FORMULATION AND DEVELOPMENT OF STATISTICAL OPTIMIZATION OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM: IN-VIVO AND IN-VITRO STUDY

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ABSTRACT:
This study focuses on the formulation and optimization of a gastro-retentive drug delivery system (GRDDS) for Lansoprazole and Clarithromycin, used in the treatment of Helicobacter pylori-associated peptic ulcers. The aim is to enhance gastric residence time and improve the local therapeutic effect through floating tablets. A design of experiment (DoE) approach, specifically Box-Behnken Design (BBD) or Central Composite Design (CCD), is used for statistical optimization. In-vitro buoyancy, drug release, and in-vivo gastric retention are evaluated to confirm the efficacy of the formulation.

Key Word- Peptic ulcer and role of H. pylori, Prolonged gastric retention, Macrolide antibiotic.

INTRODUCTION

Peptic ulcer disease (PUD), particularly those associated with Helicobacter pylori infection, remains a major gastrointestinal disorder globally. Effective treatment typically requires a combination of antibiotics and proton pump inhibitors (PPIs) to eradicate the infection and suppress gastric acid secretion. Among the therapeutic agents, Lansoprazole, a PPI, and Clarithromycin, a macrolide antibiotic, are commonly co-administered as part of triple therapy regimens. However, conventional oral delivery of these drugs poses significant challenges such as short gastric residence time, pH-dependent solubility, and limited bioavailability, which can compromise therapeutic efficacy.

To overcome these limitations, Gastroretentive Drug Delivery Systems (GRDDS) have emerged as an effective strategy. GRDDS are designed to prolong the gastric residence time of drugs, ensuring a sustained release at the site of absorption and enhancing bioavailability. This is particularly important for drugs like Lansoprazole, which is acid-labile and requires gastric localization, and Clarithromycin, whose stability is compromised in higher pH environments. By maintaining therapeutic concentrations at the site of infection, GRDDS can enhance the efficacy of H. pylori eradication therapy and reduce dosing frequency.

The success of a GRDDS depends on several formulation variables, such as polymer concentration, floating agent, and drug-polymer interaction. To systematically evaluate these variables and achieve an optimized formulation, statistical optimization techniques such as Response Surface Methodology (RSM) are employed. These approaches allow for the development of robust formulations with predictable performance through mathematical modeling and analysis of variable interactions.

This study focuses on the formulation and development of a dual-drug GRDDS for Lansoprazole and Clarithromycin, utilizing floating matrix tablets. A Design of Experiments (DoE) approach is applied to optimize the formulation parameters, followed by extensive in-vitro evaluation for buoyancy and drug release behavior. Furthermore, the in-vivo performance is assessed using suitable animal models to confirm the formulation's gastric retention and pharmacokinetic properties. The ultimate goal is to

develop an effective and statistically optimized GRDDS that can improve the treatment outcomes for peptic ulcer patients.

Gastro-retentive drug delivery systems (GRDDS) are designed to prolong the gastric residence time of drugs that are locally active in the stomach, have a narrow absorption window, or are unstable in the intestinal environment. Lansoprazole, a proton pump inhibitor, and Clarithromycin, a macrolide antibiotic, are commonly used in combination therapy for Helicobacter pylori infection and peptic ulcer treatment.

However, their therapeutic effectiveness is often limited due to their short gastric residence time and instability in intestinal PH. A floating drug delivery system that remains buoyant in the stomach could enhance bioavailability and therapeutic efficacy by maintaining drugs at the absorption site for a prolonged period.

METHODOLOGY

Material

Lansoprazole Sample from Meditab Specialities Pvt. Ltd. Satara. Purity 99%. Clarithromycin sample from Meditab Specialities Pvt. Ltd. Satara. Purity 99%. In that are Hydroxy methylcellulose (HPMC K4M K15M)(Ozone International, Mumbai), Carbopol 934P, Sodium Alginate, ethyl acrylate these polymers used (Qualigens chemicals). Sodim bicarbonate, Citric Acid (Qualigens chemicals) this are used as gas generating agent. Lactose, magnesium stearate, Talc thisexcipients used. Solvent is Ethanol, methanol. All the studies were carried in distilled water.

Formulation Method

Preparation of Floating Tablets - The floating tablets of Lansoprazole and Clarithromycin were prepared by direct compression method. Different concentrations of polymers were used to control the drug release. A mixture of drug, polymer, gas-generating agents, and excipients was blended uniformly using a mortar and pestle or a suitable blender. Magnesium stearate and talc were added as lubricants. The blend was compressed into tablets using a single-punch tablet compression machine.

Evaluation parameter

Pre- Compression Evalution

Angle of Repose- Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. And the frictional force In a loose powder or granules can be measure by angle of repose.

Angle of Repose = Tan θ = h/r

Where,

θ is the angle of repose

H is height of pile

r is radius of the base of pile

Table: 4 Relationship between Angle of repose (θ) and flow properties

Angle of Repose(θ)(degree) Flow

<25	Excellent
25-30	25-30
30-40	30-40

>40	>40

Bulk density -

Apparent bulk density was determined by pouring blend into graduated cylinder.The bulk volume and weight of powder was determined.

$\mathbf{P_b = M/ V_b}$

Where,

P_b = Bulk Density

M = Weight of sample in gm.

V_b = Final volume of blend in cm^3

Tapped density-

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times.

$\mathbf{P_t = M / V_t}$

P_t = Tapped Density

M = Weight of the sample in gm

V_t = Tapped volume of blend in cm3

Objectives and Formulation

To develop a bilayer floating tablet or a single matrix floating tablet that Protects lansoprazole from gastric acid degradation. Ensures localized, prolonged delivery of clarithromycin in the stomach. Achieves sustained drug release over 12 hours. Improves patient compliance in H. pylori eradication therapy

Drug Profile:

Drug	Class	Purpose	Stability
Lansoprazole	Proton pump inhibitor	Reduces gastric acid	Acid-labile (unstable in acid)
Clarithromycin	Macrolide antibiotic	Eradicates H. pylori	Stable in gastric pH

Two approaches are commonly used: Matrix Tablet (combined drugs in one tablet)

Bilayer Tablet (separate layers for each drug, ideal for different release behavior).

Ingredients and Role

- **Lansoprazole-** API (anti-ulcer agent)
- **Clarithromycin**- API (antibiotic)
- **HPMC K4M / K100M-** Hydrophilic polymer, controls drug release
- **Carbopol 934P-** Swelling agent, increases gastric retention
- **Sodium bicarbonate-** Gas-forming agent for floating effect
- **PVP K30-** Binder
- **Lactose / MCC**- Filler, improves compressibility
- **Citric acid-** Acid source to enhance CO_2 release
- **Magnesium stearate-** Lubricant
- **Talc-** Anti-adherent
- **Enteric coating(optional)**- Protects lansoprazole from acid

Example Formulation Composition (per tablet)

Ingredients	Quantity (mg)
Lansoprazole	30
Clarithromycin	250
HPMC K4M	90
Carbopol 934P	40
Sodium bicarbonate	50
Citric acid	20
MCC (Avicel pH 101)	80
PVP K30	10
Magnesium stearate	5
Talc	5
Total	~580 mg

Quantities may vary based on optimization and desired release profile.

Manufacturing Process

Direct Compression Method:

1. Dry Mixing: All excipients (except lubricant) are sieved and mixed thoroughly.

2. Drug Incorporation: Lansoprazole and clarithromycin added and mixed.

3. Addition of Lubricants: Magnesium stearate and talc added last.

4. Compression: Tablets compressed using a single-punch or rotary tablet press.

5. (Optional) Enteric Coating: For lansoprazole protection using polymers like Eudragit L100.

Floating Mechanism

Effervescence from sodium bicarbonate + citric acid creates CO_2 in gastric fluid.

CO_2 is trapped in the gel layer formed by HPMC, reducing tablet density and enabling floatation.

Floating Lag Time: < 2 minutes

Floating Duration: > 12 hours

Drug Release Behavior

Clarithromycin: Released in a sustained manner over 12 hours.

Lansoprazole: Protected from acid (via coating or pH modifier), released in controlled fashion.

Stability Considerations

Lansoprazole is sensitive to light, moisture, and acidic pH. Use:

Light-resistant packaging

pH buffers or enteric coating

Desiccants in packaging.

Experimental design- To optimize the formulation variables of a gastro-retentive dosage form containing Lansoprazole and Clarithromycin using Box-Behnken Design (BBD) for improved drug release and gastric retention.

Table-Independent Variables (Factors)

(Selected based on preliminary trials)

Variable	Code	Level- 1	Level- 0	Level +1
X_1	Polymer Concentration (e.g HPMC, Carbopol)	Low	Medium	High
X_2	Gas- generating agent(e.g Sodium bicarbonate)	Low	Medium	High
X_3	Binder Concentration (e.g PVP K_{30} (polyvinylpyrrolidone)	Low	Medium	High

Why Use Statistical Optimization?

Traditional "trial-and-error" methods are time-consuming, inconsistent, and do not provide insight into interactions between variables. Statistical Design of Experiments (DoE) offers a mathematical and scientific approach to:

- Minimize batch failures
- Improve drug release control
- Achieve desired tablet performance
- Reduce cost and time

Key Step in Statistical Optimization

Step	Description
Factor Selection	Choose independent (e.g., polymer %, $NaHCO_3$) and dependent (e.g., floating lag time, % drug release) variables.
Experimental Design	Use BBD, CCD to plan experiments.
Model Fitting	Fit data to a polynomial or regression model.
ANOVA Analysis	Check significance of model and variables.
Response Surface Analysis	Generate 3D surface and contour plots.
Optimization	Use desirability functions or numerical optimization.
Validation	Compare predicted and actual outcomes.

Design of Experiments (DoE) using Box-Behnken Design (BBD) or Central Composite Design (CCD):

Independent Variables:

X_1 = Polymer ratio (HPMC:Carbopol)

X_2 = Sodium bicarbonate (%)

X_3 = Drug-to-polymer ratio

Dependent Variables (Responses):

Y_1 = Floating Lag Time (FLT)

Y_2 = % Drug release at 12 h

Y_3 = Swelling index

Y_4 = Mucoadhesive strength

Steps:

1. Design experimental matrix using software (Design Expert).
2. Prepare formulations as per the design.
3. Evaluate in-vitro characteristics.
4. Analyze data using ANOVA, generate 3D plots, and optimize with desirability function.

In Vitro Evaluation Parameters

Test	**Purpose**
Floating lag time	Time taken to float (should be <1 min)
Total floating duration	Duration tablet remains buoyant (>12 h)
Swelling Index	To measure swelling property over time
Drug content uniformity	Ensure even drug distribution
n-vitro drug release study	USP Apparatus II, 0.1N HCl (pH 1.2), 12 hrs
Kinetics modeling	Zero-order, First-order, Higuchi, Korsmeyer

In Vivo Evaluation Studies

Animal Model: Albino rats or Wistar rats (for pharmacodynamic & retention study)

Objectives:

- Gastric retention time (using radiography or marker dyes)
- Pharmacokinetics (bioavailability comparison)
- Anti-ulcer effect (ethanol-induced or pylorus ligation model)

In Vivo Parameters:

Test	**Purpose**
X-ray imaging	Confirm gastric retention (barium sulfate)
Ulcer index	Assess anti-ulcer effect
AUC, Cmax, Tmax	Pharmacokinetic parameters
Histopathology	Stomach tissue integrity

Outcome

- Optimized GRDDS formulation with prolonged gastric residence.
- Sustained release profile with minimal initial burst.
- Enhanced bioavailability and therapeutic efficacy of both drugs.
- Good correlation between in-vitro and in-vivo data.

Purpose and Strategy

The main goal is to extend gastric residence time (GRT), improve bioavailability, and control release kinetics for local (e.g., H. pylori) or systemic therapy. Formulation variables like polymer type/concentration, gas-generating agent, matrix composition, drying or crosslinking methods are critically optimized. Statistical tools such as factorial design, RSM (e.g. Box–Behnken, CCD), and desirability functions are used to:

1. Screen for significant factors
2. Fit mathematical models (regression/ANOVA)
3. Identify optimal levels using surface/contour

REFERENCES

1. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release.
2. Tripathi KD. Essentials of Medical Pharmacology.
3. Bolton S, Bon C. Pharmaceutical Statistics: Practical and Clinical Applications.
4. Balaji M,Ramyakrishna N, Hanumanaik M, Scholars Research Library Formulation Development and Characterization of Enteric Coated Tablets of Lansoprazole Der Pharmacia Lettre, 2020, 12 (3): 22-38(http://scholarsresearchlibrary.com/archive.htm)
5. Veeranagoud Biradar1, Jeevan Matada Basavarajaiah2, Myat Thu Thu Win, Leneena Gudugunta, Suresh KV, Sathiyavathi Mahendra Kumar , Neeraja Turagam,Lavanya Priya. In vitro Evaluation of Gastro Retentive Drug Delivery System of Lansoprazole
6. S. Ramu, P. Chandra Gopal Reddy, D. Srinivasa Rao and G. Ramakrishna. FORMULATION AND EVALUATION OF LANSOPRAZOLE DELAYED RELEASE PELLETS IJPCBS 2015, 5(4), 860-878 Ramu et al. ISSN: 2249-9504
7. Tripathi Kamna, Likhariya Manoj, Bhadoria Juhi, Trivedi Dipali A Review on Formulation Development And Evaluation Of Lansoprazole Microspheres 2022 IJCSPUB | Volume 12, Issue 3 July 2022 | ISSN: 2250-1770 IJCSP22C1069 International Journal of Current Science (IJCSPUB) www.ijcspub.org 587
8. Julu Tripathi, Prakash Thapa, Ravi Maharjan, Seong Hoon Jeong , Current State and Future Perspectives on Gastroretentive Drug Delivery Systems Pharmaceutics. 2019 Apr 20;11(4):193. doi: 10.3390/pharmaceutics11040193
9. S.Ramu A.Suneetha Devi, D.SrinivasaRao and Ramakrishna G. Formulation And Evaluation Of Gastroretentive Clarithromycin Floating Tablets International Journal Of Pharmaceutical, Chemical And Biological Sciences Ijpcbs 2015, 5(4), 883-895 Ramu et al. ISSN: 2249-9504 883