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Research Article

DESIGN, OPTIMIZATION AND CHARACTERIZATION OF
IVABRADINE CUBOSOMES FOR CONTROLLED DRUG
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H. Vasanth Kumar³, Aakanksha Mishra³^{*1} Assistant Professor, Department of Pharmaceutical Chemistry, Malla Reddy pharmacy college, Maisammaguda, Hyderabad, Medchal, Telangana - 500100, India.² Professor and Principal, Department of Pharmaceutical Analysis, Malla Reddy pharmacy college, Maisammaguda, Hyderabad, Medchal, Telangana - 500100, India.³ Student, Malla Reddy pharmacy college, Maisammaguda, Hyderabad, Medchal, Telangana - 500100, India.**Abstract:**

The present study was aimed at the formulation and evaluation of Ivabradine-loaded cubosomes for sustained drug delivery. Cubosomes are nanostructured lipid carriers that offer advantages such as high drug-loading capacity, controlled drug release, improved stability, and enhanced bioavailability. The objective of the study was to develop a stable cubosomal formulation of Ivabradine and evaluate its physicochemical characteristics and drug release behavior. Preformulation studies including organoleptic evaluation, solubility studies, melting point determination, calibration curve preparation, and Fourier Transform Infrared (FTIR) spectroscopy were carried out. FTIR studies confirmed the compatibility of Ivabradine with the selected excipients, indicating the absence of significant drug-excipient interactions. Ivabradine-loaded cubosomes were prepared by the top-down method using glyceryl monostearate as the lipid phase and Pluronic F127 as the stabilizer. The prepared formulations were evaluated for particle size, zeta potential, surface morphology, entrapment efficiency, and in vitro drug release. The particle size of the cubosomes ranged from 169 to 183 nm, while zeta potential values ranged from -25 to -30 mV, indicating good stability of the formulations. Entrapment efficiency was found to range between 79.80% and 85.92%. In vitro drug release studies demonstrated sustained release of Ivabradine over a period of 8 hours. Among all formulations, F4 showed the best performance with a particle size of 169 nm, zeta potential of -30 mV, entrapment efficiency of 85.92%, and cumulative drug release of 98.52%. Stability studies conducted according to ICH guidelines revealed that the optimized formulation remained stable under various storage conditions, with no significant changes in drug release characteristics. The results indicate that the developed Ivabradine-loaded cubosomal formulation is a promising carrier system for sustained drug delivery and may improve therapeutic efficacy and patient compliance.

Keywords: Ivabradine, Cubosomes, Glyceryl Monooleate, Poloxamer 407, Entrapment Efficiency, Sustained Release, Nanocarrier System.

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INTRODUCTION: CUBOSOMES

Cubosomes are nanostructured lipid-based drug delivery systems formed from bicontinuous cubic liquid crystalline phases. They are composed mainly of amphiphilic lipids such as glyceryl monooleate (GMO) or phytantriol, stabilized by surfactants like Poloxamer 407. When these lipids are dispersed in water under controlled conditions, they self-assemble into a three-dimensional cubic structure containing two continuous but non-intersecting aqueous channels separated by a lipid bilayer.¹ This unique internal structure provides cubosomes with a large internal surface area and the ability to encapsulate hydrophilic, lipophilic, and amphiphilic drugs simultaneously. Due to their nanoscale size and bioadhesive nature, cubosomes enhance drug solubilization, stability, and bioavailability. Cubosomes are considered promising carriers in Novel Drug Delivery Systems (NDDS) because they can provide controlled and sustained drug release. They have been widely investigated for oral, topical, transdermal, and parenteral drug delivery applications. Their structural similarity to biological membranes also contributes to improved drug absorption and reduced toxicity.²

Controlled drug delivery systems are designed to release therapeutic agents at a predetermined rate for a specified period of time in order to maintain optimal drug concentration within the therapeutic window. Conventional dosage forms often produce fluctuations in plasma drug levels, leading to reduced efficacy and increased side effects. Therefore, there is a growing need for advanced delivery systems that can provide sustained and controlled release while improving bioavailability and patient compliance.³

Cubosomes have emerged as a promising nanostructured lipid carrier for controlled drug delivery. They are discrete nanoparticles formed from the fragmentation of bulk cubic liquid crystalline phases composed of amphiphilic lipids such as glyceryl monooleate or phytantriol, stabilized by surfactants like Poloxamer 407. Cubosomes possess a unique bicontinuous cubic structure consisting of two non-intersecting aqueous channels separated by a lipid bilayer arranged in a three-dimensional periodic pattern. This internal structure provides a large surface area and enables encapsulation of hydrophilic, lipophilic, and amphiphilic drugs. Cubosomes are versatile carriers suitable for various routes of administration, including oral, topical, ocular, and parenteral delivery. Their biocompatibility, biodegradability, and ability to improve solubility make them especially useful for poorly water-soluble drugs. Furthermore, the release rate can be modified by

adjusting formulation variables such as lipid concentration, type of stabilizer, and particle size.⁴

MATERIALS

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

METHODOLOGY:

Fourier transform infrared spectroscopy:

A small quantity of Ivabradine hydrochloride was accurately weighed and mixed thoroughly with dry potassium bromide (KBr) in a mortar and pestle. The mixture was compressed into a transparent pellet using a hydraulic press. The prepared pellet was placed in the sample holder of the FTIR spectrophotometer, and the spectrum was recorded over a range of 4000–400 cm⁻¹.

Formulation development

Top-Down Method

Table-1: Formulation development

Ingredients(mg)	F1(1:1)	F2(1:2)	F3(1:3)	F4(1:4)
Ivabradine	10	10	10	10
Glyceryl monostearate	100	200	300	400
Pluronic F-127	100	100	100	100
Ethanol	10	10	10	10
Water	q. s	q. s	q.s	q. s

Method of Preparation:⁵

Top-Down Method

Preparation of Lipid Phase

Accurately weighed quantity of glyceryl monostearate (as per formulation F1–F4) was taken in a clean beaker and melted at 60–70°C (above its melting point). Ivabradine (10 mg) was added to the molten lipid and mixed thoroughly to obtain a uniform drug–lipid mixture.

Addition of Organic Solvent

Ethanol (10 mL) was added to the molten lipid mixture to facilitate proper dissolution and uniform distribution of the drug in the lipid phase. The mixture was stirred continuously until a clear solution was obtained.

Preparation of Aqueous Phase

Pluronic F-127 (100 mg) was dissolved in a required quantity of distilled water under continuous stirring to form a clear aqueous solution. The aqueous phase was maintained at the same temperature as the lipid phase.

Formation of Bulk Cubic Phase

The molten lipid phase containing the drug was slowly added to the aqueous phase with continuous stirring at 1000–1500 rpm. The mixture was allowed to hydrate, forming a bulk cubic phase precursor, which upon homogenization produced cubosomal nanoparticles.³⁵

Homogenization (Size Reduction)

The formed bulk cubic phase was subjected to high-speed homogenization (10,000–15,000 rpm) for 5–10 minutes to reduce particle size and obtain a uniform cubosomal dispersion.

Sonication

The dispersion was further sonicated using a probe sonicator for 3–5 minutes to reduce particle size and improve uniformity.

Cooling and Storage

The final cubosomal dispersion was allowed to cool to room temperature and stored in airtight containers at refrigerated conditions until further evaluation.

Evaluation of Cubosomes:

Particle size

The particle size of Ivabradine cubosomes were determined using Dynamic Light Scattering (DLS) technique. A small quantity of cubosomal dispersion was diluted appropriately with distilled water to avoid multiple scattering effects. The diluted sample was transferred into a clean cuvette and placed in a particle size analyzer. Measurements were performed at 25°C, and the average particle size was recorded. All measurements were carried out in triplicate, and the mean values were reported.⁶

SEM analysis:

The particle shape, surface texture, and aggregation behavior were evaluated. A drop of cubosomal dispersion was placed on a clean glass slide or aluminum stub and allowed to dry at room temperature. The dried sample was coated with a thin layer of gold using a sputter coater to make it electrically conductive. The sample was then placed in the SEM chamber and observed at suitable magnifications. The shape, surface characteristics, and structural integrity of the cubosomes were recorded.

Zeta potential:

Zeta potential was measured to determine the surface charge and stability of the cubosomal dispersion. The cubosomal formulation was diluted suitably with distilled water and filled into a zeta potential cell. The sample was analyzed using a zeta potential analyzer based on electrophoretic mobility. The measurements were performed at 25°C, and the average zeta potential value was recorded. The analysis was conducted in triplicate.⁷

Entrapment efficiency:

Entrapment efficiency was determined by separating free drug from entrapped drug using centrifugation. A known volume of cubosomal dispersion was placed in centrifuge tubes and centrifuged at 15,000 rpm for 30–45 minutes. The supernatant containing free (unentrapped) Ivabradine was carefully

collected and analyzed using a UV–Visible spectrophotometer at 286 nm after suitable dilution.

$$EP = [(C_t - C_r) / C_t] * 100$$

where,

C_t, concentration of total Ivabradine,

C_r, concentration of free Ivabradine.

In vitro drug Release Study:

The in vitro drug release of Ivabradine from cubosomal formulations was carried out using the dialysis bag diffusion method. A dialysis membrane (molecular weight cut-off 12,000–14,000 Da) was soaked in distilled water for 8 hours prior to use to ensure proper hydration. An accurately measured quantity of cubosomal dispersion equivalent to a known amount of Ivabradine was placed inside the pre-soaked dialysis bag, and both ends were securely tied to prevent leakage. The dialysis bag was immersed in 100 mL of dissolution medium maintained at 37 ± 0.5°C. The medium (Phosphate buffer pH 7.4) was stirred continuously at 50–100 rpm using a magnetic stirrer to maintain uniform conditions and sink conditions throughout the experiment. At predetermined time intervals 5 mL of sample was withdrawn from the dissolution medium and immediately replaced with an equal volume of fresh pre-warmed medium to maintain constant volume and sink conditions. The withdrawn samples were filtered if necessary, suitably diluted, and analyzed using a UV–Visible spectrophotometer at the λ_{max} of Ivabradine. The cumulative percentage drug release was calculated and plotted against time to evaluate the release profile of the cubosomal formulation.⁸

Stability Studies:

Stability studies were performed according to ICH guidelines to evaluate the physical and chemical stability of the optimized cubosomal formulation. The optimized formulation was filled in airtight glass containers and stored under the following conditions: The formulation was evaluated at 0, 30, 60 and 90 days for physical appearance, particle size, entrapment efficiency and drug release.⁹

- **Long-term condition:** 25 ± 2°C / 60 ± 5% RH
- **Accelerated condition:** 40 ± 2°C / 75 ± 5% RH

RESULT & DISCUSSION:

Drug - excipient compatibility studies (FT-IR):

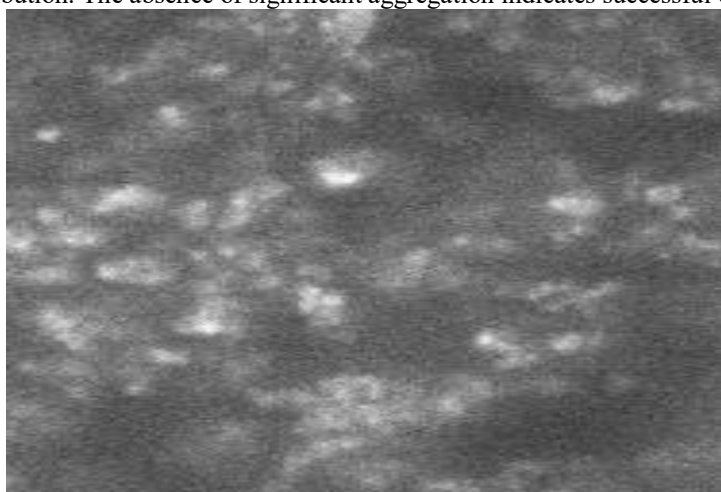
The compatibility between the Ivabradine and the selected excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug and excipients mixture, which confirmed the absence of any chemical interaction between the drug and excipients and other chemicals.

Table-3: Characteristic Peaks of Optimized formulation

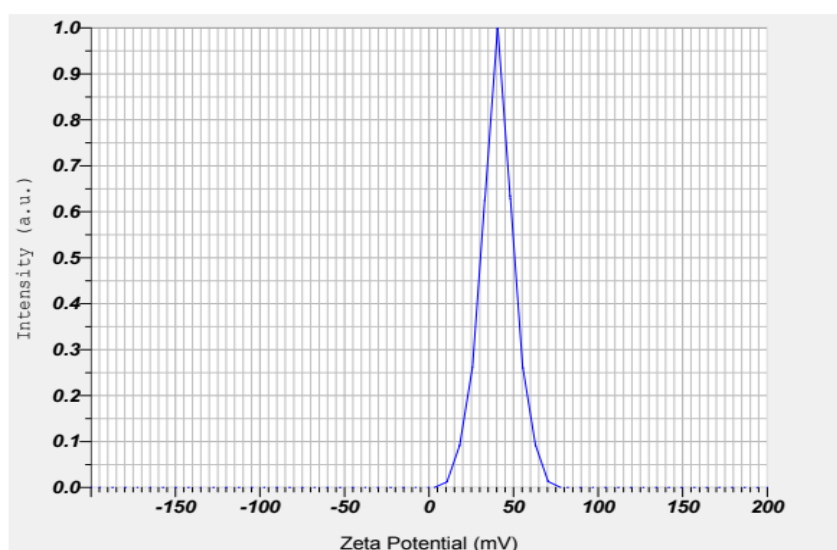
S. No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	N-H stretching	3300-3500	3432.34
2	C-H stretching	2850-3000	2978.19
3	C=O stretching	1650-1750	1730.21
4	C-N stretching	1200-1350	1274.13

EVALUATION PARAMETERS:**Determination of Vesicle morphology and Size**

SEM analysis revealed that the prepared cubosomes were nearly spherical in shape with a smooth surface and uniform particle distribution. The absence of significant aggregation indicates successful cubosome formation.

**Fig-3: SEM Analysis of optimized formulation****Particle Size and Zeta Potential**

The particle size of the formulated cubosomes ranged from 169 to 183 nm. Formulation F4 exhibited the smallest particle size (169 nm), which may contribute to improved drug release and stability. Zeta potential values ranged from -25 to -30 mV, indicating good colloidal stability of the formulations.

Zeta potential:**Fig-4: Zeta potential of optimized formulation**

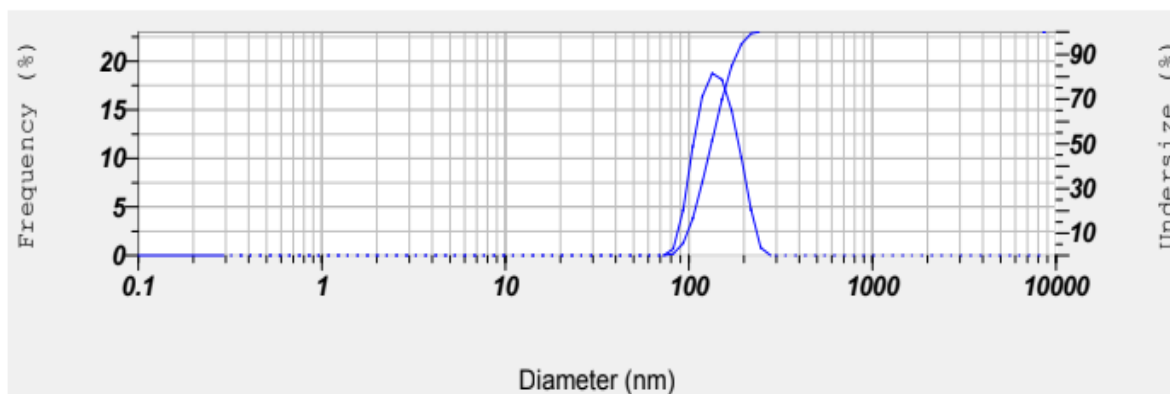


Fig-5: Particle size of optimized formulation

Table-4: Evaluation Studies of particle size and Zeta potential Cubosomes

F. No	Particle size (nm)	Zeta potential (mV)
F1	175	-25
F2	178	-29
F3	183	-26
F4	169	-30

Entrapment Efficiency:

The entrapment efficiency of all formulations was evaluated and is presented in Table 9. Entrapment efficiency ranged from 79.80% to 85.92%, with formulation F4 exhibiting the highest value (85.92%). This may be attributed to the optimized lipid-to-surfactant ratio, which facilitated efficient drug encapsulation within the cubosomal structure.

Table-5: Drug entrapment efficiency of all formulation

F.no	Drug entrapment efficiency
F1	82.39
F2	81.54
F3	79.80
F4	85.92

Entrapment efficiency ranged from 79.80% to 85.92%. Formulation F4 showed the highest entrapment efficiency (85.92%), indicating efficient incorporation of Ivabradine within the cubosomal structure.

In vitro drug release studies:

Table-6: Results of Ivabradine cubosomes of all formulations

Time(hr.)	F1	F2	F3	F4
0	0	0	0	0
1	17.12	18.15	19.25	19.62
2	24.69	28.98	36.88	37.55
3	39.86	45.86	47.55	44.78
4	47.96	52.68	58.75	50.27
5	59.45	67.85	69.38	65.28
6	70.25	71.25	75.86	72.85
7	81.26	80.45	84.40	84.64
8	93.68	94.50	95.28	98.52

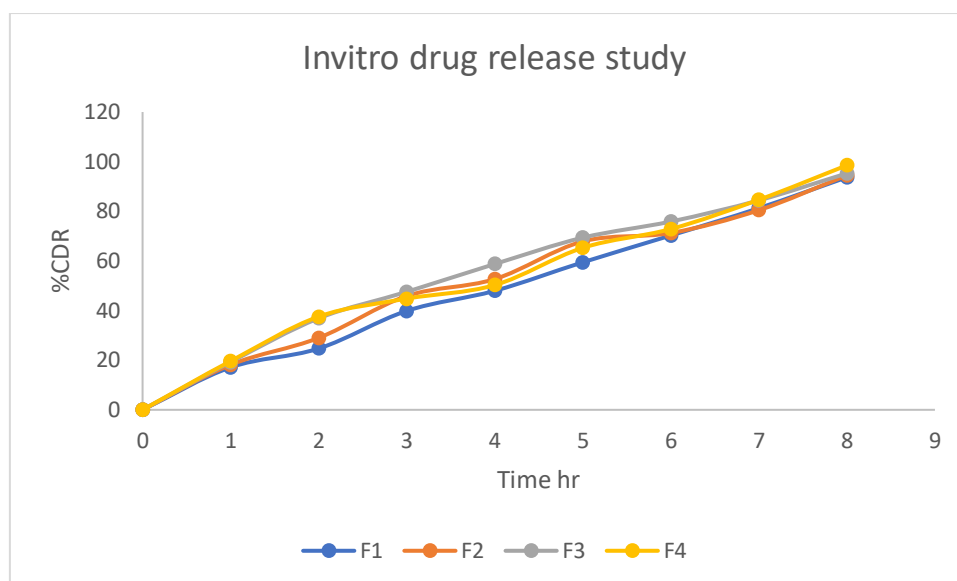


Fig-6: Drug release studies of (F1-F4) formulations

The in vitro drug release study demonstrated sustained release of Ivabradine from all cubosomal formulations over a period of 8 hours. Drug release increased gradually with time for all formulations. Among the formulations, F4 exhibited the highest cumulative drug release of 98.52% at the end of 8 hours. The enhanced release from F4 may be attributed to its optimal lipid-to-surfactant ratio, smaller particle size, and higher entrapment efficiency. These results suggest that F4 is the optimized formulation for controlled drug delivery.

Stability studies

Optimized formulations F4 was selected for accelerated stability studies as per ICH guidelines.

Table-7: Stability studies of optimized formulations at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 3 months

Formulation Code	Initial	1 st Month	2 nd Month	3 rd Month	Limits as per Specifications
F-4 (25°C/60% RH)	98.52	97.86	96.75	95.72	Not less than 85 %
F-4 (30°C/75% RH)	98.52	97.52	96.25	95.36	Not less than 85 %
F-4 (40°C/75% RH)	98.52	97.43	96.42	95.20	Not less than 85 %

SUMMARY AND CONCLUSION:

The present study was successfully carried out to formulate and evaluate Ivabradine-loaded cubosomes using the top-down method. Preformulation studies confirmed the identity, purity, and compatibility of Ivabradine with the selected excipients. FTIR studies revealed no significant drug–excipient interactions, indicating the suitability of the formulation components. Cubosomal formulations (F1–F4) were successfully prepared using glyceryl monostearate and Pluronic F127. The prepared cubosomes exhibited particle sizes in the nanometer range (169–183 nm) with satisfactory zeta potential values (–25 to –30 mV), indicating good colloidal stability. SEM analysis confirmed the formation of discrete cubosomal particles with appropriate morphology. The entrapment efficiency of the

formulations ranged from 79.80% to 85.92%, demonstrating efficient incorporation of Ivabradine within the cubosomal system. In vitro drug release studies showed sustained drug release over a period of 8 hours for all formulations. Among the formulations, F4 exhibited the highest entrapment efficiency (85.92%), smallest particle size (169 nm), highest zeta potential magnitude (–30 mV), and maximum cumulative drug release (98.52%) at the end of 8 hours. Stability studies performed according to ICH guidelines demonstrated that the optimized formulation remained stable under different storage conditions, with no significant reduction in drug release during the study period. Based on the overall evaluation results, formulation F4 was identified as the optimized formulation.

CONCLUSION:

Therefore, it can be concluded that Ivabradine-loaded cubosomes represent a promising nanocarrier system capable of providing sustained drug release, improved stability, and enhanced therapeutic performance. Further in vivo and pharmacokinetic studies may be conducted to establish the clinical potential of the optimized cubosomal formulation.

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