Journal of Animal Environment

(E-ISSN 2717-1396, ISSN 2717-1388)

Original Research Paper

FORMULATION AND CHARACTERIZATION OF GASTRORETENTIVE FLOATING MICROSPHERES OF METOPROLOL SUCCINATE

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ABSTRACT

Gastro-retentive drug delivery systems have gained considerable attention as a promising approach for prolonging gastric residence time and achieving sustained drug release. In the present study, floating microspheres of Metoprolol succinate were developed to provide controlled drug delivery and prolonged gastric retention. The microspheres were prepared by the emulsion solvent evaporation method using ethyl cellulose and Eudragit RS 100 as release-retarding polymers, calcium silicate as a buoyancy-enhancing agent, PVA as a stabilizer, and ethanol: dichloromethane (1:2) as the solvent system. Eight formulations (F1–F8) were prepared with varying polymer concentrations and evaluated for micromeritic properties, particle size, percentage yield, drug content, drug entrapment efficiency, surface morphology, floating behavior, and in-vitro drug release. The prepared microspheres showed satisfactory characteristics, with particle size ranging from 50–82 µm, percentage yield of 72–88%, drug content of 90.18–96.43%, floating duration of 7–14 h, floating lag time of 1.05–3.03 min, and drug entrapment efficiency of 72–92%. In-vitro drug-release studies demonstrated sustained drug release over 12 h, with cumulative drug release ranging from 82.80–92.15%. Among the formulations, F3 was selected as the optimized formulation, exhibiting 81% yield, 75 µm particle size, 96.43% drug content, 86% drug entrapment efficiency, 14 h floating duration, and 85.40% drug release at 12 h. Overall, the study demonstrated the successful development of floating microspheres with prolonged buoyancy and controlled drug release, and formulation F3 showed the most desirable combination of pharmaceutical characteristics, indicating its potential as a gastro-retentive system for sustained delivery of Metoprolol succinate.

Keywords: Metoprolol succinate; Floating microspheres; Gastro-retentive; Controlled release; Ethyl cellulose; Eudragit RS 100.

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Received: 25th July, 2026 | Revised: 26th August, 2026 | Accepted: 30th August, 2026 | Available Online: 2nd September, 2026

(DOI): 10.70102/AEJ.2026.18.7s.10

1. INTRODUCTION

Oral drug delivery remains one of the most widely accepted routes of administration because of its convenience, patient acceptability, and relatively simple manufacturing requirements. However, conventional oral dosage forms may exhibit limitations such as rapid gastric emptying, variable gastrointestinal transit, incomplete drug absorption, and fluctuations in plasma drug concentration. These limitations can become particularly important for drugs whose absorption is influenced by gastrointestinal residence time or whose therapeutic performance benefits from prolonged and controlled drug release. Gastroretentive drug delivery systems (GRDDS) have therefore received considerable attention as an approach for prolonging the residence of dosage forms within the stomach and improving the efficiency of oral drug delivery. Recent advances have included floating, mucoadhesive, expandable, high-density, magnetic, and other gastroretentive platforms, with floating systems remaining among the most extensively investigated approaches [1-3].

Floating drug delivery systems are designed to possess a density lower than gastric contents, allowing the dosage form to remain buoyant for an extended period while releasing the incorporated drug in a controlled manner. The prolonged gastric residence may provide several potential advantages, including sustained drug release, reduction in dosing frequency, improved utilization of the administered dose, and more consistent drug exposure. The performance of these systems is strongly influenced by formulation variables, particularly the type and concentration of polymers, particle characteristics, matrix structure, and drug–polymer interactions. Polymeric excipients such as ethyl cellulose, hydroxypropyl methylcellulose (HPMC), polyethylene oxide, alginates, chitosan, and related polymers have been investigated extensively for controlling drug release and contributing to buoyancy [4,5].

Among the various multiparticulate gastroretentive systems, floating microspheres offer particular advantages because of their small size, multiple-unit nature, relatively large surface area, and ability to distribute throughout the gastric contents. Their hollow or low-density structure can facilitate buoyancy, whereas the polymeric matrix can regulate diffusion and/or erosion of the incorporated drug. Furthermore, multiparticulate systems may reduce the risk associated with the unpredictable behavior of a single large gastroretentive unit and can provide a more reproducible drug-release pattern. Recent research continues to explore polymer selection, microsphere architecture, optimization strategies, and advanced manufacturing approaches to improve gastric retention and controlled drug delivery [4-6].

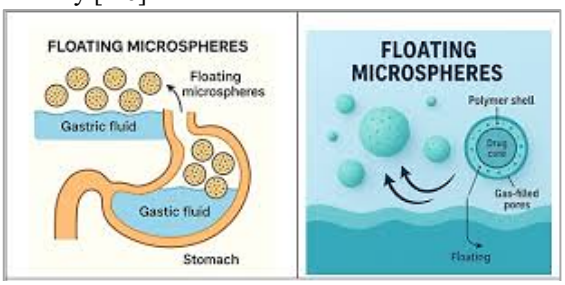

Figure No. 1: Floating Microspheres

Metoprolol succinate is a cardioselective β_1-adrenergic receptor blocker used in the management of cardiovascular conditions. Conventional Metoprolol undergoes substantial first-pass metabolism, and its plasma elimination half-life is approximately 3–7 hours. The extended-release succinate formulation is designed to provide more prolonged drug exposure than conventional Metoprolol preparations; nevertheless, development of alternative controlled-release gastroretentive systems remains of pharmaceutical interest [7]. The development of a floating multiparticulate system may provide a means of modulating drug release while maintaining the dosage form within the upper gastrointestinal region for an extended period. Previous research has demonstrated the feasibility of developing controlled-release and floating formulations of Metoprolol, supporting continued investigation of gastroretentive approaches for this drug [8].

Accordingly, the present study was undertaken to formulate and evaluate floating microspheres of Metoprolol succinate for controlled drug delivery. The developed microspheres were intended to combine prolonged gastric retention with controlled drug release. The formulation was evaluated with respect to relevant physicochemical and micromeritic characteristics, drug entrapment, buoyancy behavior, surface morphology, and in-vitro drug-release performance. The study was designed to investigate the potential of floating microspheres as a multiarticulate gastroretentive platform for achieving prolonged and controlled delivery of Metoprolol succinate.

2. MATERIALS AND METHODS

2.1 Materials

Metoprolol Succinate was obtained as a generous gift sample from Pharma Corp Inc Private Limited (Lasudia Mori, Indore). Ethyl Cellulose (MCC) was procured from Sd Fine-chem, and Eudragit RS 100 was supplied by QualiChem's. Volatile

processing solvents, including Dichloromethane (DCM), Ethanol, Chloroform, and Methanol, as well as analytical grade Hydrochloric Acid (HCl), were sourced from HiMedia Laboratories, Sd Fine-chem, and Molychem.

2.2 Method of Preparation of Floating Microspheres

Floating microspheres of Metoprolol succinate were prepared by the emulsion solvent-evaporation method. Metoprolol succinate was dispersed/dissolved with the selected polymer, either Ethyl cellulose or Eudragit RS 100, in the organic solvent system consisting of ethanol and dichloromethane. Calcium silicate was incorporated as a low-density/floating agent. The resulting polymeric dispersion was introduced into an aqueous polyvinyl alcohol (PVA) solution under continuous agitation to form an oil-in-water emulsion. The system was maintained under agitation to facilitate evaporation of the organic solvent, resulting in the formation and hardening of polymeric microspheres. The microspheres were subsequently separated, washed with suitable medium to remove adhering PVA, and dried to obtain free-flowing floating microspheres. The prepared formulations (F1–F8) were then subjected to evaluation for particle characteristics, percentage yield, drug entrapment, buoyancy, morphology, and in-vitro drug-release performance.

Table No. 1: Formulation Composition of Metoprolol Microspheres (F1-F8)

FORMULATION CODE	F1	F2	F3	F4	F5	F6	F7	F8
Drug (Metoprolol Succinate)	1000	1000	1000	1000	1000	1000	1000	1000
Ethyl Cellulose	1000	2000	3000	4000	-	-	-	-
Eudragit RS 100	-	-	-	-	1000	2000	3000	4000
Calcium Silicate	50	50	50	50	50	50	50	50
Ethanol: Dichlormethane	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2
Poly Vinyl Alcohol (%w/v)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75

2.3 Preformulation studies

1. Organoleptic Characteristics

The organoleptic characteristics of Metoprolol succinate were evaluated by visual inspection for colour, odour, appearance, and physical state. The drug was observed to be a white to almost white, crystalline powder and was practically odorless [9].

2. Melting Point

The melting point of Metoprolol succinate was determined by the capillary tube method. A small quantity of finely powdered drug was filled into a thin-walled capillary tube and gently compacted. The capillary was placed in a melting-point apparatus, and the temperature was gradually increased. The temperature at which the drug began to melt and the temperature at which complete melting occurred were noted. The experimentally determined melting point was compared with the reported value to assess the identity and purity of the drug [9,10].

3. Solubility Study

The solubility of Metoprolol succinate was qualitatively investigated in selected solvents relevant to formulation development. An accurately weighed quantity of drug was added to a fixed volume of each solvent and shaken thoroughly at room temperature. The samples were allowed to equilibrate, and the solubility was assessed based on the amount of drug dissolved. [9,11].

4. UV Spectrophotometric Analysis

UV spectrophotometric identification and calibration of Metoprolol succinate were carried out using 0.1 N HCl as the solvent. An accurately weighed quantity of Metoprolol succinate was dissolved in 0.1 N HCl and suitably diluted, and the resulting solution was scanned over 200–400 nm using a UV–Visible spectrophotometer against 0.1 N HCl as blank to determine the wavelength of maximum absorbance (λmax). The identified λmax was subsequently used for quantitative estimation.

For calibration, a standard stock solution of Metoprolol succinate was prepared in 0.1 N HCl and serially diluted to obtain different concentrations. The absorbance of each dilution was measured at the selected λmax against 0.1 N HCl as blank. A calibration curve was constructed by plotting concentration (µg/mL) versus absorbance, and the linearity of the method was evaluated from the calibration plot and correlation coefficient (R^2) [12,13].

5. FTIR Compatibility Study:

FTIR spectroscopy was performed to establish the compatibility of Metoprolol succinate with the selected formulation excipients, particularly ethyl cellulose, Eudragit RS 100, and calcium silicate. The pure drug, individual polymers/excipients, and physical drug–excipient mixtures were subjected to FTIR analysis over the appropriate mid-infrared region. The obtained spectra were examined for characteristic absorption bands of Metoprolol succinate and any substantial changes in peak position, disappearance of characteristic peaks, or appearance of new bands that could indicate chemical interaction. Metoprolol succinate has characteristic FTIR absorptions associated with its secondary alcohol, secondary amine, and methyl ether groups [9].

2.4 Evaluation of Floating Microspheres

The prepared floating microspheres of Metoprolol succinate were evaluated for their micromeritic characteristics, particle size, surface morphology, production yield, buoyancy, drug entrapment, drug content, and in-vitro drug-release behavior using established procedures for floating microspheres [14-16].

a) Micromeritic Properties

The flow properties of the prepared microspheres were assessed by determining bulk density, tapped density, angle of repose, Carr's compressibility index, and Hausner's ratio. Bulk density was determined by gently filling a known quantity of microspheres into a graduated cylinder and recording the unsettled volume, while tapped density was determined after mechanically tapping the cylinder to obtain a constant volume. The angle of repose was measured by the fixed-funnel method. Carr's index and Hausner's ratio were calculated from the bulk and tapped density values to assess the flowability and packing characteristics of the microspheres [15,16].

b) Particle Size Distribution of Microspheres

The particle size distribution of the microspheres was determined by sieve analysis. A known quantity of dried microspheres was passed through a series of standard sieves arranged in descending order of aperture size. The quantity retained on each sieve was weighed, and the percentage retained was calculated. The mean particle size was determined from the resulting particle-size distribution. Particle size is an important characteristic as it may influence the surface area, drug entrapment, buoyancy, and drug-release behavior of microspheres [15].

c) Morphological Study Using Scanning Electron Microscopy (SEM)

The morphology of the prepared microspheres was examined using scanning electron microscopy (SEM). A small quantity of dried microspheres was mounted on a suitable specimen holder and coated with a thin conductive layer where required. The samples were examined at appropriate magnifications to evaluate their shape, surface characteristics, sphericity, porosity, and surface cavities. SEM analysis was particularly useful for confirming the formation of spherical and porous structures associated with floating microspheres [14,17].

d) Determination of Percentage Yield of Microspheres

The percentage yield was determined by comparing the weight of dried microspheres recovered after preparation with the theoretical weight of drug and polymers used for the formulation. The obtained value was used to assess the efficiency of the microsphere preparation process. The percentage yield was calculated using the following equation:[18]

% Yield = (Practical yield / Theoretical yield) × 100

e) Buoyancy Studies

The buoyancy of the microspheres was evaluated by dispersing a known quantity of microspheres in the selected gastric medium maintained at 37 ± 0.5°C. The microspheres were allowed to remain in the medium for the predetermined study period. The floating microspheres were separated from the settled fraction and weighed. The floating lag time and total floating duration were also recorded where applicable. A high percentage of buoyancy and prolonged floating duration indicate satisfactory gastroretentive potential [21]. The percentage buoyancy was calculated using the following equation [19,20]:

% Buoyancy = [Weight of floating microspheres / (Weight of floating microspheres + Weight of settled microspheres)] × 100

f) Drug Entrapment Efficiency

Drug entrapment efficiency was determined by accurately weighing a known quantity of microspheres and extracting the incorporated Metoprolol succinate using a suitable solvent. The extract was appropriately diluted and analyzed using the previously developed UV spectrophotometric method. The percentage entrapment efficiency was calculated as follows:[22]

% Entrapment Efficiency = (Actual drug content / Theoretical drug content) × 100

g) Drug Content

For determination of drug content, an accurately weighed quantity of microspheres was dissolved or dispersed in a suitable solvent and appropriately diluted. The resulting solution was filtered, if necessary, and the amount of Metoprolol succinate was estimated spectrophotometrically at the previously established λmax using 0.1 N HCl as the analytical medium. The drug content was expressed as the percentage of Metoprolol succinate present in the microspheres relative to the theoretical drug amount [23].

h) In-Vitro Drug Release

The in-vitro drug-release study of Metoprolol succinate floating microspheres was carried out using a suitable USP dissolution apparatus containing the selected dissolution medium maintained at 37 ± 0.5°C. A predetermined quantity of microspheres was introduced into the dissolution medium and maintained under controlled agitation. At predetermined time intervals, a fixed volume of sample was withdrawn and immediately replaced with an equal volume of fresh dissolution medium maintained at the same temperature. The withdrawn samples were suitably diluted and analyzed spectrophotometrically at the selected λmax. The cumulative percentage of drug released was calculated and plotted against time to obtain the drug-release profile. The release data were further fitted to appropriate kinetic models to determine the probable mechanism of drug release [24,25]

3. RESULT AND DISCUSSION:

3.1 Preformulation Studies

The Preformulation studies of Metoprolol succinate were performed to establish its basic physicochemical characteristics and suitability for formulation development. Organoleptic evaluation showed that the drug was a white, crystalline and odorless powder, indicating acceptable physical characteristics. The melting point was found to be 150–151°C, which was comparable with the reported range and supported the identity and purity of the drug. [26,27]

The solubility study showed that Metoprolol succinate was freely soluble in distilled water and 0.1 N HCl, while it was sparingly soluble in ethanol, indicating better solubility in aqueous and acidic media. In UV spectrophotometric analysis, the drug exhibited maximum absorbance at 276 nm. The calibration curve showed good linearity over the investigated concentration range of 2–10 µg/mL, with the regression equation $y = 0.0921x - 0.0110$ and $R^2 = 0.9929$, confirming the suitability of the method for quantitative estimation. FTIR analysis showed the characteristic functional-group peaks of Metoprolol succinate, and their retention in the drug–polymer spectra without major changes indicated no significant chemical incompatibility between the drug and selected polymers, supporting their suitability for preparation of floating microspheres. [28]

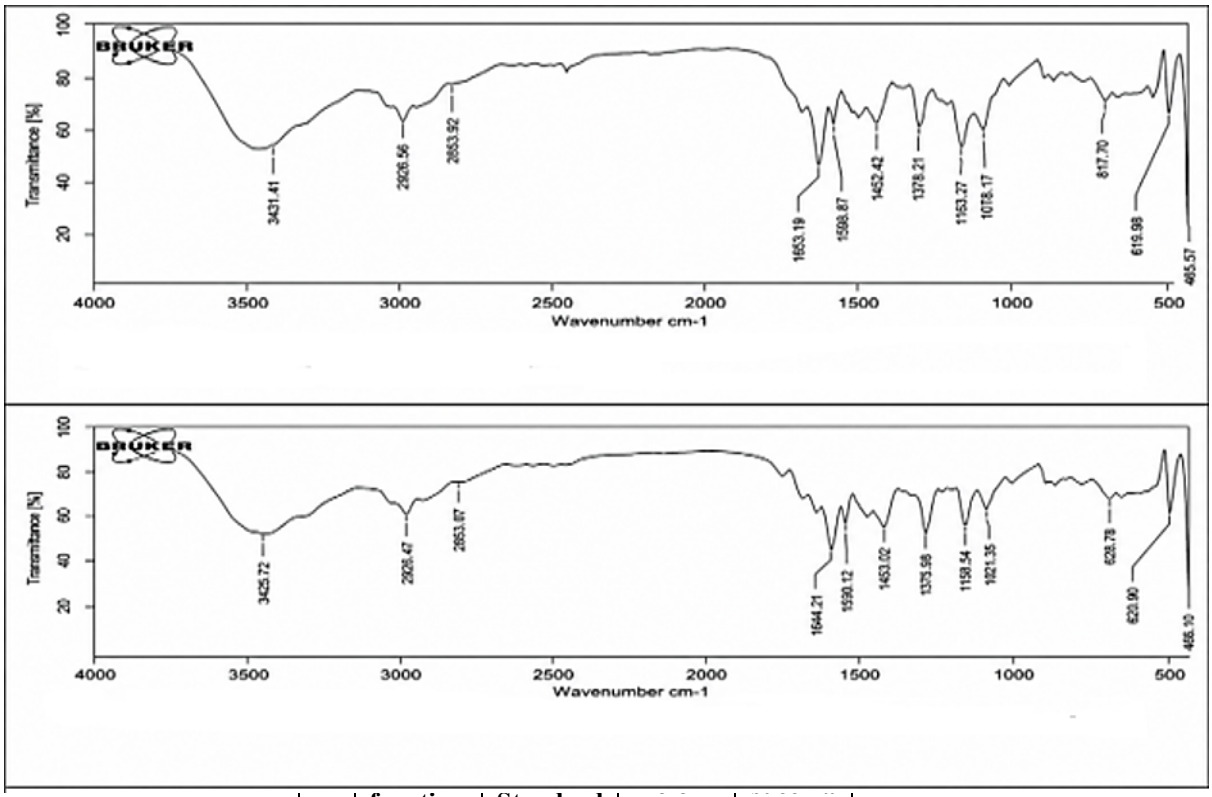

Figure No. 2: FTIR Spectra of pure Metoprolol succinate drug and Metoprolol succinate–polymer blend.

Table No. 2: FTIR characteristic peaks of Metoprolol succinate and Metoprolol succinate–polymer blend.

S. No.	functional group / structural feature	Standard characteristic range (cm^{-1})	succinate Observed peak (cm^{-1})	te + Polymer blend Observed peak (cm^{-1})
1	O–H / N–H stretching	3200–3600	3431.41	3392.72
2	Aliphatic C–H stretching	2850–3000	2926.56	2926.47
3	C=O / carboxylate-related vibration	1550–1750	1653.19	1644.21
4	Aromatic C=C / carboxylate-related vibration	1500–1620	1598.87	1590.12
6	CH_2/CH_3 bending	1350–1500	1378.21	1375.98
7	C–O / C–O–C stretching	1000–1200	1163.27	1158.54

3.2 Evaluation of Floating Microsphere of Metoprolol Succinate:

Micromeritic Properties

The prepared floating microspheres exhibited bulk density of 0.365–0.415 g/cm³, tapped density of 0.416–0.467 g/cm³, Carr's index of 10.68–14.16%, Hausner's ratio of 1.12–1.16, and angle of repose of 25.20–28.90°. These values indicate good flow and satisfactory packing characteristics of all formulations, suggesting their suitability for further processing and evaluation**.** Table No. 3 presents results of micromeritic properties of the prepared, Metoprolol succinate floating microspheres.

Table No. 3: Micromeritic properties of Metoprolol succinate

Batch	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Hausner's Ratio	Carr's Index (%)	Angle of Repose (°)	Flow Character
F1	0.365	0.418	1.15	12.68	25.20	Excellent
F2	0.367	0.416	1.13	11.78	26.06	Excellent
F3	0.405	0.460	1.14	11.96	26.35	Excellent
F4	0.392	0.448	1.14	12.50	26.95	Excellent
F5	0.395	0.455	1.15	13.19	28.90	Excellent
F6	0.415	0.467	1.13	11.13	27.60	Excellent
F7	0.410	0.459	1.12	10.68	26.35	Excellent
F8	0.382	0.445	1.16	14.16	26.95	Excellent

Percentage yield, Average particle size, and Drug content:

The prepared floating microspheres exhibited percentage yield, average particle size, and drug content in the ranges of 72–88%, 50–82 µm, and 90.18–96.43%, respectively. The increase in polymer concentration generally resulted in an increase in particle size, which may be attributed to increased viscosity of the polymeric phase during microsphere formation. The satisfactory percentage yield and relatively high drug content across all formulations indicate efficient microsphere formation and good incorporation of Metoprolol succinate into the polymeric matrix. Table No. 4 presents the percentage yield, average particle size, and drug content of the prepared Metoprolol succinate floating microspheres.

Table No. 4: Percentage yield, Average particle size, and Drug content of Metoprolol succinate floating microspheres.

S. No	Formulation	yield (%)	Average particle size (µm)	Drug content (%)
1	**F1**	72	50	90.18
2	**F2**	83	62	92.6
3	**F3**	81	75	96.43
4	**F4**	85	82	92.79
5	**F5**	84	67	93.35
6	**F6**	79	69	93.80
7	**F7**	86	73	95.2
8	**F8**	88	78	92.3

Floating ability and Drug Entrapment Efficiency:

The prepared floating microspheres exhibited floating times ranging from 7 to 14 h, with floating lag times of 1.05–3.03 min and drug entrapment efficiencies of 72–92%. The relatively short floating lag time and prolonged floating duration observed for the formulations indicate good buoyancy and potential for prolonged gastric retention. The variation in floating behavior and drug entrapment may be attributed to differences in polymer type and concentration, which can influence microsphere density, matrix formation, and drug incorporation. Overall, the results demonstrate satisfactory floating characteristics and effective entrapment of Metoprolol succinate within the polymeric microspheres. Table No. 5 represents the evaluation of the prepared floating microspheres in terms of total floating duration, floating lag time, and drug entrapment efficiency for formulations F1–F8.

Table No. 5. Floating Characteristics and Drug Entrapment Efficiency of Metoprolol Succinate Floating Microspheres

Formulation Code	Floating Time (h)	Floating Lag Time (min)	Drug Entrapment Efficiency (%)

F1	8	2.41	72
F2	12	3.03	83
F3	14	2.91	86
F4	11	2.40	92
F5	7	1.96	84
F6	10	1.58	87
F7	10.5	1.20	89
F8	9	1.05	92

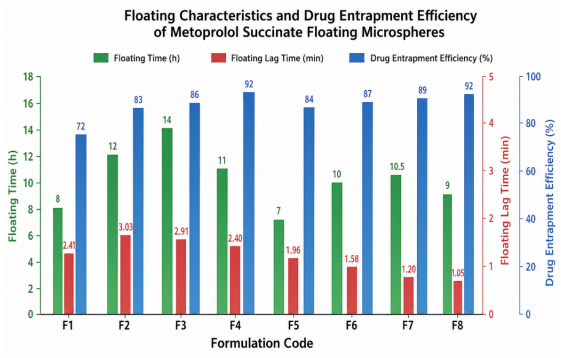

Figure No.3: Floating Characteristics and Drug Entrapment Efficiency of Metoprolol Succinate Floating Microspheres

In-vitro drug-release study:

The in vitro drug release study showed a gradual and sustained release of Metoprolol succinate from all formulations (F1–F8) over the 12 h study period. Drug release increased progressively with time, reaching 82.80–92.15% at 12 h. Among the formulations, F5 showed the highest drug release (92.15%), whereas F4 showed the lowest release (82.80%) at 12 h, indicating that polymer type and concentration influenced the release behavior. Overall, the results demonstrate the potential of the prepared floating microspheres to provide prolonged drug release over 12 h.

Table No. 5 In-vitro drug-release data of Metoprolol Succinate Floating Microspheres

Time (hrs.)	**% Cumulative Drug Release**							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	15.45	13.12	12.60	10.30	16.20	14.80	12.50	10.90
2	25.10	23.45	20.80	18.15	25.30	22.50	19.40	17.20
4	38.60	35.60	33.15	31.40	44.80	38.10	35.20	32.15
6	55.30	48.90	44.40	40.10	58.70	53.60	49.10	46.30
8	72.15	68.30	64.20	57.45	74.50	70.20	68.80	66.40
10	84.40	79.10	74.50	70.20	89.60	83.30	81.20	78.60
12	91.50	88.40	85.40	82.80	92.15	89.10	87	84.20

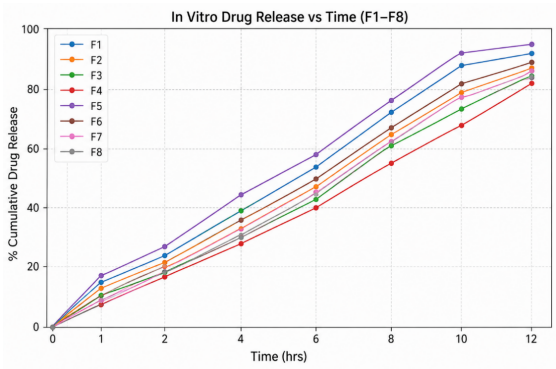

Figure No. 4: In-vitro drug-release% of Metoprolol Succinate Floating Microspheres

4. SUMMARY AND CONCLUSION:

Floating microsphere formulations F1–F8 were successfully prepared using Metoprolol succinate as the model drug, Ethyl Cellulose and Eudragit RS 100 as release-retarding polymers, calcium silicate as a buoyancy-enhancing agent, and ethanol:

dichloromethane (1:2) as the solvent system, with PVA (0.75% w/v) as the stabilizing agent. The prepared formulations were evaluated for particle size, percentage yield, drug content, floating characteristics, drug entrapment efficiency, and in vitro drug release. Among all formulations, F3 was selected as the optimized formulation based on its overall performance. F3 exhibited 81% production yield, 75 µm particle size, 96.43% drug content, 86% drug entrapment efficiency, 14 h floating duration, and a floating lag time of 2.91 min. It also showed a comparatively controlled drug-release profile, with 85.40% drug release at 12 h. Thus, F3 provided a desirable balance of high drug incorporation, prolonged buoyancy, suitable particle size, and sustained drug release, making it the most promising formulation for gastro-retentive controlled delivery of Metoprolol succinate.

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