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DEVELOPMENT AND CHARACTERIZATION OF LAPATINIB CUBOSOMAL DRUG DELIVERY SYSTEM

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Abstract:

The present study aimed to formulate, characterize, and evaluate Lapatinib-loaded cubosomes as a sustained-release nanocarrier system to improve the solubility, bioavailability, and therapeutic efficacy of Lapatinib. Cubosomes were prepared by the Top-Down method using glyceryl monostearate (GMS) as the lipid and Pluronic F-127 as the stabilizer. Eight formulations (F1–F8) were developed by varying the lipid concentration while maintaining a constant drug and surfactant ratio. SEM analysis revealed uniformly distributed, nearly spherical cubosomes with smooth surfaces. Particle size ranged from 220 to 279 nm, while zeta potential varied from −23 to −30 mV, indicating good colloidal stability. Among all formulations, F8 exhibited the smallest particle size (220 nm), highest entrapment efficiency (94.58%), and maximum cumulative drug release (98.76% after 12 hours). Drug release kinetic analysis demonstrated that the optimized formulation best fitted the Higuchi model (R^2 = 0.998), indicating diffusion-controlled sustained drug release. Accelerated stability studies conducted according to ICH guidelines showed no significant changes in the physical appearance or drug release profile, with the optimized formulation retaining more than 95% drug release after three months of storage. The findings indicate that the optimized Lapatinib-loaded cubosomal formulation is a stable and promising sustained-release drug delivery system with the potential to enhance oral bioavailability, therapeutic efficacy, and patient compliance in the management of cancer.

Keywords: *Lapatinib, cubosomes, Top-Down method, Glyceryl monostearate, In vitro drug release studies*

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INTRODUCTION:

Nanotechnology-based drug delivery systems have received considerable attention as approaches for overcoming the limitations associated with conventional lapatinib administration. Such systems can provide increased apparent solubility, enhanced drug loading, controlled drug release and improved cellular uptake.[1] Cubosomes are nanoparticles composed of highly ordered bicontinuous cubic liquid-crystalline phases, generally formed from amphiphilic lipids in the presence of a stabilizer. Their three-dimensional internal structure provides a large interfacial area and interconnected aqueous and lipid domains, allowing incorporation of hydrophilic, lipophilic and amphiphilic drugs.[2] Cubosomes have attracted particular interest in cancer drug delivery because their internal nanostructure can accommodate anticancer molecules while providing opportunities for controlled and potentially targeted drug transport.[3] The present study is focused on the development and characterization of a lapatinib-loaded cubosomal drug delivery system. The formulation is intended to exploit the unique bicontinuous cubic structure of cubosomes to improve the pharmaceutical performance of lapatinib. [4]

MATERIALS

Lapatinib was procured from Hetero Labs, Hyderabad. Glyceryl monostearate and Pluronic F-127 were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Formulation development

Table-1: Formulation development

Ingredients	F1(1:1)	F2(1:2)	F3(1:3)	F4(1:4)	F5(1:5)	F6(1:6)	F7(1:7)	F8(1:8)
Lapatinib	20	20	20	20	20	20	20	20
Glyceryl monostearate	100	200	300	400	500	600	700	800
Pluronic F-127	100	100	100	100	100	100	100	100
Ethanol	10	10	10	10	10	10	10	10
Water	q. s	q. s	q.s	q. s	q.s	q.s	q.s	q.s

Method of Preparation:

Top-Down Method[5,6]

Lapatinib-loaded cubosomes were prepared by the Top-Down Method, which involves the formation of a bulk cubic phase followed by its fragmentation into nanosized cubosome particles using high-energy homogenization. Initially, the required quantity of glyceryl monostearate (GMS) was accurately weighed according to the formulation (F1–F8) and transferred into a clean beaker. The lipid was melted at 60–70°C using a water bath. An accurately weighed quantity of 20 mg of lapatinib was dissolved in 10 mL of ethanol and added slowly to the molten lipid with continuous stirring until a clear and homogeneous lipid phase was obtained. Separately, the required quantity of Pluronic F-127 (100 mg) was dissolved in a suitable quantity of distilled water with gentle stirring to prepare the aqueous phase. The aqueous phase was maintained at the same temperature as the lipid phase to prevent premature solidification during mixing. The warm aqueous phase was gradually added to the molten lipid phase under continuous stirring using a magnetic stirrer at 1000–1500 rpm. The mixture was stirred for 30 minutes, allowing the lipid to hydrate and form a homogeneous, highly viscous bulk cubic phase. The resulting cubic phase was allowed to equilibrate at room temperature for 12–24 hours to ensure complete formation of the liquid crystalline cubic structure. The bulk cubic phase was then dispersed in the remaining distilled water and subjected to high-speed homogenization at 10,000–15,000 rpm for 10–15 minutes to reduce the particle size. The dispersion was further sonicated using a probe ultrasonicator for 5–10 minutes with intermittent cooling to obtain uniformly distributed cubosome nanoparticles having a narrow particle size distribution. The final volume of the formulation was adjusted with distilled water (q.s.) and the prepared cubosomal dispersion was allowed to cool to room temperature. The formulations were transferred into amber-colored, airtight glass containers and stored at 4–8°C until further characterization.

Evaluation of Cubosomes:

Particle Size Analysis

The average particle size and polydispersity index (PDI) of the prepared lapatinib-loaded cubosomes were determined using Dynamic Light Scattering (DLS) with a Malvern Zetasizer. The cubosomal dispersion was diluted appropriately with filtered distilled water (1:100) to avoid multiple scattering effects. The diluted sample was transferred into a disposable polystyrene cuvette and analyzed at 25 ± 1°C with a scattering angle of 90°. The average

particle size and PDI were recorded in triplicate, and the mean values were reported.[7]

Scanning Electron Microscopy (SEM) Analysis

The surface morphology and shape of the cubosomes were examined using Scanning Electron Microscopy (SEM). A drop of the optimized cubosomal dispersion was placed on a clean aluminum stub and allowed to dry at room temperature. The dried sample was sputter-coated with a thin layer of gold under vacuum to improve electrical conductivity. The coated sample was then examined under the SEM at suitable magnifications and accelerating voltage. The obtained micrographs were used to evaluate the particle shape, surface characteristics, and distribution of the cubosomes.[8]

Zeta Potential

The zeta potential of the cubosomal formulation was measured using a Malvern Zetasizer based on electrophoretic light scattering. The prepared cubosomal dispersion was diluted with distilled water and transferred into a folded capillary cell. The analysis was carried out at 25 ± 1°C, and the electrophoretic mobility of the particles was measured. The zeta potential value was automatically calculated by the instrument software and expressed in millivolts (mV). Measurements were performed in triplicate, and the average value was reported to assess the physical stability of the cubosomal dispersion.[9]

Entrapment Efficiency (%EE)

The entrapment efficiency of lapatinib-loaded cubosomes was determined by the centrifugation method. A known volume of cubosomal dispersion was transferred into centrifuge tubes and centrifuged at 15,000 rpm for 30 minutes at 4°C. After centrifugation, the supernatant containing the unentrapped (free) drug was carefully separated. The amount of free lapatinib present in the supernatant was determined using a UV–Visible spectrophotometer at the predetermined λmax after suitable dilution with the dissolution medium.[10] The percentage entrapment efficiency was calculated using the following equation:

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Total Drug} - \text{Free Drug}}{\text{Total Drug}} \times 100$$

***In vitro drug* Release Study:**

The in vitro drug release of lapatinib-loaded cubosomes was carried out using the dialysis bag diffusion method. A pre-soaked dialysis membrane (molecular weight cut-off 12,000–14,000 Da) containing an accurately measured quantity of cubosomal dispersion equivalent to the required amount of lapatinib was immersed in 250 mL of phosphate buffer (pH 6.8 or pH 7.4) maintained at 37 ± 0.5°C. The dissolution medium was stirred continuously at 100 rpm using a magnetic stirrer or USP dissolution apparatus. At predetermined time intervals (0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours), 5 mL of the dissolution medium was withdrawn and replaced with an equal volume of fresh preheated buffer to maintain sink conditions. The withdrawn samples were filtered through a 0.45 µm membrane filter, suitably diluted, and analyzed using a UV–Visible spectrophotometer at the predetermined λmax of lapatinib. The cumulative percentage drug release was calculated and plotted against time.[11]

Drug release kinetics:

The in vitro drug release data obtained from the optimized cubosomal formulation were fitted into various kinetic models to determine the mechanism of drug release. The release data were analyzed using Zero-order, First-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell kinetic models. The cumulative percentage drug release was plotted according to the mathematical equations of each model, and the regression coefficient (R^2) was calculated. The model exhibiting the highest R^2 value was considered the best fit and was used to explain the drug release mechanism. The release exponent (n) obtained from the Korsmeyer–Peppas model was used to identify whether drug release followed Fickian diffusion, non-Fickian (anomalous) transport, Case-II transport, or Super Case-II transport. This analysis provided insight into the release behavior of lapatinib from the cubosomal drug delivery system.[12]

Stability Studies[13]

The stability studies of the optimized lapatinib-loaded cubosomal formulation were carried out according to the International Council for Harmonisation (ICH) Q1A(R2) guidelines to evaluate the physical and chemical stability of the formulation during storage.

The optimized cubosomal dispersion was transferred into clean, airtight, amber-coloured glass vials and stored under the following conditions:

- 25 ± 2°C / 60 ± 5% Relative Humidity (RH) (Long-term storage)
- 40 ± 2°C / 75 ± 5% Relative Humidity (RH) (Accelerated storage)

RESULTS AND DISCUSSION:

EVALUATION PARAMETERS:

Particle Size

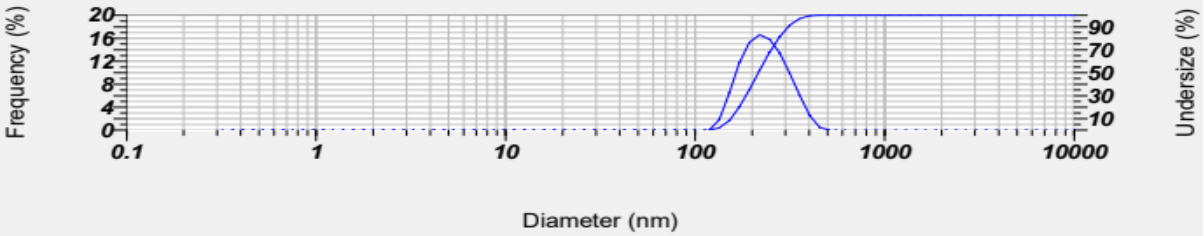

Fig-1: Particle size of optimized formulation

Determination of Vesicle morphology

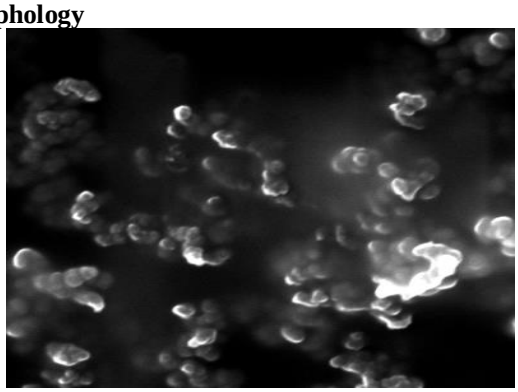

Fig-2: SEM Analysis of optimized formulation

Zeta potential:

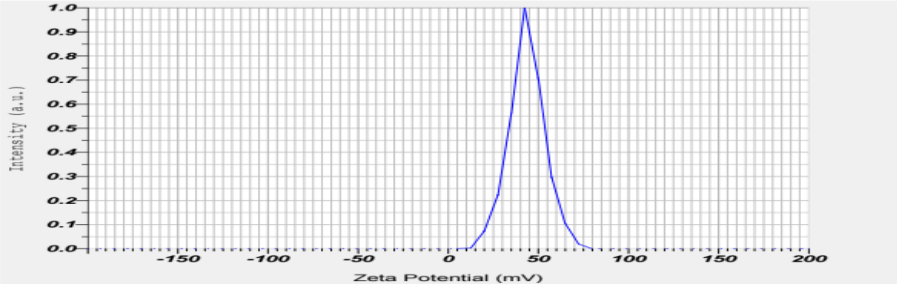

Fig-3: Zeta potential of optimized formulation

Table-2: Evaluation Studies of particle size and Zeta potential Cubosomes

F. No	Particle size (nm)	Zeta potential (mV)
F1	263	-25
F2	248	-29
F3	235	-26
F4	279	-27
F5	258	-30
F6	249	-26
F7	231	-27
F8	220	-23

Discussion

Vesicle Morphology (SEM Analysis)

The surface morphology of the optimized Lapatinib cubosome formulation was examined using Scanning Electron Microscopy (SEM). The SEM micrographs revealed that the cubosomes were nearly spherical in shape, uniformly distributed, and possessed smooth surfaces without visible aggregation or structural deformities.

Particle Size Analysis

The smaller particle size obtained with formulation F8 may be attributed to the optimum concentration of lipid and stabilizer, which facilitated efficient self-assembly of cubosomes and prevented particle aggregation. Nano-sized particles possess a larger surface area that enhances drug dissolution, promotes faster diffusion, and improves absorption across biological membranes. The narrow particle size distribution observed for the optimized formulation also indicates the uniformity and reproducibility of the preparation method.

Zeta Potential Analysis

Among all the formulations, F5 exhibited the highest negative zeta potential (−30 mV), followed by F2 (−29 mV), whereas the optimized formulation F8 showed a zeta potential of −23 mV. Although F8 exhibited a comparatively lower negative charge, its value was still within the acceptable range for stable nano-dispersions and was adequate to prevent significant particle aggregation. The combination of a small particle size (220 nm) and an appropriate zeta potential contributed to the excellent stability and uniform dispersion of the optimized formulation. Overall, the obtained zeta potential values demonstrate that the prepared cubosomes possessed satisfactory colloidal stability, ensuring maintenance of particle integrity during storage and drug release studies.

Entrapment Efficiency:

Table-3: Drug entrapment efficiency of all formulation

F.no	Drug entrapment efficiency
F1	85.69
F2	89.53
F3	91.25
F4	79.82
F5	92.25
F6	86.37
F7	93.15
F8	94.58

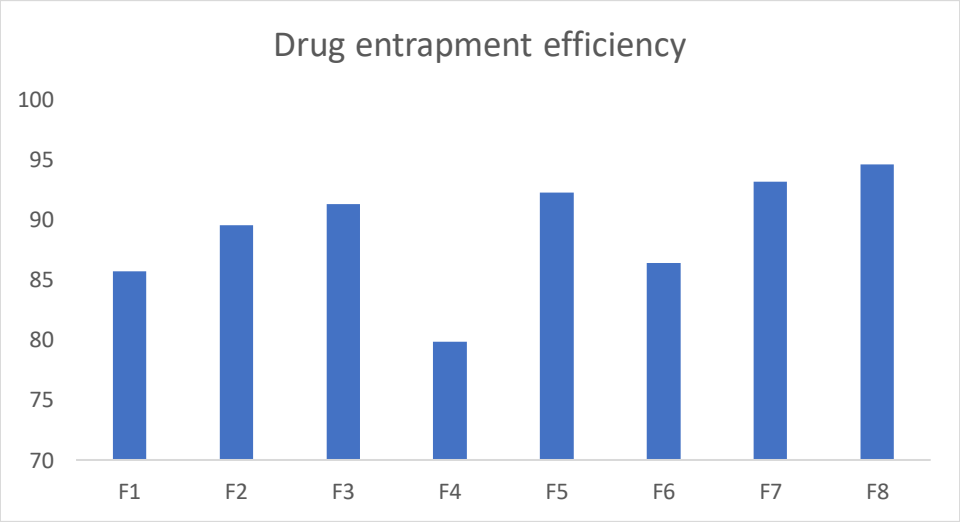

Fig-4: Drug entrapment efficiency of all formulation

Discussion:

The drug entrapment efficiency of the Lapatinib cubosome formulations (F1–F8) was determined to evaluate the ability of the cubosomal vesicles to encapsulate the drug effectively. Among all the formulations, F8 exhibited the highest drug entrapment efficiency (94.58%), followed by F7 (93.15%) and F5 (92.25%). The high entrapment efficiency observed in F8 may be attributed to the optimum concentration of lipid and stabilizer, which provided sufficient internal space for efficient drug encapsulation. Overall, the results indicate that increasing the lipid concentration improved the drug encapsulation efficiency, thereby enhancing the loading capacity of the cubosomes.

In vitro drug release studies:

Table-4: Results of Lapatinib cubosomes of all formulations

Time(hr.)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	20.19	19.85	18.76	21.18	23.59	25.19	24.31	28.49
2	35.49	34.46	35.46	36.59	38.27	37.46	33.39	37.48
3	43.57	41.19	42.27	43.78	47.48	43.18	44.78	48.69
4	55.98	54.20	56.91	57.81	58.20	51.47	52.18	57.86
6	62.37	63.19	65.49	66.98	68.97	62.35	63.50	68.49
8	73.58	75.58	76.81	77.82	76.82	74.48	71.49	78.58
10	82.19	83.15	85.49	80.98	82.19	81.37	83.25	89.69
12	92.58	93.56	94.57	93.35	95.47	92.28	97.48	98.76

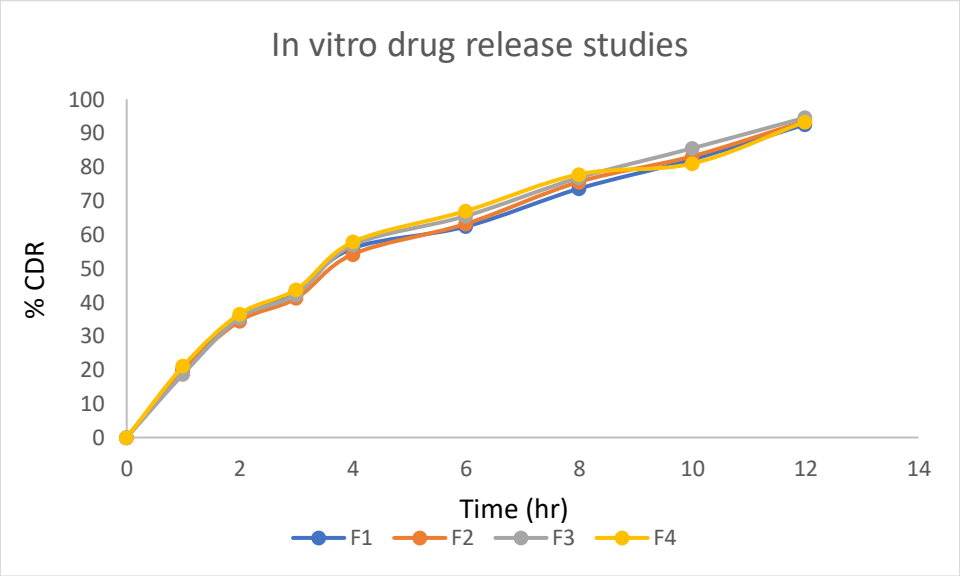

Fig-5: Drug release studies of (F1-F4) formulations

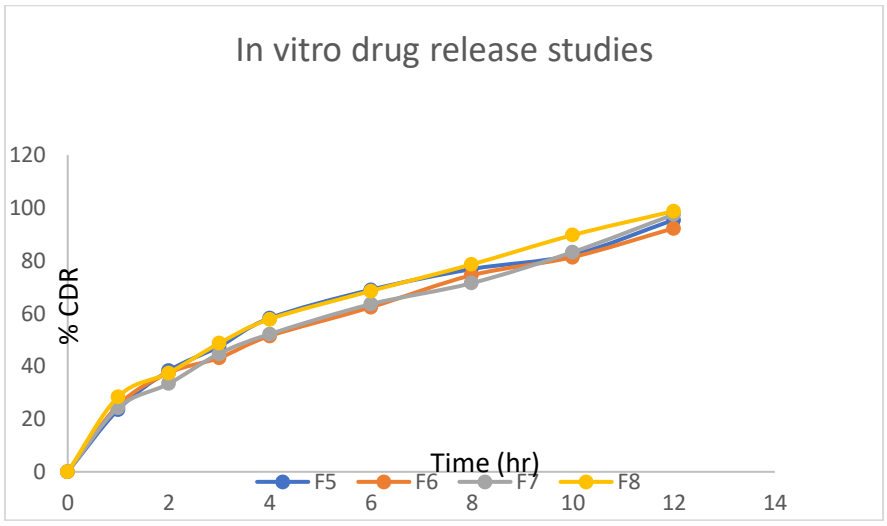

Fig-6: Drug release studies of (F5-F8) formulations

Discussion:

Among all formulations, F8 exhibited the highest cumulative drug release (98.76%), followed by F7 (97.48%), whereas F6 showed the lowest release (92.28%). The improved release profile of F8 can be attributed to its higher drug entrapment efficiency, optimum cubosomal structure, and efficient dispersion of the drug within the lipid matrix. The nano-sized cubosomes provide a larger surface area, facilitating faster diffusion of the drug into the dissolution medium while maintaining sustained release. The results indicate that formulation F8 successfully achieved prolonged drug release, making it suitable for sustained oral drug delivery.

Kinetic modelling of drug release

Zero order kinetics

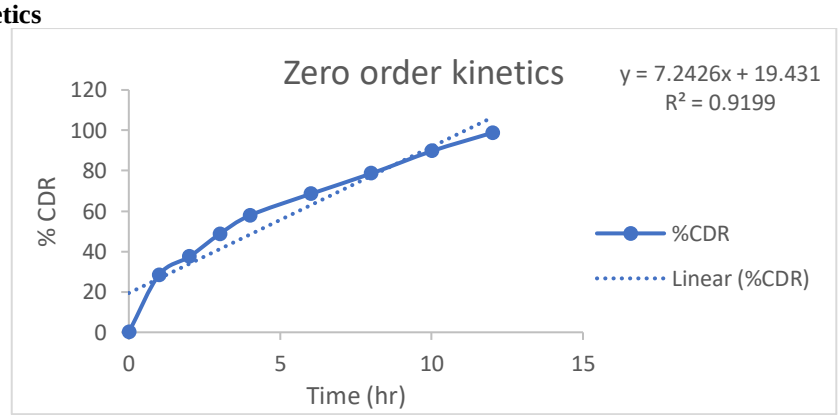

Fig-7: Zero order kinetics of optimized formulation

First order kinetics

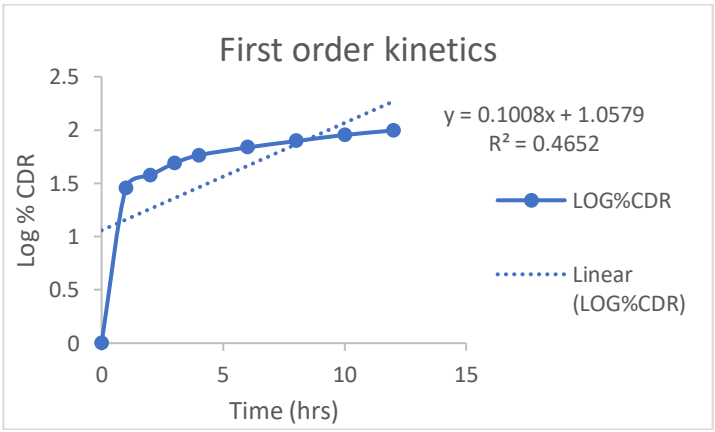

Fig-8: First order kinetics of optimized formulation

Higuchi model

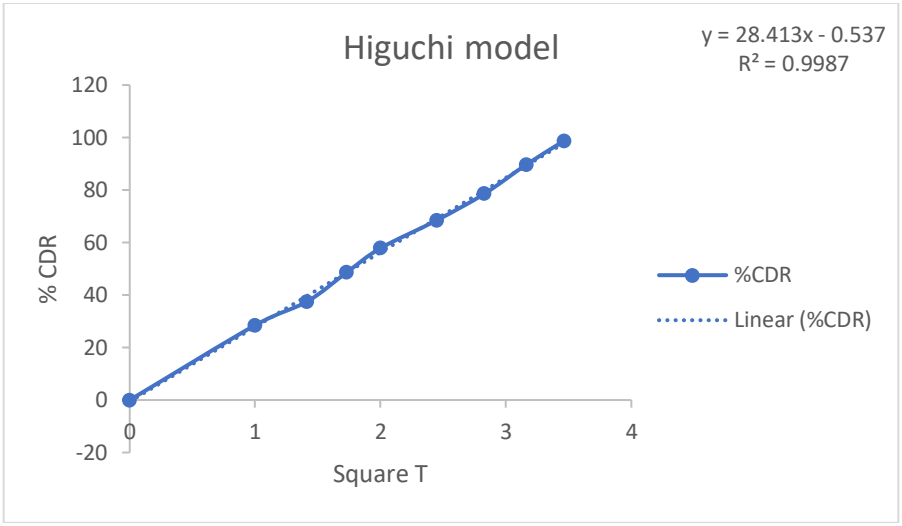

Fig-9: Higuchi model of optimized formulation

Korsmeyer peppas

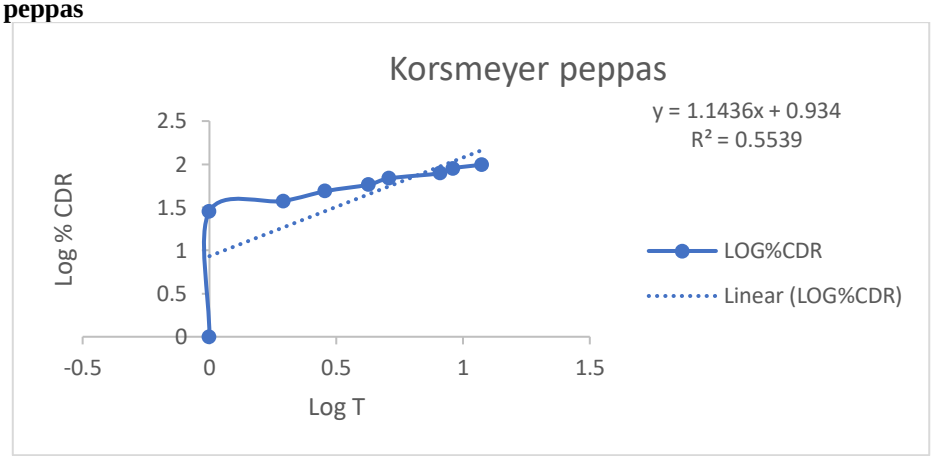

Fig-10: Korsmeyer peppas of optimized formulation

Discussion:

Among all the kinetic models, the Higuchi model showed the highest regression coefficient (R^2 = 0.998), indicating that the release of Lapatinib from the optimized cubosome formulation predominantly follows a diffusion-controlled mechanism. Drug molecules diffuse gradually through the lipid matrix of the cubosomes into the dissolution medium, resulting in sustained drug release. The comparatively lower regression coefficients obtained for the First-order and Korsmeyer–Peppas models suggest that these models are less suitable in describing the release behaviour of the optimized formulation.

Stability studies

Optimized formulations F8 was selected for accelerated stability studies as per ICH guidelines.

Table-5: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Formulation Code	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-8	98.76	97.58	96.19	95.75	Not less than 85 %
F-8	98.76	97.63	96.20	95.43	Not less than 85 %
F-8	98.76	97.15	96.53	95.16	Not less than 85 %

Discussion

The optimized formulation F8 was subjected to accelerated stability studies according to ICH guidelines at 40 ± 2°C and 75 ± 5% RH for a period of three months. The formulation was periodically evaluated for drug release.

The cumulative drug release decreased only slightly from the initial value of 98.76% to approximately 95.16–95.75% after three months of storage. Throughout the stability study, the formulation remained well above the specified acceptance limit of 85% drug release. No noticeable changes in appearance, phase separation, precipitation, or physical characteristics were observed during storage. These findings demonstrate that the optimized cubosome formulation possesses excellent physical and chemical stability under accelerated storage conditions and is suitable for long-term pharmaceutical application.

CONCLUSION:

The present investigation successfully developed and evaluated Lapatinib-loaded cubosomes as a novel sustained-release drug delivery system. Among all formulations, F8 was identified as the optimized formulation because it demonstrated the highest drug entrapment efficiency (94.58%), smallest particle size (220 nm), excellent cumulative drug release (98.76%), and satisfactory stability under accelerated storage conditions. The optimized formulation followed the Higuchi diffusion-controlled release model, indicating that drug release occurred primarily through diffusion from the cubosomal lipid matrix. The nano-sized cubosomes are expected to improve drug dissolution, gastrointestinal absorption, and oral bioavailability while providing prolonged therapeutic action and reducing dosing frequency. Overall, the developed Lapatinib cubosome formulation represents a promising nanocarrier system for sustained oral drug delivery and has the potential to enhance the clinical efficacy and patient compliance associated with Lapatinib therapy.

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