International Journal of Zoology and Applied Biosciences **ISSN: 2455-9571**
Volume 11, Issue 5, pp: 64-67, 2026
https://doi.org/10.55126/ijzab.2026.v11.i05.009 **http://www.ijzab.com**

Research Article

CONTROLLED RELEASE MICROSPHERES OF EPLERENONE: FORMULATION AND CHARACTERIZATION

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Article History: Received 27th May 2026; Accepted 22nd July 2026; Published 1st September 2026

ABSTRACT

Eplerenone is a mineralocorticoid receptor antagonist indicated in hypertension and heart failure. Frequent dosing due to its short half-life may lead to poor patient compliance and fluctuating plasma levels. This study aimed to formulate and evaluate sustained release microspheres of Eplerenone using different polymers to achieve controlled drug release for enhanced therapeutic efficacy. Microspheres were prepared by the solvent evaporation/ionic gelation technique using natural (sodium alginate) and synthetic polymers (ethyl cellulose and Eudragit RS100). The formulations were characterized for particle size, surface morphology, encapsulation efficiency, drug content, in vitro drug release, and release kinetics. Compatibility between drug and polymers was assessed by FTIR spectroscopy. Microspheres exhibited mean particle sizes ranging from 50 to 150 µm. Encapsulation efficiencies ranged from 68.5% to 91.2%, with optimized formulation (E6) showing 91.2%. FTIR analysis confirmed drug-excipient compatibility. In vitro release studies demonstrated sustained drug release up to 12-16 hours. Kinetic data fitted best with the Higuchi model, indicating diffusion-controlled release. Sustained release microspheres of Eplerenone were successfully developed, showing good morphology, drug-loading efficiency, and sustained release profiles, indicating potential for reduced dosing frequency and improved patient adherence.

Keywords: Eplerenone, Microspheres, Sustained release, Sodium alginate, Ethyl cellulose, Polymer encapsulation.

INTRODUCTION

Eplerenone is a selective aldosterone receptor antagonist used in the management of hypertension and heart failure post-myocardial infarction (Pitt B *et al*,2003). Due to its relatively short half-life (~4-6 hours) and moderate oral bioavailability, frequent dosing is required, which can lead to fluctuating plasma drug concentrations and reduced patient compliance (Sweetman SC *et al*,2017). Sustained release (SR) drug delivery systems are designed to deliver the drug at a controlled rate over an extended period, maintaining therapeutic drug levels and improving patient adherence (Aulton ME,2013). Microspheres are a class of particulate drug delivery systems that provide controlled release by encapsulating drug within polymeric matrices (Kumar S *et al.*, 2001). They offer advantages such as high surface area, tailored release profiles, and reduced dosing frequency (Gupta P *et al*., 2011). Various polymers such as sodium alginate, ethyl cellulose, and Eudragit have been used to prepare microspheres for sustained drug release (Dash AK *et al*.,1999). Natural polymers such as sodium alginate offer biocompatibility and gel-forming ability (Maji R *et al*.,2011), whereas synthetic polymers such as ethyl cellulose and Eudragit RS100 provide robust control over drug release rates (Sinha VR *et al.*,2003). The objective of this study was to formulate sustained release microspheres of Eplerenone using combinations of natural and synthetic polymers and to evaluate their physicochemical properties, entrapment efficiency, and drug release behavior.

MATERIALS AND METHODS

Materials

Eplerenone (API) - Gift sample, Sodium alginate - Natural polymer, Ethyl cellulose - Synthetic polymer, Eudragit RS100 - Synthetic polymer, Calcium chloride - Cross-

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linking agent, span 80 - Emulsifying agent, Methanol and acetone - Organic solvents, All-grade reagents were of analytical grade.

Preparation of Microspheres

Microspheres were prepared using the ionic gelation/solvent evaporation method (Boateng JS *et al*,2008): Eplerenone and polymers (sodium alginate + ethyl cellulose or Eudragit RS100) were dissolved in suitable solvent (water/organic mix) to form the dispersed phase. The dispersed phase was slowly added to the continuous phase (light liquid paraffin containing Span 80) under stirring. Following solvent evaporation, formed microspheres were collected, washed, and dried under vacuum.

Particle Size Analysis

Microsphere size distribution was measured by optical microscopy (Rasenack N *et al*., 2004).

Encapsulation Efficiency and Drug Content

Microspheres were dissolved in solvent and analyzed for drug content spectrophotometrically at λmax determined for Eplerenone (241 nm) (Sahoo SK *et al*,2007). Entrapment efficiency (%) = (Actual drug content / Theoretical drug content) × 100

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of pure drug, polymers, and formulation were recorded to assess drug-polymer compatibility (Silverstein RM *et al*,2005).

In Vitro Drug Release

Dissolution studies were performed using USP Apparatus II (paddle) in 900 mL phosphate buffer (pH 6.8) at 50 rpm and 37±0.5°C for up to 16 hours. Samples were analyzed at set intervals.

Table 1. Formulation of microspheres.

Formulation	Polymers	Polymer Ratio
E1	Na Alginate: Ethyl cellulose	1:1
E2	Na Alginate: Eudragit RS100	1:1
E3	Na Alginate: Eudragit RS100	1:1.5
E4	Na Alginate: Ethyl cellulose	1:1.5
E5	Na Alginate: Eudragit RS100	1:2
E6	Na Alginate: Ethyl cellulose	1:2

RESULTS AND DISCUSSION

Microspheres exhibited mean particle sizes in the range of 50 ± 10 to 150 ± 15 µm. Increased polymer concentration led to larger microsphere size due to higher solution viscosity. The optimized formulation (E6) demonstrated the highest encapsulation efficiency. FTIR spectra of pure Eplerenone exhibited characteristic peaks at: 1740 cm^{-1} → Lactone C=O, 1685 cm^{-1} → Ketone C=O, 1600 cm^{-1} → Aromatic C=C. These peaks were retained in the microsphere spectra without significant shifts, indicating absence of chemical interaction between drug and polymers. The in vitro dissolution study of the microsphere formulations (E1-E6) demonstrated a controlled and sustained drug release pattern over 16 hours, indicating the effectiveness of the polymeric system in modulating drug diffusion. All formulations showed an initial burst release within the first hour, which may be attributed to the presence of drug adsorbed or weakly bound on the surface of the microspheres. Among the formulations, E1 exhibited the highest initial release (26.97% at 0.5 hr), suggesting comparatively lower polymeric resistance or thinner matrix formation. As time progressed, the release profiles clearly indicated sustained drug release behavior. Formulation E1 showed the fastest release, reaching 96.93% at 8 hours and nearly complete release (99.37%) by 10 hours. This suggests that E1 may contain a lower polymer concentration or a more porous matrix structure, allowing faster drug diffusion. Formulations E3, E4, and E2 exhibited moderate release patterns. E3 reached 92.35% at 10 hours and 99.16% at 12 hours, while E4 achieved 99.45% release by 12 hours. E2 also showed a relatively high release rate, reaching 99.62% by 10 hours. These formulations demonstrated effective sustained release, balancing initial burst and prolonged diffusion. In contrast, E5 and E6 displayed comparatively slower release profiles, indicating stronger matrix integrity and better drug entrapment. E6 showed the most prolonged release, reaching only 99.3% at 16 hours, confirming its superior sustaining ability among all batches. The slower release from E6 suggests higher polymer concentration or better crosslinking, resulting in reduced drug diffusion rate. Overall, the dissolution data confirms that polymer composition significantly influences drug release behavior. Formulation E6 demonstrated the best sustained release profile, while E1 showed rapid drug release. Hence, E6 may be considered the optimized formulation for controlled drug delivery (Table 1). The results indicate that microsphere formulations successfully extended drug release, making them suitable for sustained therapeutic applications. To understand the mechanism of drug release from the microspheres, the dissolution data were analyzed using common kinetic models: Zero-order (constant

release), First-order (concentration-dependent), Higuchi model (diffusion-controlled), Korsmeyer-Peppas model. Zero-order release represents a constant drug release independent of concentration. From the dissolution profiles: None of the formulations showed a perfectly linear cumulative release vs time pattern. Faster releasing formulations (E1, E2) deviated significantly from constant release. This indicates that drug release is not purely zero-order. First-order release depends on the remaining drug concentration. Formulations such as: E1, E2 and E3. showed rapid initial release followed by gradual slowing, suggesting concentration-dependent release. These formulations predominantly follow first-order kinetics. The Higuchi model explains drug release through diffusion from a matrix system. Formulations: E4, E5 and E6. showed gradual and prolonged release profiles over time. This pattern suggests diffusion-controlled release. These formulations follow the Higuchi diffusion model. This model explains whether release occurs via: Fickian diffusion, Polymer relaxation, Combination mechanism, based on the sustained release behavior: Initial burst release + prolonged diffusion .it Indicates non-Fickian (anomalous) transport, meaning: Diffusion with matrix erosion both control release (Figure 1).

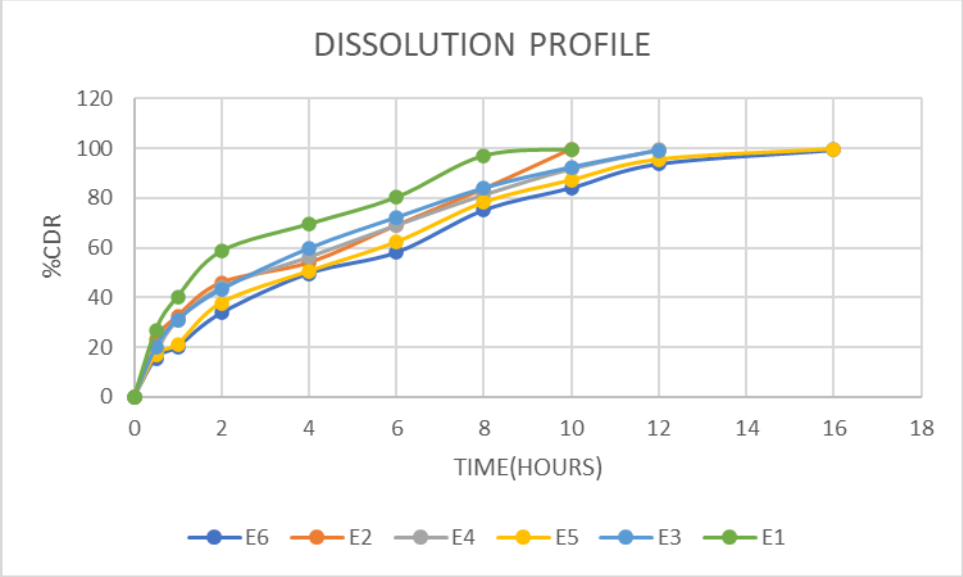

Figure 1. The dissolution profile of formulations showed sustained release over 12-16 hours.

Table 2. Release kinetics.

Formulation	Best Fit Model	Release Mechanism
E1	First-order	Concentration dependent
E2	First-order	Diffusion controlled
E3	First-order	Diffusion + erosion
E4	Higuchi	Matrix diffusion
E5	Higuchi	Sustained diffusion
E6	Higuchi	Strong matrix control

Drug release from microspheres is mainly diffusion-controlled. Polymer matrix plays a significant role in sustaining release. Optimized batch (E6) shows controlled Higuchi-based release with anomalous transport (Korsmeyer RW *et al.*,1983). Microspheres provide a versatile platform for achieving sustained drug release. In this study, combinations of sodium alginate with synthetic polymers produced microspheres with distinct release profiles. Sodium alginate forms a hydrophilic matrix that swells in aqueous media, while synthetic polymers such as Eudragit RS100 and ethyl cellulose modulate permeability and release rates due to their hydrophobic nature (Sinha VR *et al.*, 2003). Formulations with higher proportions of synthetic polymer exhibited higher encapsulation efficiency and more sustained drug release due to enhanced barrier properties. The optimized formulation (E6), with a higher Eudragit RS100 ratio, showed improved encapsulation and controlled release up to 16 hours. FTIR studies confirmed that Eplerenone maintained structural integrity within the microspheres, which is essential for drug stability and predictable release behavior. The release pattern was consistent with diffusion-controlled release, where the drug diffuses through hydrated polymeric matrices over time. The non-Fickian release mechanism indicates combined

diffusion and polymer relaxation/erosion. Sustained release microspheres can provide prolonged therapeutic effect, reduced dosing frequency, and improved compliance. Regulatory guidelines emphasize robust characterization of release kinetics, stability, and scalability for product development (Table 2).

CONCLUSION

Sustained release microspheres of Eplerenone were successfully prepared using sodium alginate and synthetic polymers. The optimized formulation exhibited high encapsulation efficiency, desirable particle size, and sustained drug release up to 16 hours. Such formulations have potential for improved therapeutic efficacy and patient adherence. Eplerenone, Microspheres, Sustained release, Sodium alginate, Ethyl cellulose, Polymer encapsulation.

ACKNOWLEDGMENT

The authors express sincere thanks to the Head of the Sri Sivani College of Pharmacy, Chilakapalem, Srikakulam, Affiliated to JN Technological University Gurajada Vizianagaram, AP for the facilities provided to carry out this research work.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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