<0.001, **p<0.01, and *p<0.05 justify the significance

PHARMACODYNAMIC STUDIES

EFFECT OF OPTIMIZED CUR-SLN ON DIABETES MELLITUS

All the groups of rats except group 1 were given an STZ dose (60 mg/kg) to induce diabetes. The mean fasting blood glucose levels of blood samples taken at 0, 7, 14, 21, and 28 days were calculated for all the experimental groups; data is shown in table STZ successfully induced diabetes in animals, with fasting glucose levels >200 mg/dl when significantly ($p<0.001$) than non-diabetic control. Group I (Non-diabetic control), treated with blank SLN, was

observed with a stable mean blood glucose level throughout the study. By the end of study group II (Diabetic control- STZ (60 mg/kg)), animals were fully diabetic with a mean blood glucose level of 309.4±3.528 at a significance of ($p<0.001$) compared to non-diabetic control. A significant reduction in mean blood glucose level (from 234.2±7.621 mg/dl to 141.8±4.290 mg/dl) was observed in Group III animals (pure drug suspension) than inthe diabetic control group. Curcumin reduced the blood glucose level up to 40% by the end of the 28th day. A significant change ($p<0.001$) in mean blood glucose level (272.0±2.795mg/dl - 106.4±6.908mg/dl) was observed in the animals of Group IV (optimized formulation Cur-SLN) compared to diabetic control animals (group II), and animals received pure drug suspension (group III). The optimized Cur-SLN reduced the blood glucose level by 60 % by the end of the 28th day. The mean blood glucose level of group IV animals was almost similar to non-diabetic control animals by the 21st day.

Table 6: Mean Blood Glucose Level (mg/dl) in experimental groups during the pharmacodynamics study (optimized Cur-SLN)

S. No.	Treatment	BLOOD GLUCOSE LEVEL (mg/dl)				
		0 Day	7 Day	14 Day	21 Day	28 Day
1	Group I (Non-diabetic control)	104.1±2.433	109.7±4.439	107.1±3.548	111.0±4.306	109.4±2.835
2	Group II (Diabetic control- STZ (60 mg/kg))	294.1±3.599***	299.7±4.751	304.1±4.404	307.0±4.410	309.4±3.528***
3	Group III (STZ (60 mg/kg) + Pure Drug Suspension)	234.2±7.621***	221.6±5.520***	175.8±4.209***	164.2±4.958***	141.8±4.290***
4	Group IV (STZ (60mg/kg) + optimized Cur-SLN)	272.0±2.795***	184.3±5.236***	127.4±5.095***	112.2±6.831***	106.4±6.908***

Values are expressed as Mean±SD (n=6), One-way ANOVA followed by Bonferroni test, and ***p<0.001, **p<0.01, and *p<0.05 justify the significance

EFFECT OF OPTIMIZED CUR-SLN ON BODY WEIGHT

The changes in body weight after 28 days of treatment are shown in table 7. No difference was observed in the bodyweight of non-diabetic control animals. At the same time, body weight was drastically decreased in diabetic control animals and found significant compared to non-diabetic control ($p<0.001$). Compared to diabetic control, the pure drug suspension and optimized Cur-SLN significantly ($p<0.001$) increased the body weight. The body weight of animals receiving optimized Cur- SLN was more improved than pure curcumin suspension after 28 days of treatment with a significance level of $p < 0.05$.

Table 7 : Body weight (gm) in experimental groups during the pharmacodynamic study (optimized Cur-SLN)

S. No.	Treatment	Body Weight (gm)	
		Initial	Final
1	Group I (Non-diabetic control)	198.4±5.553	201.9±7.865
2	Group II (Diabetic control- STZ (60 mg/kg))	220.5±9.950	172.8±8.221***
3	Group III (STZ (60 mg/kg) + Pure Drug Suspension)	201.0±3.367	209.5±8.426***
4	Group IV (STZ (60 mg/kg) + Optimized Cur-SLN)	206.8±5.315	225.0±5.888***

Values are expressed as Mean±SD (n=6), One-way ANOVA followed by Bonferroni test, and ***p<0.001, **p<0.01, and *p<0.05 justify the significance

STABILITY STUDIES

The data for the stability studies over six months period. During this period, no changes were observed in the physical appearance of the Cur-SLN, while a slight decrease was observed in % entrapment efficiency at both temperature conditions. The optimized formulation particle size changed from 119.7 to 120.8 nm at 25ºC ± 2ºC/60% ± 5% RH and from 119.7 nm to 125.9 nm at accelerated conditions after 180 days of storage.

Table 8: Stability profile of optimized Cur-SLN over six months

		25°C ± 2°C/60% ± 5% RH			40°C ± 2°C/75% ± 5% RH		
S. No.	Time (Days)	Physical Appearance	Entrapment Efficiency ± SD (%)*	Particle Size (nm)	Physical Appearance	Entrapment Efficiency ± SD (%)*	Particle Size (nm)
1.	0	Yellow-colored suspension throughout the study	81.93±0.974	119.7	Yellow- colored suspension throughout the study	81.93±0.974	119.7
2.	30		81.67±1.65	119.7		80.95±1.78	119.9
3.	60		81.20±1.12	120.2		79.60±1.45	120.6
4.	90		80.88±1.32	120.2		79.35±1.63	123.4
5.	180		80.45±1.72	120.8		78.93±1.22	125.9

*Values are expressed as Mean±SD

CONCLUSION:

This study aimed to improve curcumin's bioavailability and anti-diabetic efficacy by developing a solid lipid nanoparticle (SLN) oral delivery system. Curcumin's poor solubility and bioavailability limit its effectiveness in managing diabetes. Despite curcumin's natural anti-diabetic potential, its effectiveness is hindered by its poor solubility and bioavailability. In the SLN preparation, the stabilizer concentration (1%), sonication time, and sonication amplitude were maintained constant. The independent variables, including drug concentration, lipid concentration, and surfactant concentration, were analyzed using ANOVA to determine the optimal values for dependent variables such as particle size and percentage entrapment efficiency. The model demonstrated significance for both particle size and entrapment efficiency, as indicated by the F-value and P-value. The polynomial equation and response surface plots revealed that particle size increases with higher lipid and drug concentrations, while it decreases with an increase in surfactant concentration. Conversely, the percentage entrapment efficiency was found to increase with higher lipid concentration, with a slight enhancement in entrapment efficiency also noted.

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