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Formulation and Assessment of Novel Ivabradine Hydrochloride Microspheres Using Synthetic Polymers

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Abstract

The research centers on developing Ivabradine hydrochloride microspheres through solvent evaporation with synthetic polymers including cellulose acetate, ethyl cellulose, and eudragit RS100. The research tries to make the drug more effective medicinally while managing its release pattern. Various features of manufactured microspheres underwent evaluation through tests for drug loading assessment and measurement of encapsulation efficiency exams as well as morphological examination and particle dimension assessments. Researchers evaluated Ivabradine HCl microsphere controlled drug release patterns through laboratory-based testing assessments. The development of Ivabradine HCl microspheres using the solvent evaporation method succeeded with the combination of cellulose acetate, ethyl cellulose, and eudragit RS100 in ratios of 1:1, 1:1.5, and 1:2. SEM results verified that the microspheres maintained consistent spherical shapes among uniformly distributed particles. The in vitro dissolution investigation showed Ivabradine HCl released at a greater rate when exposed to pH 7.4 solution than when placed in solutions of pH 1.2 & 5.5. The controlled release of drug process of microspheres reached 90% and continued throughout twelve hours of evaluation in phosphate buffer solution maintained at pH 7.4. Microspheres made using 1:2 ratio of cellulose acetate together with span 80 achieved optimal controlled release throughout a 12-hour period. All tests showed that drug-excipient reactions did not occur which points to the formulation's stable state. The research data suggests that Ivabradine HCl microsphere technology demonstrates capabilities as an efficient controlled-release delivery system and enhanced medication compliance platform.

Keywords: Ivabradine hydrochloride, Microspheres, Solvent evaporation, Particle size, Drug loading, Encapsulation efficiency

Introduction

Microspheres exist as round-shaped particles whose typical dimensions fall between 1 and 1000 micrometers according to (1,2). Drugs delivered through microspheres have become a common technology in numerous scientific applications especially through drug delivery systems mainly because of these unique properties (3-5). Through encapsulation microspheres function as drug delivery units that enable timed drug distribution which enhances both drug availability and effectiveness (6). The versatility of microspheres enables them to function as carriers which deliver therapeutic and diagnostic drugs through effective targeted systems with controlled release mechanisms (7,8).

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Medical experts use Ivabradine hydrochloride to treat chronic heart failure together with angina pectoris and sinus tachycardia (9). The action of ivabradine hydrochloride targets If currents inside the sinoatrial node pacemaker cells (10). Ivabradine determines a reduced heart rate through its mechanism which controls the movement of sodium and potassium ions thereby decreasing depolarization rate (11-13). The heart rate control mechanism of Ivabradine operates independently from blood pressure regulation and myocardial output along with cardiac conduction (14).

The preparation of Ivabradine hydrochloride microspheres through solvent evaporation technique using synthetic polymers such as cellulose acetate, ethyl cellulose, and eudragit RS100 (15-17) brings multiple important advantages:

- The main advantage of incorporating microspheres in this formulation is achieving controlled drug release kinetics for Ivabradine HCl. The improved bioavailability of this formulation through microsphere technology creates long-term therapeutic outcomes which results in fewer medication administrations and better patient adherence (18).
- The release technique controls drug levels in bloodstreams to minimize side effect risks and toxicities. A controlled drug delivery system maintains a steady therapeutic level throughout an extended period because the drug releases gradually (19).
- Microsphere formulations made from cellulose acetate and ethyl cellulose and eudragit RS100 protect molecules of Ivabradine hydrochloride by preventing environmental factors from degrading it which extends its storage duration (20).
- The microspheres provide a delivery method which allows medical personnel to control where Ivabradine HCl releases in the gastrointestinal tract for better bioavailability and therapeutic effects (21).
- Industrial use becomes viable because the solvent evaporation method applied for this formulation enables scalable and affordable manufacturing at large scales (22).
- Drug loading efficiencies and desired release profiles exist within reach because this formulation allows adjustments of polymers' type and concentration (23).

This research demonstrates Ivabradine HCl microspheres function as an innovative drug delivery method that delivers controlled medication distribution with high efficiency and convenience for patients (24,25).

Main objective of this research implements development & evaluation of Ivabradine hydrochloride microspheres formed using synthetic polymers cellulose acetate, ethyl cellulose along with eudragit RS100 through solvent evaporation method. Ivabradine's therapeutic efficacy and bioavailability together with reduced side effects will be the main outcomes of developing a controlled-release delivery system by achieving sustained drug release.

The main focus of this research project contains two parts: developing Ivabradine hydrochloride microspheres by combining cellulose acetate with ethyl cellulose and eudragit RS100 through solvent evaporation while studying drilling parameters and solution

Table 1: Formulation of Ivabradine HCl microspheres

Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ivabradine (mg)	100	100	100	100	100	100	100	100	100
Cellulose acetate (mg)	100	150	200	--	--	--	--	--	--
Ethyl cellulose (mg)	--	--	--	100	150	200	--	--	--
Eudragit RS100 (mg)	--	--	--	--	--	--	100	150	200
Span 80 (%)	1	1	1	1	1	1	1	1	1

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evaporation parameters. A range of tests will be performed on the microspheres to determine their dimensions, shape, drug content, uptake rate and release profile measurements in vitro. The stability between Ivabradine HCl and excipients will be determined through DSC and FTIR examinations. Studies of drug release kinetics will determine which drug delivery method provides sustained drug release while achieving therapeutic advantages.

Materials and Methods

Drugs and Chemicals

Ivabradine hydrochloride arrived as a gift donation from Shree Icon Pharmaceutical Laboratories operating in Vijayawada. The suppliers Yarrow Chem Products in Mumbai delivered cellulose acetate together with ethyl cellulose and eudragit RS100. The laboratory obtained all chemicals and solvents including sodium hydroxide, potassium dihydrogen orthophosphate, methanol, dichloromethane, chloroform, liquid paraffin, and span 80 from S.D. Fine-Chem Limited in Mumbai. The research utilized analytical-grade solvents together with all AR chemicals.

Preparation of Ivabradine HCl loaded microspheres

The preparation of Ivabradine hydrochloride-loaded microspheres happened by applying the solvent evaporation method with cellulose acetate, ethyl cellulose, and eudragit RS100 as components. Scientists combined all polymers with methanol and dichloromethane solutions at 25°C while using 300rpm of stirring force to obtain homogenous solutions. The mixed polymer solutions reached complete homogeneity before combining them together. The clear drug solution obtained from stirring with 300 rpm in methanol allowed slow addition into the polymer mixture which also stirred at 300 rpm for maintaining uniformity. A mixture of 1% Span 80 and liquid paraffin required 500rpm of stirring to achieve its external phase preparation. A gradual addition of drug-polymer solution took place into liquid paraffin with span 80 at 40°C under 800 rpm stirring. The mixture needed 3 hours of stirring to finish the evaporation process of all organic solvents. The microsphere isolation process started with solvent removal and included three rounds of hexane wash followed by 24 hours of oven drying at 45°C. The layout describing the microsphere formulation procedure can be found in Table 1.

Characterization

Percentage yield determination

The researchers obtained the weight of dried microspheres to determine percentage yield based on this calculation:
Percentage yield = Weight of microspheres / Total weight of drug and polymer x 100

Drug loading and entrapment efficiency

Measurement of drug amount present in microspheres required dissolving 100 mg microspheres in 100 mL phosphate buffer at pH 7.4 during a 12-hour incubation at 37°C. UV-Vis spectrophotometer measurements with 0.45 µm syringe filtration steps analyzed solution at 286 nm. The microsphere drug loading determination required the usage of this equation:

The calculation involves dividing the microsphere weight by their total weight to obtain the percentage drug loading.

The method to determine entrapment efficiency required the following calculation:

The calculation for entrapment efficiency requires division of the difference between drug added and the amount of unentrapped drug by drug added followed by multiplication by 100.

Micromeritic properties of microspheres

Microsphere flow evaluations included measuring angle of repose together with bulk density & tapped density and compressibility index and Hausner's ratio. The researchers utilized the below equations to measure these properties.

Angle of repose, $\theta = \tan^{-1}(\text{height/radius})$

The microsphere bulk density calculation consists of the microsphere

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weight measurement divided by their volume measurement.

Tapped density provides ratio between microsphere weight & its bulk volume.

Compressibility index = Tapped density – Bulk density / Tapped density x 100

Hausner's ratio = Tapped density / Bulk density

Determination of particle size

Research workers measured microsphere mean size through optical microscope that had pre-calibrated ocular & stage micrometer. The evaluation of hundred particles took place for every formulation.

Fourier transform infrared spectroscopy (FTIR)

Evaluation based on FTIR spectroscopy helped assess drug-excipient compatibility and detect their mutual interactions to anticipate drug-excipient bonding properties. A Bruker FTIR spectrophotometer analyzed both pure drug and polymers together with unloaded and loaded microspheres for examination. Disclosures of the samples occurred at wavelengths from 4000 to 500 cm^{-1}.

Scanning electron microscopy (SEM)

A double adhesive stub allowed researchers to place microspheres on one side for gold dust coating as a preparation method for SEM analysis. The Hitachi S-3700N scanning electron microscope evaluated surface characteristics and morphology of loaded and unloaded microspheres through multiple magnification points.

Thermal analysis

The drug nature within various formulations came to light after DSC analysis was performed on pure drug, cellulose acetate and ethyl cellulose and eudragit RS100 and unloaded microspheres and Ivabradine-loaded microspheres. A joint procedure using the STD Q600 DSC Analyzer (USA) took place during analysis. A 4-5 mg sample of crushed microspheres received assessment after placing it in aluminum pans that were sealed for analysis. The analysis procedure involved heating the microsphere samples from 40°C to 350°C at 10°C/min under 100 mL/min of nitrogen gas stream through the equipment which was calibrated with indium.

In vitro drug release profile

In vitro drug release examination of Ivabradine-loaded microspheres occurred on USP XXIII dissolution paddle equipment under 100 rpm rotation speed at 37 ± 0.5°C. A portion of 100 mg accurately weighed microspheres received placement in cellulose dialysis membrane before membrane was tied to paddles. Three different dissolution pools of phosphate buffer solution at pH 1.2, 5.5 & 7.4 had 900 mL volume. The dissolution medium received samples through nine specific time points spanning from 0.5 to 1, 2, 3, 4, 6, 8, 10, and 12 hours. The absorbance measurements for Ivabradine took place using a UV-Vis spectrophotometer at 286 nm for 5 mL sample aliquots. Fresh phosphate buffer solution with equivalent volume served to keep the dissolution medium in sink conditions. The drug concentration measurements took place in three repetitions and the quantitative values were obtained from a calibration curve for standard solutions.

Drug release kinetics

In vitro drug release data can be analyzed using several kinetic models, each offering a different approach to understanding the release mechanism:

- Zero-order model: The release follows a constant rate, described by the equation Ft=K0tF_t = K_0 t, where FtF_t represents the fraction of the drug released at time tt, and K0K_0 is the zero-order release rate constant.
- First-order model: The release follows an exponential decay, given by ln

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(1−F)=−K1t\ln(1 - F) = -K_1 t, where FF is the fraction of drug released at time tt, and K1K_1 is the release constant associated with first-order kinetics.

- Higuchi model: This model describes drug release through a square root of time dependence, represented as F=K2t1/2F = K_2 t^{1/2}, where K2K_2 is Higuchi's constant, and FF is the fraction of the drug released at time tt.
- Korsmeyer-Peppas model: This model accounts for drug release through a power-law expression: MtM=K3tn\frac{M_t}{M} = K_3 t^n, where MtM_t is the amount of drug released at time tt, MM is the total drug released at infinite time, K3K_3 is the Korsmeyer-Peppas constant, and nn is the diffusion exponent.

In the case of microspheres, the value of nn helps identify the release mechanism:

If nn is less than 0.43, the release mechanism follows Fickian (Case I) diffusion.

If nn falls between 0.43 and 0.85, the release mechanism is non-Fickian (Case II), which suggests a zero-order drug release pattern.

Results and Discussion

% Entrapment efficiency & percentage yield of microspheres

Oil-in-oil (O/O) solvent evaporation approach was used to prepare Ivabradine-loaded microspheres in current research. Researchers selected this method because both drug substance & polymers had solubility in dichloromethane & methanol. Solution contained homogeneous mixtures of Cellulose acetate, ethyl cellulose, eudragit RS100, Ivabradine dissolving in methanol. prepared solution was transferred to a 1% span 80 solution of external phase under conditions of 800 rpm stirring at 40°C for three hours. Microspheres obtained from solution after solvent evaporation completed. Microsphere collection process included cleaning particles 3 times through n-hexane washes to eliminate excess oil. Drying process lasted for one night inside oven set at room temperature conditions.

Percentages of entrapment efficiency reached 96.46, 97.77 & 97.95 respectively when producing Ivabradine HCl microspheres with different ratios of cellulose acetate while percentage yields stood at 92.35, 94.56, & 98.69. Ivabradine HCl microspheres encapsulated with ethyl cellulose displayed entrapment efficiencies exceeding 97% while achieving percentage yields exceeding 94%. At different ratios tested efficacy reached 97.12% for 97.12% yield, 98.22% for 95.24% yield & 98.21% for 98.18% yield respectively. Entrapment efficiency (%) of Ivabradine HCl microspheres prepared with eudragit RS100 at different ratios reached 98.08, 98.35, & 97.70 while corresponding percentage yields amounted to 96.14, 97.38, & 98.29. Ivabradine HCl Formulation data presented in Table 2 displays trapped drug amounts & yield results from different polymer compositions.

Particle size & morphology of microspheres

The studies utilized scanning electron microscopy (SEM) to examine microsphere shape together with surface morphology. microsphere images in Figure 1 presented spherical shapes along with smooth surfaces regardless of whether particles contained loading materials or not. Table shows mean particle sizes of different microsphere formulations as displayed in Table 3. As formulations contained more polymer their microsphere particles became larger.

Table 2: Results of entrapment efficiency & percentage yield of microspheres

Formulation	% Entrapment efficiency	Percentage yield
F1	96.46	92.35
F2	97.77	94.56
F3	97.95	98.69
F4	97.12	94.67
F5	98.22	95.24
F6	98.21	98.18
F7	98.08	96.14
F8	98.35	97.38
F9	97.70	98.29

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Micromeritic properties microspheres

The micromeritic property assessment comprised bulk & tapped density measurements & evaluations of compressibility index & Hausner's ratio & angle of repose assessments of all 9 formulations. Compressibility index values extended between 11 & 15 which indicated proper flow characteristics. flow properties appeared good based on Hausner's ratio values between 1.12 & 1.18. All measured angle of repose values flanked by 25° to 30° show that microspheres exhibit superior flow abilities. A table presents test results Table 4.

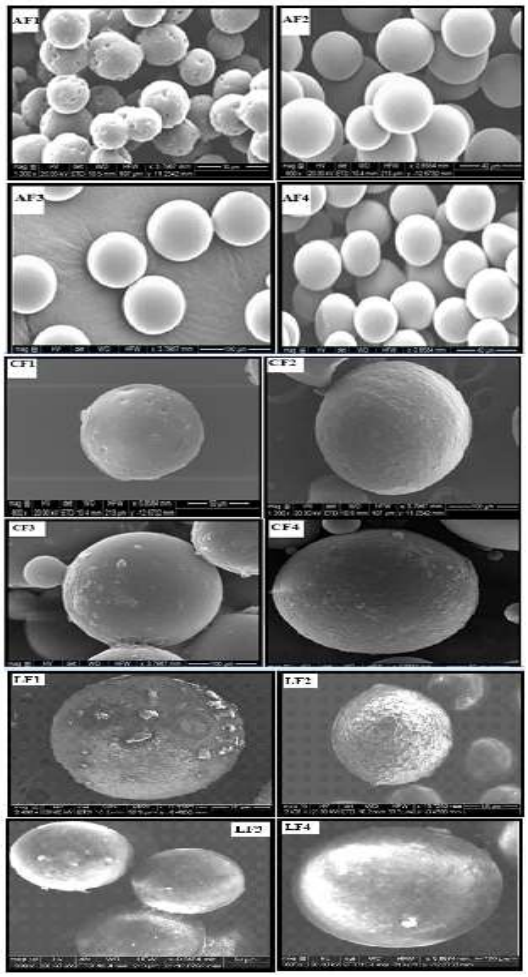

Figure 1: SEM images of Ivabradine-loaded microspheres prepared by using cellulose acetate, ethyl cellulose, eudragit RS100 with drug & polymer

Fourier transform infrared spectroscopy (FTIR)

Figure 2 presents the FTIR spectra of Ivabradine HCl along with its individual components-cellulose acetate, ethyl cellulose, and Eudragit RS100—and both empty and drug-loaded microspheres. The FTIR spectrum of Ivabradine HCl shows several key characteristic peaks: O-H stretching bands at 3061 cm^{-1}, C-H asymmetric stretching bands at 1585 cm^{-1}, C=O stretching bands at 1565 cm^{-1}, C-O-C asymmetric bending bands at 743 cm^{-1}, and C-O-C symmetric bending bands at 3061 cm^{-1}.

When Ivabradine HCl was mixed with cellulose acetate, the IR spectrum displayed O-H stretching bands at 3065 cm^{-1}, C-H asymmetric stretching bands at 1594 cm^{-1}, C=O stretching bands at 1568 cm^{-1}, C-O-C asymmetric bending bands at 750 cm^{-1}, and C-O-C symmetric bending bands at 3065 cm^{-1}. The FTIR spectrum of the drug combined with ethyl cellulose showed O-H stretching bands at 3063 cm^{-1}, C-H asymmetric stretching bands at 1591 cm^{-1}, C=O stretching bands at 1565 cm^{-1}, C-O-C asymmetric bending bands at 748 cm^{-1}, and C-O-C symmetric bending bands at 3063 cm^{-1}.

Table 3: Results of mean particle size & shape of microspheres

Formulation	Particle size (µm)	Shape
F1	561.28	Spherical
F2	579.16	Spherical
F3	588.26	Spherical
F4	522.17	Spherical
F5	548.28	Spherical
F6	568.19	Spherical
F7	503.56	Spherical
F8	521.37	Spherical
F9	546.61	Spherical

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For the drug mixed with Eudragit RS100, the FTIR spectrum revealed O-H stretching bands at 3067 cm^{-1}, C-H asymmetric stretching bands at 1594 cm^{-1}, C=O stretching bands at 1568 cm^{-1}, C-O-C asymmetric bending bands at 749 cm^{-1}, and C-O-C symmetric bending bands at 3067 cm^{-1}.

Finally, the FTIR spectra of Ivabradine-loaded microspheres demonstrated stability between the drug and polymer, indicating the presence of chemical bonds formed within the microsphere system.

Differential scanning calorimetery (DSC)

DSC analysis was performed to investigate melting characteristics of drug & polymers. DSC curve showed an endothermic peak at 194.96°C, indicating melting point of Ivabradine HCl, while drug-loaded microspheres did not exhibit any such peak. Similarly, endothermic peaks for cellulose acetate, ethyl cellulose, & eudragit RS100 were observed at 247.91°C, 242.68°C, & 198.34°C, respectively. These results suggest that drug particles are distributed within polymer matrix. DSC curves of (A) Ivabradine HCl, (B) Cellulose acetate, (C) Ethyl cellulose, & (D) Eudragit RS100 microspheres are shown in Figure 3.

In vitro drug release

Drug release behaviour of microspheres depends on network properties of utilized polymers through their chemical makeup as well as network configuration & release environment. Research studied Ivabradine hydrochloride as primary drug for release kinetics evaluation across all 9 developed formulations while varying their polymer content. Tables 5-7 show in vitro drug release profiles of Ivabradine HCl microspheres that contain cellulose acetate, ethyl cellulose & eudragit RS100 ratios at 1:1, 1:1.5, & 1:2 respectively. In vitro drug release research showed how launch rate of drug from microspheres evolved across time from 0.5 to 12 hours as a result of different polymer combinations & ratios. Microsphere porosity decreased as solution viscosity increased because polymer wall thickened with higher viscosity. length of drug release extends when polymer concentration increases because it creates longer diffusion path distances. Because of thick polymeric barrier dissolution medium took longer to penetrate into microsphere which caused reduced drug release from polymer matrices leading to extended drug release duration. Drug release mechanism transformed from diffusion-controlled control to erosion as drug particles experienced dissolution buffer at pH 7.4.

Table 4: Results of angle of repose, bulk density, tapped density, compressibility index & Hausner's ratio

Formulation	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%)	Hausner's ratio
F1	28.04±0.12	0.419±0.018	0.503±0.020	14.16±0.59	1.12±0.012
F2	28.96±0.17	0.429±0.021	0.507±0.025	14.93±0.46	1.18±0.019
F3	29.02±0.18	0.442±0.023	0.511±0.031	14.24±0.51	1.17±0.013
F4	25.22±0.16	0.439±0.018	0.512±0.026	14.24±0.71	1.16±0.011
F5	27.36±0.15	0.445±0.011	0.522±0.019	13.94±0.52	1.17±0.083
F6	28.85±0.18	0.478±0.017	0.580±0.023	14.58±0.45	1.18±0.010
F7	27.46±0.15	0.452±0.019	0.543±0.023	14.75±0.53	1.20±0.012
F8	28.12±0.12	0.469±0.021	0.571±0.022	17.86±0.46	1.19±0.013
F9	29.30±0.18	0.479±0.023	0.583±0.018	17.95±0.49	1.22±0.009

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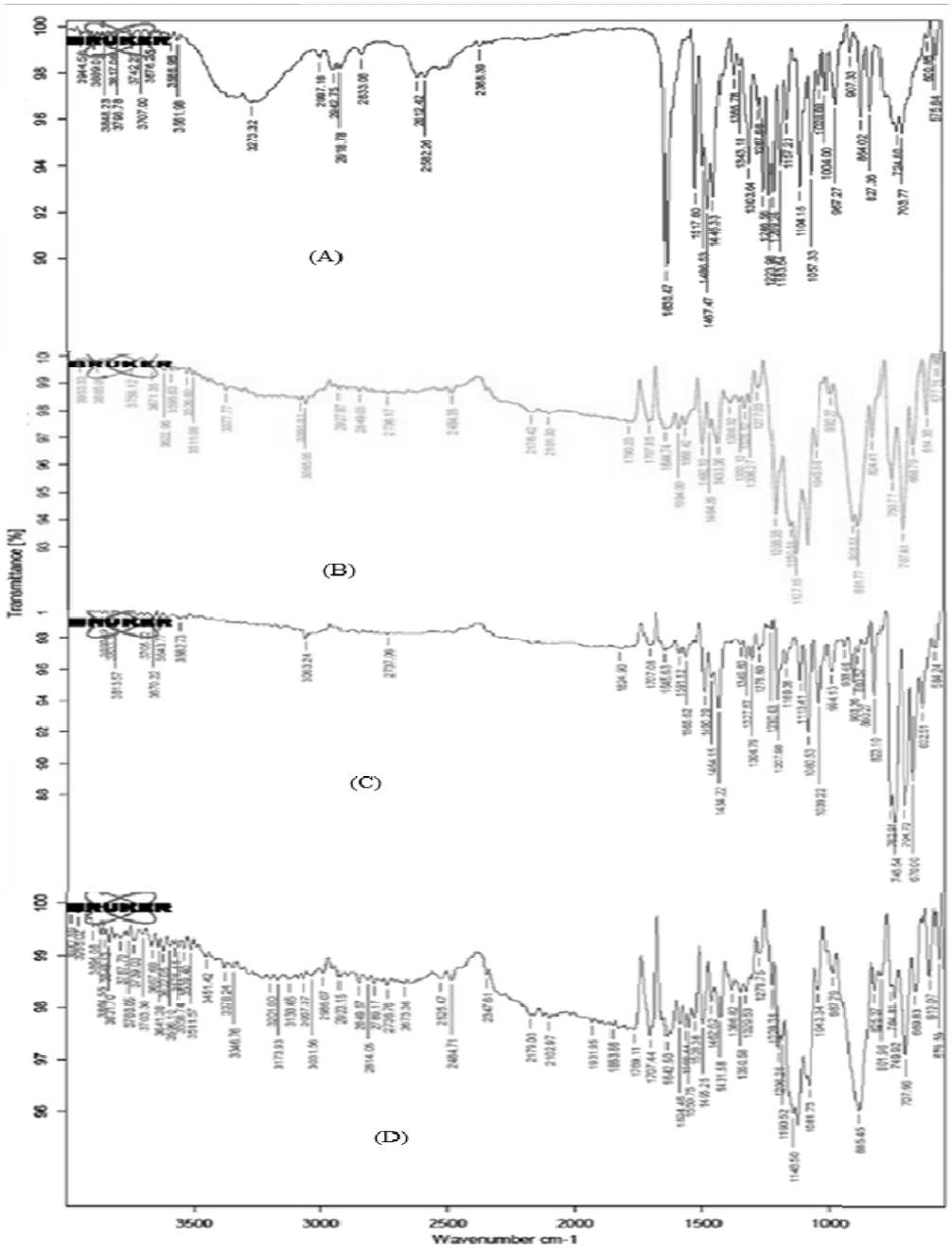

Figure 2: FTIR spectra of (A) Ivabradine HCl, (B) Cellulose acetate, (C) Ethyl cellulose, (D) Eudragit RS100 microspheres

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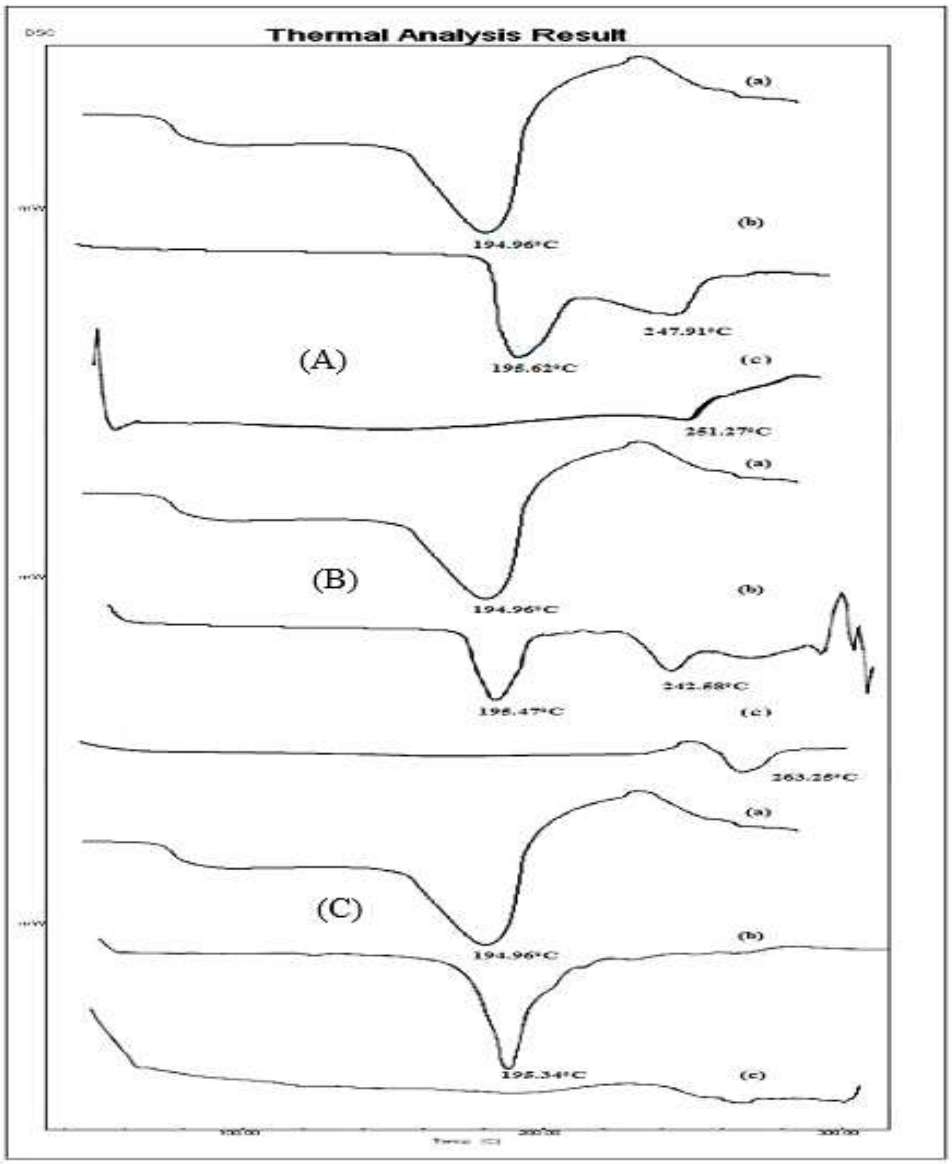

Figure 3: DSC Thermogram of (A) Ivabradine HCl, (B) Cellulose acetate, (C) Ethyl cellulose, (D) Eudragit RS100 microspheres

Drug release kinetics

Tables 8 demonstrate in vitro drug release analysis through four different kinetic models which include zero-order & first-order & Higuchi & Korsmeyer-Peppas models. Researchers chose best release model through R^2 regression coefficient analysis. Research established zero-order

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Table 5: *In vitro* drug release data of Ivabradine HCl microspheres prepared with cellulose acetate in different ratios

Time (hrs.)	% Drug release		
	F_1	F_2	F_3
0.5	8.03±0.03	7.34±0.03	6.90±0.02
1	12.49±0.02	11.85±0.04	10.97±0.03
1.5	16.97±0.04	15.95±0.03	14.94±0.05
2	21.53±0.02	20.52±0.02	19.43±0.07
2.5	26.12±0.03	24.85±0.03	23.51±0.03
3	30.68±0.05	29.14±0.06	27.60±0.04
3.5	35.25±0.03	33.46±0.04	31.66±0.03
4	39.54±0.03	37.74±0.02	35.67±0.02
4.5	43.98±0.04	41.91±0.03	39.58±0.03
5	49.44±0.02	47.12±0.05	43.89±0.02
5.5	53.62±0.04	51.02±0.03	48.16±0.03
6	58.19±0.03	55.33±0.02	52.20±0.05
6.5	62.85±0.05	59.72±0.04	56.33±0.03
7	67.74±0.02	63.38±0.07	60.41±0.02
7.5	73.14±0.04	66.70±0.03	64.76±0.03
8	78.57±0.03	70.83±0.06	66.89±0.04
8.5	84.03±0.02	74.99±0.04	71.02±0.02
9	89.51±0.04	79.17±0.02	75.18±0.03
9.5	95.03±0.05	84.62±0.03	79.36±0.06
10	99.94±0.01	90.11±0.04	83.56±0.02
10.5		95.00±0.02	87.77±0.05
11		99.27±0.05	92.01±0.02
11.5			95.65±0.04
12			99.42±0.03

Table 6: *In vitro* drug release data of Ivabradine HCl microspheres prepared with ethyl cellulose in different ratios

Time (hrs.)	% Drug release		
	F4	F5	F6
0.5	10.91±0.03	9.99±0.02	8.25±0.03

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1	19.99±0.02	18.36±0.05	16.62±0.02
1.5	25.06±0.04	22.51±0.02	19.14±0.03
2	29.36±0.03	26.44±0.02	23.40±0.06
2.5	34.03±0.06	30.52±0.05	27.34±0.02
3	39.18±0.02	34.73±0.02	30.95±0.03
3.5	44.02±0.05	38.73±0.03	35.64±0.02
4	48.42±0.02	43.45±0.05	39.64±0.02
4.5	53.77±0.05	47.84±0.02	43.09±0.05
5	59.26±0.07	52.84±0.05	47.49±0.02
5.5	65.15±0.04	57.75±0.04	51.67±0.05
6	69.86±0.05	62.10±0.05	56.22±0.02
6.5	75.32±0.02	66.83±0.02	60.34±0.05
7	80.00±0.03	70.42±0.03	65.05±0.02
7.5	85.05±0.05	75.30±0.02	68.29±0.05
8	90.70±0.06	79.98±0.05	72.12±0.02
8.5	95.57±0.02	84.91±0.03	75.85±0.03
9	99.08±0.04	90.33±0.02	80.76±0.02
9.5		94.38±0.03	86.04±0.04
10		99.27±0.05	90.42±0.05
10.5			94.82±0.02
11			99.85±0.03

Table 7: *In vitro* drug release data of Ivabradine HCl microspheres prepared with eudragit RS100 in different ratios

Time (hrs.)	% Drug release		
	F7	F8	F9
0.5	8.12±0.03	7.97	7.78±0.04
1	13.24±0.04	12.74±0.04	12.36±0.02
1.5	18.17±0.02	17.41±0.02	16.84±0.03
2	23.18±0.04	22.17±0.05	21.40±0.02
2.5	28.22±0.03	26.95±0.02	25.99±0.02
3	33.23±0.04	31.70±0.04	30.55±0.02
3.5	38.01±0.02	36.47±0.03	35.12±0.03
4	42.75±0.05	40.95±0.02	39.41±0.02

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4.5	47.27±0.03	45.58±0.04	43.85±0.03
5	53.32±0.02	51.25±0.02	49.31±0.04
5.5	57.96±0.05	55.62±0.03	53.48±0.03
6	62.99±0.04	60.39±0.03	58.06±0.02
6.5	68.83±0.03	65.07±0.04	62.72±0.04
7	78.65±0.03	69.08±0.02	67.10±0.02
7.5	88.53±0.04	76.38±0.03	72.50±0.05
8	99.07±0.06	83.72±0.02	77.92±0.04
8.5		92.36±0.04	83.38±0.02
9		99.15±0.05	88.86±0.03
9.5			94.37±0.04
10			99.28±0.03

Table 8: Drug release kinetic data of Ivabradine HCl microspheres

Formulation	Zero order		First order		Higuchi model		Korsmeyer Peppas	
	R^2	K_0	K_1	R^2	K_H	R^2	R^2	n
F1	0.9990	0.491	0.024	0.6859	8.261	0.9271	0.9968	0.8732
F2	0.9983	0.455	0.016	0.8085	9.201	0.9352	0.9983	0.8651
F3	0.9965	0.427	0.020	0.7450	8.956	0.9355	0.9989	0.8594
F4	0.9907	0.644	0.025	0.8211	7.238	0.9569	0.9956	0.7385
F5	0.9895	0.583	0.019	0.8206	8.921	0.9573	0.9971	0.7508
F6	0.9925	0.510	0.016	0.8353	8.674	0.9506	0.9964	0.7643
F7	0.9926	0.556	0.015	0.7407	6.972	0.9089	0.9941	0.8882
F8	0.9968	0.528	0.020	0.7705	7.371	0.9197	0.9960	0.8804
F9	0.9990	0.497	0.018	0.7991	8.278	0.9278	0.9971	0.8750

model R^2 values between 0.9895 & 0.990 whereas first-order model R^2 values spanned from 0.7450 through 0.8353. R^2 values measured for Higuchi model reached from 0.9089 to 0.9573 while Korsmeyer-Peppas model showed R^2 values spanning from 0.9941 to 0.9989. Drug release pattern matched first-order drug release model according to obtained results. Obtained results showed that drug release followed first-order model most accurately. Release exponent (n) values calculated from Korsmeyer-Peppas model consisted of numbers between 0.7385 & 0.8882. Release mechanism exhibited non-Fickian characteristics because measured values spanned from 0.7385 through to 0.8882.

Conclusion

Using, a solvent evaporation method researchers successfully synthesized Ivabradine-loaded microspheres from cellulose acetate, ethyl cellulose, & eudragit RS100 in

1:1, 1:1.5, & 1:2 ratios. SEM imaging revealed microspheres had spherical distributions & showed homogeneous dispersion across analysis field. Drug release studies using in vitro dissolution methods showed that drug-loaded formulations displayed drug-release behavior which depended on solution pH. Drug release measurements showed Ivabradine HCl released more effectively at pH 7.4 than it did at other tested conditions of pH 1.2 & 5.5. Analysis using differential scanning calorimetry showed that every Ivabradine formulation contained drug substance in an amorphous form. Drug release studies revealed that microspheres could emit drug continuously for 12 hours within pH 7.4 phosphate buffer solution until all formulations released more than 90% of drug. Formulation produced by using cellulose acetate at a concentration ratio of 1:2 with Span 80 as surfactant achieved greatest medication release control over 12 hours among all nine formulations produced. When microspheres contained a drug-to-polymer ratio of 1:2 they released drug more slowly than when ratio was set to 1:1 & 1:1.5. drug release timing from cellulose acetate-based microspheres proved slower than what ethyl cellulose & eudragit RS100 based microspheres produced. Researched results demonstrated that higher amounts of coating materials produced decreased rates of drug delivery. Prepared pH-responsive Ivabradine-loaded microspheres demonstrate suitable characteristics for utilization in controlled medication delivery applications.

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Conflicts of Interest

The authors declare no conflicts of interest in this work.

References

1. Mohini, Y., Trushali, A.M., Vaishnavi, J., Otari, K. (2024). A review on microspheres as a promising drug carrier. *Journal of Drug Delivery and Therapeutics,* 14(7), 120-128. doi: https://doi.org/10.22270/jddt.v14i7.6656
2. Gautam, T.I., Shrikant, D.P., Roshini, S., Dipti, P. (2023). Current trends in microspheres: A review. *Journal of Drug Delivery and Therapeutics,* 13(1), 183-194. doi: https://doi.org/10.22270/jddt.v 13i1.5915
3. Yawalkar, A.N., Pawar, M.A., Vavia, P.R. (2022). Microspheres for targeted drug delivery - A review on recent applications. *Journal of Drug Delivery Science and Technology,* 75, 103659. doi: https://doi.org/10.1016/j.jddst.2022.103659
4. Athira, K., Vineetha, K., Kamath, K.K., Shabaraya, A.R. (2022). Microspheres as a novel drug delivery system – A review. *International Journal of Pharmaceutical Sciences Review and Research,* 75(1), 160-166. doi: 10.47583/ijpsrr.2022.v75i01.027
5. Sunny, P., Rajeshwar, P.K., Dinesh, P.A., Gorantli, C.C. (2020). A review on microspheres: Types, methods of preparation, effects of process variables & applications. *American Journal of PharmTech Research,* 10(4), 123-140. doi: 10.46624/ajptr.2020.v10.i4.011
6. Gurung, B.D., Kakar, S. (2020). An overview on microspheres. *International Journal of Health and Clinical Research,* 3(1), 11-24.
7. Kaustubh, V.G., Manohar, D.K., Kiran, V.C., Vaishnavi, P.A., Naziya, I.K. (2019). A review on microsphere & it's application. *Asian Journal of Pharmaceutical Research,* 9(2), 123-129. doi: 10.5958/2231-5691.2019.00020.0
8. Chitra, S., Suresh, P., Madhu, S., Pandey, B.L. (2013). Design & evaluation of microspheres: A review. *Journal of Drug Delivery Research,* 2(2), 18-27.
9. Haechl, N., Ebner, J., Hilber, K., Todt, H., Koenig, X. (2019). Pharmacological profile of bradycardic agent Ivabradine on human cardiac ion channels. *Cellular Physiology & Biochemistry*, 53, 36-48. doi: 10.33594/000000119

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10.5530/ctbp.2025.2s.1

10. Koruth, J.S., Anuradha, L., Pinney, S., Reddy, V.Y., Srinivas, D.S. (2017). Clinical use of Ivabradine. *Journal of the American College of Cardiology*, 70(14), 1777-1784. doi: 10.1016/j.jacc.2017.08.038
11. Kaski, J.C., Gloekler, S., Ferrari, R., Fox, K., Levy, B.I., Komajda, M., Vardas, P., Camici, P.G. (2018). Role of Ivabradine in management of stable angina in patients with different clinical profiles. *Open Heart*, 5, e000725. doi: 10.1136/openhrt-2017-000725
12. Sulfi, S., Timmis, A.D. (2006). Ivabradine – First selective sinus node I(f) channel inhibitor in treatment of stable angina. *International Journal of Clinical Practice*, 60(2), 222-228. doi: 10.1111/j.1742-1241.2006.00817.x
13. Difrancesco, D., Camm, J.A. (2004). Heart rate lowering by specific & selective I(f) current inhibition with Ivabradine: A new therapeutic perspective in cardiovascular disease. *Drugs*, 64(16), 1757-1765. doi: 10.2165/00003495-200464160-00003
14. Eswarudu, M.M., Lakshmana Rao, A., Vijay, K. (2022). Development & validation of a LC-MS/MS method for simultaneous quantification of Ivabradine & Metoprolol in rat plasma. *Journal of Pharmacological and Toxicological Methods*, 116, 107186. doi: 10.1016/j.vascn.2022. 107186
15. Majeed, A., Ranjha, N.M., Hanif, M., Abbas, G., Khan, M.A. (2017). Development & evaluation of Ivabradine HCl-loaded polymeric microspheres prepared with eudragit L100-55 (methacrylic acid-ethyl acrylate copolymer) & ethyl cellulose for controlled drug release. *Acta Poloniae Pharmaceutica*, 74(2), 565-578.
16. Poorva, P., Vishnu, P. (2024). Formulation & evaluation of mucoadhesive buccal tablet of Ivabradine hydrochloride. *International Journal of Creative Research Thoughts*, 12(5), d63-d88.
17. Akash, V., Shravani, G., Venkatesh, V., Gayathri, P., Hema, G. (2022). Preparation & characterization of microspheres of Ivabradine hydrochloride using natural, semi-synthetic, & synthetic polymers. *International Journal of Green Pharmacy*, 16(4), 397-402. doi: https://doi.org/10.22377/ijgp.v16i4.3350
18. Sagar, N.F., Nitin, B.G. (2019). *In vitro* & *in vivo* evaluation of Ivabradine loaded microsphres prepared by multiple emulsion solvent evaporation method. *International Journal of Pharmacy and Biological Sciences*, 9(4), 315-322. doi: https://doi.org/10.21276/ijpbs.2019.9.4.35
19. Lodhi, M., Dubey, A., Narayan, R., Prabhu, P., Priya, S. (2013). Formulation & evaluation of buccal film of Ivabradine hydrochloride for treatment of stable angina pectoris. *International Journal of Pharmaceutical Investigation*, 3(1), 47-53. doi: 10.4103/2230-973X. 108963
20. Prashant, S. (2012). Formulation & evaluation of Ivabradine hydrochloride loaded ethyl cellulose microspheres. *International Journal of Pharmaceutical Research and Development*, 4(10), 57-63.
21. Vinod, B., Trupti, K., Rishikesh, B. (2023). Formulation development & evaluation of mouth dissolving film of Ivabradine HCl. *International Journal of Pharmaceutical Sciences*, 1(8), 79-88. doi: 10.5281/zenodo.8244885
22. Prashant, S., Mani, T.T., Goswami, S., Pradeep, S. (2019). Comparative evaluation of Ivabradine hydrochloride loaded natural & synthetic microspheres. *Journal of Pharmaceutical Research & Education*, 4(1), 368-379.
23. Prashant, S., Senthil Kumar, S.K., Parthiban, S., Peeyush., Mani, T.T. (2012). Formulation & evaluation of Ivabradine hydrochloride loaded egg albumin microspheres. *Journal of Pharmaceutical Research & Opinion*, 2(2), 25-28.
24. Lakshmi, G.N.A., Rajitha, G.N.L., Lakshmana Rao, A. (2018). Formulation & evaluation of Efavirenz mucoadhesive microspheres. *Advance Research in Pharmaceuticals & Biologicals,* 8(1), 920-934.
25. Balakrishna, T., Kiranmayee, P., Lakshmana Rao, A. (2023). Formulation development & evaluation of Stavudine mucoadhesive microspheres. International Journal of Research in Pharmacy and Chemistry. 13(1), 23-28. doi: https://dx.doi.org/10.33289/IJRPC.17.1.2023.13(5).