Available online on 15.8.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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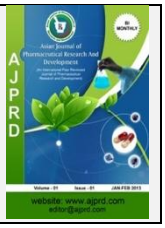

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Review Article

Gastro-retentive Floating Tablets For Leprosy: Current Trends and Challenges

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A B S T R A C T

Leprosy, also known as Hansen's disease, is a chronic infectious condition caused by Mycobacterium leprae, primarily affecting the skin, peripheral nerves, mucosa of the upper respiratory tract, and eyes. Despite its ancient origin and significant social impact, leprosy remains a public health concern in several endemic regions. This review explores the historical background, pathogenesis, and current World Health Organization (WHO)-recommended diagnostic and therapeutic strategies for leprosy. Emphasis is placed on multidrug therapy MDT), which includes dapsone, rifampicin, and clofazimine, as the cornerstone of treatment. The article further examines the role of gastroretentive drug delivery systems (GRDDS) in optimizing the pharmacokinetics and therapeutic efficacy of anti-leprosy agents. GRDDS are innovative oral formulations designed to prolong gastric residence time, thereby enhancing drug absorption in the upper gastrointestinal tract. Floating drug delivery systems (FDDS), a subclass of GRDDS, are particularly suitable for drugs like rifampicin, which exhibit narrow absorption windows or instability in the intestinal environment.The review discusses the mechanisms of gastroretention, including low-density floating, mucoadhesion, swelling, and high-density systems. Special focus is given to floating tablet technologies, their formulation strategies for leprosy management, and the various types of FDDS such as effervescent and non-effervescent systems. Key challenges in the development of floating tablets including formulation stability, drug loading efficiency, in vivo buoyancy, and patient variability are also outlined. Finally, the review highlights ongoing advancements and potential future directions in the integration of GRDDS with anti-leprosy therapy.

Keywords: Leprosy, multidrug therapy, Gastro-retentive system, gastric retention, floating tablets, controlled release, Bioavailability, formulation, hydrodynamic balance, buoyancy, drug delivery.

A R T I C L E I N F O: Received 12 Feb. 2025; Review Complete 18 April. 2025; Accepted 12 June 2025. ; Available online15 August. 2025

Cite this article as:

Mahale R, Deore S, Jadhav S, Mahajan S, Gastro-retentive Floating Tablets For Leprosy: Current Trends and Challenges, Asian Journal of Pharmaceutical Research and Development. 2025; 13(4):106-116, DOI: http://dx.doi.org/10.22270/ajprd.v13i4.1599

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INTRODUCTION

Leprosy, historically regarded as one of the most ancient and misunderstood diseases, has been a significant public health and social issue across human civilizations. The earliest evidence of leprosy dates back to approximately 2000 BCE, with findings in the skeletal remains of individuals from regions like India and China showing signs of bone deformities typically associated with the disease. Ancient Indian texts, such as the *Sushruta Samhita* and the *Charaka Samhita*, contain some of the oldest written records that detail symptoms consistent with leprosy, categorizing it under the umbrella of chronic skin diseases marked by disfigurement, sensory loss, and deformity [1]. Leprosy has also been prominently mentioned in early Egyptian and Chinese medical writings, where it was described as a disfiguring disease affecting the skin and peripheral nerves. In ancient Egypt, the Ebers Papyrus (circa 1550 BCE) makes indirect references to skin conditions that modern scholars believe to be related to leprosy. Moreover, one of the most culturally significant historical references to leprosy appears in the Bible, where the term "tzaraath" is frequently used to describe conditions believed by many to represent leprosy, although some scholars argue that this may have included a variety of dermatological disorders. Nevertheless, the association between leprosy and impurity, sin, or divine punishment deeply influenced cultural attitudes toward the disease for centuries [2].

During the Middle Ages, leprosy became a feared and highly stigmatized illness across Europe, Africa, and Asia. The lack of scientific understanding at the time led to patients being isolated from their communities. The establishment of "leper houses" or "leprosariums" became a common public health response, where those afflicted were forced to live in segregated colonies, often under religious oversight. In

Europe alone, hundreds of such leprosariums were constructed, where patients endured not only the physical suffering from the disease but also intense social ostracization and spiritual condemnation. Patients were often required to wear distinct clothing or carry bells to announce their presence, reinforcing their exclusion and public shaming [3]. A turning point in the history of leprosy came in 1873, when Norwegian physician Gerhard Armauer Hansen discovered *Mycobacterium leprae*, the bacterium responsible for the disease. This was a watershed moment in medical microbiology, as it marked the first time a bacterium was identified as the causative agent of a chronic human disease. Hansen's discovery shifted the understanding of leprosy from a condition associated with curses and moral failings to one with a tangible infectious etiology, thereby laying the groundwork for more scientific approaches to its diagnosis and treatment [4].

Figure 1: Leprosy

Despite this breakthrough, leprosy remained a major public health burden well into the 20th century, particularly in tropical and subtropical regions where conditions of poverty, malnutrition, and poor sanitation perpetuated its spread. Before the advent of antibiotic therapies, leprosy continued to ravage entire communities, causing deformities, disabilities, and reinforcing the cycle of social stigma. It was not until the mid-20th century, with the discovery of dapsone and later the introduction of multi-drug therapy (MDT) by the World Health Organization (WHO) in the 1980s, that significant strides were made in controlling and curing leprosy [5]. The historical trajectory of leprosy is not just a chronicle of medical advancements, but also a reflection of societal attitudes toward disease, disability, and marginalized populations. The disease has shaped laws, policies, and public health infrastructure across continents, and even influenced cultural representations of illness in literature and art. While modern medicine has significantly reduced its global prevalence, leprosy's historical legacy continues to influence public perceptions and the lived experiences of those affected today [6].

Etiological Agent: *Mycobacterium leprae*

The causative organism of leprosy is *Mycobacterium leprae*, a slow-growing, acid-fast, obligate intracellular bacterium that exhibits a unique set of biological and pathological features distinguishing it from other mycobacteria. It was first discovered in 1873 by Gerhard Armauer Hansen, making it the first bacterium to be linked to a chronic infectious human disease. As a result, leprosy is also commonly referred to as Hansen's disease in his honor [7].

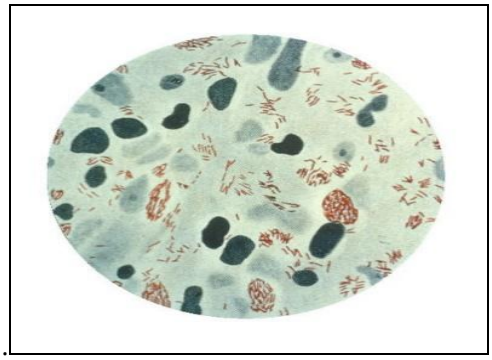

Figure 2: *Mycobacterium leprae*

The transmission of *M. leprae* predominantly occurs via the respiratory route, particularly through inhalation of infectious droplets from untreated multibacillary patients. There is also supporting evidence for the possibility of transmission through prolonged skin-to-skin contact and environmental reservoirs, although these routes remain less well-defined. Additionally, zoonotic transmission from infected armadillos has been documented in specific geographic regions, including parts of the southern United States and Brazil. From a pathogenic perspective, *M. leprae* has a remarkable ability to modulate the host immune response. The outcome of infection largely depends on the host's immune competency [8].

Global Epidemiology and Burden

Leprosy remains a public health concern in several parts of the world despite significant progress in its control and management over recent decades. Globally, the disease is endemic in tropical and subtropical regions, with its distribution largely influenced by socioeconomic conditions, access to healthcare, and public health infrastructure. The World Health Organization (WHO) has classified leprosy as one of the neglected tropical diseases (NTDs) due to its strong association with poverty, poor sanitation, and limited access to medical services, particularly in marginalized communities [9]. According to the most recent data from the WHO, approximately 200,000 new cases of leprosy are reported annually worldwide, although the actual burden is believed to be higher due to underreporting, lack of surveillance systems, and social stigma deterring patients from seeking early diagnosis and treatment. The majority of cases are concentrated in a few countries, notably India, Brazil, and Indonesia, which together account for more than 70% of the global disease burden. India alone contributes nearly 60% of all new leprosy cases, making it the most heavily affected nation despite extensive national and international efforts to reduce transmission [10].

While leprosy was once highly prevalent across Europe, North America, and East Asia during ancient and medieval times, concerted public health interventions and improved socioeconomic conditions have significantly reduced its incidence in most developed regions. However, the disease continues to persist in certain pockets of Africa, South-East Asia, and Latin America, where factors such as overcrowding, poor nutrition, and inadequate healthcare delivery systems facilitate sustained transmission [11]. The

epidemiology of leprosy is marked by its slow, insidious progression and long incubation period, often extending up to 5 to 20 years. This prolonged latency complicates timely detection and allows the disease to silently circulate within communities before clinical symptoms become evident. Moreover, children under the age of 15 account for a significant proportion of new cases in endemic areas, which indicates ongoing transmission and highlights gaps in effective control measures [12].

Gender disparities are also observed in the global burden of leprosy. Males are more frequently affected than females, possibly due to a combination of biological susceptibility and social factors, such as gender-based differences in healthcare-seeking behavior. Furthermore, the disease is disproportionately concentrated in lower-income populations, with individuals from rural areas and informal settlements being most vulnerable due to limited access to health education and early diagnostic services [13].

The global burden of leprosy extends beyond mere case counts. The disease contributes significantly to physical disability, social exclusion, and economic hardship for affected individuals and their families. Leprosy-related disabilities, especially when coupled with societal stigma, severely impact patients' quality of life and their ability to participate fully in social and economic activities [14]. In many endemic regions, affected individuals face discrimination in education, employment, and community life, perpetuating a vicious cycle of poverty and social isolation. In response to this burden, international initiatives such as the WHO's Global Leprosy Strategy 2021–2030 aim to promote early case detection, strengthen health systems, reduce stigma, and provide disability-inclusive care. The strategy also places special emphasis on interrupting transmission, improving community awareness, and ensuring equitable access to healthcare services for vulnerable populations [15].

Pathogenesis and Disease Mechanisms

Mycobacterium leprae primarily targets cooler body sites such as the skin, peripheral nerves, upper respiratory mucosa, and eyes. It enters through the nasal mucosa or broken skin and binds to Schwann cells via laminin and phenolic glycolipid-1 (PGL-1) receptors [16]. Once inside Schwann cells, it subverts host defenses to replicate, causing demyelination and axonal injury, leading to nerve dysfunction and sensory loss. The host's immune response dictates disease progression: a strong Th1-type response (IFN-γ, IL-2) activates macrophages, forming granulomas and containing infection, typical of tuberculoid leprosy. In contrast, a Th2-skewed humoral response (IL-4, IL-5, IL-10) leads to ineffective bacterial clearance and widespread dissemination seen in lepromatous leprosy [17]. M. leprae evades innate immunity by inhibiting phagosome-lysosome fusion and suppressing oxidative bursts and TNF-α production. Infected Schwann cells dedifferentiate, promoting bacterial survival and contributing to chronic inflammation and fibrosis. Acute immunologic reactions may occur: Type 1 (reversal) reactions involve heightened Th1 responses with inflammation of lesions, while Type 2 (ENL) reactions involve immune complex deposition causing systemic symptoms [18]. Progressive nerve damage results in muscle wasting, deformities likeclaw hand and foot drop, and chronic complications such as non-healing ulcers.

Diagnostic Approaches

Leprosy diagnosis is mainly clinical, guided by WHO's cardinal signs: skin patches with sensory loss, thickened peripheral nerves, and positive skin smears for acid-fast bacilli. Examination includes inspecting skin lesions and palpating nerves like the ulnar and common peroneal for enlargement or tenderness. Sensory testing with cotton wisps, pins, and tuning forks assesses touch, pain, and vibration [19]. Slit-skin smears stained by Ziehl-Neelsen technique help detect bacilli and estimate bacterial load through the bacterial index. Skin biopsies show granulomas with few bacilli in tuberculoid forms and foamy macrophages with abundant bacilli in lepromatous leprosy. PCR detects *M. leprae* DNA with high sensitivity, especially when smears are negative. Serological tests for PGL-1 antibodies assist in screening but have limited diagnostic reliability. In nerve-dominant cases without skin lesions, nerve conduction studies and ultrasonography help assess nerve damage. Fine-Needle Aspiration Cytology (FNAC) from nerves is useful in pure neuritic leprosy. Combining clinical and lab methods ensures early, accurate diagnosis and effective treatment classification [20].

Treatment Modalities and WHO Guidelines

Leprosy is treated using WHO-recommended multi-drug therapy (MDT), which effectively kills *Mycobacterium leprae*and prevents drug resistance. WHO classifies leprosy as paucibacillary (PB) or multibacillary (MB) based on the number of skin lesions and smear results. PB cases receive rifampicin monthly and daily dapsone for six months. MB cases are treated with monthly rifampicin and clofazimine, plus daily clofazimine and dapsone for 12 months. Rifampicin rapidly reduces bacterial load, dapsone inhibits folate synthesis, and clofazimine adds anti-inflammatory effects. Corticosteroids are used to manage nerve inflammation and reversal reactions, while thalidomide helps control ENL but is used with caution due to teratogenicity. Supervised monthly dosing and directly observed therapy (DOT) improve adherence and outcomes. WHO recommends single-dose rifampicin (SDR) for contacts of new patients to prevent transmission. Supportive care includes physiotherapy, wound care, and psychosocial support. MDT is provided free to all patients under WHO's global leprosy elimination strategy [21].

Global Control Programs and Future Directions

Global control programs, led by WHO and supported by governments and NGOs, have played a key role in reducing the global burden of leprosy since the 1980s through Multi-Drug Therapy (MDT). The WHO declared leprosy eliminated as a public health problem in 2000, defined as a prevalence below 1 case per 10,000 population. Despite this, the disease remains in some regions, especially in low- and middle-income countries. The Global Leprosy Strategy 2021–2030, "Towards Zero Leprosy," focuses on halting transmission, early diagnosis, and preventing disabilities [22]. It promotes single-dose rifampicin (SDR) chemoprophylaxis for contacts and encourages integration of leprosy care into general health systems. Active case detection and public awareness campaigns help reduce stigma and diagnostic delays. The

Global Leprosy Programme supports national programs with technical guidance and workforce training. NGOs like The Leprosy Mission International and ILEP contribute to detection, treatment, and rehabilitation. Future directions include better diagnostics such as PCR and point-of-care tools. Vaccine development is ongoing, with focus on BCG enhancement and subunit vaccines. Disability prevention and social inclusion are prioritized for improved quality of life. Achieving zero leprosy will require strong political will, sustainable funding, and innovations in public health [23]

Gastroretentive Drug Delivery System (GRDDS)

The concept of gastroretentive drug delivery systems (GRDDS) has emerged as a promising strategy to overcome the limitations associated with conventional oral drug formulations, particularly for drugs that exhibit site-specific absorption in the stomach or upper small intestine. By prolonging gastric retention time, GRDDS ensures extended drug release in the stomach, leading to improved bioavailability, enhanced therapeutic efficacy, and better patient compliance. The development of GRDDS is particularly beneficial for drugs that have a narrow absorption window in the upper gastrointestinal tract, are poorly soluble at higher pH conditions, or require localized action in the stomach. Various gastroretentive approaches, including floating, mucoadhesive, high-density, and expandable systems, have been designed to enhance the gastric residence time of orally administered drugs, thereby optimizing their pharmacokinetic and pharmacodynamic profiles [24].

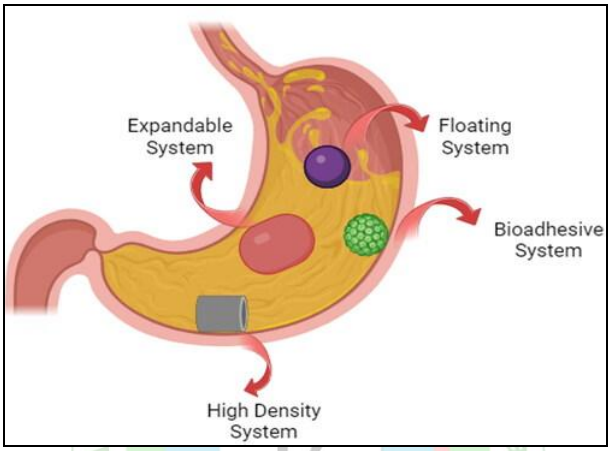

Figure 3: Gastroretentive drug delivery (GRDDS)

Introduction to Gastroretentive Drug Delivery and Its Importance

Oral drug delivery remains the most widely preferred and commonly used route for drug administration due to its non-invasive nature, ease of use, cost-effectiveness, and high patient compliance. However, one of the significant challenges associated with conventional oral drug formulations is the short gastric residence time, which often results in incomplete drug absorption, poor bioavailability, and suboptimal therapeutic efficacy. The rapid gastric emptying process, which varies depending on factors such as fed or fasted states, gastric motility, and individual physiological differences, limits the time available for drug dissolution and absorption. This limitation particularly affects drugs that exhibit site-specific absorption in the stomach or upper small intestine, leading to reduced therapeutic effects and necessitating frequent dosing to maintain drug concentrations within the desired therapeutic window. Gastroretentive drug delivery systems (GRDDS) have been developed to overcome these limitations by prolonging gastric retention time, thereby enhancing drug dissolution, absorption, and therapeutic efficacy. These systems are particularly useful for drugs that have a narrow absorption window in the upper gastrointestinal tract, are poorly soluble in the alkaline pH of the intestine, or require localized action in the stomach to achieve their therapeutic effects. By ensuring that the drug remains in the stomach for a prolonged period, GRDDS allows for sustained and controlled drug release, leading to improved bioavailability, reduced dosing frequency, and better patient adherence to therapy [25].

The need for gastroretentive formulations arises due to several pharmacokinetic and pharmacodynamic challenges associated with conventional oral drug delivery. Many drugs exhibit pH-dependent solubility, meaning their solubility is significantly reduced in the alkaline environment of the small intestine. Weakly basic drugs, for example, dissolve readily in acidic conditions but become less soluble as they transit into the intestine, resulting in poor and incomplete absorption. For such drugs, maintaining a longer gastric residence time allows them to remain in a favorable acidic environment, ensuring better dissolution and absorption before passing into the intestine. Additionally, certain drugs exert local therapeutic effects in the stomach and require extended contact with the gastric mucosa for optimal efficacy. Examples include proton pump inhibitors, mucosal protective agents, and antibiotics used for Helicobacter pylori eradication therapy. Conventional dosage forms often fail to retain the drug at the site of action for a sufficient duration, leading to reduced drug efficacy and frequent dosing requirements. GRDDS addresses this issue by prolonging drug retention in the stomach, ensuring maximum therapeutic effect, and improving the overall treatment outcome.

Another critical consideration is for drugs with a short biological half-life. Many drugs are rapidly metabolized and eliminated from the body, necessitating frequent administration to maintain consistent therapeutic levels. Conventional dosage forms often result in peaks and troughs

in plasma drug concentrations, which can lead to reduced efficacy, increased side effects, and poor patient compliance. GRDDS provides a solution by allowing for sustained and controlled drug release, reducing the frequency of administration and minimizing fluctuations in drug levels, thereby enhancing patient adherence and optimizing therapeutic efficacy. From a pharmacokinetic perspective, GRDDS can also be beneficial for drugs that undergo first-pass metabolism. Some drugs are extensively metabolized in the liver before reaching systemic circulation, leading to reduced bioavailability. By prolonging gastric retention and ensuring gradual drug release, GRDDS can minimize first-pass metabolism and improve overall drug bioavailability, making the formulation more effective in achieving therapeutic outcomes [26].Gastroretentive drug delivery systems (GRDDS) are crucial for treating gastric ulcers, gastroesophageal reflux disease (GERD), and *H. pylori* infections, ensuring localized drug action in the stomach. Drugs like antibiotics and acid-suppressing medications benefit from prolonged gastric retention, enhancing efficacy and reducing resistance. GRDDS strategies include floating, mucoadhesive, high-density, and expandable formulations to maintain sustained drug release. These systems minimize dose-related side effects, improve safety, and optimize therapeutic outcomes. Reduced dosing frequency enhances patient convenience and adherence, especially in long-term treatments. GRDDS offer a promising solution to overcome the limitations of conventional oral drug formulations [27].

Physiological Challenges of Gastric Retention and Drug Absorption

The effectiveness of gastroretentive drug delivery systems (GRDDS) is significantly influenced by various physiological factors that govern gastric retention time, gastric motility, and drug absorption. While GRDDS offers a promising strategy to improve drug bioavailability and therapeutic efficacy, certain physiological challenges must be addressed to ensure successful drug retention in the stomach and controlled drug release. These challenges arise due to the complex and dynamic nature of the gastrointestinal (GI) tract, which is subject to continuous variations in pH, enzymatic activity, gastric emptying patterns, and mucosal interactions. Understanding these physiological barriers is essential for designing optimized GRDDS formulations capable of overcoming rapid gastric emptying and absorption limitations [28].

Gastric Emptying and Variability in Retention Time

Gastric emptying, which varies with fed or fasted state, meal composition, individual physiology, and gastric motility patterns, is a key determinant of how long a drug remains in the stomach [38]. In the fasted state, migrating myoelectric complexes (MMCs) cycle every 90–120 minutes, with a strong Phase III peristaltic wave that clears residual contents and can rapidly expel any dosage form present. Conversely, in the fed state, motility slows and gastric emptying is delayed, prolonging retention of solid and semi-solid formulations. However, factors such as meal viscosity, caloric load, and fat content modulate this effect: high-fat meals further delay emptying, whereas liquid meals may accelerate clearance of floating systems. Thus, GRDDS must be designed to withstand strong MMC contractions and perform reliably across diverse dietary and physiological conditions [29]

Gastric pH Variability and Its Impact on Drug Solubility

Gastric pH fluctuates with fed or fasted states, disease conditions, and individual physiology, profoundly influencing drug solubility, dissolution, and stability. In the fasted stomach (pH 1–2), weakly basic drugs dissolve readily, whereas acid-sensitive compounds risk degradation. After eating, pH rises to around 3.5–5, which can impair the solubility and bioavailability of drugs requiring highly acidic media—especially in patients on proton pump inhibitors or those with hypochlorhydria. Gastroretentive formulations must therefore remain stable under low pH to avoid premature drug breakdown, and acid-sensitive proteins or peptides often need protection from acidic hydrolysis. Strategies such as polymer coatings, enteric layers, and pH-responsive release mechanisms are essential to safeguard these drugs and achieve controlled, extended release within the stomach[30].

Effect of Gastric Mucus and Enzymatic Activity

The gastric mucus barrier protects the stomach lining but poses a challenge for mucoadhesive systems due to continuous mucus turnover, requiring formulations that adhere firmly despite clearance. Choice of polymers like chitosan, carbopol, or alginate is key to enhancing bioadhesion and extending gastric residence. Gastric enzymes such as pepsin can degrade sensitive drugs especially proteins and peptides before absorption. To prevent enzymatic breakdown, GRDDS may incorporate enzyme inhibitors, protective coatings, or encapsulation techniques. These strategies together ensure sustained retention and effective delivery of vulnerable drug molecules in the stomach [31].

Role of Pyloric Sphincter and Size of the Dosage Form

The pyloric sphincter, located at the junction between the stomach and the small intestine, acts as a gatekeeper regulating gastric emptying. Drug particles and formulations smaller than 2 mm in diameter tend to pass through the pyloric sphincter easily, limiting their gastric retention. GRDDS must be designed to achieve a size large enough to prevent rapid passage through the pylorus while maintaining patient comfort and ease of swallowing. Expandable drug delivery systems, which swell upon contact with gastric fluids, are effective in overcoming this limitation, ensuring prolonged gastric retention by preventing premature emptying into the small intestine [32].

Variability in Gastric Blood Flow and Absorption Dynamics

Although the stomach is not the primary site for drug absorption, some drugs exhibit optimal absorption in the gastric region, particularly those that are weakly acidic, highly lipophilic, or unstable in intestinal conditions. However, variability in gastric blood flow can influence drug absorption rates. Factors such as age, disease states, and medication interactions can alter gastric microcirculation, affecting drug uptake from the stomach. GRDDS formulations must be designed to maintain prolonged drug release and ensure sufficient time for absorption, regardless of fluctuations in gastric blood flow [33].

Patient-Specific Variability and Disease Conditions

Physiological differences among patients introduce another challenge in the development of GRDDS. Elderly patients, individuals with gastrointestinal disorders, and patients with altered gastric motility may exhibit significant variability in gastric retention time, acid secretion, and motility patterns. Conditions such as gastroparesis, gastric ulcers, and diabetic neuropathy can delay gastric emptying, prolonging drug retention and affecting the predictability of drug release profiles. Conversely, conditions such as hyperthyroidism and stress-induced hypermotility can accelerate gastric emptying, reducing the effectiveness of gastroretentive formulations. Furthermore, patients on concomitant medications such as proton pump inhibitors (PPIs) or antacids may experience altered gastric pH and enzyme activity, impacting drug solubility and bioavailability. These factors must be considered when designing GRDDS to ensure consistent and predictable drug release across diverse patient populations [34].

Mechanisms of Gastroretention

The effectiveness of gastroretentive drug delivery systems (GRDDS) depends on their ability to prolong the residence time of a drug in the stomach, ensuring sustained and controlled drug release. Given the dynamic nature of gastric emptying, various strategies have been developed to enhance gastric retention and optimize drug absorption. These mechanisms include floating drug delivery systems, mucoadhesive systems, expandable and swellable formulations, and high-density systems. Each of these approaches utilizes different principles to prevent premature gastric emptying, allowing drugs to remain in the stomach for an extended duration and ensuring therapeutic effectiveness. Selecting the appropriate gastroretentive mechanism depends on factors such as drug solubility, physicochemical properties, gastric motility patterns, and patient-specific physiological conditions [35].

Floating Drug Delivery Systems.

Floating drug delivery systems (FDDS) are one of the most commonly used gastroretentive technologies, designed to remain buoyant in the gastric fluid while gradually releasing the drug in a controlled manner. These systems prevent premature gastric emptying by maintaining a lower density than the gastric contents, ensuring that the drug remains in the stomach for an extended period. Floating systems are particularly beneficial for drugs that have low solubility in the alkaline pH of the intestine or require prolonged gastric residence to achieve effective absorption. Effervescent floating systems function by incorporating gas-generating agents such as sodium bicarbonate, citric acid, or tartaric acid. Upon contact with gastric fluids, these agents undergo a chemical reaction, releasing carbon dioxide gas, which becomes trapped within the polymeric matrix of the dosage form. This trapped gas reduces the density of the formulation, causing it to float on the gastric contents. Effervescent systems can be formulated as single-layered or multi-layered tablets, with the latter offering better control over drug release kinetics. Non-effervescent floating systems, in contrast, do not rely on gas generation but instead use low-density polymers such as hydroxypropyl methylcellulose (HPMC), polyethylene oxide, and ethyl cellulose. These polymers hydrate and swell upon exposure to gastric fluids, forming a gel-like structure that reduces the formulation's density and maintains buoyancy. While floating systems provide significant advantages in ensuring prolonged gastric retention, their effectiveness is influenced by several factors, including gastric motility, food intake, and variations in gastric fluid composition among individuals. Additionally, ensuring consistent floating behavior and preventing premature drug release are challenges that must be addressed during formulation development [36].

Mucoadhesive Systems for Prolonged Gastric Retention

Mucoadhesive (bioadhesive) systems employ polymers such as chitosan, alginate, carbopol, hydroxypropyl methylcellulose (HPMC), and polyethylene glycol (PEG) to form strong interactions via hydrogen bonds, electrostatic attractions, and hydrophobic forces with the gastric mucin layer, thereby anchoring the dosage form at the site of absorption for prolonged drug release and enhanced bioavailability . The efficacy of these systems relies on polymer concentration, hydration capacity, and the intrinsic mucoadhesive strength of the polymer mucin interface. However, the stomach's continuous mucus turnover and the presence of digestive enzymes like pepsin can compromise adhesion and degrade the polymer matrix over time. Optimizing the choice and ratio of mucoadhesive polymers, along with formulation strategies such as crosslinking or co-polymer blends, is essential to overcome these barriers, ensuring robust gastric retention and sustained therapeutic delivery[37].

Expandable and Swellable Systems in GRDDS

Expandable and swellablegastroretentive systems leverage size increase upon contact with gastric fluids to resist pyloric passage and prolong stomach retention: expandable devices employ biodegradable elastomers that unfold into large structures, ensuring extended mucosal contact and sustained drug release, while swellable formulations use hydrophilic polymers such as crosslinkedpolyacrylates, sodium carboxymethylcellulose, and hydrocolloids to absorb fluid and expand severalfold .This swelling and unfolding delay gastric emptying and maintain controlled release, but the systems must possess sufficient mechanical strength to withstand powerful gastric contractions without fragmenting and be optimized to avoid patient discomfort or obstruction. Careful selection and tuning of polymer composition, crosslinking density, and expansion kinetics are therefore essential to balance safety, comfort, and therapeutic efficacy in these advanced GRDDS [38].

High-Density Systems for Delayed Gastric Emptying

High-density gastroretentive systems remain in the stomach's lower region by having a density above that of gastric fluids (>2.5 g/cm³), resisting premature emptying. Incorporating heavy excipients like barium sulfate, zinc oxide, titanium dioxide, or iron oxide anchors the dosage form despite gastric motility. These systems are ideal for drugs requiring prolonged local gastric exposure but can be affected by individual variations in motility and stomach contents. Uniform drug distribution within the dense matrix and maintaining structural integrity under peristaltic forces are key formulation challenges. Careful optimization of excipient type, particle size, and matrix composition is essential to

maximize retention time while ensuring consistent drug release.[39].

Advantages of Floating Tablets in Controlled Drug Release

1. **Prolonged Gastric Retention Time** – Remain buoyant in the stomach for extended periods, ensuring sustained drug release and longer therapeutic action.
2. **Improved Drug Bioavailability** – Enhance absorption of pH-dependent drugs by maintaining them in the acidic gastric environment.
3. **Controlled and Sustained Drug Release** – Provide gradual drug release, reducing the need for frequent dosing and maintaining steady therapeutic levels.
4. **Reduced Plasma Drug Level Fluctuations** – Maintain consistent drug concentrations in the bloodstream, avoiding peaks and troughs that can cause toxicity or inefficacy.
5. **Enhanced Efficacy for Gastric Disorders** – Ensure higher local drug concentration for conditions like ulcers, GERD, and H. pylori infection by targeting the gastric region.
6. **Minimized Drug Wastage and Enhanced Absorption** – Prevent premature gastric emptying, ensuring complete dissolution and optimal drug utilization.
7. **Reduced Dosing Frequency and Improved Compliance** – Support less frequent dosing, making treatment easier for patients and improving adherence.
8. **Effective for Drugs with Narrow Absorption Windows** – Retain drugs in specific GI regions where absorption is most effective, maximizing therapeutic benefit.
9. **Reduced Food-Drug Interaction Impact** – Provide more consistent absorption profiles by mitigating the influence of food on gastric emptying.
10. **Potential for Combination and Dual-Release Therapy** – Allow co-formulation of multiple drugs with tailored release profiles for enhanced treatment efficiency

Floating drug delivery systems offer multiple advantages in ensuring prolonged gastric retention, controlled drug release, improved bioavailability, and better therapeutic outcomes. These benefits make floating tablets a valuable approach for the treatment of gastric disorders, drugs with pH-dependent solubility, and medications with narrow absorption windows. However, successful formulation of floating tablets requires careful selection of excipients, polymers, and buoyancy-enhancing agents to achieve optimal floating behavior and controlled release characteristics. The next section will discuss the challenges associated with the formulation and development of GRDDS, highlighting the critical factors that need to be addressed to ensure effective and reproducible floating drug delivery systems [40,41].

Material used to prepare gastro-retentive floating tablet.

1. **Polymers (Matrix Formers):-** Polymers like HPMC, xanthan gum, and guar gum form the tablet matrix and control drug release through swelling and gel formation. When exposed to gastric fluids, they swell, creating a barrier that slows drug diffusion. HPMC K100M is commonly used for sustained release. Natural gums also enhance viscosity and floating ability. These polymers ensure prolonged gastric retention by maintaining tablet shape and buoyancy.
2. **Gas-Generating Agents:-**Sodium bicarbonate, often combined with citric or tartaric acid, reacts with stomach acid to produce CO_2. This gas becomes trapped in the swollen matrix, reducing the tablet's density. The resultant buoyancy allows the tablet to float and remain in the stomach longer. This mechanism supports prolonged drug absorption in the upper GI tract. Proper balance of acids and bases ensures optimal floating lag time and duration.
3. **Fillers/Diluents:-**Fillers like lactose and microcrystalline cellulose (MCC) add bulk and improve compressibility of the formulation. MCC also enhances mechanical strength and can help modulate floatation when used properly. Lactose is water-soluble and may influence the drug's release rate. agents help maintain tablet size, integrity, and flow during processing.
4. **Binders:-**Binders such as PVP K30 and starch paste help hold the ingredients together, ensuring tablet strength and uniformity. PVP also contributes slightly to controlled drug release when used in hydrophilic matrices. Gelatin and starch provide cohesive strength during granulation and compression. Proper binder concentration prevents tablet breakage. They are essential for ensuring tablet durability through storage and handling.
5. **Lubricants &Glidants:-**Magnesium stearate and talc are added in small amounts to reduce friction during tableting and improve powder flow. Lubricants prevent sticking to punches and dies, ensuring smooth ejection. Glidants like colloidal silicon dioxide enhance flowability of powders. They don't affect drug release significantly but are critical for consistent manufacturing. Overuse can, however, retard drug release or affect tablet hardness.
6. **Buoyancy Enhancers:-**Buoyancy enhancers such as beeswax and ethyl cellulose reduce the tablet's density or increase porosity, aiding floatation. These hydrophobic substances trap air or resist wetting, keeping the tablet afloat. Used with polymers, they improve floating lag time and total floating duration. Waxes like cetyl alcohol or stearic acid are also used. They are especially useful in non-effervescent floating tablet designs.
7. **Active ingredients:-** used in gastroretentive floating tablets are typically drugs with a narrow absorption window, poor solubility in higher pH, or that act locally in the stomach. Examples include dapsone**,** metformin**,** ciprofloxacin**,** ranitidine**,**propranolol**,** andlevodopa. These drugs benefit from prolonged gastric retention, which enhances their absorption and bioavailability. Floating tablets allow the drug to remain in the stomach for extended periods, releasing the drug slowly. This approach is especially useful for drugs with short half-lives or requiring controlled release at the upper GI level [42-43].

Preparation of floating tablet

The preparation of floating tablets by wet granulation involves a systematic sequence of steps to ensure tablet quality and buoyancy. First, all ingredients are accurately weighed as per the formula, followed by dry mixing of the active pharmaceutical ingredient and excipients for 10–15 minutes to ensure uniform distribution. A binder solution is then prepared in purified water and homogenized to achieve a

consistent mixture. This solution is gradually added to the dry blend with mixing until cohesive wet granules are formed. The granules are dried in a tray or fluidized bed dryer at 40–50°C until the moisture content is reduced below 2%. After drying, the granules are passed through an appropriate mesh sieve to ensure uniform particle size. The sieved granules are blended with suitable lubricants and glidants for 5–10 minutes to improve flow properties. The final blend is compressed into tablets using a rotary tablet press, and critical parameters like weight, hardness, thickness, and buoyancy are monitored. The tablets are then subjected to a buoyancy test in simulated gastric fluid to confirm their floating ability. Finally, the tablets are packaged in moisture-protective containers and evaluated through quality control tests such as friability, dissolution, and weight uniformity to ensure they meet required specifications [44-47].

Evaluation test for gastro-retentive floating tablets.

Weight Variation:-After the tablets are compressed, individual tablets are weighed and compared with the average tablet weight. This test ensures uniformity in the amount of drug and excipients per tablet. Significant variation could lead to inconsistent dosing and therapeutic failure. According to pharmacopeial limits, no more than two tablets should deviate by more than the permitted percentage. It is a critical quality control step during batch production.

Hardness Test:-The hardness or crushing strength of the tablet is evaluated using a tablet hardness tester. This test ensures that the tablet is strong enough to withstand handling, packaging, and transportation without breaking or chipping. Tablets that are too hard may not disintegrate properly, while too soft tablets may crumble prematurely. The results are expressed in kg/cm² or Newtons.

Friability Test:-Tablets are rotated in a friabilator, usually for 100 revolutions at 25 rpm, to simulate the mechanical stress of handling. The percentage of weight loss is measured to evaluate tablet durability. A friability of less than 1% is generally acceptable. This test is particularly important for ensuring physical stability during packaging and shipping.

Content Uniformity:-A sample of tablets is analyzed to determine the drug content in individual units. This ensures that each tablet delivers a consistent dose, especially important for potent drugs like dapsone. It is typically performed using UV-visible spectrophotometry or HPLC. The acceptable range is usually 85% to 115% of the label claim for individual dosage units.

Swelling Index:-Tablets are placed in simulated gastric fluid and removed at specific time intervals to measure their weight gain. This reflects the hydration and swelling behavior of polymers used in the formulation. Swelling is critical as it supports the buoyancy and controls drug release. The swelling index is calculated as: (Finalweight–Initialweight)/Initialweight×100(Final weight – Initial weight) / Initial weight × 100(Finalweight–Initialweight)/Initialweight×100

Buoyancy Test (Floating Lag Time and Total Floating Time):-The floating lag time is the time the tablet takes to rise to the surface, while total floating time is the duration it remains afloat in 0.1 N HCl at 37°C. This test determines the ability of the tablet to remain in the stomach for a prolonged time. A short lag time and long floating duration indicate effective gastroretention.

In-vitro Drug Release:-Using USP Type II (paddle) dissolution apparatus, tablets are subjected to testing in simulated gastric fluid (pH 1.2) at 37°C. Samples are collected at predetermined intervals and analyzed for drug content. This provides the drug release profile over time, which helps determine whether the formulation achieves sustained or controlled release.

Stability Study:- Stability tests are conducted under ICH-recommended conditions (e.g., 40°C ± 2°C / 75% RH ± 5%) for specified durations (e.g., 1, 3, and 6 months). These tests assess changes in physical appearance, drug content, buoyancy, and release profile. Stability data ensures the formulation maintains its safety, efficacy, and quality throughout its shelf life.

In Vivo Drug Release Studies:-These are carried out in suitable animal models or human subjects to confirm the in-vitro performance. Techniques like gamma scintigraphy or radiographic imaging may be used to observe tablet location and gastric retention. Pharmacokinetic studies are conducted to determine parameters such as Cmax, Tmax, AUC, and bioavailability. These studies validate the gastroretentivebehavior and sustained drug release in real physiological conditions [48-49]

Gastro-retentive floating tablet for leprosy management

Gastroretentive floating tablets represent a major advancement over conventional oral dosage forms in the treatment of leprosy, especially for drugs that exhibit pH-dependent solubility and are primarily absorbed in the upper gastrointestinal (GI) tract. In conventional dosage forms, the drug often passes quickly through the stomach into the intestine, where absorption may be limited due to a less favorable pH environment. This can result in inconsistent bioavailability, fluctuating plasma drug levels, and the need for frequent dosing, which significantly affects patient compliance, particularly in long-term treatments required for chronic diseases like leprosy. In contrast, gastroretentive floating tablets are designed to remain buoyant in gastric fluid for extended durations by incorporating gas-generating agents and swelling polymers, allowing them to float and stay in the stomach for 12–24 hours. This prolonged gastric residence time enhances drug absorption by keeping the drug in the region of optimal uptake, thereby leading to improved bioavailability, more stable plasma concentrations, and reduced dosing frequency. The controlled-release nature of these tablets also minimizes peak-trough fluctuations, reducing the risk of side effects and improving the overall therapeutic effect. For diseases like leprosy, where long-term, consistent therapy is critical to prevent drug resistance, relapse, and transmission, gastroretentive systems offer a more efficient, patient-friendly, and therapeutically effective approach. They simplify the dosing regimen, improve adherence especially in populations with limited healthcare access and contribute to better disease management and eradication strategies.

Challenges in the Formulation and Development of GRDDS

The development of gastroretentive drug delivery systems (GRDDS) presents several challenges that must be carefully addressed to ensure effective and reliable drug retention in the stomach. The complexity of gastric physiology, variability in gastric motility, and patient-specific factors make it difficult to design a universal formulation that consistently performs across different individuals. Additionally, the physicochemical properties of the drug, selection of excipients, and the type of gastroretentive mechanism employed play crucial roles in determining the success of GRDDS. Overcoming these challenges requires extensive formulation optimization, in-vitro and in-vivo testing, and advanced drug delivery technologies to enhance the stability, efficacy, and reproducibility of these systems. One of the major challenges in GRDDS development is the variability in gastric emptying time. Gastric emptying is highly dynamic and influenced by several factors, including the fed or fasted state, the composition of the meal, gastric motility, and individual patient physiology. In a fasted state, the stomach undergoes cyclic contractions known as the migrating myoelectric complex (MMC), which can rapidly push dosage forms into the small intestine. In contrast, the presence of food delays gastric emptying, allowing a longer retention time. This variability makes it difficult to predict how long a gastroretentive formulation will remain in the stomach, leading to inconsistent drug release and absorption patterns. To address this, GRDDS formulations must be designed to function optimally regardless of gastric motility variations, ensuring prolonged retention under both fasting and fed conditions. Another significant challenge is achieving sufficient buoyancy or adhesion in floating and mucoadhesive systems. Floating drug delivery systems rely on low-density materials to maintain buoyancy in gastric fluids, preventing them from being rapidly emptied into the intestine. However, fluctuations in gastric fluid volume, composition, and peristaltic activity can affect the buoyancy of the dosage form, leading to unpredictable floating behavior. Similarly, mucoadhesive formulations must adhere to the gastric mucosa for prolonged periods, but the continuous turnover of mucus, along with enzymatic degradation and gastric secretions, can weaken adhesion, causing premature drug detachment. Optimizing the polymer composition, viscosity, and hydration properties of the formulation is critical to improving the reliability of these gastroretentive mechanisms [50].

The mechanical integrity and swelling properties of expandable and swellable GRDDS pose additional formulation challenges. Expandable systems rely on size expansion after ingestion to prevent passage through the pylorus, but these formulations must be strong enough to withstand gastric contractions without breaking apart. If the expansion is insufficient, the dosage form may be prematurely emptied from the stomach, reducing its effectiveness. On the other hand, excessive expansion may cause gastric obstruction, leading to safety concerns. The choice of polymeric materials, crosslinking agents, and swelling kinetics must be carefully optimized to achieve the desired expansion behavior while ensuring patient safety. Controlling the drug release profile is another critical issue in GRDDS formulation. The goal of gastroretentive drug delivery is to provide sustained and controlled drug release over an extended period, but achieving a consistent and predictable release rate can be difficult. Factors such as drug solubility, polymer composition, tablet matrix porosity, and hydration dynamics all influence drug release kinetics. Highly soluble drugs may be released too quickly, defeating the purpose of prolonged gastric retention, while poorly soluble drugs may exhibit erratic or incomplete dissolution. Formulation strategies such as using hydrophilic polymers, coating techniques, and multi-layered dosage forms must be employed to modulate the release rate and ensure sustained drug availability.

The impact of gastric pH and enzymatic activity also presents formulation challenges. The stomach's pH varies significantly depending on the presence or absence of food, the use of acid-reducing medications, and individual physiological conditions. For instance, patients on proton pump inhibitors (PPIs) may have a higher gastric pH, affecting the dissolution and solubility of certain drugs. Similarly, the presence of pepsin and other gastric enzymes can degrade sensitive drugs before absorption, reducing their therapeutic effectiveness. GRDDS must be formulated to withstand these variations by incorporating pH-sensitive coatings, enzyme inhibitors, or protective polymeric matrices that ensure drug stability throughout gastric retention. Manufacturing and scalability issues further complicate the development of GRDDS. Unlike conventional oral formulations, gastroretentive systems require specialized excipients, complex processing techniques, and stringent quality control measures to ensure reproducibility. The use of effervescent agents in floating systems, for example, requires precise control over the ratio of gas-forming agents to maintain the desired buoyancy. Similarly, mucoadhesive and expandable formulations require highly specific polymeric compositions and optimized mechanical properties to function effectively. The cost of raw materials and the complexity of manufacturing processes can increase production expenses, making large-scale commercialization challenging.

Patient-specific factors and inter-individual variability further influence the effectiveness of GRDDS. Differences in age, gender, disease state, gastric motility disorders, and concurrent medication use can all impact the performance of gastroretentive formulations. For example, patients with gastroparesis (delayed gastric emptying) may experience prolonged drug retention, leading to unintended accumulation and potential toxicity. Conversely, hypermotile gastric conditions may result in rapid gastric emptying, reducing the intended effectiveness of GRDDS. Ensuring that these formulations work effectively across diverse patient populations requires personalized formulation approaches and comprehensive clinical studies. Regulatory challenges must also be considered in the development of GRDDS. Since gastroretentive formulations involve advanced drug delivery technologies, they require rigorous evaluation for safety, efficacy, and in-vivo performance. Regulatory agencies such as the FDA and EMA require detailed pharmacokinetic studies, stability assessments, and patient safety evaluations before approving gastroretentive products for clinical use. Demonstrating consistent gastric retention, controlled drug release, and reproducible therapeutic effects is essential to obtaining regulatory approval and ensuring widespread clinical adoption. The formulation and development of GRDDS involve multiple challenges related

to gastric physiology, drug solubility, polymer selection, drug release kinetics, manufacturing feasibility, and patient variability. Addressing these challenges requires a multi-disciplinary approach, incorporating innovative formulation strategies, advanced polymer technologies, and rigorous in-vitro and in-vivo evaluations. By optimizing these parameters, GRDDS can provide more effective and patient-friendly drug delivery solutions, improving therapeutic outcomes and ensuring better management of gastric and systemic diseases [51].

Summary and Conclusion:- Gastro-retentive floating tablets are a helpful improvement in treating leprosy because they stay in the stomach longer and slowly release the drug where it can be best absorbed. Unlike regular tablets that pass quickly through the digestive system, floating tablets stay at the top of the stomach and allow the drug to work for a longer time. This helps keep the right amount of drug in the body, making the treatment more effective. It also means patients may not need to take the drug as often, which can improve how well they stick to the treatment. These tablets are made with special materials that swell and float, allowing for a steady release of the drug. Because of these benefits, floating tablets are a superior option compared to regular tablets for managing long-term leprosy. While formulation and physiological challenges remain, ongoing research and innovation are paving the way for the successful development of optimized floating systems tailored to the specific needs of chronic disease therapies like leprosy.

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