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Research Article

Formulation, development, and evaluation of chitosan mucoadhesive microspheres of Atenolol, a selective Beta blocker

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Abstract

Atenolol, a selective β₁-adrenergic blocker, requires chronic administration for hypertension and related cardiovascular disorders. Conventional oral dosage forms may lead to plasma peak–trough fluctuations and frequent dosing. The present work aimed to develop chitosan-based mucoadhesive microspheres of atenolol to achieve prolonged gastrointestinal residence and sustained drug release. Microspheres were prepared using ionotropic gelation with sodium tripolyphosphate (TPP) as a cross-linking agent. Formulations (F1–F6) were optimized by varying polymer and cross-linker levels. Prepared microspheres were evaluated for percentage yield, particle size, drug loading, entrapment efficiency, flow properties, swelling index, mucoadhesive strength, in-vitro wash-off, surface morphology (SEM), in-vitro drug release, and release kinetics. Microspheres were discrete and spherical, showing acceptable flow and significant mucoadhesion. The optimized formulation (F2) exhibited high yield, satisfactory entrapment, strong mucoadhesion, and sustained release up to 12 h. Release kinetics indicated diffusion-dominant release with swelling contribution, consistent with Higuchi and Korsmeyer–Peppas behavior. The study concludes that chitosan mucoadhesive microspheres represent a promising controlled oral delivery platform for atenolol.

Keywords: Atenolol; Chitosan; Mucoadhesion; Microspheres; Ionotropic gelation; Controlled release.

1. Introduction

Oral drug delivery remains the most preferred route of administration due to its convenience, patient compliance, cost-effectiveness, and safety [1]. Despite these advantages, conventional oral dosage forms often suffer from several limitations, including short gastrointestinal residence time, variable absorption, frequent dosing, and plasma concentration fluctuations, which may compromise therapeutic efficacy, particularly in the management of chronic diseases. These challenges have driven continuous research toward the development of advanced oral drug delivery systems capable of providing controlled and predictable drug release [2].

Controlled drug delivery systems are designed to maintain plasma drug concentrations within the therapeutic window for prolonged periods, thereby reducing dosing frequency and minimizing adverse effects associated with peak–trough fluctuations. Among these systems, multiparticulate dosage forms, such as microspheres, have gained significant attention due to their ability to distribute uniformly throughout the gastrointestinal tract, reduce the risk of dose dumping, and improve reproducibility of drug absorption compared to single-unit systems [3].

Mucoadhesive drug delivery systems represent a promising approach to enhance the performance of oral controlled release formulations. These systems adhere to the mucosal surfaces of the gastrointestinal tract, thereby prolonging residence time at the site of absorption and potentially improving drug bioavailability. Mucoadhesion occurs through physicochemical interactions between the polymer and mucin, including hydrogen bonding, electrostatic interactions, and polymer chain interpenetration. The selection of an appropriate mucoadhesive polymer is therefore crucial for the success of such systems [4].

Chitosan, a natural, biodegradable, and biocompatible polymer obtained by deacetylation of chitin, has emerged as an excellent candidate for mucoadhesive drug delivery. Owing to its cationic nature, chitosan exhibits strong electrostatic interaction with negatively

charged mucosal surfaces, resulting in enhanced mucoadhesion. Additionally, chitosan possesses swelling, film-forming, and permeation-enhancing properties, which further support its application in oral controlled drug delivery systems. These characteristics make chitosan particularly suitable for the formulation of mucoadhesive microspheres [5].

Microspheres are spherical particulate systems, typically ranging from 1 to 1000 µm in size, in which the drug is either dispersed or encapsulated within a polymeric matrix. Chitosan-based microspheres prepared by ionotropic gelation offer several advantages, including mild processing conditions, avoidance of organic solvents, high drug entrapment efficiency, and suitability for heat- or moisture-sensitive drugs. By modulating polymer concentration and cross-linking density, the drug release profile from microspheres can be precisely controlled [6].

Atenolol is a selective β_1-adrenergic receptor blocker widely prescribed for the treatment of hypertension, angina pectoris, and other cardiovascular disorders. It is a hydrophilic drug with moderate oral bioavailability and requires long-term administration. Conventional immediate-release formulations of atenolol may lead to fluctuating plasma drug levels, necessitating multiple daily doses and potentially affecting patient adherence. A controlled release formulation capable of maintaining consistent therapeutic levels would therefore be beneficial in improving treatment outcomes [7].

Several studies have explored sustained-release and gastroretentive formulations of atenolol; however, many of these systems lack strong mucoadhesive properties, resulting in limited gastrointestinal retention and suboptimal absorption. Incorporation of mucoadhesive characteristics using chitosan-based microspheres offers a rational strategy to overcome these limitations by combining prolonged residence time with controlled drug release [8].

In this context, the present study focuses on the formulation, development, and evaluation of chitosan mucoadhesive microspheres of atenolol using the ionotropic gelation technique. The study aims to optimize formulation variables, evaluate physicochemical and mucoadhesive properties, investigate in-vitro drug release behavior, and elucidate the release kinetics [9]. The successful development of such a system may provide an effective controlled oral delivery platform for atenolol, with the potential to enhance therapeutic efficacy and patient compliance in long-term antihypertensive therapy [10].

2. Materials and Methods

2.1 Materials

- **Drug:** Atenolol (API, pharmaceutical grade)
- **Polymer:** Chitosan (medium MW; degree of deacetylation as per supplier)
- **Cross-linker:** Sodium tripolyphosphate (TPP)
- **Other reagents:** Glacial acetic acid, distilled water, 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), and analytical grade chemicals.

2.2 Method of Preparation (Ionotropic Gelation)

Chitosan was dissolved in 1–2% v/v acetic acid under stirring to obtain a homogeneous solution. Atenolol was dissolved/dispersed in the polymer solution. The drug–polymer solution was added dropwise into aqueous TPP solution under mechanical stirring, producing instantaneous ionic cross-linking and microsphere formation. Microspheres were cured for a fixed time, collected by filtration/centrifugation, washed with distilled water, dried, and stored in a desiccator.

2.3 Formulation Design

Six formulations (F1–F6) were prepared by varying chitosan and TPP levels.

Table 1. Formulation design (F1–F6)

Formulation	Drug: Polymer	Chitosan level	TPP level
F1	1:1	Low	Low
F2	1:2	Medium	Low
F3	1:3	High	Low
F4	1:1	Low	Medium
F5	1:2	Medium	Medium
F6	1:3	High	High

3. Evaluation of Microspheres

3.1 Percentage Yield

3.2 Particle Size

Mean particle size was measured by optical microscopy using an ocular micrometer (n≈100 particles).

3.3 Surface Morphology (SEM)

Dried microspheres were gold sputter-coated and examined under SEM to observe shape and surface texture.

3.4 Drug Loading and Entrapment Efficiency

Microspheres were crushed, extracted in suitable medium, filtered, and analyzed by UV spectrophotometry.

3.5 Flow Properties

Bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose were determined by standard methods.

3.6 Swelling Index

3.7 Mucoadhesive Strength

Mucoadhesive strength was measured using ex-vivo mucosa (e.g., goat intestinal mucosa) using a modified balance/force measurement approach.

3.8 In-Vitro Wash-Off Test

Microspheres were applied to mucosa mounted on a slide and subjected to vertical movement in dissolution/disintegration apparatus; % retained after fixed time was recorded.

4. In-Vitro Drug Release

Dissolution was performed using USP apparatus (commonly Type II) at 37±0.5°C. Release media included SGF pH 1.2 followed by phosphate buffer pH 6.8 (two-stage approach). Samples were withdrawn at intervals and analyzed spectrophotometrically. Cumulative % release was calculated.

5. Release Kinetic Modeling

Release data were fitted to:

- **Zero-order**
- **First-order**
- **Higuchi model**
- **Korsmeyer–Peppas model** (to interpret mechanism via n value for spherical systems)

6. Results and Discussion

6.1 Percentage Yield and Particle Size

Table 2. Yield and particle size

Formulation	Yield (%)	Particle size (µm)
F1	78.4 ± 1.2	310 ± 15
F2	85.6 ± 1.0	365 ± 18
F3	88.9 ± 1.3	420 ± 20
F4	80.1 ± 1.5	330 ± 16
F5	83.7 ± 1.1	380 ± 19
F6	86.4 ± 1.4	445 ± 22

Discussion: Increasing chitosan concentration increased viscosity, producing larger microspheres and improving yield. Higher cross-linking tended to stabilize microspheres, reducing processing losses.

6.2 Drug Loading and Entrapment Efficiency

Table 3. Drug loading and entrapment

Formulation	Drug loading (%)	Entrapment efficiency (%)
F1	18.2 ± 0.9	65.4 ± 1.5
F2	21.8 ± 1.0	78.6 ± 1.2
F3	23.4 ± 1.1	82.3 ± 1.4
F4	19.1 ± 0.8	68.2 ± 1.6
F5	22.0 ± 1.0	75.9 ± 1.3
F6	23.9 ± 1.2	80.1 ± 1.5

Discussion: Entrapment improved with polymer content due to stronger matrix formation. Excess cross-linking may restrict drug distribution and reduce effective loading beyond an optimum.

6.3 Flow Properties

Table 4. Flow indices

Formulation	Carr's index (%)	Hausner ratio	Angle of repose (°)
F1	15.2	1.18	27.6
F2	13.1	1.15	25.9
F3	16.4	1.20	29.3
F4	14.8	1.17	26.8
F5	13.9	1.16	26.2
F6	17.0	1.21	30.1

Discussion: Spherical shape generally supported good flow; higher polymer/cross-linking increased interparticle cohesion slightly.

6.4 Swelling, Mucoadhesion, and Wash-Off

Table 5. Swelling and mucoadhesive performance

Formulation	Swelling index(%)	Mucoadhesive strength (g)	Retained after 6 h(%)
F1	62.5 ± 2.1	18.6 ± 0.9	42
F2	71.8 ± 2.3	24.2 ± 1.0	61
F3	78.6 ± 2.5	28.5 ± 1.1	68
F4	65.2 ± 2.0	20.1 ± 0.8	48
F5	70.4 ± 2.2	23.6 ± 1.0	57
F6	75.9 ± 2.6	27.2 ± 1.2	65

Discussion: Mucoadhesion increased with chitosan level due to electrostatic interaction between cationic chitosan and mucin. F2 provided strong adhesion with controlled swelling, suitable for sustained release without excessive matrix relaxation.

6.5 SEM Morphology

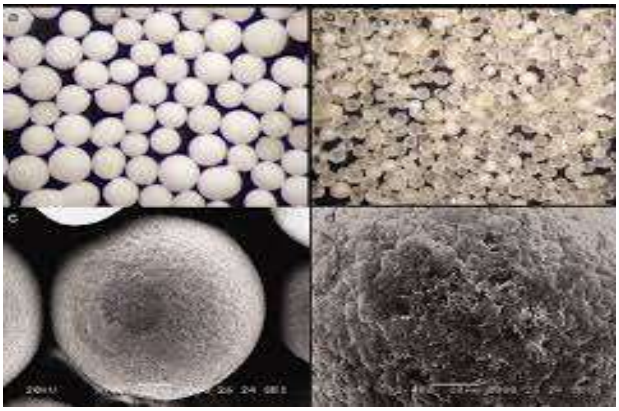

Figure 1. SEM images of Atenolol-loaded chitosan microspheres

Caption: Microspheres appeared spherical with smooth to slightly rough surfaces, indicating successful formation via ionotropic gelation and supporting controlled release performance.

6.6 In-Vitro Drug Release Profile

Table 6. Cumulative % drug release

Time (h)	F1	F2	F3	F4	F5	F6
0.5	18.4	12.6	9.8	16.9	13.8	10.5
1	28.7	21.4	16.2	26.1	22.6	17.9
2	42.5	35.8	28.4	39.7	36.1	30.2
4	63.9	54.6	45.3	60.1	55.7	48.8
6	78.2	69.8	60.7	74.5	70.2	64.3
8	92.6	83.4	72.1	88.9	84.7	76.8
12	98.4	94.2	86.5	96.1	93.3	88.9

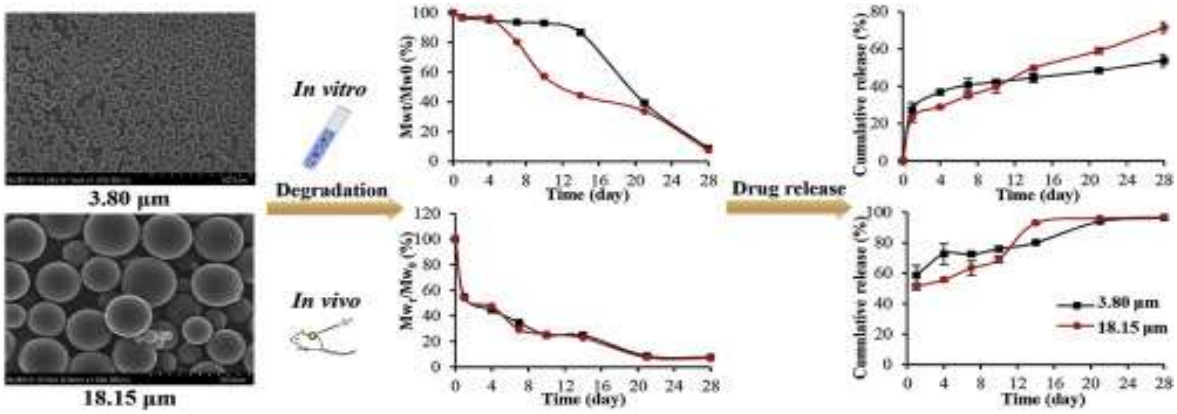

Figure 2. Cumulative % drug release vs time (F1–F6)

Caption: Formulations showed an initial phase followed by sustained release. F2 achieved controlled release (~94% at 12 h) with reduced burst effect compared to low-polymer batches.

Discussion: Lower polymer matrices released faster due to reduced diffusion path length and lower cross-link density, whereas higher polymer/cross-link systems showed retarded release. F2 presented a balanced controlled release profile.

6.7 Release Kinetics

Table 7. Best-fit kinetics (R^2) and Peppas exponent (n)

Formulation	R^2 (Zero)	R^2 (First)	R^2 (Higuchi)	R^2 (Peppas)	n
F1	0.932	0.951	0.978	0.985	0.41
F2	0.945	0.962	0.991	0.993	0.58
F3	0.938	0.955	0.987	0.990	0.63
F4	0.934	0.949	0.975	0.982	0.44
F5	0.941	0.958	0.986	0.989	0.56
F6	0.936	0.953	0.984	0.988	0.61

Discussion: Higuchi and Peppas models showed the highest R^2, indicating diffusion-dominant release with polymer swelling contribution. Peppas n values for most batches suggested non-Fickian transport (diffusion + relaxation/swelling). F2 exhibited controlled release with consistent mechanism.

7. Conclusion

Chitosan mucoadhesive microspheres of atenolol were successfully developed using ionotropic gelation. Formulation variables (polymer and cross-linker levels) significantly influenced microsphere size, entrapment efficiency, mucoadhesion, and drug release. The optimized batch (F2) demonstrated desirable physicochemical properties, strong mucoadhesion, sustained release up to 12 h, and diffusion-dominant release kinetics with swelling contribution. The developed microspheres offer a promising oral controlled delivery approach for atenolol to potentially improve therapeutic consistency and patient compliance.

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