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Probiotic formulation and Quality Delivery System of Proton pump inhibitor

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ABSTRACT :

Since their debut into pharmacotherapy, proton pump inhibitors (PPIs) have been widely utilized to treat a variety of disorders characterized by excessive stomach acid output. Despite this, there are still unmet demands in terms of availability for patients of all ages. Their low stability prevents the creation of formulations with easily adjustable doses. The purpose of this review is to outline the discovery and development of PPIs, explore formulation problems, and offer current solution formulation development. The review discusses the physicochemical features of PPIs, their relationship to pharmacokinetic and pharmacodynamic qualities, and their stability, including the identification of the most essential variables influencing them. Furthermore, the options for qualitative and quantitative investigation of PPIs are briefly discussed.

This evaluation also defines commercial PPI-containing medicines available in the United States and Europe. The majority of the review focuses on presenting the state-of-the-art in the development of novel formulations with PPIs, including nanoparticles, microparticles, minitablets, pellets, bilayer, floating, and mucoadhesive tablets, as well as parenteral, transdermal, and rectal preparations. It also predicts future potential for the development of PPI dose formulations. It is aimed specifically at researchers creating new formulations involving PPIs, as it addresses the most critical formulary concerns that must be considered before making a formula selection decision. It might assist in avoiding superfluous efforts in this procedure and selecting the finest. The study also includes an up-to-date database of literature on pharmaceutical formulation technology using PPIs.

This study focuses on the formulation of a synergistic delivery system combining PPIs and probiotics. The goal is to achieve a dual benefit: the effective suppression of gastric acid and the maintenance of a healthy gut microbiota.

Proton Pump Inhibitors (PPIs) are a widely used class of drugs for acid-related disorders. However, their long-term use poses risks such as gut dysbiosis and nutritional deficiencies. Integrating probiotics into PPI therapy offers potential to mitigate these issues.

Keywords- Proton pump inhibitors; delayed-release pills; enteric coating; Eudragit; omeprazole, pantoprazole, and lansoprazole

INTRODUCTION

Proton Pump Inhibitors (PPIs) are antisecretory medicines [1, 2]. Along with histamine H2-receptor antagonists and potassium-competitive acid blockers (PCAB), they are used to treat gastroesophageal reflux disease (GERD) and other conditions characterized by excessive stomach acid production [3,4,5,6]. According to the IQVIA study on Medicine Spending and Affordability in the United States, omeprazole and pantoprazole were among the top 20 most often prescribed medications in 2020 [7]. Furthermore, in the United Kingdom, omeprazole was the most used antisecretory medicine in 2021, with over 35 million items distributed [8]. Despite their widespread usage in pharmacotherapy, there are still unmet demands in terms of adequate dose forms for patients of all ages.

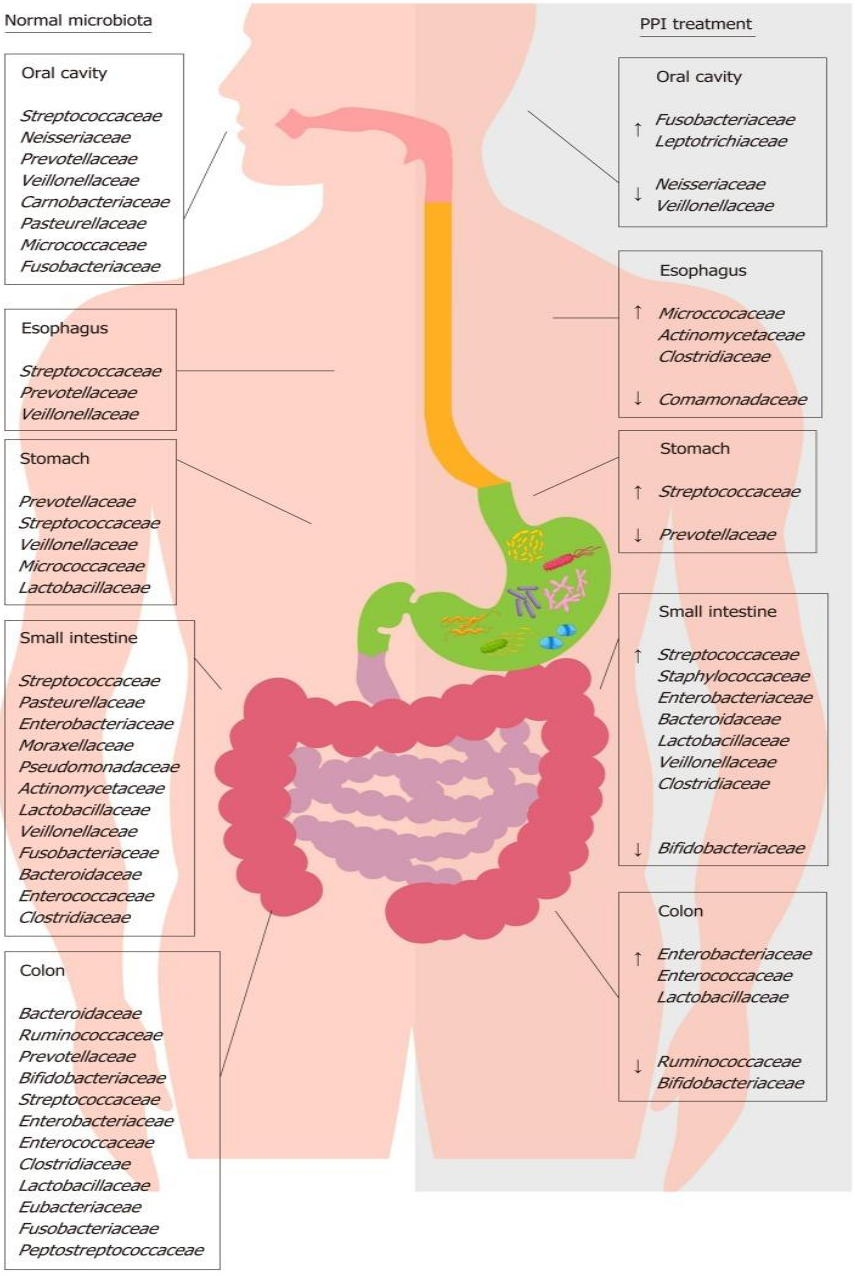
It is critical to increase the availability of more advanced formulations that are simple to prepare and administer, such as minitablets, orodispersible tablets, and films, particularly those incorporating functional micro- or nanoparticles. Standard enteric-coated tablets or capsules are not appropriate for all people, resulting in typical issues such as dosage adjustments, crushing, or grinding of such forms. Additionally, it has a detrimental impact on patients' compliance and drug adherence. The majority of currently produced formulations are aimed at overcoming these challenges and improving the efficacy and safety of PPI treatment.

The purpose of this study is to summarize the historical context of proton pump inhibitor discovery and development, address formulation concerns linked to this medication class, show modern solutions, and evaluate future potential and challenges in formulation development.

The physicochemical features of PPIs are briefly presented, with a focus on their pharmacokinetic and pharmacodynamic qualities, stability, and qualitative or quantitative analytical methods. We investigated the content and formulation of PPI-containing commercial medicines. The most important section of this review discusses the various approaches to developing different dosage forms with PPIs, including nanoparticles,

microparticles, minitablets, pellets, bilayer tablets, gastroretentive tablets, and mucoadhesive tablets, as well as dosage forms administered via non-oral routes such as parenteral, transdermal, and rectal preparations.

Proton pump inhibitors (PPIs) are widely used to treat acid-related gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. However, prolonged use of PPIs has been associated with adverse effects, including dysbiosis of the gut microbiome, leading to infections, reduced nutrient absorption, and other complications. The introduction of probiotics alongside PPIs presents a novel approach to mitigating these side effects while enhancing therapeutic outcomes.



The distribution of the main bacterial families in the human microbiota under healthy conditions and during proton pumps inhibitor therapy. This diagram depicts the impact of proton pump inhibitor (PPI) medication on the makeup of gut microbiota families. The left side of the picture depicts the main bacterial families under normal physiological settings, whereas the right side depicts the rise (↑) and reduction (↓) in bacterial families in the gut microbiota following PPI therapy. PPI: proton pump inhibitor.

The current review aims to synthesize the most recent findings on the influence of PPIs on the gut microbiota, with a focus on different sections of the gastrointestinal (GI) tract, and to address the potential significance of the related dysbiosis in the etiology of multiple GI illnesses. This study aims to gain a better understanding of how PPIs may affect human homeostasis through gut microbiota imbalance.

Currently, little information has been published on the relationship between PPI usage and oral microbiota makeup. One study showed that, in healthy volunteers, a four-week esomeprazole administration of PPI caused an increase of Fusobacterium and Leptotrichia in the periodontal pocket, associated with a decrease of Neisseria and Veillonella in saliva and a parallel increase of Streptococcus in fecal samples; this suggests that PPIs may cause both oral and gut microbiota changes.

Based on these data, the oral cavity could represent a potential source of microbiota information related to oral and non-oral disorders; it could also be an important indicator of dysbiosis in other areas of the GI tract.

AIM AND OBJECTIVES

To innovate and optimize a dual-delivery system combining probiotics and proton pump inhibitors (PPIs) that ensures effective acid suppression, restores gut microbiota balance, and enhances patient safety and compliance through a scientifically designed, patient-centric formulation. Probiotic formulations can be produced to supplement proton pump inhibitors (PPIs) by improving gastrointestinal delivery and decreasing PPI-related negative effects. Probiotics are encapsulated in biocompatible matrices or delivered via specialized technologies to protect them throughout transit and direct them to the small intestine. These formulations may help restore gut microbial balance, minimize dysbiosis, and perhaps increase PPI adherence.

OBJECTIVES-

To better characterize the nationwide distribution of proton-pump inhibitor (PPI) prescriptions and to communicate evidence-based recommendations for utilizing probiotics as an adjuvant to PPIs in a variety of therapeutic settings.

1. *Formulation Development*
2. *Delivery System Optimization*
3. *Quality Assurance*
4. *Therapeutic Efficacy*
5. *Regulatory Compliance*
6. *Cost-Effectiveness*

Main objective of the study-

1. To formulate tablet dosage form of a proton pump inhibitor.
2. To enteric-coat the above tablet to make it delayed release dosage form.
3. To film coat enteric coated tablet with alginic acid.
4. To evaluate the physicochemical parameters of the formulation(s) and invitro drug release profile.
5. To subject the most satisfactory formulation(s) based on the above studies for accelerated stability studies.

RESEARCH METHODOLOGY

The prospective research focuses on designing and optimizing a dual-delivery system that integrates Probiotic with proton pump inhibitors (PPIs) to address the adverse effects associated with acid suppression therapy. The study will emphasize enhancing the stability, viability, and therapeutic efficiency of Probiotic alongside controlled PPI release using advanced delivery techniques and a Quality by Design (QbD) approach.

Primary Goal of the Research-

1. To design a dual-delivery system combining PPIs and Probiotic for effective acid suppression and gut health restoration.
2. To ensure the viability of Probiotic and their targeted delivery to the intestine.
3. To optimize the formulation using QbD principles, ensuring stability and therapeutic efficacy.
4. To evaluate the safety, stability, and cost-effectiveness of the developed formulation.

Research Step-

1. Selection of Model Components

- *Proton Pump Inhibitor (PPI)*: Omeprazole is selected as the model PPI due to its established efficacy and widespread use in treating acid-related disorders.
- *Probiotic*: Strains of Lactobacillus acidophilus and Bifidobacteriumbifidum are chosen for their proven benefits in restoring gut microbiota balance and reducing gastrointestinal complications.
- Assessing physicochemical properties and compatibility between the PPI and Probiotic.
- Determining the stability of Probiotic in acidic and intestinal conditions.

2. Pre-Formulation Studies-

i. *Physicochemical Characterization*:
   - Evaluate the solubility, pH stability, and compatibility of omeprazole and probiotics.
   - Conduct Differential Scanning Calorimetry (DSC) and Fourier-Transform Infrared Spectroscopy (FTIR) to identify potential interactions.

ii. *Probiotic Viability*: Assess the stability of probiotic strains under simulated gastric and intestinal conditions.

3. Formulation Development-

i. *Step 1*: Design a dual-layered delivery system:
   - *Layer 1*: Enteric-coated layer containing omeprazole to ensure acid resistance and controlled release in the intestine.
   - *Layer 2*: Microencapsulated probiotics using polymers such as alginate or chitosan to enhance viability and ensure targeted intestinal release.

ii. *Step 2*: Use Quality by Design (QbD) principles to optimize critical formulation parameters:
   - Polymer concentration.
   - Coating thickness.
   - Drug-to-polymer ratio.

4. Process Optimization-

i. *Encapsulation Techniques*:
   - Optimize micro encapsulation methods (e.g., spray drying or extrusion) for probiotic protection.

ii. *Coating Technology*:
   - Apply fluidized bed coating for PPI layers to achieve uniform enteric coating and controlled-release properties.

5. Evaluation of Drug Delivery System-

In Vitro Evaluation

i. *Drug Release Studies*:
   - Conduct dissolution tests in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) to evaluate controlled release and stability.

ii. *Probiotic Viability*:
   - Assess survival rates of probiotics post-formulation under acidic and intestinal pH conditions**.**

In Vivo Studies

i. Conduct animal studies to evaluate the therapeutic efficacy of the combined formulation:
   - Measure the reduction in gastric acidity.
   - And improvement in microbiota diversity.
   - Assess safety, tolerability, and clinical outcomes.

6. Analytical Testing

i. *Analytical Techniques*:
   - Use High-Performance Liquid Chromatography (HPLC) for PPI content analysis.
   - Conduct viable cell count assays for probiotics.

7. Validation and Scale-Up

I. Validate the optimized formulation process through reproducibility studies.
II. Develop scalable manufacturing protocols suitable for commercial production.

8. Regulatory and Quality Assurance

i. Ensure compliance with guidelines from the Central Drugs Standard Control Organization (CDSCO) and the World Health Organization (WHO).

ii. Document critical process parameters (CPPs) and critical quality attributes (CQAs) to meet regulatory standards.

9. Evaluation of Cost-Effectiveness

i. Analyze production costs and explore strategies for economic scalability in the Indian pharmaceutical industry.

Expected Consequence

1. A novel dual-delivery system with:
   - Controlled release of PPIs for effective acid suppression.
   - Enhanced viability and targeted delivery of probiotics.
2. Improved therapeutic outcomes, including reduced PPI-associated dysbiosis and improved gastrointestinal health.
3. Scalable and cost-effective formulation tailored for the Indian pharmaceutical industry.

Significance of Research

This study is expected to advance the field of gastrointestinal therapeutics by addressing the limitations of conventional PPI therapy. The integration of probiotics into the delivery system offers a patient-centric approach, promoting better clinical outcomes, reduced side effects, and enhanced gut health.

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