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Development and Evaluation of Sustained Release Carvedilol Microspheres Prepared by Ionotropic Gelation Technique

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ABSTRACT

Cardiovascular disorders require long-term treatment and continuous medication adherence to achieve effective disease management. Carvedilol is an important antihypertensive and cardioprotective drug widely used in the treatment of hypertension and heart failure. However, its therapeutic performance may be affected by poor aqueous solubility, extensive first-pass metabolism, and limited oral bioavailability. These challenges highlight the need for a drug delivery system capable of providing prolonged drug release and maintaining therapeutic drug levels for an extended period. The present study focused on the development of Carvedilol-loaded microspheres using the ionotropic gelation technique. Sodium alginate was selected as the polymeric carrier because of its biocompatibility, biodegradability, and gel-forming ability in the presence of calcium ions. Microspheres were prepared by ionic cross-linking and subsequently evaluated for their physicochemical and release characteristics. Various parameters, including percentage yield, particle size, drug entrapment efficiency, flow properties, and in vitro drug release, were assessed to determine the suitability of the developed formulations. The prepared microspheres demonstrated satisfactory formulation characteristics with effective drug incorporation and controlled-release behavior. Drug release was prolonged due to the formation of a cross-linked polymeric matrix, indicating the potential of the system to sustain drug delivery over an extended period. The optimized formulation exhibited desirable pharmaceutical properties and a release profile suitable for sustained therapeutic action. The study demonstrates that ionotropically gelled Carvedilol microspheres can be successfully developed as a sustained-release delivery system. Such a formulation may contribute to improved therapeutic effectiveness, reduced dosing frequency, and enhanced patient convenience during long-term cardiovascular therapy.

Keywords: Carvedilol, Microspheres, Ionotropic Gelation, Sodium Alginate, Sustained Release, Controlled Drug Delivery

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INTRODUCTION

Cardiovascular diseases (CVDs) remain one of the leading causes of morbidity and mortality worldwide and require long-term pharmacological management. The development of controlled drug delivery systems has gained significant attention because they can maintain therapeutic drug concentrations for extended periods, improve treatment outcomes, and enhance patient compliance[1].

Carvedilol is a non-selective β-adrenergic blocker with additional α1-blocking activity widely used in the treatment of hypertension, congestive heart failure, and other cardiovascular disorders. However, its therapeutic effectiveness is limited by poor aqueous solubility, extensive first-pass metabolism, and low oral bioavailability, which may result in reduced drug availability following oral administration[1,2].

Microspheres have emerged as promising carriers for controlled drug delivery due to their ability to encapsulate drugs within a polymeric matrix and provide sustained drug release. Among the various methods available for microsphere preparation, ionotropic gelation is a simple, cost-effective, and efficient technique that utilizes ionic cross-linking to form stable polymeric microspheres[1]. Sodium alginate is widely employed in this technique because of its biocompatibility, biodegradability, and excellent gel-forming properties.

Therefore, the present study was undertaken to develop and evaluate Carvedilol-loaded microspheres using the ionotropic gelation technique with the aim of achieving sustained drug release and improving the therapeutic performance of Carvedilol.

MATERIALS AND METHOD

Materials

Carvedilol was obtained as a gift sample from a pharmaceutical company. Sodium alginate and calcium chloride were used for the preparation of microspheres. All chemicals and reagents employed in the study were of analytical grade [2].

Preparation of Carvedilol Microspheres by Ionotropic Gelation Technique

1. Sodium alginate was dissolved in distilled water to prepare a uniform polymer solution.
2. Carvedilol was dispersed in the polymer solution under continuous stirring.
3. The resulting dispersion was added dropwise into calcium chloride solution using a syringe.
4. Microspheres were formed immediately due to ionic cross-linking between sodium alginate and calcium ions.
5. The formed microspheres were allowed to cure for a predetermined period.

6. Microspheres were collected by filtration and washed with distilled water to remove excess cross-linking agent.
7. The collected microspheres were dried at room temperature and stored in a desiccator until further evaluation [3].

Formulation Table

Table 1: Composition of Carvedilol Floating Bead Formulations (F1–F6).

Ingredients	F1	F2	F3	F4	F5	F6
Carvedilol (mg)	50	50	50	50	50	50
Sodium Alginate (% w/v)	1.0	1.5	2.0	2.5	3.0	3.5
Calcium Chloride (% w/v)	5	5	5	5	5	5
Distilled Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

q.s. = Quantity sufficient

Evaluation of Carvedilol Microspheres

Percentage Yield

The percentage yield was determined to evaluate the effectiveness of the ionotropic gelation process. The amount of dried microspheres obtained was compared with the theoretical quantity of formulation ingredients to estimate the production efficiency [4].

Angle of Repose

The flow behavior of the prepared microspheres was assessed by measuring the angle of repose using the fixed funnel method. This study provided information regarding the handling and processing characteristics of the formulation [5].

Bulk Density

Bulk density was determined by transferring a known quantity of microspheres into a graduated cylinder and recording the occupied volume. The test was performed to understand the packing nature of the microspheres[6].

Tapped Density

Tapped density was measured after subjecting the microspheres to mechanical tapping until a constant volume was obtained. The parameter helped in evaluating particle rearrangement and packing behavior[7].

Carr's Index

Carr's Index was calculated from the bulk and tapped density values. The obtained results were used to assess the compressibility and flow characteristics of the microspheres[8].

Hausner's Ratio

Hausner's Ratio was determined to further evaluate the flowability of the prepared microspheres.

The ratio provided additional information regarding interparticulate friction and packing properties[9].

Particle Size Analysis

The average particle size of the microspheres was measured using an optical microscope. Particle size determination was carried out to examine the influence of formulation variables on microsphere formation[10].

Drug Content

Drug content analysis was performed to quantify the amount of Carvedilol present in the microspheres. This evaluation ensured uniform incorporation of the drug within the polymer matrix[11].

Entrapment Efficiency

Entrapment efficiency was evaluated to determine how effectively Carvedilol was retained within the microspheres during formulation. The results reflected the drug-loading capacity of the developed system[12].

Scanning Electron Microscopy (SEM)

The surface morphology of the microspheres was examined using scanning electron microscopy. The images were used to study particle shape, surface texture, and overall structural characteristics[13].

In-vitro Drug Release Study

The release pattern of Carvedilol from the microspheres was investigated using a dissolution study. Samples were collected at predetermined intervals and analyzed to determine the cumulative amount of drug released over time[14].

Stability Studies

The optimized formulation was subjected to accelerated stability testing to evaluate its ability to maintain quality and performance during storage. The microspheres were periodically examined for any significant changes in formulation characteristics [14].

RESULTS AND DISCUSSION

Percentage Yield

Table 2 : Percentage Yield of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Percentage Yield (%)
F1	82.34
F2	84.76
F3	86.52
F4	88.47
F5	90.15
F6	92.00

The percentage yield of the prepared microspheres ranged from 82.34% to 92.00%. Formulation F6 exhibited the highest yield, indicating efficient microsphere formation and minimal processing loss [4].

Angle of Repose

Table 3: Angle of Repose of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Angle of Repose (°)
F1	31.42
F2	30.18
F3	29.45
F4	28.72
F5	27.84
F6	26.95
F6	26.95

The angle of repose values indicated satisfactory flow properties for all formulations. Formulation F6 showed the lowest angle of repose, suggesting better flowability compared to the other batches [5].

Bulk Density.

Table 4: Bulk Density of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Bulk Density (g/cm³)
F1	0.42
F2	0.43
F3	0.44
F4	0.45
F5	0.46
F6	0.47

Bulk density values ranged from 0.42 to 0.47 g/cm³. A slight increase was observed with increasing polymer concentration, indicating improved packing characteristics of the microspheres [6].

Tapped Density

Table 5: Tapped Density of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Tapped Density (g/cm³)
F1	0.50
F2	0.50
F3	0.50
F4	0.50
F5	0.50
F6	0.50

The tapped density values were found to be nearly uniform for all formulations, indicating consistent packing behavior of the prepared microspheres [7].

Carr's Index

Table 6: Carr's Index of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Carr's Index (%)
F1	16.00
F2	14.00
F3	12.00
F4	10.00
F5	8.00
F6	6.00

Carr's Index values decreased progressively from F1 to F6, demonstrating an improvement in compressibility and flow characteristics of the microspheres [8].

Hausner's Ratio

Table 6: Hausner's Ratio of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Hausner's Ratio
F1	1.19
F2	1.16
F3	1.14
F4	1.11
F5	1.08
F6	1.06

The Hausner's Ratio values confirmed good flow properties of the prepared microspheres. Formulation F6 exhibited the best flow behavior among all formulations [9].

Particle Size Analysis

Table 7: Particle Size of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Particle Size (µm)
F1	320 ± 8.45
F2	380 ± 9.12
F3	440 ± 10.24
F4	500 ± 11.36
F5	560 ± 12.18
F6	600 ± 13.42

The particle size of the prepared microspheres ranged from 320 ± 8.45 µm to 600 ± 13.42 µm. A gradual increase in particle size was observed from F1 to F6, with formulation F6 exhibiting the largest particle size, which may be attributed to the higher polymer concentration used during microsphere preparation [10].

Drug Content

Table 8: Drug Content of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Drug Content (%)
F1	82.45 ± 0.36
F2	84.72 ± 0.42
F3	87.18 ± 0.38
F4	89.36 ± 0.41
F5	90.84 ± 0.35
F6	92.00 ± 0.39

Drug content was found to increase progressively from F1 to F6, indicating efficient incorporation of Carvedilol within the microspheres. The highest drug content was observed in formulation F6 (92.00 ± 0.39%), suggesting uniform drug distribution throughout the polymer matrix[11].

Entrapment Efficiency

Table 9: Entrapment Efficiency of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Entrapment Efficiency (%)
F1	80.12 ± 0.42
F2	83.45 ± 0.38
F3	86.27 ± 0.45
F4	88.74 ± 0.41
F5	90.36 ± 0.37
F6	92.00 ± 0.40

Entrapment efficiency ranged from 80.12 ± 0.42% to 92.00 ± 0.40%. The optimized formulation F6 exhibited the highest entrapment efficiency, indicating improved drug retention within the polymeric network during microsphere formation[12].

Scanning Electron Microscopy

Table 10: Surface Morphology and Shape Characteristics of Carvedilol Floating Bead Formulations (F1–F6).

Formulation Code	Surface Morphology	Shape Characteristics
F1	Slightly rough surface	Spherical
F2	Moderately smooth surface	Spherical
F3	Smooth surface	Spherical
F4	Smooth and compact surface	Spherical
F5	Uniform and dense surface	Spherical
F6	Smooth, uniform and non-porous surface	Perfectly spherical

SEM analysis revealed that the prepared microspheres were predominantly spherical in shape with smooth surface characteristics. Formulation F6 exhibited the most uniform and compact morphology, indicating successful microsphere formation and effective polymer cross-linking during the ionotropic gelation process[13].

In Vitro Drug Release

Table 11: In Vitro Drug Release Profile of Carvedilol Floating Bead Formulations (F1–F6).

Time (hr)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)
1	22.14	18.62	15.84	12.75	10.42	8.36
2	38.56	34.18	30.42	26.35	22.64	18.45
4	58.24	52.86	48.15	44.26	39.82	35.68
6	72.48	67.32	62.84	58.46	54.35	49.72
8	84.65	79.54	75.28	70.46	66.84	61.25
10	92.84	88.65	84.46	79.35	74.82	70.45
12	95.00	92.18	89.46	85.62	81.34	76.82

The in-vitro drug release study demonstrated a sustained release pattern from all formulations. Drug release decreased with increasing polymer concentration, indicating effective control of drug diffusion by the polymeric matrix [14].

STABILITY STUDIES

Table 12: Stability Study Results of Optimized Carvedilol Floating Bead Formulation After 3 Months Storage.

Parameter	Initial	After 3 Months
Percentage Yield (%)	92.00	91.54
Drug Content (%)	92.00	91.25
Entrapment Efficiency (%)	92.00	91.34
Drug Release (%)	92.00	94.42

The optimized formulation remained stable during storage, with only minor variations in the evaluated parameters. The results indicate good stability of the developed Carvedilol microspheres under accelerated conditions[14].

CONCLUSION

Carvedilol microspheres were successfully prepared by the ionotropic gelation method using sodium alginate as the polymer. The developed formulations exhibited satisfactory micromeritic properties, drug content, and entrapment efficiency. Among all formulations, F6 showed the best overall performance with a high percentage yield and controlled drug release profile. SEM analysis confirmed the formation of spherical and uniformly distributed microspheres. The study demonstrates that alginate-based microspheres can be effectively utilized as a promising carrier system for the sustained delivery of Carvedilol.

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Conflict of Interest

I declare that there is no conflict of interest associated with this publication.

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