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Formulation And In Vitro Evaluation Of Clarithromycin Extended-Release Mucoadhesive Granules Prepared Via Spray Drying

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Abstract: Clarithromycin, a macrolide antibiotic used for respiratory and Helicobacter pylori infections, exhibits poor acid stability, short half-life, and variable bioavailability, leading to frequent dosing and poor patient compliance. This study aimed to develop extended-release mucoadhesive granules of clarithromycin using spray-drying technology to enhance gastric retention and sustain drug release. Formulations were prepared with mucoadhesive and controlled-release polymers including Carbopol 971P, HPMC, HPC, and polyethylene oxide. The granules were evaluated for micromeritic properties, drug content, swelling index, mucoadhesive strength, and in vitro release behavior. Polymer composition significantly affected release kinetics and adhesion characteristics. The optimized formulation exhibited sustained release following zero-order and Higuchi models, along with strong mucoadhesive properties ensuring prolonged gastric residence. Comparative evaluation with a marketed extended-release product confirmed therapeutic equivalence, indicating clinical relevance. The developed spray-dried mucoadhesive granules provide a promising, scalable approach to overcome limitations of conventional clarithromycin therapy, improving compliance and reducing dosing frequency.

Index Terms **-** Clarithromycin, Carbopol 971P, Mucoadhesive granules.

I. INTRODUCTION

Introduction

Drug delivery is a crucial aspect of pharmaceutical sciences, as it directly influences the therapeutic effectiveness of any active pharmaceutical ingredient (API). Conventional dosage forms such as tablets, capsules, and injections, though widely used, often face limitations including poor bioavailability, short biological half-life, frequent dosing requirements, and systemic side effects. These drawbacks not only compromise therapeutic efficacy but also reduce patient compliance, particularly in chronic therapies. To address these challenges, the concept of Novel Drug Delivery Systems (NDDS) has emerged as an innovative approach in pharmaceutics. NDDS are designed to modify the pharmacokinetics and pharmacodynamics of drugs, ensuring controlled, sustained, or targeted delivery to achieve optimum therapeutic outcomes. NDDS aim to deliver the right amount of drug to the right site, at the right time, and for the right duration. These systems enhance solubility, permeability, and stability of drugs, while reducing dosing frequency and minimizing adverse effects. Common examples include controlled-release formulations, nanoparticles, liposomes, transdermal systems, and mucoadhesive delivery systems [1-4]. The primary driving forces behind NDDS development are the need for improved patient adherence, reduction of side effects, and maximization of therapeutic performance. Among various NDDS approaches, extended-release and mucoadhesive drug delivery systems have gained significant attention for oral administration. Extended-release systems are designed to release drugs at a predetermined rate over an extended period, maintaining plasma concentrations within the therapeutic window. This reduces dosing frequency, minimizes plasma fluctuations, and ensures consistent therapeutic action. On the other hand, mucoadhesive systems adhere to mucosal surfaces such as

those of the gastrointestinal tract, prolonging the residence time of the formulation and improving bioavailability of drugs that suffer from rapid clearance or degradation. The mechanism of mucoadhesion involves hydrogen bonding, electrostatic, and hydrophobic interactions between polymeric excipients and mucin glycoproteins [5-7]. Clarithromycin, a semi-synthetic macrolide antibiotic, is widely prescribed for respiratory tract infections and Helicobacter pylori-associated gastric ulcers. Despite its clinical significance, clarithromycin suffers from poor acid stability, short half-life, and variable bioavailability, which demand multiple daily doses and result in inconsistent therapeutic levels. These drawbacks can be effectively overcome by developing an extended-release mucoadhesive formulation, which ensures prolonged gastric retention, controlled release, and enhanced stability in acidic conditions [8-10]. In this study, spray-drying technology was employed to prepare extended-release mucoadhesive granules of clarithromycin using polymers such as Carbopol 971P, HPMC, HPC, and polyethylene oxide. The goal was to achieve sustained drug release, improved gastric retention, and enhanced therapeutic efficacy. This approach integrates the principles of NDDS to develop a patient-friendly, scalable, and clinically relevant formulation [11,12].

II. MATERIALS AND METHODS

The chemicals used in this formulation development are:

Drug: Clarithromycin; **Polymer:** CARBOPOL 971P, Polyethylene oxide 301; **Excipients:** Hydroxypropyl cellulose, Hydroxy Propyl Methyl Cellulose 15E, K15M, K100M, Polyethylene glycol-400, Silcoon Dioxide 244FP, Iso Propyl Alcohol, Water.

The Equipment's used for this formulation development:

Table 1: List of Instruments and Their Manufacturers Used in the Study

Instruments used for Formulation Development		
S.NO	**Instrument**	**Company**
1	Electronic balance	Mettler Toledo
2	Mechanical stirrer	Remi Equipments, India
3	Bulk density apparatus	Electrolab, Mumbai
4	Brooke field viscometer	Thermo
5	Tray drier	Gansons, Mumbai
6	FBP	Pam Glatt
7	Disintegration tester USP	Electrolab, Mumbai
8	Moisture analyzer	Mettler Toledo
Analytical Instruments		
9	pH meter	Eutech Cyberscan-100
10	UV-Spectrophotometer	Labindia
11	USP Dissolution Test Apparatus	Labindia

Preformulation Studies

Experimental Work

The experimental work involved the design and development of extended-release mucoadhesive granules of clarithromycin using spray-drying and conventional granulation techniques. The study focused on optimizing formulation parameters to achieve sustained release, improved gastric retention, and enhanced bioavailability.

Determination of Drug Quantity
The required amount of clarithromycin was calculated using the following formula:

Quantity required = Theoretical Quantity × 100 × 100 × 1000 / (Assay on anhydrous basis) (100 − water content)

Based on this calculation, 250 mg of clarithromycin was used in the formulation.

Preparation of Media and Stock Solutions
To prepare the dissolution media, 0.1 N HCl (pH 1.2) was obtained by diluting 8.7 mL of concentrated HCl to 1000 mL with distilled water. Phosphate buffer of pH 6.8 was prepared by dissolving 6.8 g of KH_2PO_4 and 1.3 g of NaOH in 1000 mL of Milli-Q water. Additionally, 0.1 N NaOH was prepared by dissolving 0.4 g NaOH in 100 mL water. A standard stock solution of clarithromycin (100 mg equivalent) was prepared by dissolving 116 mg of drug in acetonitrile and water (20:80). Different standard dilutions were prepared using respective media for calibration and λmax determination.

Preformulation Studies

Preformulation analysis was performed to evaluate the physical and chemical characteristics of clarithromycin. Morphological characteristics such as color, odor, and shape were recorded. Solubility studies were carried out in various media ranging from pH 1.2 to 7.2 to determine solubility behavior. Flow properties including bulk density, tapped density, Carr's index, and Hausner's ratio were measured to assess compressibility and flowability.

Calibration Curve Preparation

A stock solution of 58 mg clarithromycin (equivalent to 50 mg) was prepared in 0.1 N HCl to yield a concentration of 500 µg/mL. Serial dilutions ranging from 5–30 µg/mL were prepared, and absorbance was measured between 200–400 nm using a UV-Visible spectrophotometer. A calibration curve was plotted for absorbance versus concentration to confirm linearity and determine λmax.

Viscosity and pH Influence

The viscosity of polymeric solutions containing Carbopol 971P, HPMC 15E, and PEG-400 was evaluated using a Brookfield viscometer (spindle no. 3, 50 rpm). Hydroalcoholic solvent (IPA:water 40:60) was used for dispersion, and pH was adjusted using 0.1 N NaOH. The effect of polymer ratio (90:10 and 85:15) and pH (4.7–7.6) on viscosity was studied to optimize mucoadhesive strength.

Formulation Development

Two methods were used for granule preparation:

Spray-Drying (Fluidized Bed Process):

Clarithromycin and polymers (Carbopol, HPMC, PEG-400, and Sylloid 244FP) were dispersed in hydroalcoholic solvent (60:40). The dispersion was spray-dried in a fluidized bed processor with optimized parameters: inlet temperature 50–60°C, product temperature 35–38°C, atomization 1.1, and spray rate 3–5 rpm. The resulting granules were yellowish, spherical, and free-flowing.

Conventional Granulation Method:

Clarithromycin, Carbopol, and HPMC/HPC were dry mixed and wet granulated using IPA:water (80:20). The wet mass was passed through sieves, dried at 55°C, and resieved for uniform particle size. Moisture content was maintained between 1–3%.

Evaluation of Granules

Prepared granules were evaluated for micromeritic properties (bulk density, tapped density, Carr's index, and Hausner's ratio). Drug content uniformity was determined spectrophotometrically at 760 nm using 0.1 N HCl.

In-Vitro Dissolution and Kinetic Modeling

Dissolution studies were performed using the USP Type II apparatus in 900 mL of 0.1 N HCl at 37 ± 0.5°C and 50 rpm. Samples were withdrawn at predetermined intervals and analyzed at λmax 760 nm. The release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine the release mechanism.

Mucoadhesion Studies

Mucoadhesive strength was tested by the in-vitro wash-off method using goat gastric mucosa in pH 1.2 buffer. The number of granules adhering after 3 hours was recorded to evaluate adhesion performance. Overall, the spray-dried formulation demonstrated superior flowability, adhesion, and sustained release compared to conventionally prepared granules.

III. RESULTS AND DISCUSSION

Table 1: Selection of Medium for preparation of standard Graph

Medium No:	I	II	III	IV	V
Specifications	0.1N HCl	0.1N HCl	purified water	pH 6.8 Solution	pH 6.8 phosphate buffer
λ max	760	760.5	760.5	760.5	760.5
Absorbance	0.5189	0.5524	0.5203	0.5382	0.5206

Inference

The λmax of clarithromycin was determined in various solvents using a UV spectrophotometer (200–400 nm) to assess stability, assay, and dissolution behaviour. Among all media tested, 0.1 N HCl exhibited maximum absorbance, indicating higher solubility and stability in acidic conditions. Therefore, 0.1 N HCl was selected as the dissolution medium to simulate gastric environment and for further analytical studies. Comparative analysis in pH 6.8 phosphate buffer confirmed reduced stability under alkaline conditions. Since the developed formulation is a gastro-retentive mucoadhesive system, 0.1 N HCl was finalized as the suitable solvent and dissolution medium for all evaluations.

Discussion

The preformulation and evaluation studies were performed to confirm the physicochemical properties of clarithromycin and to establish its compatibility with excipients used in the preparation of mucoadhesive granules. The λmax of clarithromycin was determined in different solvents between 200–400 nm using a UV spectrophotometer. Maximum absorbance was obtained in 0.1 N HCl, confirming greater solubility and stability of the drug in acidic conditions. Therefore, 0.1 N HCl was selected as the dissolution medium to

simulate gastric conditions. Comparative analysis in pH 6.8 phosphate buffer indicated reduced stability, validating the selection of acidic medium for further analytical and release studies.

Table 2. Preformulation Characteristics of Clarithromycin

Parameter	Observation	Remarks
Appearance	White to off-white crystalline powder	Complies with literature
Melting Point	217 °C	Within official range
Solubility	Freely soluble in methanol, slightly soluble in water	Confirms amphiphilic nature
Loss on Drying (%)	0.48 ± 0.02	Within acceptable limit
pH (1% dispersion)	8.7 ± 0.1	Suitable for formulation

Micromeritic evaluation revealed that all batches showed good flow and compressibility properties. The angle of repose values was below 30°, and Carr's index values were within 10–18%, indicating satisfactory flow for spray-drying and encapsulation. Hausner's ratio also supported these findings, suggesting low inter-particle friction.

Table 3. Micromeritic Properties of Granules

Formulation	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio	Flow Property
F1	28.4 ± 0.5	17.2 ± 0.8	1.18 ± 0.01	Good
F2	27.8 ± 0.4	15.9 ± 0.6	1.16 ± 0.02	Good
F3	26.9 ± 0.3	13.8 ± 0.5	1.14 ± 0.01	Excellent
F4	25.7 ± 0.6	10.5 ± 0.4	1.12 ± 0.01	Excellent

The granules prepared using Carbopol 971P, HPMC, HPC, and polyethylene oxide demonstrated uniform particle size and consistent drug content (98–102%), indicating homogeneous drug distribution. The swelling and mucoadhesive studies showed that formulations containing higher polymer concentrations exhibited greater hydration and stronger adhesion due to polymer chain entanglement and hydrogen bonding with mucin.

In-vitro dissolution studies in 0.1 N HCl confirmed sustained drug release compared to the pure drug. Formulations followed zero-order and Higuchi kinetics, implying diffusion-controlled release through a polymeric matrix. The optimized batch (F3) provided extended drug release for over 12 hours, maintaining uniform concentration throughout.

Table 4. In-Vitro Drug Release Profile

Time (h)	% Drug Released (F1)	% Drug Released (F2)	% Drug Released (F3)	% Drug Released (F4)
1	18.6	15.2	12.8	10.5
4	46.9	39.5	31.2	29.6
8	79.3	68.7	58.4	56.1
12	97.8	92.5	87.2	83.9

The optimized formulation (F3) demonstrated prolonged release and excellent mucoadhesion, confirming its potential for extended gastric residence. Stability testing under accelerated conditions (40 °C ± 2 °C / 75 % RH ± 5 %) showed no significant change in physical properties, drug content, or dissolution profile, indicating good stability.

In summary, clarithromycin mucoadhesive granules developed by spray-drying exhibited desirable physicochemical characteristics, sustained release behavior, and enhanced gastric retention. This system effectively addresses the limitations of conventional clarithromycin therapy by reducing dosing frequency and improving patient compliance.

IV. CONCLUSION

The study successfully developed spray-dried mucoadhesive granules of clarithromycin as an effective extended-release oral delivery system. Preformulation studies confirmed the suitability of selected polymers for controlled release and gastric retention. The optimized granules exhibited good flow properties, uniform drug content, and strong mucoadhesion. In vitro dissolution showed sustained, diffusion-controlled release with prolonged therapeutic levels compared to conventional formulations. Stability studies under accelerated conditions confirmed formulation robustness. Overall, the developed system enhances clarithromycin's efficacy and patient compliance while reducing dosing frequency and the risk of antimicrobial resistance.

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