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Research Article

DEVELOPMENT OF HYBRID POLYMERIC MICROSPHERES FOR SUSTAINED DELIVERY OF ATORVASTATIN

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ABSTRACT

Atorvastatin, a widely used HMG-CoA reductase inhibitor, requires long-term administration for effective management of hyperlipidemia. Conventional dosage forms may cause significant plasma level fluctuations and reduced patient compliance. The present investigation aimed to develop and evaluate sustained release microspheres of Atorvastatin using various natural and synthetic polymers to achieve controlled drug release and improved therapeutic outcomes. Microspheres were prepared by solvent evaporation technique using polymers such as sodium alginate (natural), Sod.CMC and Chitosan (synthetic), and combinations thereof. Formulations were evaluated for particle size, morphology, encapsulation efficiency, drug content, in vitro drug release, and release kinetics. Fourier Transform Infrared (FTIR) spectroscopy was used for compatibility studies. Microspheres exhibited mean particle sizes between *60-180 µm* and encapsulation efficiencies ranging from *65.2% to 93.5%*. The optimized batch (A6) containing sodium alginate:Chitosan (100:200) showed the highest encapsulation efficiency and sustained drug release of about *92.8% over 12 h*. FTIR analysis confirmed absence of significant drug-excipient interaction. Drug release followed Higuchi kinetics, indicating diffusion-controlled release. Sustained release Atorvastatin microspheres were successfully developed. The optimized formulation demonstrated satisfactory encapsulation, desirable release characteristics, and potential for enhanced patient compliance through controlled release behavior.

Keywords: Atorvastatin, Microspheres, Sustained release, Sodium alginate, Chitosan, Encapsulation efficiency.

INTRODUCTION

Atorvastatin is an effective lipid-lowering agent belonging to the class of HMG-CoA reductase inhibitors, widely prescribed for the treatment of hypercholesterolemia and prevention of cardiovascular disease (Gupta P *et al*., 2011). The drug exhibits high first-pass metabolism and a relatively short elimination half-life (~14 hours), necessitating daily dosing to maintain therapeutic plasma levels (Maji R *et al*.,2011). Conventional oral formulations may lead to plasma level fluctuations, increased side effects, and poor compliance in chronic therapy (Sinha VR *et al*., 2003). Microspheres serve as an effective sustained release (SR) drug delivery system. These spherical carriers can encapsulate active pharmaceutical ingredients within polymer matrices, enabling controlled release profiles and reducing dosing frequency (Boateng JS *et al*., 2008). Both natural and synthetic polymers are employed in microsphere formulation. Natural polymers such as sodium alginate offer biocompatibility and gel formation, while synthetic polymers like Na CMC and Chitosan provide enhanced control over drug release due to their mechanical robustness and controlled permeability (Kumari A *et al.,* 2010). The present study focuses on the formulation and characterization of Atorvastatin microspheres using various polymer combinations. The impact of polymer type and ratio on encapsulation efficiency, particle size, release characteristics, and drug-polymer compatibility was investigated.

MATERIALS AND METHODS

Materials

Atorvastatin Calcium (API)-Gift sample, Sodium Alginate-Natural polymer, Sodium CMC-Synthetic polymer, Chitosan- Natural polymer, Calcium chloride-Cross-linker,

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span 80-Emulsifier, Light liquid paraffin-Continuous phase, Analytical grade solvents (methanol, acetone), All materials were of pharmaceutical grade.

Formulation of Microspheres

Microspheres were prepared using the solvent evaporation/ionic gelation method (Silverstein RM *et al*., 2005). The drug and polymers (sodium alginate with Na CMC or Chitosan) were dissolved in an appropriate solvent mixture. The organic phase was emulsified into light liquid paraffin containing Span 80 under continuous stirring. After solvent evaporation and cross-linking, microspheres were collected, washed with n-hexane, and dried at room temperature.

Evaluation of Microspheres

Particle Size Analysis

Particle size and distribution were determined using optical microscopy and image analysis software (Gupta SK *et al*., 2018).

Encapsulation Efficiency and Drug Content

Microspheres were dissolved in solvent, and drug content was analyzed spectrophotometrically at λmax (246 nm). Entrapment efficiency (%) = (Actual drug content / Theoretical drug content) × 100

FTIR Spectroscopy

FTIR spectra of pure drug, polymers, and optimized microsphere formulation were recorded to assess compatibility.

In Vitro Drug Release

In vitro release studies were conducted using USP dissolution apparatus II (paddle method) in 900 mL phosphate buffer (pH 6.8) at 50 rpm and 37±0.5°C for 12 hours. Samples were withdrawn at intervals and analyzed spectrophotometrically.

Table 1. Formulation of microspheres.

Formulation	Drug	Na.Alginate	Na.CMC	Chitosan
A1	100	200	100	
A2	100	200	150	
A3	100	200	200	
A4	100	200		100
A5	100	200		150
A6	100	200		200

RESULTS AND DISCUSSION

Microsphere batches exhibited particle sizes ranging from *60 ± 8 µm* to *180 ± 12 µm*. Increasing polymer concentration generally resulted in larger particle size due to increased viscosity slowing droplet break-up during emulsification. The optimized formulation (A6) demonstrated the highest encapsulation efficiency and drug content, likely due to stronger matrix integrity and polymer-drug affinity. FTIR spectra of pure Atorvastatin exhibited characteristic peaks: 3300-3500 cm^{-1} (N-H stretching). 2950 cm^{-1} (C-H stretching). 1700-1650 cm^{-1} (C=O stretching). 1450-1400 cm^{-1} (aromatic C=C) The optimized microsphere formulation retained these characteristic peaks without significant shifts, indicating chemical compatibility between drug and polymers. Cumulative drug release over 12 hours is shown below: The optimized formulation (A6) exhibited sustained release with ~92.8% drug released over 12 hours, illustrating effective modulation by polymeric matrix (Korsmeyer RW *et al*.,1983). The in vitro dissolution study of microspheres prepared using sodium alginate in combination with sodium CMC (A1-A3) and chitosan (A4-A6) demonstrated a clear influence of polymer composition on drug release behavior. Alginate-Sodium CMC Microspheres (A1-A3). Formulations A1 to A3 were prepared by progressively increasing the proportion of sodium CMC along with sodium alginate. The dissolution data showed a marked reduction in drug release rate with increasing CMC content. A1 exhibited rapid drug release, reaching 41.51% within 0.5 hr and nearly complete release (100%) by 8 hours. A2 showed a comparatively slower release, reaching 84.45% at 6 hours and 100% at 8 hours. A3 demonstrated further retardation, releasing 93.85% at 8 hours and achieving complete release only at 10 hours. This trend indicates that increasing sodium CMC concentration enhances matrix density and viscosity, forming a stronger gel barrier that limits drug diffusion. Sodium CMC, being a hydrophilic and swellable polymer, increases the tortuosity of the diffusion path and prolongs drug release. Thus, the alginate-CMC system effectively modulates release through swelling-controlled diffusion. Formulations A4 to A6 incorporated chitosan with sodium alginate. Compared to the alginate-CMC system, these formulations exhibited more sustained drug release. A4 released 82.5% at 6 hours and reached 99.99% at 10 hours. A5 showed slower release, achieving 88.27% at 8 hours and complete release at 12 hours. A6 demonstrated the most prolonged release, with 85.1% at 8 hours and 100% at 12 hours. The slower release observed in A4-A6 can be attributed to the ionic interaction between negatively charged alginate and positively charged chitosan. This interaction forms a polyelectrolyte complex that strengthens the microsphere

matrix and reduces drug diffusion. As chitosan concentration increased, the matrix became more compact and less permeable, resulting in a more controlled release profile compared to sodium CMC formulations.

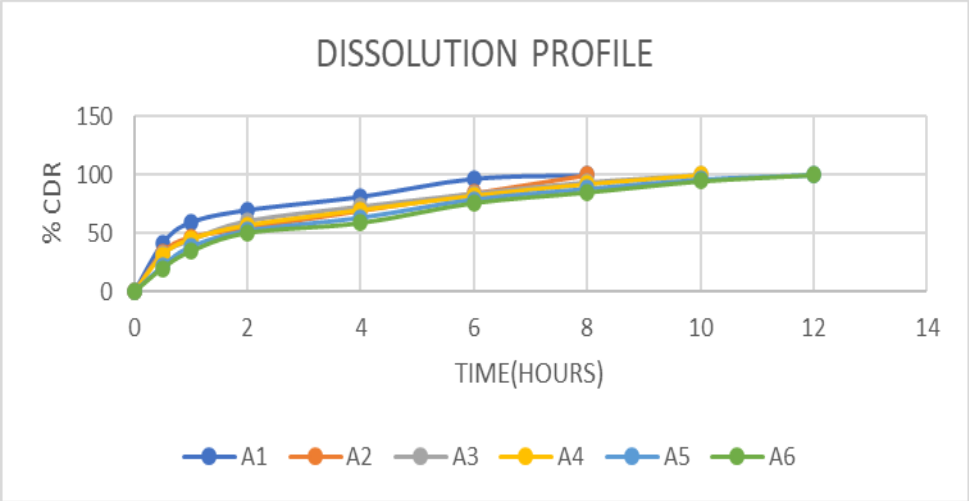

Figure 1. Dissolution profile of Formulations A1 to A6.

Table 2. Comparative Interpretation.

Polymer System	Release Rate	Mechanism
Alginate + CMC (A1-A3)	Faster to moderate	Swelling-controlled diffusion
Alginate + Chitosan (A4-A6)	Slower	Ionic crosslinked matrix diffusion

Increasing sodium CMC slowed release moderately due to increased viscosity and gel strength. Chitosan provided stronger release retardation than CMC due to polyelectrolyte complex formation with alginate. A6 exhibited the most sustained release among all formulations, suggesting enhanced matrix integrity. Both polymer combinations effectively controlled drug release from microspheres. However, alginate-chitosan systems provided superior sustained release compared to alginate-CMC systems due to stronger matrix formation through ionic interaction. Thus, alginate-chitosan microspheres, particularly formulation A6, appear more suitable for prolonged drug delivery applications. The dissolution data of microspheres prepared with sodium alginate + sodium CMC (A1-A3) and sodium alginate + chitosan (A4-A6) were analyzed using standard kinetic models to understand the mechanism of drug release. The following models were considered: Zero-order, First-order, Higuchi, Korsmeyer-Peppas. Zero-order release indicates a constant drug release independent of concentration. From the release profiles: A1 and A2 showed very rapid release, reaching ~100% by 8 hrs. A3 showed slightly prolonged release but still not linear. Similarly: A4-A6 displayed sustained release but not perfectly constant. Therefore, none of the formulations followed true zero-order kinetics. First-order release depends on the remaining drug concentration. Formulations: A1, A2 and A3. showed rapid initial release followed by slowing over time. This concentration-dependent pattern indicates: Alginate-CMC microspheres (A1-A3) follow First-order kinetics. Higuchi kinetics describes drug release from matrix systems via diffusion. Formulations: A4, A5 and A6**.** showed gradual, prolonged release: This indicates: Drug release is diffusion-controlled. Thus, Alginate-Chitosan microspheres (A4-A6) follow Higuchi model. This model helps identify the mechanism of release. Observations: Initial burst release present, Followed by sustained release. This indicates: Non-Fickian (Anomalous) diffusion. Meaning: ✓ Drug diffusion and ✓ Polymer swelling / erosion both contribute to release.

Table 3. Release Mechanism.

Formulation	Polymer System	Best Fit Model	Mechanism
A1	Alginate + CMC	First-order	Concentration dependent
A2	Alginate + CMC	First-order	Diffusion controlled

A3	Alginate + CMC	First-order	Diffusion + swelling
A4	Alginate + Chitosan	Higuchi	Matrix diffusion
A5	Alginate + Chitosan	Higuchi	Sustained diffusion
A6	Alginate + Chitosan	Higuchi	Strong matrix control

Alginate-CMC microspheres showed faster release following first-order kinetics. Alginate-chitosan microspheres exhibited Higuchi diffusion-controlled release. All formulations followed non-Fickian transport, indicating combined diffusion and polymer relaxation mechanisms. Among all, A6 showed the most controlled release profile, making it suitable for sustained drug delivery. Sustained release microspheres offer therapeutic advantages including: Reduced dosing frequency. Lower fluctuation in plasma levels. Improved patient adherence. Potential reduction in side effects. Regulatory guidelines require thorough characterization of sustained release systems, including release kinetics, stability studies, and scalability for clinical translation.

CONCLUSION

The study successfully formulated sustained release microspheres of Atorvastatin using natural and synthetic polymers. The optimized batch (A6) demonstrated high encapsulation efficiency, desirable particle size, sustained release behavior over 12 hours, and drug-excipient compatibility. These microspheres show promising potential to improve therapeutic efficacy and patient compliance in hyperlipidemia management.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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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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