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Research Article

Design, Prepare and in Vitro Evaluation of Lapatinib Solid Lipid Nanoparticles

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ABSTARCT.

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ABSTRACT

The present study was aimed at the formulation and evaluation of Lapatinib-loaded Solid Lipid Nanoparticles (SLNs) using the hot homogenization followed by ultrasonication method to achieve improved drug encapsulation and sustained drug release. Lapatinib is an anticancer drug with poor aqueous solubility, which may limit its pharmaceutical performance. Solid lipid nanoparticles offer a promising lipid-based drug delivery approach due to their nanosized structure, biocompatibility, and ability to incorporate poorly water-soluble drugs. FTIR studies indicated the absence of significant drug-excipient interactions. Eight formulations (F1–F8) were prepared using different concentrations of Glyceryl Monostearate (GMS), while maintaining constant concentrations of Lapatinib, Poloxamer 407, and Span 80. The prepared formulations were evaluated for particle size, entrapment efficiency, zeta potential, surface morphology, and in-vitro drug release. The results revealed that particle size ranged from 112 to 190 nm, entrapment efficiency ranged from 85.37% to 95.18%, and zeta potential ranged from −22 to −35 mV. Among all formulations, F7 exhibited the most favorable characteristics, with a particle size of 112 nm, entrapment efficiency of 95.18%, and zeta potential of −35 mV. In-vitro drug release studies demonstrated sustained drug release over 12 hours, with formulation F7 showing the maximum cumulative drug release of 97.18%. Drug release kinetics indicated that the Higuchi model provided the best fit, with an R^2 value of 0.984, suggesting a predominantly diffusion-controlled release mechanism.

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Stability studies conducted for three months under different storage conditions demonstrated that the optimized formulation maintained drug release above 85%.In conclusion, Lapatinib-loaded solid lipid nanoparticles were successfully formulated, and F7 was identified as the optimized formulation based on its physicochemical characteristics, high entrapment efficiency, sustained drug release, and acceptable short-term stability.

INTRODUCTION

Nanotechnology-based drug-delivery systems have emerged as promising approaches for overcoming several limitations associated with poorly water-soluble anticancer agents. Among these systems, lipid nanoparticles have attracted considerable interest because of their ability to incorporate lipophilic drugs within a lipid matrix, their relatively good biocompatibility, and the possibility of modifying drug-release characteristics.[1]Lipid-based Nano systems may also protect incorporated drugs from degradation and provide a platform for improving their pharmaceutical performance.[2] Solid lipid nanoparticles (SLNs) are colloidal carriers generally composed of physiologically acceptable lipids that remain solid at both room and body temperatures and are stabilized using suitable surfactants.[3] Lapatinib is an orally active small-molecule tyrosine kinase inhibitor used in the treatment of selected human epidermal growth factor receptor 2 (HER2)-positive breast cancers. Considering the poor aqueous solubility of lapatinib and the potential advantages of lipid-based nanocarriers, the present study was undertaken to design, prepare, and evaluate lapatinib-loaded solid lipid nanoparticles.[4] The formulation is intended to achieve effective incorporation of lapatinib into a solid lipid carrier and obtain desirable nanoscale characteristics and drug-release behavior.[5] The prepared formulations will be evaluated for physicochemical properties, particle size, zeta potential, entrapment efficiency, morphology, in vitro drug release, release kinetics, and stability. The study is expected to provide a systematic basis for the development of an optimized SLN-based delivery system for lapatinib. [6]

MATERIALS

Lapatinib was procured from Hetero Labs, Hyderabad Glyceryl Monostearate (GMS), Poloxamer 407 and Span 80 were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

Method of preparation of Lapatinib loaded nanoparticles:

Table None: 1: Composition of Lapatinib for Preparation of Solid Lipid Nanoparticles

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Lapatinib(mg)	10	10	10	10	10	10	10	10
Glyceryl Monostearate (GMS) (mg)	100	200	300	400	500	600	700	800
Poloxamer 407 (mg)	100	100	100	100	100	100	100	100
Span 80(mg)	1	1	1	1	1	1	1	1
Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Preparation of Lapatinib Solid Lipid Nanoparticles[7]

Method: Hot Homogenization Followed by Ultrasonication

Accurately weigh Lapatinib and Glyceryl Monostearate. Melt the lipid in a beaker at approximately 70–75°C, which is above the melting point of the lipid. Lapatinib is then dispersed in the molten lipid phase under continuous magnetic stirring until a clear and uniform mixture is obtained. Similar hot homogenization approaches are widely used for SLN preparation. In a separate vessel, prepare the aqueous phase by dissolving Poloxamer 188 and Span 80 in distilled water and heating it to the same temperature as the lipid phase (70–75°C). Maintaining equal temperatures prevents premature lipid solidification during emulsification. The hot aqueous phase is then slowly added to the molten lipid phase under high-speed homogenization using a homogenizer operating at 10,000–15,000 rpm

for 10–15 minutes to produce a coarse oil-in-water emulsion. The resulting emulsion is subjected to probe ultrasonication for 5–10 minutes to reduce particle size and obtain a nanoemulsion. Ultrasonication helps achieve nanoparticles in the nanometer range with narrow size distribution. The hot nanoemulsion is immediately cooled to room temperature or placed in an ice bath with continuous stirring. Upon cooling, the lipid recrystallizes, resulting in the formation of Lapatinib-loaded solid lipid nanoparticles. The dispersion is then stored at 4°C for further characterization.

Evaluation of Lapatinib loaded nanoparticles:

Particle size The average particle size and polydispersity index (PDI) of the prepared Lapatinib-loaded SLNs are determined using Dynamic Light Scattering (DLS) employing a particle size analyzer (e.g., Malvern Zetasizer). Accurately transfer 0.1 mL of the SLN dispersion into a volumetric flask and dilute appropriately with distilled water to avoid multiple scattering effects. The diluted sample is placed in a disposable cuvette and analyzed at 25°C. Measurements are performed in triplicate and the mean particle size and PDI are recorded.[8]

Zeta potential

The zeta potential of the SLN formulation is measured using a Zeta Potential Analyzer equipped with electrophoretic light scattering. A suitable quantity of the SLN dispersion is diluted with deionized water and transferred into a folded capillary cell. The sample is analyzed at 25°C under standard operating conditions. Measurements are carried out in triplicate and the average zeta potential value is reported.[9]

SEM analysis

The surface morphology and shape of Lapatinib-loaded SLNs are examined using Scanning Electron Microscopy (SEM). A small amount of freeze-dried SLN powder is mounted on an aluminum stub using double-sided adhesive carbon tape. The sample is then coated with a thin layer of gold or platinum using a sputter coater under vacuum conditions to improve conductivity. The coated sample is observed under SEM at suitable magnifications, and photomicrographs are recorded.[10]

Drug encapsulation efficiency

The drug encapsulation efficiency of Lapatinib-loaded SLNs is determined by the ultracentrifugation method. A known volume (e.g., 5 mL) of the SLN dispersion is transferred into centrifuge tubes and centrifuged at 15,000–20,000 rpm for 30–45 minutes at 4°C. The supernatant containing free (unentrapped) drug is carefully collected and analyzed spectrophotometrically at the λmax of Lapatinib or by HPLC. The amount of free drug present in the supernatant is determined from a previously prepared calibration curve. The encapsulated drug is calculated by subtracting the free drug from the total drug added during formulation.[11]

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount entrapped}}{\text{Total drug loaded}} \times 100$$

In-vitro drug release studies[12]

In vitro release study of the formulated Solid lipid nanoparticles was carried out by using diffusion cell through membrane as a dialysis membrane. Diffusion cell with inner diameter 24mm was used for the study. 1 mL formulation was placed in donor compartment and freshly prepared 7.4 phosphate buffer was placed in receptor compartment. Dialysis membrane was mounted in between donor and receptor compartment. The position of the donor compartment was adjusted so that the membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 1mL of sample was withdrawn from receiver compartment after 1, 2, 3, 4, 5, 6, 8, 10 & 12 hrs and same volume of fresh medium was replaced. The withdrawn samples were diluted to 10mL in a volumetric flask with distilled water and analysed by UV spectrophotometer.

Drug release kinetics[13]

The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and Koresmeyer Peppas model (equation 4).

i) Zero order kinetics:

$$R = K_o t \text{ -- (1)}$$

R=cumulative percent drug

Ko=zero order rate constant

ii) First order kinetics

$\log C = \log Co - K_1 t / 2.303$ -- (2)

where C = cumulative percent drug

K_1 = first order rate constant

iii) Higuchi model

$R = K_H t^{0.5}$ -- (3)

Where R = cumulative percent drug

K_H = higuchi model rate constant

iv) Korsmeyer peppas model:

$M t / M \alpha = K_k t^n$

$\log M t / M \alpha = \log K_k + n \log t$ -- (4)

where K_k = korsermeyer peppas rate constant

'M t / M α' is the fractional drug , n = diffusional exponent, which characterizes the mechanism of drug.

The obtained regression co-efficient (which neared 0.999) was used to understand the pattern of the drug from the Solid lipid nanoparticles.

Stability Studies[14]

The stability studies of the optimized Lapatinib-loaded Solid Lipid Nanoparticles are carried out according to the International Council for Harmonisation (ICH) guidelines to evaluate the physical and chemical stability of the formulation during storage. The optimized SLN formulation is packed in airtight glass containers and stored under different storage conditions, namely refrigerated conditions (4 ± 2°C), room temperature conditions (25 ± 2°C/60 ± 5% RH), and accelerated conditions (40 ± 2°C/75 ± 5% RH).

RESULTS AND DISCUSSION

Particle size

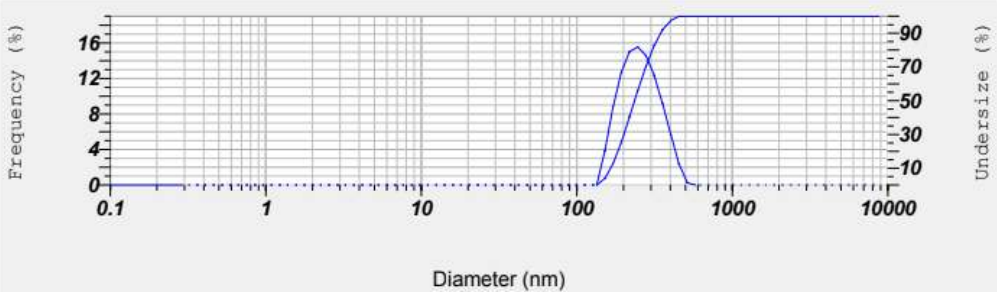


Figure None: 1: Particle Size of Optimized Formulations

Determination of Zeta potential:

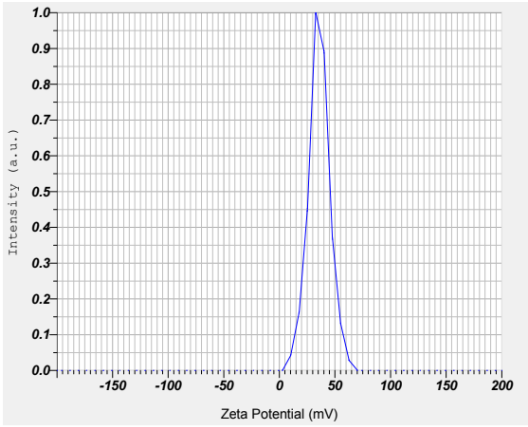


Figure None: 2: Zeta Potential of Optimized Formulation

Scanning Electron Microscopy:

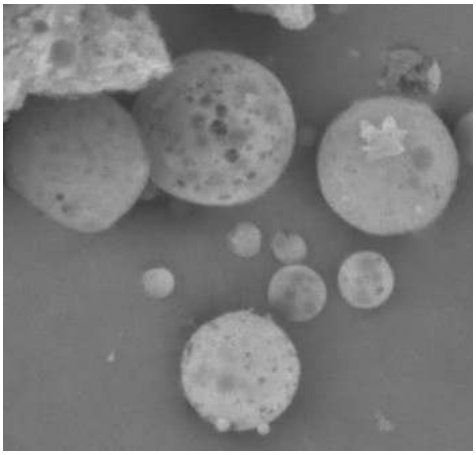


Figure None: 3: SEM Analysis of Nanoparticles

Characterization of Nanoparticles of Lapatinib

Table None: 2: Evaluation Studies of Solid Lipid Nanoparticles

F. no	Particle size (nm)	Entrapment Efficiency (%)	Zeta Potential(mV)
F1	189	85.37	-22
F2	175	86.95	-28
F3	162	90.12	-31
F4	155	89.73	-27
F5	190	91.53	-28
F6	187	93.25	-29
F7	112	95.18	-35
F8	136	88.61	-23

Entrapment efficiency

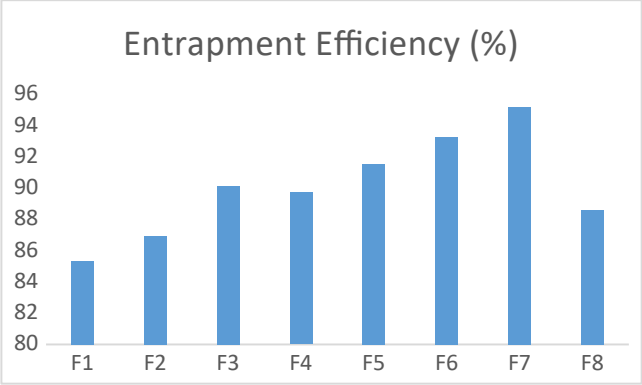


Figure None: 4: In Vitro Drug Entrapment Efficiency Studies

DISCUSSION

The prepared lapatinib-loaded solid lipid nanoparticles (SLNs) were evaluated for particle size, entrapment efficiency, and zeta potential. The results are presented in Table-8. The particle size of the formulations ranged from 112 to 190 nm, indicating the formation of nano-sized lipidic carriers. F1 showed a particle size of 189 nm, while F2, F3, and F4 exhibited particle sizes of 175, 162, and 155 nm, respectively. F5 and F6 showed slightly higher particle sizes of 190 and 187 nm. Among all formulations, F7 showed the lowest particle size of 112 nm, followed by F8 with 136 nm. The reduction in particle size may be attributed to efficient homogenization/sonication and suitable lipid–surfactant interactions, which promote the formation of smaller and more uniform nanoparticles. The entrapment efficiency (EE) of lapatinib-loaded SLNs ranged from 85.37% to 95.18%. F1 exhibited an EE of 85.37%, whereas F2, F3, and F4 showed 86.95%, 90.12%, and 89.73%, respectively. F5 and F6 demonstrated higher entrapment efficiencies of 91.53% and 93.25%. The maximum entrapment efficiency was observed for F7 (95.18%), while F8 showed 88.61%. The relatively high entrapment efficiency suggests effective incorporation of the lipophilic lapatinib into the lipid matrix. The higher value observed with F7 may be related to favorable drug–lipid compatibility and an appropriate lipid-to-surfactant ratio, which can reduce drug partitioning into the external aqueous phase during SLN preparation.

The zeta potential values ranged from −22 to −35 mV. F1 exhibited a zeta potential of −22 mV, while F2, F3, F4, F5, and F6 showed values of −28, −31, −27, −28, and −29 mV, respectively. F7 showed the highest negative zeta potential of −35 mV, whereas F8 showed −23 mV. The negative surface charge indicates the presence of negatively charged groups or components at the nanoparticle interface. The relatively higher magnitude of zeta potential observed in F7 suggests better electrostatic repulsion between particles, which can contribute to reduced aggregation and improved physical stability of the dispersion.

In-vitro Dissolution Study

Table None: 3: *In-vitro* Release Data of Tablet F_1 to F_8

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	17.56	16.83	17.16	18.16	15.49	17.45	19.57	16.97
2	28.10	29.17	27.69	29.15	25.46	32.16	30.15	27.46
3	36.56	38.25	39.61	37.29	43.56	45.16	43.25	35.68
4	45.14	48.91	52.16	50.13	50.18	51.13	55.12	47.81
6	66.20	68.13	68.20	69.55	65.78	68.43	72.16	58.91
8	73.69	75.60	77.82	78.14	76.98	73.59	82.20	72.35
10	85.10	84.19	87.48	88.49	87.50	81.20	89.10	83.10
12	93.39	94.10	95.86	94.78	92.36	96.58	97.18	96.39

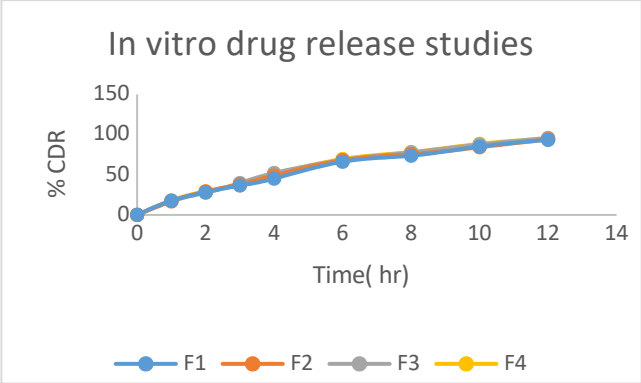


Figure None: 5: In Vitro Drug Release Studies of F1-F4 Formation

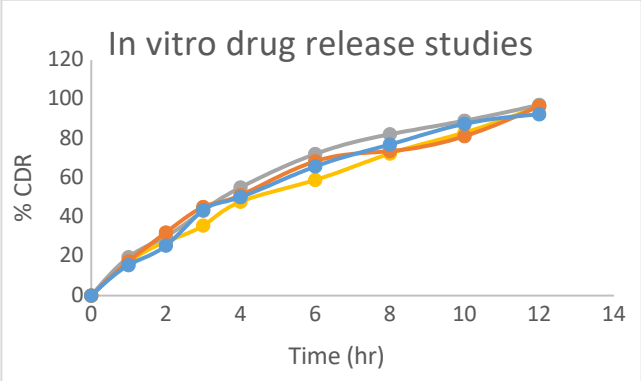


Figure None: 6: In Vitro Drug Release Studies of F5-F8 Formation

DISCUSSION

Overall, all formulations demonstrated sustained drug release over the 12-hour study period. F7 showed the highest cumulative drug release of 97.18% at 12 hours, indicating a relatively efficient drug-release profile among the tested formulations.

Kinetic modelling of drug release

All the 8 formulation of prepared Lapatinib SLN were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

Zero order kinetics

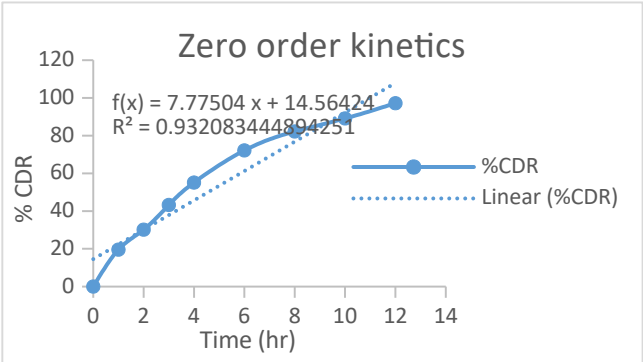


Figure None: 7: Zero Order Kinetics of Optimized Formulation

First order kinetics

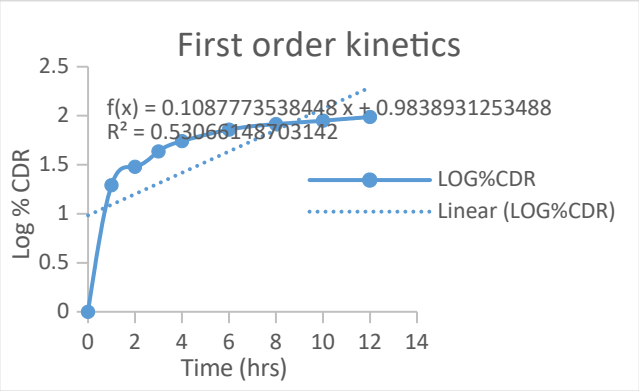


Figure None: 8: First Order Kinetics of Optimized Formulation

Higuchi model

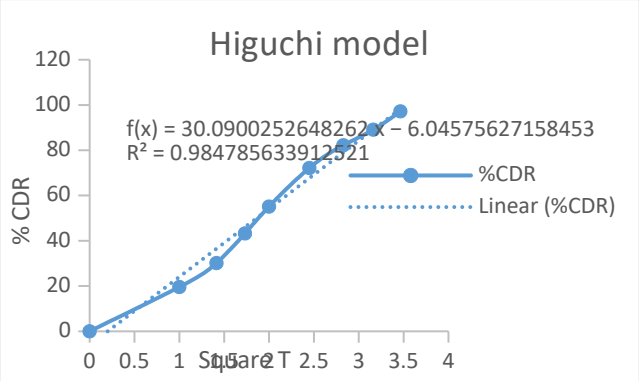


Figure None: 9: Higuchi Model of Optimized Formulation

Korsmeyer peppas

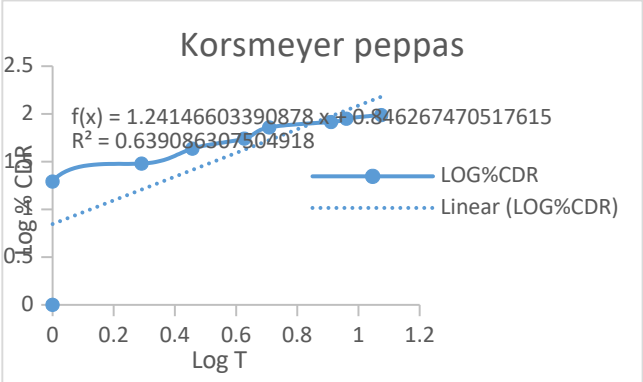


Figure None: 10: Korsmeyer Peppas of Optimized Formulation

The kinetic values obtained for formulation F7 were shown. The values of invitro release were attempted to fit into various mathematical models.

Regression values are higher with Zero order release kinetics. Therefore, all the SLN Zero order release kinetics. Therefore, all the follow first order release kinetics.

DISCUSSION

Kinetic modelling of the optimized formulation F7 showed that the drug release followed mainly Higuchi diffusion kinetics, as indicated by the highest regression coefficient (R^2 = 0.982). This suggests that the drug release mechanism is primarily diffusion-controlled from the solid lipid matrix rather than concentration-dependent release. The zero-order model also showed relatively good fit, indicating a controlled release profile.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-7 after 3 months.

Table None: 4: Results of Stability Studies of Optimized Formulation F7

Formulation Code	Parameters	Initial	1st Month	2nd	3rd	Limits as per Specifications
F-7	25⁰C/60%RH	97.18	96.82	95.67	94.75	Not less than 85%
F-7	30⁰C/75% RH	97.18	96.81	95.15	94.11	Not less than 85%
F-7	40⁰C/75% RH	97.18	96.15	95.30	94.03	Not less than85%

DISCUSSION

Stability studies of formulation F7 under different storage conditions (25°C/60% RH, 30°C/75% RH, and 40°C/75% RH) showed no significant changes in drug content over three months. The drug content remained above 95% in all conditions, indicating good physical and chemical stability of the formulation. The slight decrease observed over time may be due to minor degradation or lipid matrix rearrangement, but overall the formulation remained stable within acceptable limits.

CONCLUSION

The present study successfully demonstrated the formulation and evaluation of Lapatinib-loaded Solid Lipid Nanoparticles using the hot homogenization followed by ultrasonication method. Eight formulations were developed by varying the concentration of Glyceryl Monostearate, and their physicochemical characteristics and in-vitro drug release profiles were systematically evaluated. Among the eight formulations, F7 was identified as the optimized formulation based on its favorable evaluation parameters, including a minimum particle size of 112 nm, maximum entrapment efficiency of 95.18%, and zeta potential of −35 mV. The optimized formulation also exhibited sustained drug release, achieving 97.18% cumulative drug release over 12 hours. The drug release kinetics indicated that the Higuchi model provided the best fit, suggesting a predominantly diffusion-controlled drug release mechanism. Furthermore, the stability studies conducted over three months demonstrated that the optimized formulation maintained acceptable drug release characteristics under the investigated storage conditions. Thus, the developed Lapatinib-loaded SLNs demonstrated promising physicochemical properties, efficient drug encapsulation, sustained drug release, and satisfactory short-term stability. The formulation may serve as a potential lipid-based nanocarrier for further investigation of Lapatinib delivery. However, further studies, including in-vitro cytotoxicity, cellular uptake, pharmacokinetic evaluation, biodistribution, blood-brain barrier transport, and in-vivo antitumor efficacy studies, are necessary to establish its suitability for targeted brain delivery and clinical applications. Therefore, it can be concluded that formulation F7 represents a promising optimized Lapatinib-loaded solid lipid nanoparticle formulation for further pharmaceutical and biological evaluation.

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