FORMULATION AND EVALUATION OF SILYMARIN-LOADED SODIUM ALGINATE NANOPARTICLES FOR ENHANCED ORAL DELIVERY

M. Magesh kumar*, A. Vasanthan[1]

M. Magesh kumar, Department of Pharmaceutics, Sri Vijay Vidyalaya College of Pharmacy, Dharmapuri - 636 807, Tamilnadu, India

A. Vasanthan, Department of Pharmaceutics, Sri Vijay Vidyalaya College of Pharmacy, Dharmapuri - 636 807, Tamilnadu, India

*Address correspondence to
M. Magesh kumar
Department of Pharmaceutics,
Sri Vijay Vidyalaya College of Pharmacy,
Dharmapuri - 636 807, Tamilnadu, India
Email Id: kumarmagesh162@gmail.com
Phone: 8310316775

ABSTRACT

This study focuses on the formulation and evaluation of silymarin-loaded sodium alginate nanoparticles to enhance the oral bioavailability of silymarin, a hepatoprotective natural compound limited by poor water solubility and low absorption. Nanoparticles were prepared using the solvent desolvation method while varying stirring speeds to optimize critical parameters such as particle size, entrapment efficiency, and polydispersity index (PDI). The optimized formulation achieved a mean particle size of 150 ± 0.32 nm, high entrapment efficiency of 86.65 ± 0.65%, and a PDI of 0.103 ± 0.12, indicating excellent uniformity and stability. FTIR studies confirmed compatibility between drug and polymer. The zeta potential of −34.87 ± 0.67 mV ensured colloidal stability by preventing aggregation. In vitro drug release studies demonstrated a significantly improved dissolution profile, with ~89% cumulative release over 12 hours compared to 49.22% for the pure drug, featuring an initial burst followed by sustained release. Kinetic modeling indicated that the Korsmeyer-Peppas model best described the release behavior, suggesting super case II transport. These findings highlight the ability of sodium alginate nanoparticles to protect silymarin from gastrointestinal degradation, improve solubility, and sustain drug release, ultimately enhancing its oral bioavailability. Overall, this nanoparticulate delivery system offers a promising strategy for overcoming the limitations of silymarin's pharmacokinetics, providing a safer and more effective approach for hepatoprotection and supporting its potential use in managing liver disorders.

KEY WORDS: Silymarin, Sodium Alginate, Nanoparticles, Oral Bioavailability

INTRODUCTION

Oral bioavailability is the fraction of an orally administered drug that reaches the systemic circulation in its active form. Typically, it is stated as a percentage of the dose that was given. It shows how quickly and to what degree the active component is absorbed and made available at the site of action [1].

Many drugs exhibit poor oral bioavailability due to factors such as low aqueous solubility, poor permeability, chemical instability in the gastrointestinal tract, and extensive first-pass metabolism. To achieve therapeutic efficacy at lower doses, decrease dosing frequency, minimize patient response variability, increase patient compliance, and cut total treatment costs, oral bioavailability must be improved [2,3].

To overcome these issues, novel drug delivery systems such as nanoparticles, liposomes, phytosomes, solid lipid nanoparticles, nano emulsions, and self-emulsifying drug delivery systems (SEDDS) are being extensively explored. In order to greatly increase the therapeutic efficiency of natural substances, these systems seek to improve permeability, increase solubility, prevent enzymatic degradation, and accomplish targeted delivery to the liver [4,5].

Nanoparticle-based drug delivery systems have emerged as a transformative approach in the treatment of hepatic disorders. Therapeutic drugs' solubility, stability, and bioavailability can all be increased by utilizing nanoscale carriers [6,7].

Moreover, nanoparticles can offer targeted delivery to hepatic tissues, sustained drug release, and reduced systemic toxicity. Specifically, polymeric offers a secure and efficient framework for creating treatments that preserve the liver. There is great potential for improving liver protection and encouraging the regeneration of injured hepatocytes by the encapsulation of herbal bioactive in nanoparticulate systems [8,9].

AIM AND OBJECTIVE

To formulate and evaluate sodium alginate nanoparticles loaded with silymarin in order to improve the drug's oral bioavailability.

- To formulate silymarin-loaded sodium alginate nanoparticles for enhanced oral bioavailability and hepatoprotective efficacy
- To carry out formulation optimization studies.
- To carry out an evaluation study for prepared nanoparticles, such as particle size, drug entrapment efficiency, zeta potential, in vitro drug release studies, and in vitro drug release kinetic studies.

DRUG AND POLYMER PROFILE

SILYMARIN

Silymarin is an active ingredient derived from the Asteraceae family plant Silybum marianum, also referred to as milk thistle. Silymarin flavonolignan, which includes silydianin, silychristin, silybin A and B, and iso silybin A and B, makes up about 70–80% of plants. Silymarin is used as an adjuvant therapy for cirrhosis, jaundice, hepatitis, and liver illnesses associated with alcohol. It has also been shown to have anticancer properties.

SODIUM ALGINATE

Sodium alginate is extracted from brown seaweed (e.g., *Laminaria*, *Macrocystis*) and it is also known as algin, alginic acid sodium salt. It is Non-toxic, bioadhesive, mucoadhesive, mild gelation conditions and easy chemical modification. Widely used in drug delivery (e.g., nanoparticles, beads, gels), wound healing, food industry, and tissue engineering.

METHODOLOGY

PRE-FORMULATION STUDIES

Physical characteristics

By visual examination, the drug was tested for its physical characteristics like colour, odour and texture.

Solubility test

The drug Silymarin powder (10mg) was taken in a test tube, and solubility in ethanol, methanol, chloroform, dichloromethane and water was tested.

Analytical estimation of drug content

Preparation of stock solution

The standard stock solution of silymarin was prepared by accurately weighing 100mg of silymarin was dissolving it in 100 ml of ethanol to make 1000 µg/ml. The standard stock solution was scanned in the range of 200 to 400nm in a UV spectrophotometer [10].

Construction of the calibration curve of silymarin

From the standard stock solution of silymarin 0, 2, 4, 6, 8, 10. 12, 14, 16, and 4ml were withdrawn to a 10ml volumetric flask and made up to volume with phosphate buffer pH 7.4 to get the concentration range of 2-16ug/ml. the absorbance of this solution was measured at 288nm using a UV-visible spectrometer. phosphate buffer pH 7.4 was used as blank. The calibration curve was plotted between concentration and absorbance.

Formulation of silymarin-loaded sodium alginate nanoparticles by desolvation method

Sodium alginate was dissolved in 10 ml of distilled water. Silymarin dissolved in 10 ml of ethanol. combine the silymarin and sodium alginate solution, and the pH level was adjusted to four. Under continuous stirring, 10 ml of ethanol was added dropwise to the silymarin-sodium alginate solution. The endpoint was determined by the appearance of turbidity in the solution. 2% sodium tripolyphosphate was then added. For 12 h, the stirring was maintained to allow the nanoparticles to cross-link. Centrifuging the generated solution for 30 minutes, discarding the supernatant solution, and collecting the precipitate, which was dried in room temperature and stored in the refrigerator for subsequent evaluation [11].

Drug excipient compatibility study

FTIR studies were carried to study the presence of functional groups on the synthesized nanoparticles. The Fourier transform infrared (FTIR) spectra of synthesized nanoparticles were measured by a thermos shimadzu FTIR spectrometer with the KBR pellet technique ranging from 4000 cm^{-1} to 400 cm^{-1} [12].

Determination of particle size

The particle size and particle size distribution of the prepared nanoparticles were determined using a Malvern particle size analyzer (e.g., Malvern Zetasizer Nano series, Malvern Instruments Ltd., UK). The analysis was performed at a controlled temperature of 25 °C [13].

Determination of zeta potential

The zeta potential of the nanoparticle suspension was measured using a Malvern Zetasizer. The sample was diluted with an appropriate electrolyte solution to ensure suitable conductivity. Approximately 1 mL of the diluted sample was filled into a disposable zeta cell. Measurements were performed at 25 °C, and the instrument software calculated the electrophoretic mobility and converted it to zeta potential using the Smoluchowski equation [14].

Determination of drug entrapment efficiency

The entrapment efficiency of the silymarin in the nanoparticle is determined by the separation of drug from the supernatant liquid containing non-associated drug obtained after centrifugation. Drug content measured by using UV spectrometry [11]. To calculate the drug entrapment efficiency, the following formula was applied,

$$\mathrm{DEE\%} = \frac{\text{Total amount of silymarin used} - \text{Amount of free silymarin}}{\text{Total amount of silymarin used}} \times 100$$

***In vitro* drug release study**

The *in vitro* drug release study of the prepared nanoparticles was carried out using the Type II (paddle) dissolution apparatus. Pure drug suspension, optimized nanoparticles, were placed in dialysis bags and placed in a dissolution vessel. The dissolution medium consisted of 900 mL of phosphate buffer (pH 7.4) maintained at a temperature of 37 ± 0.5 °C to mimic physiological conditions. The paddle was rotated at a constant speed of 50 rpm to ensure uniform mixing. At predetermined time intervals. 10 mL aliquots of the dissolution medium were withdrawn using a syringe fitted with a 0.45 µm filter to remove undissolved particles. The withdrawn volume was immediately replaced with an equal volume of fresh dissolution medium pre-warmed to 37 °C to maintain sink conditions. The collected samples were analyzed using a UV-Visible spectrophotometer at the drug's maximum absorbance wavelength (288 nm), and the cumulative percentage of drug release was calculated [11].

***In vitro* drug release kinetics**

In order to understand the mechanism of drug release, *in vitro* drug release data were used to kinetic models such as zero order, first order and Higuchi model, and Korsmeyer-Peppas model [15].

Zero order

This model can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms. The dosage forms following this profile release the same amount of drug by unit of time and this model can be expressed as,

$$Qt = Qo + Kt$$

Qt= amount of drug dissolved in time

"t" Qo=initial amount of drug in the solution

K= Zero order release constant

First order

The pharmaceutical dosage forms following this dissolution profile, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish. The following relation can be used to express this model,

$$\log Qt = \log Qo + Kt / 2.303$$

Qt- amount of drug dissolved in time "t"

Qo- initial amount of drug in the solution

Kt = first order release constant

Higuchi model

This model helps to study the release mechanism of water-soluble and less water-soluble drugs incorporated in semi-solid and solid matrixes. The mathematical expression for drug release is,

$$Q = [\, D\,(2C-Cs)\, Cs.t\,]^{1/2}$$

Whereas,

Q - cumulative % of drug released in time in time

"t"- per unit area.

C - Initial drug concentration

C - Drug solubility in the matrix media

D- diffusion coefficient. Assuming that diffusion co-efficient and other parameter remain constant during release, the above equation reduces to,

$$Q = Kt/2.$$

Thus, for diffusion-controlled release mechanism, a plot of cumulative % of drug released vs square root of time should be linear. The linearity of the plots can be checked by carrying out linear regression analysis and determination of regression co efficient of the plot.

Korsmeyer-peppa's model

To verify the fact that whether the diffusion follows ficks law or not, the drug release data can also plotted against log time according to peppa's equation. The drug release can be expressed as,

$$Q= K\,t\,n$$

Taking the log on both sides of the equation

$$\text{Log } Q= \text{Log } k+ n \log t$$

Whereas,
Q is the cumulative % drug release
t is the time
n is the slope of the linear plot of log Q vs log t
The n^0 value can be used to characterize the diffusional release mechanism, and the data is given in Table 1.

Table 1: Diffusion exponent and Diffusion mechanism

Diffusion exponent (n)	Diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Non fickian diffusion
0.89	Case 2 transport
Higher than 0.89	Super case 2 transport

RESULT AND DISCUSSION

Physical characteristics

The physical characteristics of colour, odour, and texture of silymarin were carried out, and it is a light yellow coloured powder in appearance, odourless, and crystalline.

Solubility

A solubility test for silymarin was carried out in different solvents, such as ethanol, methanol, chloroform, dichloromethane, water, and the results are given in Table 2.

Table 2: Solubility test of silymarin in various solvents

SI. No	Solvent	Soluble	Sparingly Soluble	Insoluble
1	Ethanol	Soluble	Not sparingly Soluble	Insoluble
2	Methanol	Soluble	Not sparingly Soluble	Insoluble
3	Chloroform	Not soluble	Sparingly soluble	Insoluble
4	Dichloromethane	Soluble	Not sparingly Soluble	Insoluble
5	Water	Not soluble	Not sparingly Soluble	Insoluble

Analytical estimation of drug content

The silymarin stock solution of 100 µg/ml was prepared and the UV-Visible absorption spectra for the sample were taken in the range of 200-400nm for λmax using double-beam UV spectrophotometer. The maximum absorption of silymarin was found to be at 288nm.

Construction of a calibration curve of silymarin

Linearity was obtained between 2-16 µg/ml concentration of silymarin, and the regression value (R^2) was found to be 0.9999. That obeys Beer Lambert's law at the concentration between 2-16 µg/ml and its selected for drug quantification studies.

Table 3: Concentration and absorbance for the calibration curve of silymarin at 288nm.

Concentration (µg/ml)	Absorbance at 288 nm
2	0.1022
4	0.2031
6	0.3033
8	0.4042
10	0.5041
12	0.6095
14	0.7019
16	0.8018

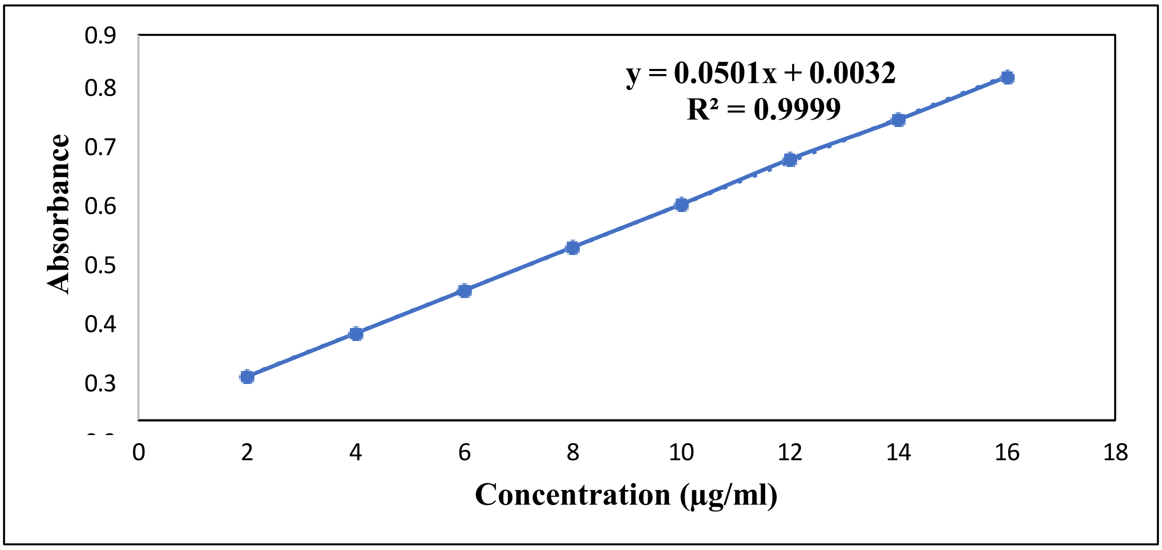

Figure 1: Calibration graph of silymarin

Formulation of silymarin-loaded sodium alginate nanoparticles by the solvent desolvation method

Silymarin-loaded sodium alginate nanoparticles were successfully formulated using the solvent desolvation technique, a robust and widely applied method for producing polymeric nanoparticles with controlled properties. In this study, a total of five formulations (F1–F5) were systematically developed employing the One Variable at a Time (OVAT) approach to isolate and understand the influence of stirring speed on critical nanoparticle characteristics. Importantly, the drug, polymer quantity, and cross-linker concentration were maintained constant across all batches to ensure that the observed variations in nanoparticle properties were solely attributable to changes in stirring speed.

The rationale for selecting stirring speed as the independent variable is grounded in its well-documented and significant impact on particle size, drug entrapment efficiency, and polydispersity index (PDI). Higher stirring speeds typically generate greater shear forces and improved mixing, promoting the formation of smaller, more uniform nanoparticles with potentially enhanced drug encapsulation. Conversely, lower speeds may lead to larger particle sizes with broader size distributions due to insufficient mixing energy. By systematically varying stirring speed while controlling other formulation parameters, this study aims to optimize the preparation conditions for silymarin-loaded sodium alginate nanoparticles to achieve desirable physicochemical characteristics suitable for improved oral delivery.

Table 4: Composition table for the formulation of silymarin loaded sodium alginate nanoparticles

Formulation Code	Drug (mg)	Sodium Alginate (mg)	Sodium tripolyphosphate (%)	Stirring Speed (rpm)
F1	140	100	0.1	400
F2	140	100	0.1	600
F3	140	100	0.1	800
F4	140	100	0.1	900
F5	140	100	0.1	1000

Formulation optimization by the OVAT approach

Five formulations (F1–F5) of silymarin-loaded sodium alginate nanoparticles were prepared using the solvent desolvation method, maintaining constant concentrations of drug, polymer, and cross-linker across all batches. The findings indicated that increasing the stirring speed resulted in reduced particle size, enhanced drug entrapment efficiency, and a lower polydispersity index (PDI).

Among these, formulation F5 was selected as the optimized formulation due to its desirable particle size, high entrapment efficiency, and low PDI. The optimized formulation was further characterized for drug–polymer compatibility, zeta potential, and *in vitro* drug release profile.

Table 5: Observed outcomes for F1 to F5

Formulations	Particle Size (nm)	Drug entrapment efficiency	PDI
F1	550± 0.76	50± 0.32	0.787± 0.23
F2	400± 0.89	61± 1.08	0.643± 0.57
F3	300± 1.03	68± 0.34	0.532± 0.47
F4	250± 0.45	74± 0.76	0.321± 0.23
F5	150± 0.32	86.65±0.65	0.103± 0.12

Drug–polymer compatibility study

Drug polymer compatibility was assessed by using the FTIR method.

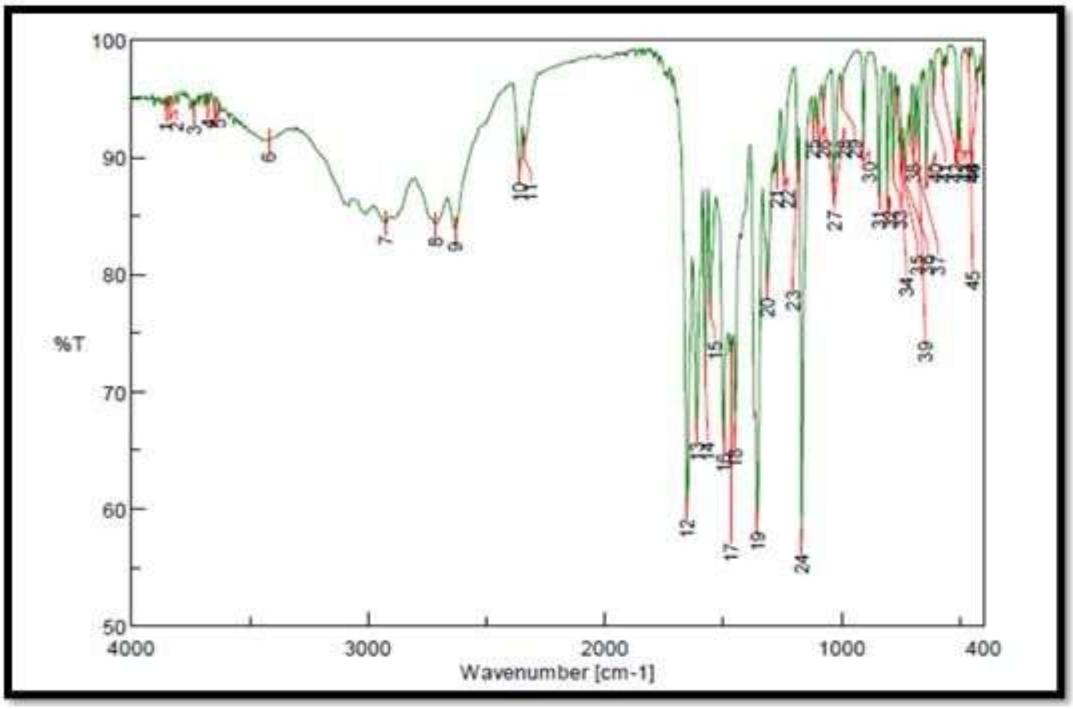

Figure 2: FTIR spectrum of pure drug

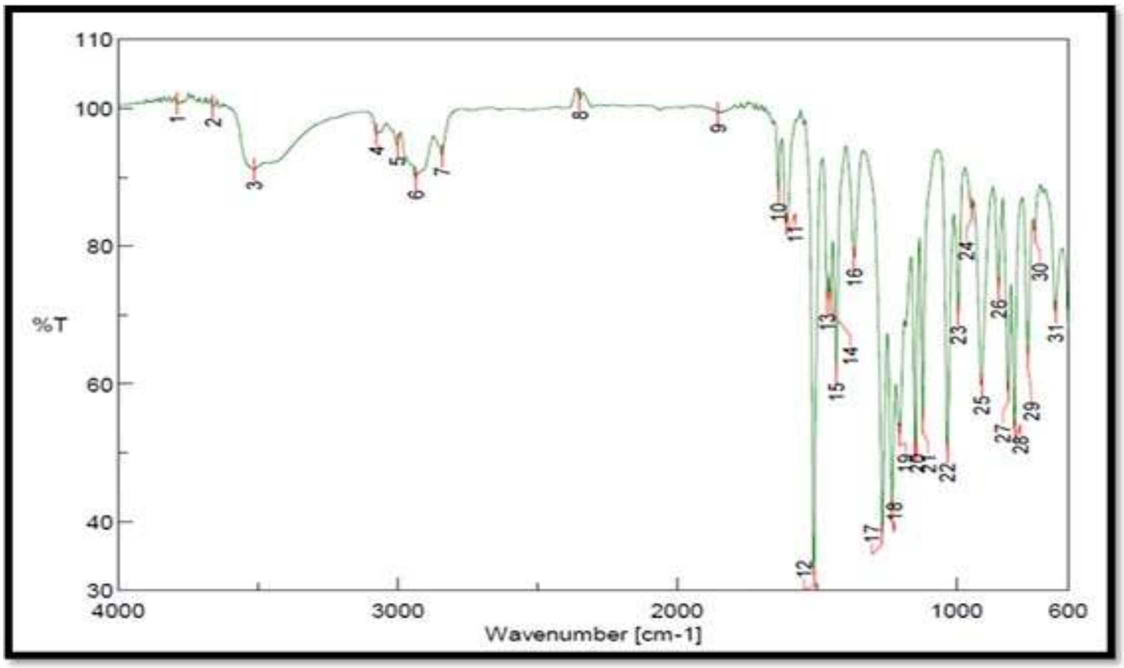

Figure 3: FTIR spectrum of sodium alginate

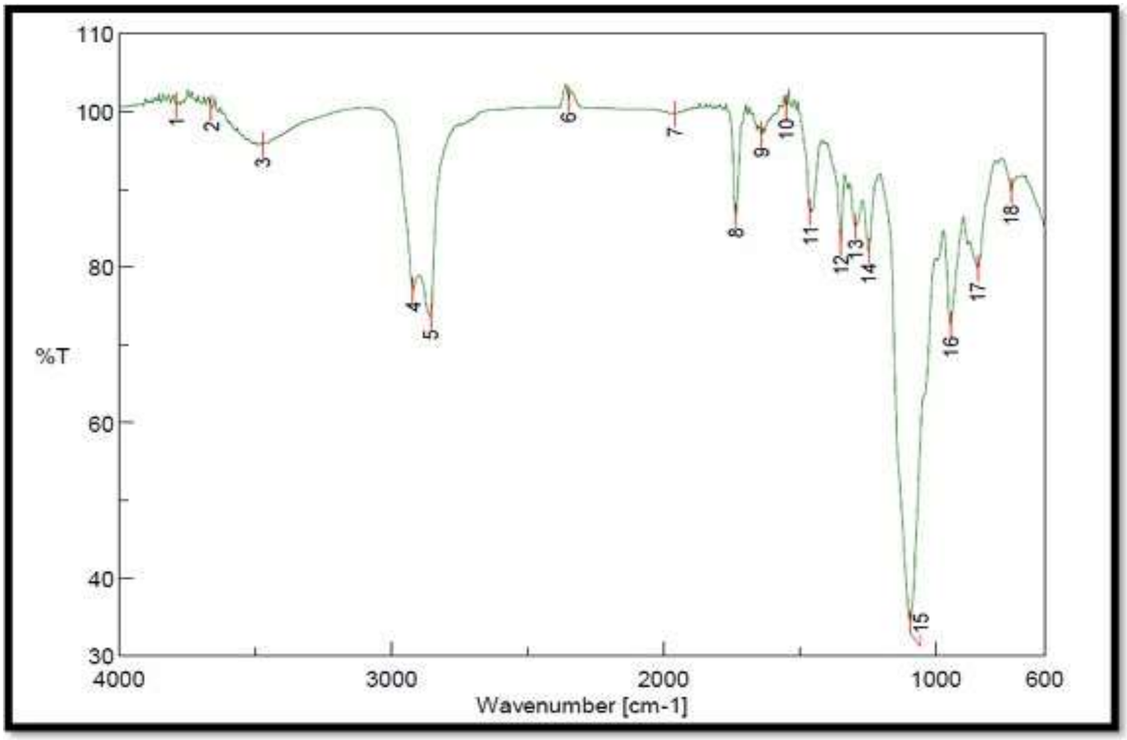

Figure 4: FTIR spectrum of optimized nanoparticle

The FTIR spectrum of the optimized formulation showed the characteristic peaks of pure drug, sodium alginate, and its functional groups. This finding reveals that drug-polymer are compatible.

Determination of particle size

The optimized silymarin-loaded sodium alginate nanoparticles with 150.32 ± 0.32 nm size can significantly enhance oral bioavailability. Their small size increases surface area for dissolution, improves mucosal adhesion, and facilitates better intestinal absorption. The alginate matrix protects silymarin from degradation and enables controlled release, leading to sustained plasma levels and reduced first-pass metabolism. Overall, this nanoformulation offers an effective strategy to improve the oral delivery of poorly soluble silymarin.

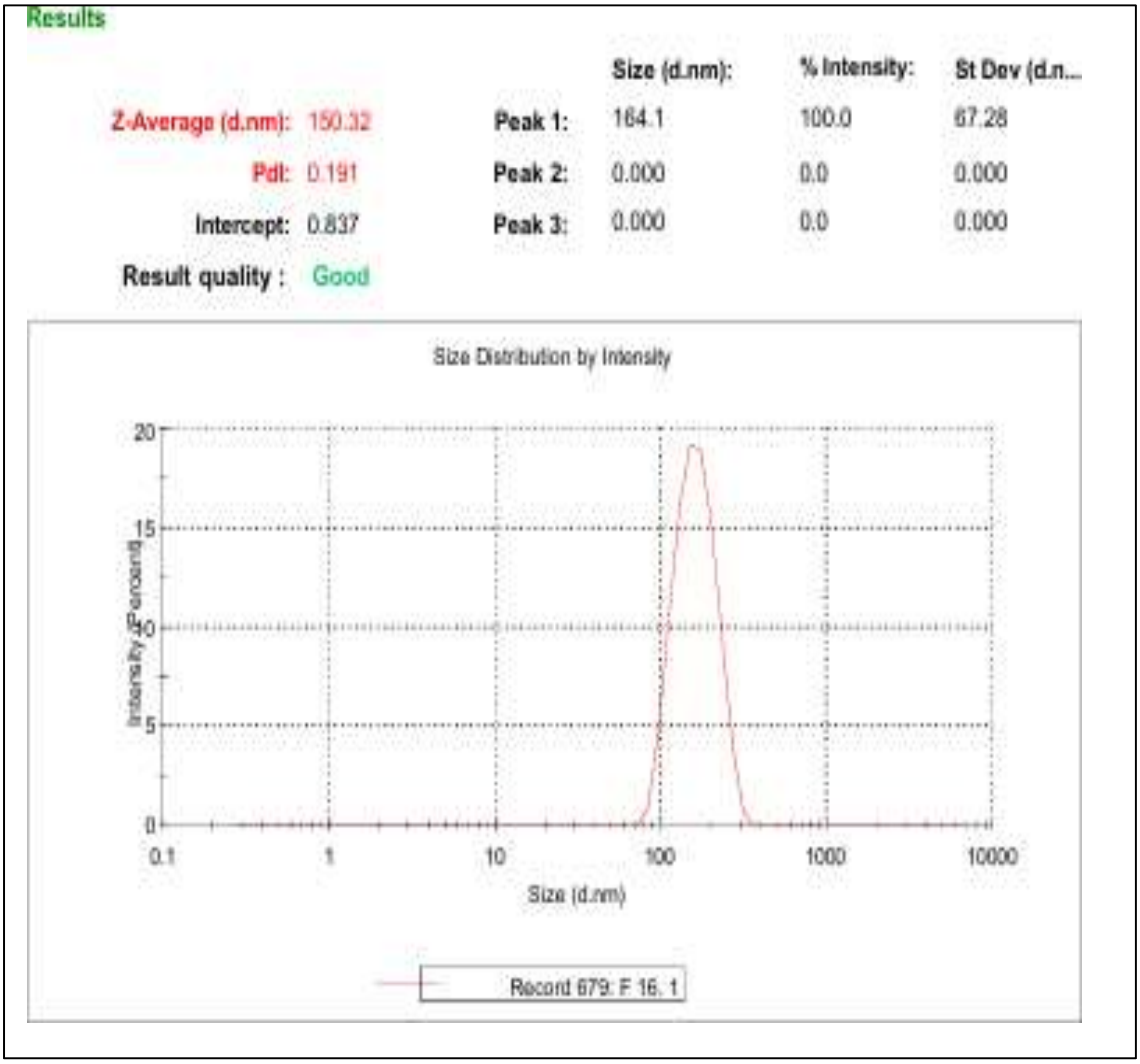

Figure 5: Particle size of optimized nanoparticles

Determination of PDI

In this study, the optimized silymarin-loaded sodium alginate nanoparticles exhibited a PDI value of 0.103± 0.12, indicating a highly uniform and monodisperse particle distribution. Such low PDI reflects excellent formulation stability and consistency, which is critical for predictable drug release and absorption profiles. The uniformity ensures reproducible performance, enhances mucosal interaction, and supports improved oral bioavailability of silymarin by minimizing variability in nanoparticle behavior within the gastrointestinal tract.

Drug entrapment efficiency

In this study, the optimized silymarin-loaded sodium alginate nanoparticles achieved a high drug entrapment efficiency of 86.65±0.65%. This effective encapsulation ensures sufficient drug loading within the polymer matrix, enabling controlled release and protecting silymarin from degradation, which supports improved oral bioavailability.

Zeta potential

In this study, the optimized silymarin-loaded sodium alginate nanoparticles exhibited a zeta potential of −34.87±0.67 mV, indicating strong electrostatic repulsion that enhances nanoparticle stability by preventing aggregation. Improved stability supports better dispersion and solubility in gastrointestinal fluids, which in turn facilitates consistent absorption and enhances the oral bioavailability of silymarin.

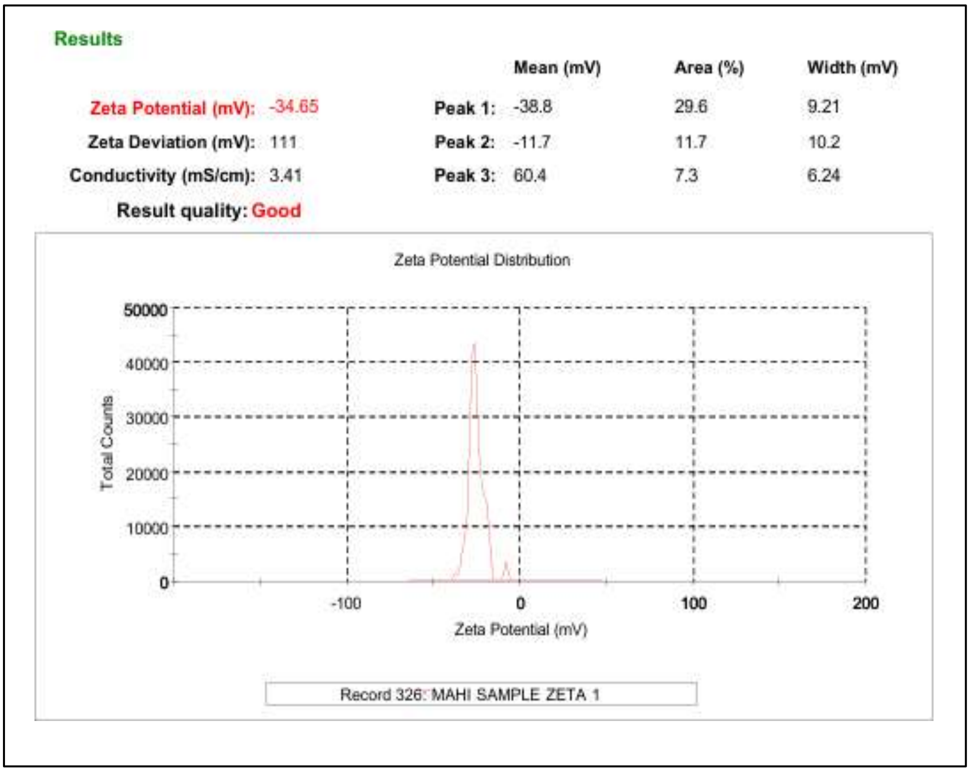

Figure 6: Zeta potential of optimized nanoparticles

***In Vitro* drug release**

Table 6: *In vitro* drug release profile for pure drug, optimized nanoparticles

Time (Hours)	Cumulative % of drug released	
	Optimized nanoparticles (%)	Pure drug suspension (%)
0	0	0
2	57.67±1.22	20.65±0.88
4	63.37±0.42	27.41±0.21
6	69.79±0.43	30.51±0.54
8	76.43±0.65	38.52±0.36
10	80.05±0.38	44.4±0.45
12	89.14±0.42	49.22±0.08

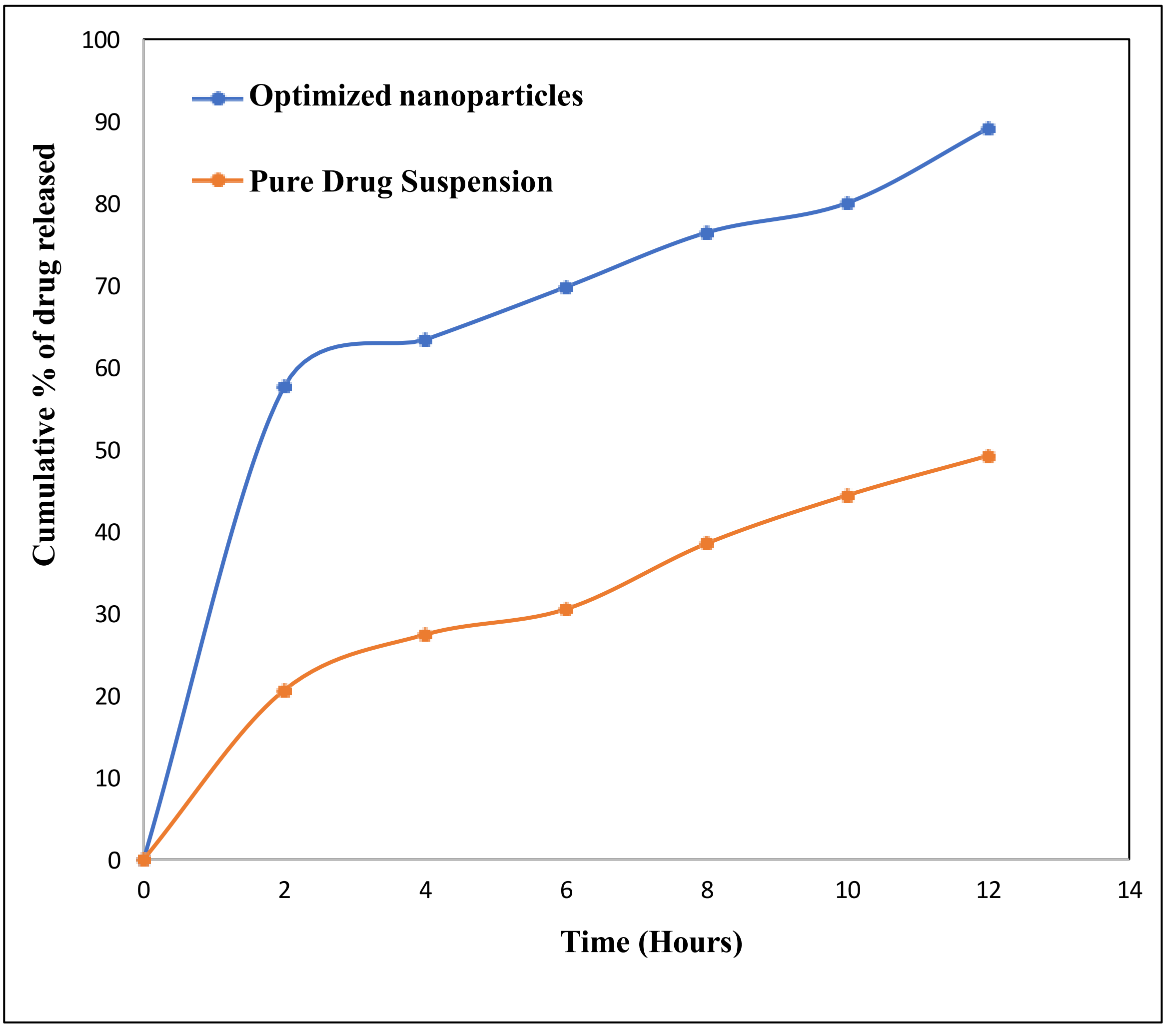

Figure 7: *In vitro* drug release profile for optimized nanoparticles, pure drug suspension

The *in vitro* dissolution study was conducted to compare the drug release behavior of the pure drug suspension and the optimized nanoparticles. The pure drug suspension exhibited poor dissolution, with only 49.22 ± 0.08 of the drug released over 12 hours, which is attributed to its inherent low aqueous solubility as a BCS Class II compound. Remarkably, the optimized nanoparticles system showed a significantly enhanced dissolution profile, with a total of 89.14 ± 0.42 % drug release within 12 hours. Notably, the optimized nanoparticles exhibited a burst release of 57.67 ± 1.22 within the first 2 hours, likely due to the rapid diffusion of surface-associated drug and the increased surface area of the nanoparticles. This initial burst was followed by a sustained release pattern, maintaining a consistent release rate over the remaining study period.

In vitro drug release kinetics

Table 7: Zero order kinetics model for optimized nanoparticles

Time	% of drug release
0	0
2	57.67
4	64.22
6	71.13
8	74.41
10	81.25
12	89.14

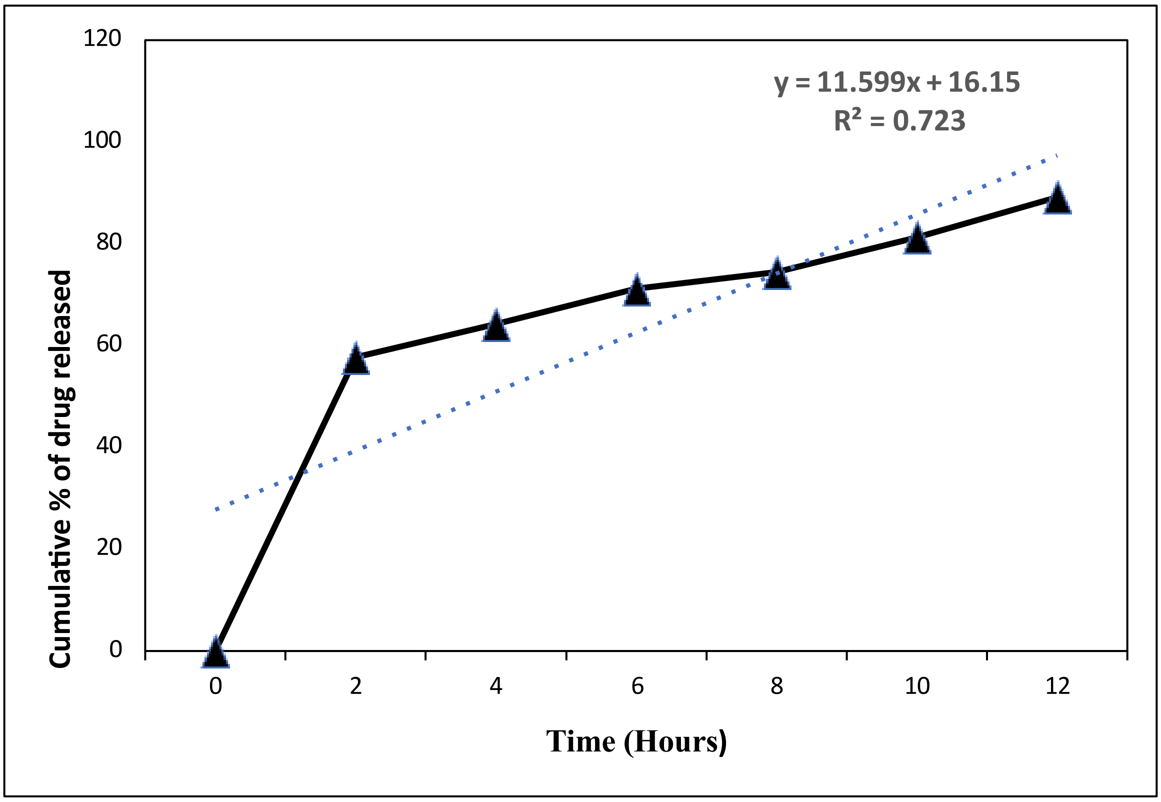

Figure 8: Zero-order model

Table 8: First order model for optimized nanoparticles

Time	Cumulative % of drug unreleased (CDUR)	Log CDUR
0	100	2
2	42.33	1.62
4	35.78	1.55
6	28.87	1.46
8	25.59	1.4
10	18.75	1.27
12	10.86	1

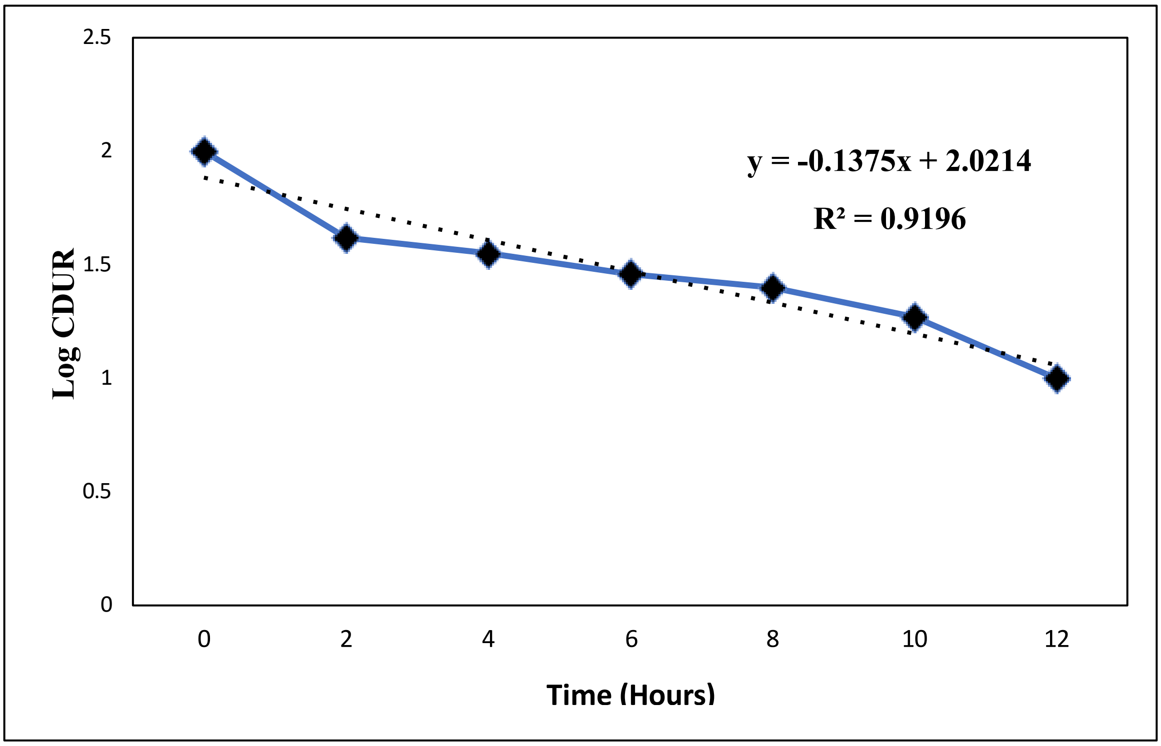

Figure 9: First-order model

Table 9: Korsmeyer-Peppas model for optimized nanoparticles

Time	Log T	Log CDUR
0	0	2
2	0.3	1.62
4	0.6	1.55
6	0.7	1.46
8	0.9	1.4
10	1	1.27
12	1.07	1

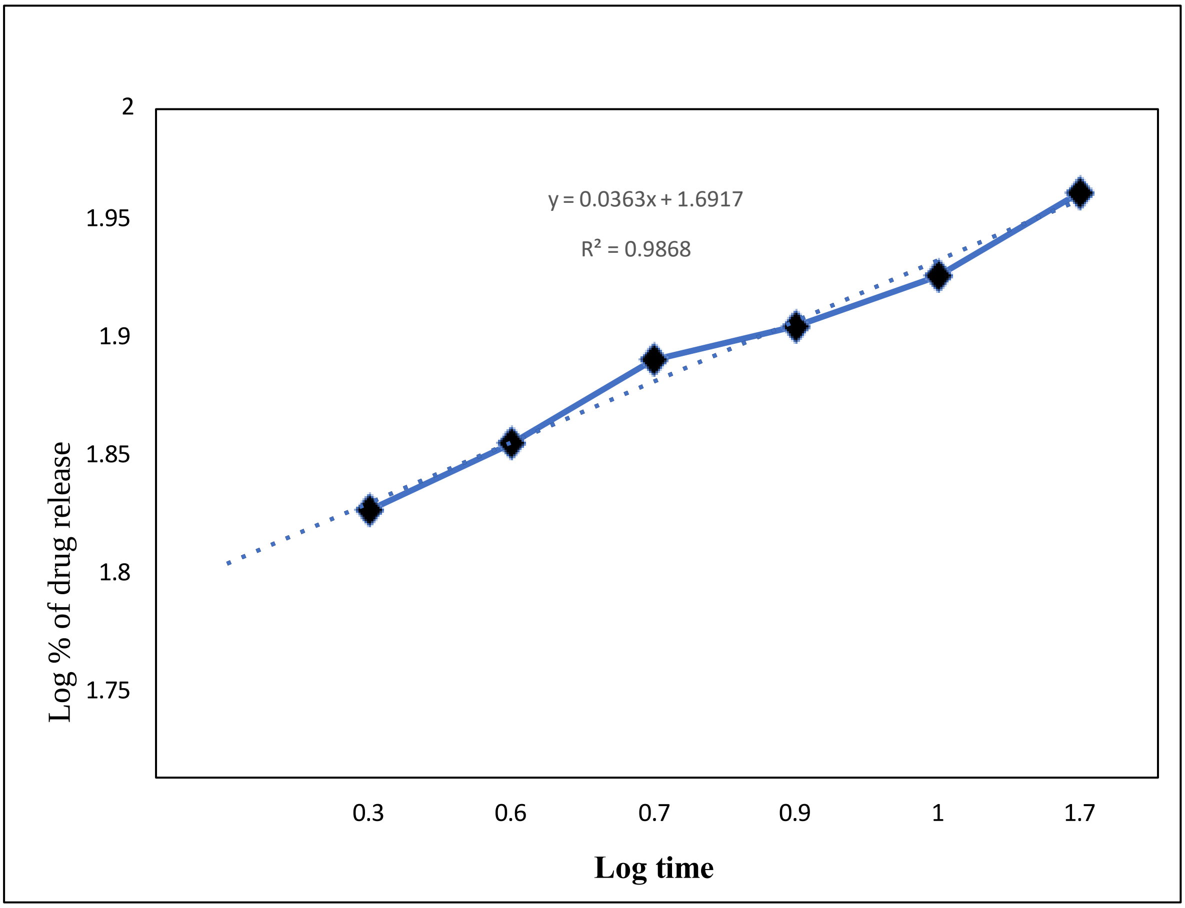

Figure 10: Korsmeyer-Peppas model

Table 10: Higuchi model for optimized nanoparticles

Time	Square root of time	Log cum % drug release
0	0	0
2	1.41	1.76
4	2	1.8
6	2.44	1.85
8	2.82	1.87
10	3.16	1.9
12	3.46	1.95

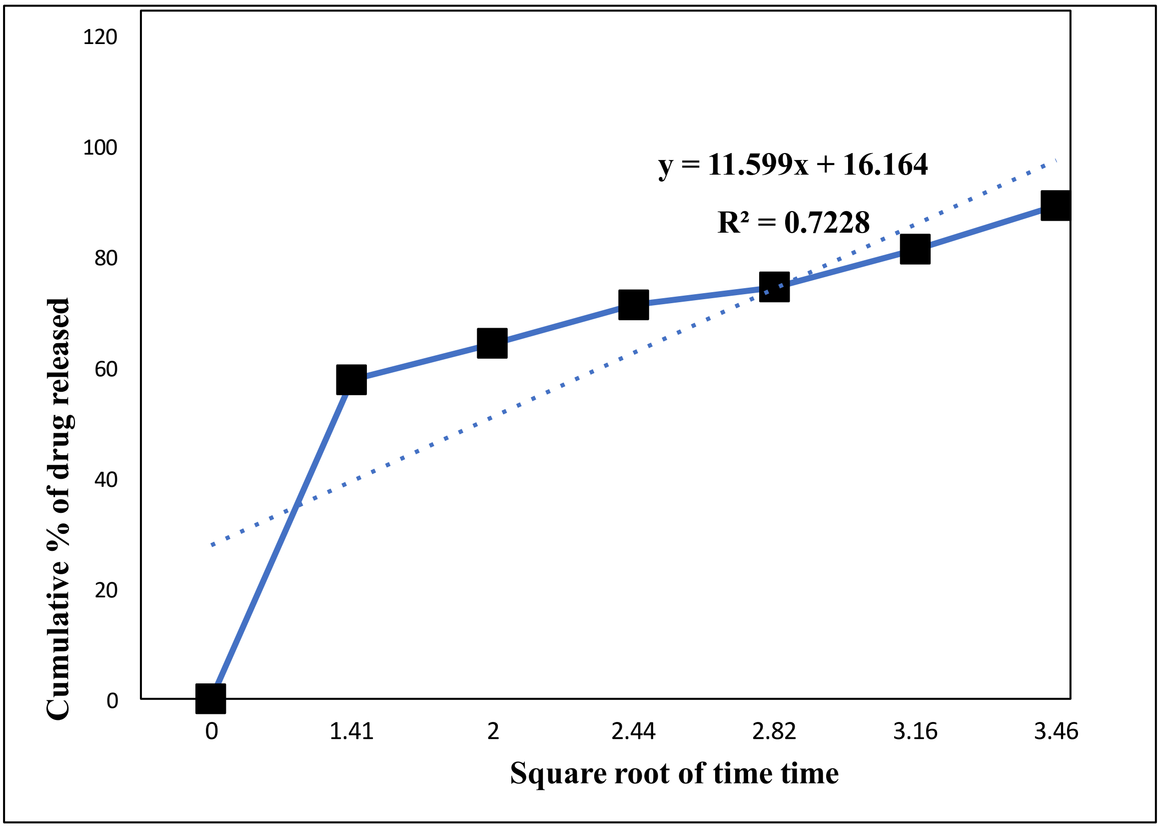

Figure 11: Higuchi model

The results found that the Korsmeyer-Peppas model exhibited the highest R^2 value (9868) compared to other models. Our findings showed optimized ASNPs in the Korsmeyer-Peppas model showed the highest R^2 and n value of 1.69 in the dissolving medium. As suggested by the Korsmeyer model, silymarin can be released from optimized nanoparticles through super case 2 transport. silymarin release process in nanoparticles involves substantial matrix swelling and diffusion in the dissolution medium.

CONCLUSION

The present study successfully formulated and evaluated silymarin-loaded sodium alginate nanoparticles with the objective of enhancing the oral bioavailability of silymarin, a hepatoprotective flavonolignan complex known for its poor aqueous solubility and limited gastrointestinal absorption. The nanoparticles were developed using the solvent desolvation technique and optimized through the One Variable at a Time (OVAT) approach. Among the prepared formulations (F1–F5), formulation F5 exhibited superior characteristics with a particle size of 150.32 ± 0.32 nm, entrapment efficiency of 86.65 ± 0.65%, and a PDI of 0.103 ± 0.12, indicating uniformity and stability of the prepared nanoparticles.

FTIR analysis confirmed the absence of any major chemical interaction between silymarin and sodium alginate, thereby establishing the compatibility of drug and polymer. The zeta potential value of −34.87 ± 0.67 mV reflected strong electrostatic repulsion and excellent colloidal stability, ensuring resistance to aggregation and improved storage potential. The optimized nanoparticles demonstrated a biphasic in vitro drug release profile, characterized by an initial burst release followed by a sustained release phase, with a total cumulative drug release of 89.14% within 12 hours compared to 49.22% for the pure drug suspension.

Drug release kinetics followed the Korsmeyer–Peppas model, suggesting a super case II transport mechanism, which indicates that both diffusion and polymer relaxation governed the release process. This sustained release behavior effectively minimizes dosing frequency and maintains prolonged therapeutic concentrations. The nanoscale size, uniformity, and controlled release nature of the optimized nanoparticles suggest that the formulation can protect silymarin from enzymatic degradation and improve intestinal permeability, thereby significantly enhancing its oral bioavailability.

Overall, the study demonstrates that sodium alginate-based nanoparticles provide an efficient, biocompatible, and biodegradable carrier system for silymarin delivery. The developed nano formulation successfully addressed the solubility and bioavailability challenges associated with silymarin, offering an innovative and promising platform for improving therapeutic efficacy in liver protection and related disorders. Future studies involving *in vivo* pharmacokinetic and pharmacodynamic evaluations are recommended to further validate the clinical potential and long-term stability of the optimized formulation.

REFERENCES

1. Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 14th ed. New York: McGraw-Hill Education; 2018. Chapter 2.
2. Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines. 2022 Aug 23;10(9).
3. Amidon G.L., Lennernäs H., Shah V.P., Crison J.R. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 1995;12:413–420.
4. Krishnaiah Y.S. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J. Bioequiv. Availab. 2010;2:28–36.
5. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, Porter CJ. Strategies to address low drug solubility in discovery and development. Pharmacol Rev. 2013 Jan;65(1):315-499.
6. Setyawati DR, Sekaringtyas Gao W, Thamphiwatana S, Angsantikul P, Zhang L. Nanoparticle approaches against bacterial infections. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2014 Nov- Dec;6(6):532-47.
7. FC, Pratiwi RD, Rosyidah A, Azhar R, Gustini N, Syahputra G, Rosidah I, Mardliyati E, Tarwadi, El Muttaqien S. Recent updates in applications of nanomedicine for the treatment of hepatic fibrosis. Beilstein J Nanotechnol. 2024 Aug 23;15:1105-1116.
8. Thapa, R.K., Kim, J.O. Nanomedicine-based commercial formulations: current developments and future prospects. *J. Pharm. Investig.* 53, 19–33 (2023).
9. Bai X, Su G, Zhai S. Recent Advances in Nanomedicine for the Diagnosis and Therapy of Liver Fibrosis. *Nanomaterials*. 2020;10(10):1945.
10. Sandip D.Firke, Nikhil Patel, Sanjay J.Surana, Sunjaykumar B.Bari. Method development and validation of Silymarin in bulk and pharmaceutical formulation by UV- spectrophotometric area under curve method (AUC). Analytical chemistry an Indian Journal vol:3, Issue 3 2015 [100-104].
11. M. Nallamuthu, Umadevi S. 2025. "Abiraterone acetate loaded sodium alginate nanoparticles for improving aqueous solubility and dissolution of abiraterone acetate: preparation and formulation optimization by central composite design, characterization". International journal of applied pharmaceutics. 17(4):268-78.
12. Bunaciu AA, Aboul-Enein HY, Fleschin S. Application of Fourier transform infrared spectrophotometry in pharmaceutical drugs analysis. Appl Spectrosc Rev. 2010;45(3):206–19
13. Ismail R, Sovány T, Gácsi A, Ambrus R, Katona G, Imre N, Csóka I. Synthesis and statistical optimization of poly (Lactic-co-glycolic acid) Nanoparticles encapsulating GLP analog designed for oral delivery. Pharm Res. 2019; 36 (7):99.
14. Yang KY, Hwang du H, Yousaf AM, Kim DW, Shin YJ, Bae ON, Kim YI, Kim JO, Yong CS, Choi HG. Silymarin-loaded solid nanoparticles provide excellent hepatic protection: physicochemical characterization and in vivo evaluation. Int J Nanomedicine. 2013;8:3333-43.
15. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm. 2010 May-Jun;67(3):217-23.