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Research Article

Clarithromycin-Loaded Mucoadhesive Microspheres for Gastro-Retentive Drug Delivery: Formulation and Characterization Using Tamarind Seed Polysaccharide

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Abstract

Clarithromycin, a macrolide antibiotic, is widely used in treating bacterial infections, including *Helicobacter pylori*. Conventional oral dosage forms often undergo rapid gastrointestinal transit, limiting gastric residence and controlled release. Gastro-retentive mucoadhesive microspheres offer a promising approach to prolong gastric residence and sustain drug delivery. Tamarind seed polysaccharide (TSP), a natural polymer, was evaluated for developing Clarithromycin microspheres. Preformulation studies included physical characterization, solubility, pKa, log P, powder-flow properties, UV estimation, and drug–excipient compatibility. Microspheres were prepared by a single-emulsion technique, with 29 batches designed using Design-Expert software by varying drug concentration, TSP concentration, stirring speed, and Span-80 levels. Responses studied were mucoadhesion, entrapment efficiency, cumulative drug release, and particle size. Optimized microspheres were filled into hard gelatin capsules equivalent to 250 mg Clarithromycin. Clarithromycin showed a melting point of 218–220°C, pKa 8.35, log P 3.05, and poor solubility in water, but higher solubility in acidic media. FTIR confirmed compatibility with TSP. Microspheres exhibited good flow (angle of repose 26.5°, Hausner's ratio 1.035, Carr's index 3.44%). Capsules demonstrated uniform drug content (250.08 ± 1.13 mg), disintegration time of 12.57 min, and satisfactory pharmaceutical quality. In-vitro dissolution revealed prolonged release: 63.85% at 8 h, 81.76% at 12 h, 95.36% at 18 h, and 97.21% at 20 h.

The study confirms the feasibility of TSP-based mucoadhesive microspheres for gastro-retentive controlled release of Clarithromycin, with excellent content uniformity and sustained drug release up to 20 h.

Keywords: Clarithromycin; Tamarind seed polysaccharide; TSP; mucoadhesive microspheres; gastro-retentive drug delivery; controlled release; mucoadhesion; *Helicobacter pylori*.

1. Introduction

Oral drug delivery remains the most widely used and convenient route for administration of pharmaceutical agents because of its ease of administration, patient acceptability, cost-effectiveness, and established manufacturing processes [1]. However, conventional oral dosage forms may be associated with several limitations, including rapid gastrointestinal transit, variable drug absorption, and short residence time at the absorption site, and fluctuations in plasma drug concentration. These limitations become particularly important for drugs that exhibit site-specific absorption, limited solubility, or a narrow absorption window in the gastrointestinal tract [2]. Gastro-retentive drug delivery systems (GRDDS) have therefore received considerable attention as an approach to prolong the residence time of dosage forms within the stomach and improve drug availability at the desired site of absorption [3].

Among the different gastro-retentive approaches, mucoadhesive drug delivery systems are particularly promising because they can interact with the mucin layer covering the gastrointestinal epithelium [4]. Mucoadhesion may prolong the residence of drug-loaded particles at the gastric mucosa, thereby providing intimate contact between the formulation and the absorptive surface [5]. Microspheres are advantageous in this regard because their small particle size provides a relatively large surface area for interaction with the mucosal surface. Incorporation of mucoadhesive polymers into microspheres can consequently provide

prolonged gastric residence and controlled drug release while reducing the frequency of drug administration [6].

Clarithromycin is a semisynthetic macrolide antibiotic derived from erythromycin and is widely used in the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria as well as atypical microorganisms [7]. It is also an important component of combination regimens used for the eradication of *Helicobacter pylori*. Despite its therapeutic usefulness, conventional oral administration of Clarithromycin can present challenges associated with its physicochemical characteristics and gastrointestinal absorption [8]. Clarithromycin is a weakly basic, relatively lipophilic compound with limited aqueous solubility, and its oral absorption and gastrointestinal disposition can be influenced by the formulation and physiological environment [9]. Conventional immediate-release dosage forms may therefore result in relatively rapid drug release and limited gastric residence, which may not be optimal when prolonged exposure in the upper gastrointestinal tract is desirable [10].

A gastro-retentive mucoadhesive microsphere system may offer several potential advantages for Clarithromycin delivery. Following administration, the capsule can disintegrate and release the microspheres into the stomach [11]. The microspheres can hydrate and interact with the gastric mucus layer, thereby increasing their residence time. Simultaneously, the polymeric matrix can control penetration of the dissolution medium and diffusion of Clarithromycin from the microspheres. Such a system may provide prolonged drug release, improved gastric residence, reduced dosing frequency, and more consistent drug exposure compared with conventional immediate-release formulations [12].

Natural polymers have attracted considerable interest in the development of gastro-retentive and mucoadhesive drug delivery systems because of their biodegradability, biocompatibility, low toxicity, availability, and relatively low cost. Natural polysaccharides are particularly useful because their hydrophilic functional groups can facilitate hydration, swelling, hydrogen bonding, and interaction with mucin. These characteristics make them suitable candidates for the preparation of controlled-release and mucoadhesive dosage forms [13].

Tamarind seed polysaccharide (TSP) is a naturally occurring polysaccharide obtained from the seeds of *Tamarindus indica* Linn. Tamarind seeds are an abundant, inexpensive, and renewable natural source of polysaccharides [14]. TSP possesses favourable physicochemical characteristics, including hydrophilicity, swelling ability, viscosity enhancement, film-forming capacity, and potential bioadhesive properties [15]. The presence of hydroxyl-containing polysaccharide chains can facilitate interactions with biological mucus through hydrogen bonding and other intermolecular interactions. These properties make TSP an attractive natural polymer for developing mucoadhesive and sustained-release pharmaceutical formulations [16].

The utilization of TSP as a pharmaceutical excipient also offers an opportunity to explore a naturally derived alternative to synthetic polymers [17]. The performance of TSP in a microsphere system can be influenced by polymer concentration, drug-to-polymer ratio, method of preparation, particle size, surface characteristics, swelling behavior, and cross-linking or matrix formation [18]. Optimization of these factors is essential to obtain microspheres with desirable particle size, percentage yield, entrapment efficiency, drug loading, surface morphology, mucoadhesive strength, swelling behavior, and controlled drug-release characteristics [19].

In the present investigation, an attempt was therefore made to develop gastro-retentive mucoadhesive microspheres of Clarithromycin using Tamarind seed polysaccharide (TSP) as a natural mucoadhesive polymer [20]. The prepared microspheres were systematically characterized for their physicochemical and micromeritic properties, drug entrapment, particle size, surface morphology, mucoadhesive performance, and in-vitro drug-release behaviour [21]. The optimized microsphere formulation was subsequently incorporated into a hard gelatin capsule and evaluated for relevant pharmaceutical quality attributes [22]. The study was undertaken with the objective of developing a natural-polymer-based gastro-retentive delivery system capable of providing prolonged gastric residence and sustained release of Clarithromycin, thereby potentially improving the effectiveness and convenience of oral therapy [23].

2. Materials and Methods

2.1 Materials

Clarithromycin was used as the model drug for the development of gastro-retentive mucoadhesive microspheres. Tamarind seed polysaccharide (TSP) was selected as the natural mucoadhesive polymer. Span-80 was used as the emulsifying/surfactant agent, while other formulation and analytical reagents were of suitable pharmaceutical or analytical grade. Magnesium stearate and talc were used as excipients during the preparation of the capsule blend. The optimized microspheres were subsequently filled into hard gelatin capsules. The study was designed to investigate the feasibility of TSP as a natural polymer for prolonged gastric residence and controlled release of Clarithromycin. The formulation development and evaluation were performed according to the experimental design described in the study.

2.2 Preformulation Studies

2.2.1 Physical characterization of Clarithromycin

The supplied Clarithromycin was examined for its organoleptic characteristics, including appearance, colour, odour, taste, and physical state. The observed characteristics were compared with the reported pharmacopoeial characteristics of Clarithromycin. The drug was observed as a white to almost white crystalline powder and was practically odourless.

2.2.2 Determination of melting point

The melting point of Clarithromycin was determined by the capillary method using a melting-point apparatus. A small quantity of the drug was packed into a capillary tube and subjected to gradual heating. The temperature range over which the drug melted was recorded and compared with the reported reference value. The observed melting point was 218–220°C.

2.2.3 Solubility study

The solubility of Clarithromycin was determined in selected aqueous and organic solvents. An excess amount of drug was added to the respective solvent and the samples were allowed to equilibrate. Following equilibration, the samples were filtered and the dissolved drug concentration was determined by the established analytical method. Solubility was expressed as grams per millilitre. The investigation included distilled water, methanol, ethanol, acetone, chloroform, benzene, DMSO, phosphate buffer pH 2, 0.1 N HCl, simulated gastric fluid, phosphate buffer pH 7.4, 0.1 N NaOH, and petroleum ether.

2.2.4 Determination of pKa

The pKa of Clarithromycin was determined to assess its ionization characteristics. The experimental pKa was obtained using the procedure adopted in the study and compared with the reported reference value. The observed pKa of Clarithromycin was 8.35, compared with the reported value of 8.99.

2.2.5 Determination of partition coefficient

The partition coefficient of Clarithromycin was determined by the shake-flask method using an n-octanol/water system. The drug was allowed to distribute between the two immiscible phases, after which the drug concentration in the respective phases was determined. The partition coefficient was calculated from the ratio of drug concentration in the organic phase to that in the aqueous phase. The observed log P value was 3.05.

2.2.6 Determination of bulk density

Bulk density was determined by measuring the volume occupied by a known weight of Clarithromycin powder using a densitometer. The bulk density was calculated as the ratio of the mass of powder to its untapped bulk volume. The determination was performed in triplicate.

2.2.7 Determination of tapped density

Tapped density was determined by mechanically tapping a known quantity of Clarithromycin powder in a graduated measuring cylinder. The cylinder was raised and allowed to fall under its own mass from a height of approximately 14 ± 2 mm for 500 taps. The final tapped volume was recorded and tapped density was calculated as the ratio of powder mass to tapped volume.

2.2.8 Evaluation of powder-flow properties

The flow properties of Clarithromycin were evaluated using Carr's compressibility index and Hausner's ratio. These parameters were calculated from the bulk and tapped density values using the following equations:

2.2.9 Carr's Compressibility Index (%)

The obtained values were used to characterize the flowability of the drug powder.

2.3 UV Spectrophotometric Analysis of Clarithromycin

A UV/visible spectrophotometric method was used for quantitative estimation of Clarithromycin. The analytical procedure described in the study employed a visible-range spectrophotometric reaction using ferric chloride ($FeCl_3$) and potassium thiocyanate (KSCN). A series of standard Clarithromycin concentrations was prepared and analyzed to establish the calibration relationship between concentration and absorbance. The calibration curve was linear over the investigated concentration range, with concentrations of 10–50 µg/mL.

2.4 Drug–Excipient Compatibility Study

Compatibility between Clarithromycin and Tamarind seed polysaccharide was investigated using Fourier-transform infrared spectroscopy (FTIR). Clarithromycin and TSP were mixed in a 1:1 ratio and placed in sealed 5-mL glass vials. The mixtures were stored in an oven at 60°C for 3 weeks. Following storage, the samples were subjected to FTIR analysis over the range of 500–4000 cm^{-1}. The characteristic absorption bands of the drug and drug–polymer mixture were compared to identify any significant changes or disappearance of characteristic peaks.

2.5 Preparation of Tamarind Seed Polysaccharide

Tamarind seed polysaccharide was used as the natural mucoadhesive polymer for microsphere preparation. The isolated/processed TSP was incorporated into the formulation according to the experimental design. The polymer concentration was treated as one of the principal formulation variables during optimization.

2.6 Preparation of Clarithromycin Mucoadhesive Microspheres

Clarithromycin-loaded mucoadhesive microspheres were prepared by the single-emulsion technique. Clarithromycin and TSP were incorporated into the formulation according to the experimental design, while Span-80 was used as the surfactant/emulsifying agent. The

formulation and processing variables were systematically varied to obtain microspheres with desirable mucoadhesive and controlled-release properties.

A total of 29 experimental batches were generated using Design-Expert software. The formulation responses investigated were percentage mucoadhesion (Y_1), drug entrapment efficiency (Y_2), cumulative drug release at 8 h (Y_3), and microsphere size (Y_4).

2.7 Optimization of Microsphere Formulation

Design of Experiments (DoE) was employed to evaluate the effects of the selected formulation and process variables on the characteristics of the microspheres. The experimental responses were analyzed using Design-Expert software. The optimization process was performed by evaluating the influence of drug concentration, TSP concentration, stirring speed, and Span-80 concentration on mucoadhesion, drug entrapment efficiency, cumulative drug release, and microsphere size.

The optimized formulation was selected based on the desired combination of the investigated responses. The optimized microspheres were subsequently used for preparation of the capsule dosage form.

2.8 Evaluation of Clarithromycin Mucoadhesive Microspheres

The prepared microspheres were evaluated for their pharmaceutical and formulation characteristics, including particle size, drug entrapment efficiency, percentage mucoadhesion, and in-vitro drug release. These responses were used during formulation optimization.

2.8.1 Evaluation of micromeritic properties

The flow properties of the prepared microspheres were evaluated by determining angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's compressibility index. The determinations were performed in triplicate and expressed as mean ± standard deviation.

2.9 Preparation of Capsule Dosage Form

The optimized Clarithromycin mucoadhesive microspheres were incorporated into hard gelatine capsules. Each capsule contained approximately 625 mg of Clarithromycin-loaded microspheres, equivalent to 250 mg of Clarithromycin. Magnesium stearate and talc were incorporated into the blend as pharmaceutical excipients. The composition per capsule was:

Ingredient	Quantity per capsule
Clarithromycin mucoadhesive microspheres	625 mg, equivalent to 250 mg Clarithromycin
Magnesium stearate	15 mg
Talc	10 mg
Total fill weight	650 mg

The microspheres and excipients were blended to obtain a uniform formulation blend, which was subsequently filled into hard gelatin capsules.

2.10 Evaluation of the Capsule Formulation

2.10.1 Disintegration test

The prepared Clarithromycin mucoadhesive microsphere capsules were subjected to a disintegration test under pharmacopoeial conditions. The time required for complete disintegration of the capsule was recorded. Complete disintegration was considered when no residue, except fragments of insoluble coating or capsule shell, remained on the apparatus screen.

2.10.2 Weight variation test

The filled capsules were individually weighed and the average capsule weight was calculated. The percentage deviation of each capsule from the average weight was determined and compared with the applicable pharmacopoeial acceptance criteria. The test was performed on 20 capsules.

2.10.3 Content uniformity

Content uniformity was determined by estimating the amount of Clarithromycin present in individual capsules. A weighed quantity of the mucoadhesive microsphere blend equivalent to 10 mg of Clarithromycin was dissolved in 100 mL of 0.1 N HCl and kept for 24 h. The resulting solution was filtered through a 0.45-µm membrane filter, and the filtrate was analyzed using a UV-visible spectrophotometer. The amount of Clarithromycin present in each sample was calculated from the established calibration curve.

2.10.4 In-vitro dissolution study

The in-vitro drug-release behavior of the prepared Clarithromycin mucoadhesive microsphere capsules was investigated using a suitable dissolution testing procedure. Samples were withdrawn at predetermined time intervals and analyzed for Clarithromycin content using the established analytical method. The cumulative percentage of drug released was calculated at each sampling interval and plotted against time to obtain the dissolution profile. The dissolution performance of the prepared formulation was also compared with that of a marketed modified-release Clarithromycin tablet.

2.10.5 Drug-Release Kinetic Analysis

The dissolution data obtained from the optimized formulation were fitted to different mathematical models to characterize the mechanism and kinetics of Clarithromycin release. The release data were evaluated using zero-order, first-order, Higuchi, and Hixson–Crowell models. The model providing the best fit based on the correlation coefficient was considered indicative of the predominant release kinetics. The optimized formulation was therefore investigated to determine whether drug release was governed predominantly by concentration-dependent release, diffusion

through the hydrated polymeric matrix, or matrix erosion/changes in surface area.

2.11 Statistical Analysis

All experimental determinations were performed in triplicate wherever applicable, and the results were expressed as mean ± standard deviation (SD). Design-Expert software was used for experimental design, statistical analysis, evaluation of formulation variables, and optimization of the microsphere formulation. The responses investigated included percentage mucoadhesion, drug entrapment efficiency, cumulative drug release, and microsphere size.

3. Results and Discussion

3.1 Preformulation Studies of Clarithromycin

The preformulation studies were performed to establish the physicochemical characteristics of Clarithromycin before formulation development. The drug was characterized by organoleptic properties, melting point, solubility, pKa, partition coefficient, bulk density, tapped density, powder-flow properties, UV spectrophotometric analysis, and drug–excipient compatibility. These studies provided the basis for selecting appropriate formulation conditions for development of Clarithromycin-loaded gastro-retentive mucoadhesive microspheres.

Table 1. Physical and physicochemical characteristics of Clarithromycin

S. No.	Parameter	Observed result	Interpretation
1	Appearance	White to almost white crystalline powder	Characteristic
2	Odour	Practically odourless	Complies
3	Taste	Bitter	Characteristic
4	Physical state	Crystalline powder	Characteristic
5	Melting point	218–220°C	Consistent with reference
6	pKa	8.35	Weakly basic drug
7	Log P	3.05	Moderately lipophilic
8	Molecular formula	$C_{38}H_{69}NO_{13}$	—
9	Molecular weight	747.95 g/mol	—

The physical appearance of the drug was consistent with the reported characteristics of Clarithromycin. The observed melting point of 218–220°C was close to the reported range of 217–220°C, supporting the identity and physical integrity of the drug. The experimentally determined pKa of 8.35 and log P of 3.05 were also reasonably close to the respective reported values.

3.2 Solubility Study

The solubility study showed considerable variation in the solubility of Clarithromycin in different solvents. The drug exhibited very low solubility in distilled water, whereas considerably higher solubility was observed in acidic media and selected organic solvents.

Table 2. Solubility profile of Clarithromycin

S. No.	Solvent/medium	Solubility (g/mL), Mean ± SD
1	Distilled water	0.0036 ± 0.0001
2	Methanol	0.368 ± 0.021
3	Ethanol	0.517 ± 0.016
4	Acetone	0.764 ± 0.025
5	Chloroform	0.184 ± 0.008
6	Benzene	0.0140 ± 0.008
7	DMSO	0.632 ± 0.014
8	Phosphate buffer pH 2	0.581 ± 0.019
9	0.1 N HCl, pH 1.2	0.782 ± 0.013
10	Simulated gastric fluid	0.756 ± 0.015
11	Phosphate buffer pH 7.4	0.01780 ± 0.006
12	0.1 N NaOH	0.02370 ± 0.006
13	Petroleum ether	0.00021 ± 0.00002

Values are expressed as mean ± SD (n = 3).

The aqueous solubility of Clarithromycin was only 0.0036 ± 0.0001 g/mL, whereas its solubility increased markedly in acidic conditions, reaching 0.782 ± 0.013 g/mL in 0.1 N HCl and 0.756 ± 0.015 g/mL in simulated gastric fluid. The relatively higher solubility under acidic conditions is relevant to the proposed gastro-retentive system because the formulation is intended to remain in the gastric environment.

3.3 Micromeritic Properties of Clarithromycin

The bulk density of Clarithromycin was found to be 0.42 g/mL, while the tapped density was 0.909 g/cm³. The calculated Carr's compressibility index and Hausner's ratio were 42.132% and 1.727, respectively.

Table 3. Micromeritic properties of Clarithromycin

S. No.	Parameter	Observed value
1	Bulk density	0.42 g/mL
2	Tapped density	0.909 g/cm³
3	Carr's compressibility index	42.132%
4	Hausner's ratio	1.727

The relatively high Carr's index and Hausner's ratio indicate poor flow characteristics of the untreated drug powder. This finding supported the need to convert the drug into a more suitable multiparticulate system. Following microsphere formation, the flow properties improved considerably, facilitating subsequent capsule filling.

3.4 UV Spectrophotometric Analysis

The standard calibration curve of Clarithromycin was prepared in 0.1 N HCl over a concentration range of 10–50 µg/mL.

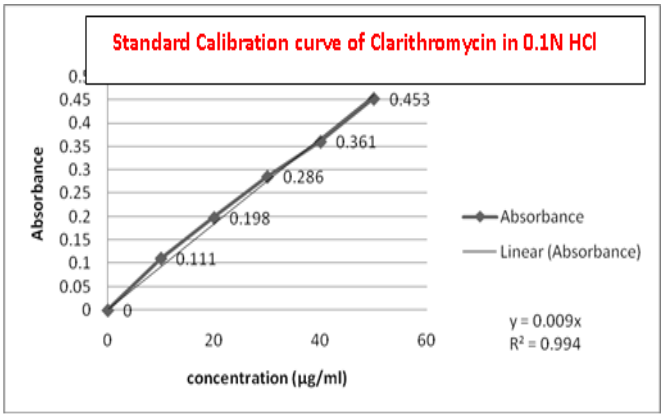

Figure 1: Standard Calibration curve of Clarithromycin in 0.1N HCl.

The absorbance increased progressively with increasing Clarithromycin concentration. The coefficient of determination (R^2 = 0.994) indicated a strong linear relationship between concentration and absorbance over the investigated range. The analytical method was therefore considered suitable for estimation of Clarithromycin during formulation and dissolution studies.

3.5 Drug–Excipient Compatibility Study

The compatibility of Clarithromycin with TSP was investigated by FTIR spectroscopy. Characteristic peaks of Clarithromycin were observed at 1051.01, 1169.58, 1106.52, 1731.76, and 2976.59 cm^{-1}, corresponding to characteristic functional-group vibrations. These characteristic bands were retained in the Clarithromycin–TSP mixture.

Table 5. FTIR characteristics of Clarithromycin–TSP mixture

S. No.	Wavenumber (cm^{-1})	Characteristic vibration
1	1051.01	C–O stretching
2	1169.58	C–H stretching
3	1106.52	C–O–C stretching
4	1731.76	C=O stretching
5	2976.59	O–H stretching

No significant alteration in the characteristic peak positions was observed after mixing Clarithromycin with TSP. This indicated the absence of a significant drug–polymer interaction under the conditions investigated and supported the suitability of TSP for further formulation development.

3.6 Preparation and Optimization of Mucoadhesive Microspheres

Clarithromycin-loaded mucoadhesive microspheres were prepared by the single-emulsion technique. Design-Expert software was employed to generate 29 formulation batches. Four formulation/process variables were investigated: Clarithromycin concentration (X_1), TSP concentration (X_2), stirring speed (X_3), and Span-80 concentration (X_4). The principal responses evaluated were percentage mucoadhesion (Y_1), drug entrapment efficiency (Y_2), cumulative drug release at 8 h (Y_3), and microsphere size (Y_4).

The experimental design provided a systematic approach for evaluating the effect of formulation and process variables on microsphere performance. The optimized formulation was selected based on the desired combination of mucoadhesion, drug entrapment, controlled drug release, and microsphere size.

3.7 Micromeritic Properties of Optimized Microspheres

The optimized Clarithromycin mucoadhesive microspheres showed considerably improved flow properties compared with the untreated drug.

Table 6. Micromeritic properties of Clarithromycin mucoadhesive microspheres and final blend

Parameter	Mucoadhesive microspheres	Final microsphere blend
Angle of repose (°)	26.5 ± 0.21	21.3 ± 0.14
Bulk density (g/cm³)	0.952 ± 0.011	0.958 ± 0.013
Tapped density (g/cm³)	0.986 ± 0.016	1.052 ± 0.019
Hausner's ratio	1.035	1.098
Carr's index (%)	3.44	9.3

Values are expressed as mean ± SD (n = 3).

The microspheres exhibited an angle of repose of 26.5 ± 0.21°, Carr's index of 3.44%, and Hausner's ratio of 1.035, indicating good flow characteristics. The final blend also showed satisfactory flow, with an angle of repose of 21.3 ± 0.14°, Carr's index of approximately 9.3%, and Hausner's ratio of 1.098.

The improved flow behavior of the microspheres compared with the original Clarithromycin powder was advantageous for capsule filling. Addition of talc and magnesium stearate further contributed to the handling properties of the final blend.

3.8 Formulation of Clarithromycin Microsphere Capsules

The optimized microspheres were successfully incorporated into hard gelatin capsules. Each capsule contained approximately 625 mg of Clarithromycin-loaded microspheres equivalent to 250 mg of Clarithromycin, along with 15 mg magnesium stearate and 10 mg talc.

Table 7. Composition of Clarithromycin mucoadhesive microsphere capsule

S. No.	Ingredient	Quantity/capsule
1	Clarithromycin mucoadhesive microspheres	625 mg, equivalent to 250 mg Clarithromycin
2	Magnesium stearate	15 mg
3	Talc	10 mg
Total fill weight		**650 mg**

The final formulation was successfully converted into a capsule dosage form, providing a convenient method for oral administration of the optimized mucoadhesive microspheres.

3.9 Evaluation of Capsule Formulation

3.9.1 Disintegration test

The disintegration time of the prepared capsules ranged from 11.8 to 13.2 min, with a mean value of 12.57 ± 0.53 min.The relatively low variation in disintegration time indicated reproducible capsule performance. Disintegration of the capsule permits release of the microspheres into the gastrointestinal environment, where the TSP-containing microspheres can hydrate and establish contact with the gastric mucus layer.

3.9.2 Weight variation test

The weight variation test was performed on 20 capsules. All capsules were reported to be within the permissible pharmacopoeial limit. The satisfactory weight uniformity demonstrated consistent filling of the microsphere blend into the capsule shells. This may be attributed to the favourable flow properties of both the microspheres and final blend.

3.9.3 Content uniformity test

The Clarithromycin content of individual capsules ranged from 248.6 to 252.0 mg, corresponding to 99.44–100.80% of the theoretical drug content. The mean drug content of 250.08 ± 1.13 mg demonstrated excellent agreement with the theoretical dose of 250 mg. The low standard deviation and narrow range of individual drug-content values indicated uniform distribution of Clarithromycin within the microspheres and satisfactory filling of the capsules.

3.9.4 In-vitro Dissolution Profile

The in-vitro dissolution study demonstrated a gradual and prolonged release of Clarithromycin from the prepared mucoadhesive microsphere capsules.

The formulation released 16.84 ± 1.24% of Clarithromycin during the first hour and subsequently exhibited gradual drug release. At 8 h, cumulative release was 63.85 ± 1.69%, increasing to 81.76 ± 1.47% at 12 h and 95.36 ± 1.16% at 18 h. The cumulative drug release reached 97.21 ± 1.08% at 20 h.

The observed release pattern indicates that the TSP matrix was effective in retarding Clarithromycin release. The initial release can be attributed to drug located at or close to the surface of the microspheres, while the subsequent prolonged release may be associated with hydration and swelling of the polymeric matrix followed by diffusion of Clarithromycin through the hydrated polymer network. Progressive matrix relaxation or erosion may also contribute to the later stage of drug release.

The prolonged release up to 20 h is particularly important for the intended gastro-retentive system because it indicates that the microspheres can maintain drug release for an extended period after administration. Such a release pattern may reduce the rapid fluctuations associated with conventional immediate-release dosage forms and may provide prolonged exposure of the gastric mucosa to Clarithromycin.

3.9.5 Release Kinetic Analysis

The dissolution data were analyzed using zero-order, first-order, Higuchi, and Hixson–Crowell models to characterize the kinetics and mechanism of drug release. The study also included comparative kinetic plots between the prepared formulation and a marketed modified-release Clarithromycin tablet.

The use of multiple kinetic models allowed assessment of whether drug release was primarily associated with concentration-dependent processes, diffusion through the polymeric matrix, or changes in the surface area and dimensions of the releasing system. The Higuchi model is particularly relevant to polymeric microspheres because diffusion through a hydrated polymer matrix can be an important contributor to drug release. The final interpretation of the predominant release mechanism should be based on the experimentally obtained correlation coefficients for each kinetic model.

The results demonstrate the successful development of a Clarithromycin-loaded gastro-retentive mucoadhesive microsphere system using Tamarind seed polysaccharide. Preformulation studies confirmed the physicochemical identity of Clarithromycin and demonstrated its low aqueous solubility and pH-dependent solubility. The FTIR compatibility study showed retention of the characteristic drug peaks in the Clarithromycin–TSP mixture, indicating compatibility between the drug and polymer. The microsphere formulation improved the handling characteristics of Clarithromycin, as demonstrated by the markedly lower Carr's index and Hausner's ratio compared with the untreated drug. The optimized microspheres and their final blend demonstrated satisfactory flow, which facilitated uniform capsule filling. The resulting capsules showed acceptable disintegration, satisfactory weight uniformity, and excellent content uniformity.

Most importantly, the formulation provided a prolonged Clarithromycin release profile extending to 20 h, with 97.21 ± 1.08% cumulative drug release at the end of the dissolution study. The controlled-release behavior can be attributed to the hydrophilic polymeric nature of TSP, hydration and swelling of the polymer matrix, and subsequent diffusion and gradual relaxation/erosion of the microsphere matrix.

Thus, the combined results support Tamarind seed polysaccharide as a promising natural polymer for gastro-retentive mucoadhesive delivery of Clarithromycin. The developed microsphere-loaded capsule demonstrated satisfactory pharmaceutical characteristics and prolonged in-vitro drug release. Further in-vivo studies, particularly gastric-retention and pharmacokinetic investigations, would be necessary to confirm whether the observed in-vitro advantages translate into improved gastrointestinal residence and therapeutic performance.

Table 8. Summary of Evaluation of Clarithromycin Mucoadhesive Microsphere Capsules

S. No.	Evaluation parameter	Result
1	Disintegration test	12.57 ± 0.53 min
2	Weight variation	Within permissible pharmacopoeial limit
3	Content uniformity	100.03 ± 0.45%
4	Mean Clarithromycin content	250.08 ± 1.13 mg/capsule
5	Drug content range	99.44–100.80%
6	Drug release at 8 h	63.85 ± 1.69%
7	Drug release at 12 h	81.76 ± 1.47%
8	Drug release at 18 h	95.36 ± 1.16%
9	Drug release at 20 h	97.21 ± 1.08%

4. Conclusion

The present study successfully developed gastro-retentive mucoadhesive microspheres of Clarithromycin using Tamarind seed polysaccharide (TSP) as a natural mucoadhesive polymer. The optimized microspheres demonstrated satisfactory micromeritic properties and were successfully incorporated into hard gelatin capsules. The prepared capsules exhibited acceptable disintegration, uniform weight, excellent drug-content uniformity (100.03 ± 0.45%), and prolonged in-vitro drug release, achieving 97.21 ± 1.08% release at 20 h. Overall, the findings indicate that TSP is a promising natural polymer for developing a mucoadhesive, controlled-release gastro-retentive delivery system for Clarithromycin. Further in-vivo studies are warranted to confirm gastric retention and therapeutic performance.

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