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Engineering Floating Tablets for NSAIDs-Induced Peptic Ulcers: Insights from Design to Optimization.

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Abstract: Peptic ulcer disease (PUD) remains an important gastrointestinal disorder that is characterised by ulcers in the stomach or duodenum that extend into the mucosa and the underlying layers. The previous few decades have seen a significant shift in the Etiology. While H. pylori infection was historically the leading cause, regular use of non-steroidal anti-inflammatory drugs (NSAIDs), like aspirin and other anti-platelets have been recognised predominant cause of PUD in current therapeutic practice. The treatments primarily focus on eradication of *H. pylori* and reducing the gastric acid secretion with proton pump inhibitors, H2 antagonist and using mucosal protective agents like misoprostol particularly for NSAIDs induced ulcers. Traditional oral medication administration often shows limited therapeutic efficacy due to rapid gastric emptying and short residence time, resulting lower concentration at target site. Floating tablets as gastroretentive system has emerged as promising approach of enhancing gastric retention thus improving bioavailability. The tablets are designed to stay afloat in the stomach juice for extended periods, providing delayed release of medication and prolonged therapeutic action directly at the site of ulceration. The various formulation approaches involved in floating tablets are effervescent and non-effervescent systems, by employing different polymers like HPMC, ethyl cellulose, Carbopol desired buoyancy and prolong drug release can be achieved. This formulation approaches offers a number of benefits, including enhanced patient compliance, reduce systemic side effects and enhanced protection of gastric mucosa through sustain local action.

Index Terms - Peptic Ulcer Disease (PUD), Floating Tablets, NSAIDs, Gastric Retention, Sustained Release, HPMC Polymers.

1. Introduction

Peptic ulcer disease (PUD) is caused by an imbalance in protective and abrasive factors; it is characterized by acid-induced lesions in digestive tract predominantly affecting the stomach and first segment of duodenum. The breakdown of mucosa and cells that release gastric acid that constitute the stomach lining and protects stomach cells from gastric acid, is referred to as Peptic ulcer disease. The erosion continues to the mucosa muscularis. The primary causes of this type of ulcer are Helicobacter Pylori infection and prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs). Historically, predominant cause of peptic ulcer was H. pylori infection, however prolong use of NSAIDs, including aspirin and other anti-platelets has emerged as leading cause of PUD in current therapeutic practice. **[1]** Treatments for H.

pylori involve its eradication using antibiotics and acid suppressing agents whereas for NSAIDs induced ulcers involves drugs like H2 antagonists, PPIs, cytoprotective agents like misoprostol. **[2]**
Peptic ulcer therapy using traditional medication delivery methods shows rapid gastric emptying thus sub optimal concentration present at the target site. One of the promising approaches for its treatment would be floating tablets as a gastroretentive system. The tablets are constructed in a fashion that they remain buoyant in the stomach, providing prolong release of the drug, enhancing gastric retention and improving bioavailability at the site of action. The mechanism involved in a floating tablet is based on two technologies: effervescent and non-effervescent system. Gas-generating substances like sodium carbonate, tartaric acid, and citric acid are used in the effervescent system to produce carbon dioxide, which decreases the system's density and makes it float.

Whereas, gel- forming agents or cellulose compounds that are extremely swellable are employed in non-effervescent system. **[3]** While developing floating tablet it's essential to understand factors that affects duration of gastric retention, important variables influencing oral dosage form's gastric retention include dosage form density, size, shape as well as aspects of food consumption such as its type, caloric value and frequency.**[4]** Moreover, the design of floating tablets can also be influenced by different polymers and excipients. Polymers of natural origin includes, alginates, xanthan gum, guar gum, pectin's, chitosan, etc. **[5]** Semi synthetic polymers like HPMC, Ethyl cellulose, NaCMC are commonly employed in the floating technology. Synthetic polymers include Polyethylene glycol (PEG), polyethylene oxide (PEO) and carbomers. Other excipient includes gas generating agents, diluent, flow promoters. These polymers and excipients in an optimized combination are necessary for the successful creation of floating tablet formulations. Following formulation development, the tablets are assessed according to pharmacopeial standards for several assessment metrics, such as total floating time (TFT), floating lag time (FLT), dissolution studies, hardness, friability and weight variation.**[6]** A floating medicine delivery device offers a number of advantages, such as increased bioavailability, suitability for medications like misoprostol that need local action, and decreased dose frequency, which eventually improves patient compliance. According to recent research, floating tablets have become a useful strategy for medications with a restricted window of absorption and pH-dependent solubility. This review comprehensively explores the mechanisms, formulation strategies, evaluations with recent advances in floating drug delivery system with focus on their application for drugs like misoprostol in treating NSAIDs- induced peptic ulcers. **[7]**

PATHOPHYSIOLOGY OF PEPTIC ULCER DISEASE:

A complex balance between aggressive (acid, pepsin, H. pylori, NSAIDs) and defensive (mucus barrier, bicarbonate secretion, prostaglandins, epithelium regeneration) forces stomach mucosa to be intact. Mucosal damage advances from superficial erosions to deep ulcers that penetrate mucosa muscularis, when this equilibrium is shifted towards aggressive forces.

The main causes of PUD include H. pylori infection as well as use of medications like NSAIDs. Since its discovery, H. pylori, a Gram-negative, spiral-shaped, microaerophilic bacterium, has become a major gastrointestinal tract pathogen. Inflammation is induced in gastric mucosa due to its capacity to colonize in it. The bacteria are able to thrive in GIT through production of ammonia, hence neutralizing gastric acid locally, this persistent infection leads to active gastritis. The bacterium has also ability to produce various enzymes as well as cytotoxic agents that directly injures epithelial cells.**[8]**
Whereas the main pathogenic mechanism involved in NSAIDs- induced peptic ulcers involves inhibition of enzymes like cyclooxygenases which are cox- 1 and cox - 2. This inhibition leads to reduced prostaglandin synthesis. Prostaglandins play role in preserving the integrity of the stomach mucosa through various mechanisms like mucus and bicarbonate production and circulation in the stomach mucosa. The inhibition leads to reduction in these, thus leading to gastric mucosal damage. In addition to this NSAIDs are also involved in direct mucosal injury mechanism, due to physicochemical

characteristics of NSAIDs they directly impair mucosal integrity. These medications cause cellular harm by disrupting mucus, phospholipids and cell membranes. Encounter to luminal aggressive elements, such as acid, pepsin, food particles, bile, and maybe H. pylori, accelerates this early impairment of mucosal defence. Thus, increasing need for mucosal protective agents.**[9]**

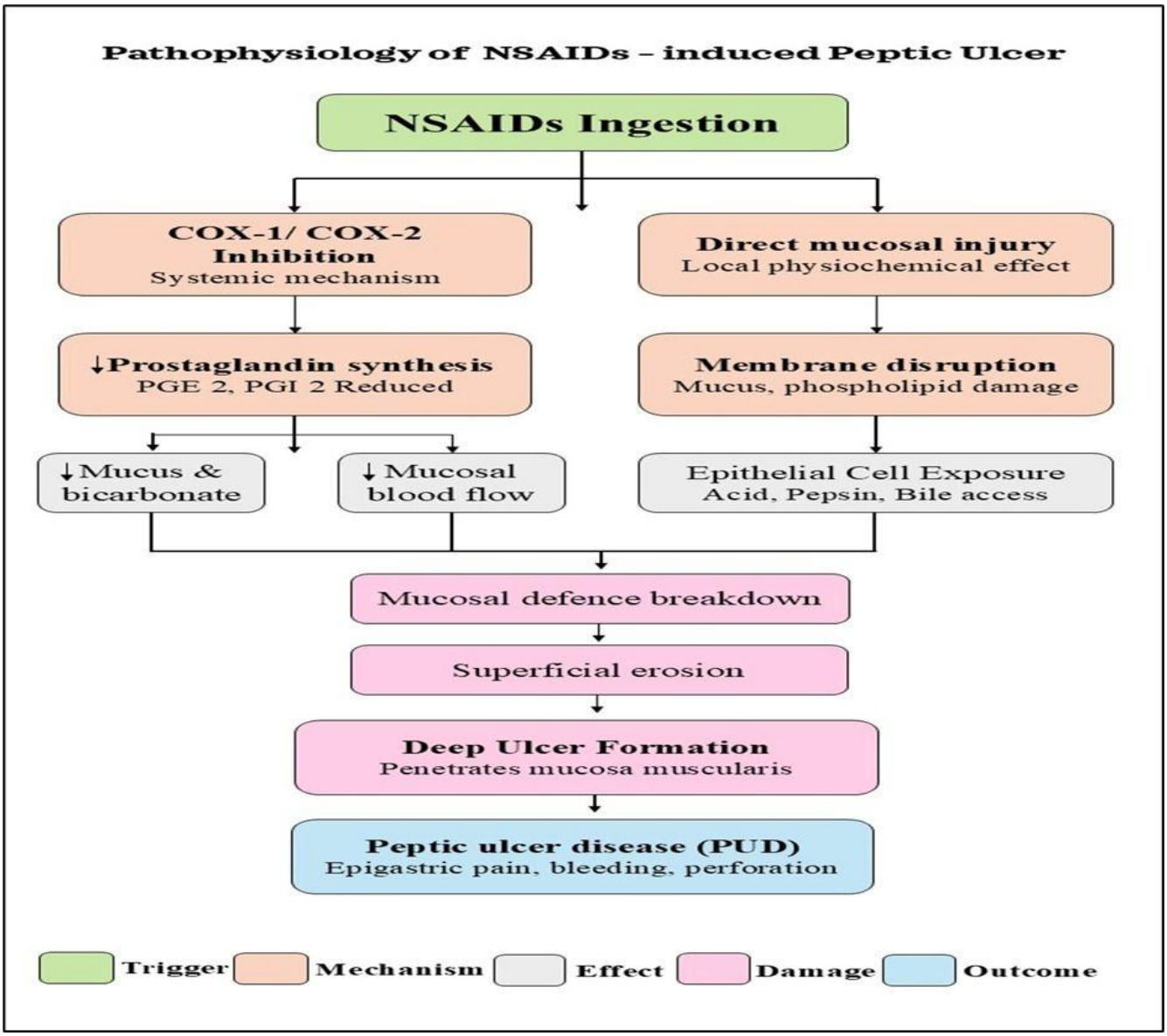

Figure 1: Pathophysiology of NSAIDs induced Peptic Ulcer

CONVENTIONAL TREATMENTS AND ITS LIMITATIONS:

The conventional peptic ulcer therapy targets either aggressive factors or defensive factors but commonly faces challenges with restoring NSAIDs- induced mucosal depletion, thus requiring an innovative drug delivery system.

The H. Pylori eradication includes triple therapy that commonly involves drugs such as PPIs, and two antibiotics for 7- 14 days. If the first therapy fails the second line is given that includes levofloxacin based triple therapy.

Class	Example	Mechanism	Limitation
PPIs	Omeprazole, Pantoprazole, rabeprazole	Irreversible inhibition of Hydrogen/ Potassium ATPase pump.	Adverse effects like Vitamin B12 deficiency, unable to prevent reoccurrence of NSAIDs induced ulcers.
H2 Antagonists	Cimetidine, famotidine, ranitidine	Blocks histamine receptors at parietal cells	Weaker acid suppression
Cytoprotective agents	Misoprostol (PGE1 analog)	Increase mucus and bicarbonate production	Short half-life, rapid gastric emptying
	Sucralfate	Physical Barrier	Poor compliance, no prostaglandin replacement.
	Bismuth	Cytoprotection and antibacterial	Less effective

Table 1: Treatments and Limitations

Whereas for NSAIDs induced ulcers, the therapy involves drugs like PPIs, H2 antagonists, gastroprotective or cytoprotective agents. Of these, PPIs are most often recommended medications and have various side effects too. Also, gastric acid inhibition by PPIs affects uptake of various vitamins and minerals. Misoprostol, as gastroprotective agent have side effects like diarrhea due to its rapid absorption also; shows less effect due to rapid gastric emptying. However, it can be used for restoring mucosal depletion caused due to NSAIDs. You can accomplish this by formulating it as a floating drug delivery system.**[8]**

INSIGHTS TO SYSTEM DESIGNED FOR GASTRIC RETENTION:

The purpose of a gastroretentive system for drug delivery is to extend the amount of time that drugs stay in the stomach. As drug retention time can significantly influence drug's absorption. There are several kinds of GRDDS, such as floating system, raft-forming systems, bio- adhesive systems, swelling / expandable systems, high density system, magnetic system. Each system works on different driving forces; floating system works on the ability of polymer to float and should have total density of system less then stomach content. Polymers make up the raft forming system that when comes in contact with stomach fluid forms viscous cohesive gel, as each liquid expands a raft is formed. Bio adhesive system works by adhering to bio adhesive substances, mucus or mucosal surfaces. These systems enable to

combine a particular medication method with bio-adhesive materials, this enables the device to abide by the walls and inhibit the emptying of the stomach. As the name suggests, an expandable system modifies its form and volume to achieve a longer stomach residency duration. The density of a high-density systems is roughly 3gm/ cm3 and are stored in the stomach's lining epithelium, where they can withstand peristaltic motions. When their density increases to between 2.4 and 2.8 g/cm3, it is possible to store these systems in the lower abdomen.**[10]**

The GRDDS helps to extend the duration of stomach occupancy for the medications with a limited window of absorption in the GIT, locally active drugs like misoprostol, unstable substances in colonic environment. Thus, such a kind of system provides site- specific delivery, better bioavailability along with reduced dosing in contrast to traditional dose formulations.**[11]**

MECHANISM GOVERNING FLOATATION AND DRUG RELEASE:

The floating medication delivery device stays buoyant in the stomach without altering the pace of gastric emptying because its bulk density is lower than that of gastric contents. Among GRDDS, floating systems are able to achieve buoyancy via two main approaches, effervescent and non-effervescent approach thus reducing density below gastric contents (1.004 g/cm3) for prolonged retention. Effervescent system contains volatile liquids and gas-producing substances as its main components. Hydrophilic polymers are mixed with sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid in the gas-generating floating system. When this system arrives into touch with the gastric fluid, the effervescent agent reacts with the gastric fluid, releasing CO2. Its hydrocolloid matrix, which gives the tablet buoyancy and affects the drug release characteristics, traps the released CO2 gas. Volatile liquids, such ether and cyclopentane, are added to an inflatable chamber in volatile liquid systems. These liquids volatilize at body temperature, enabling the stomach chamber to expand.**[12]**

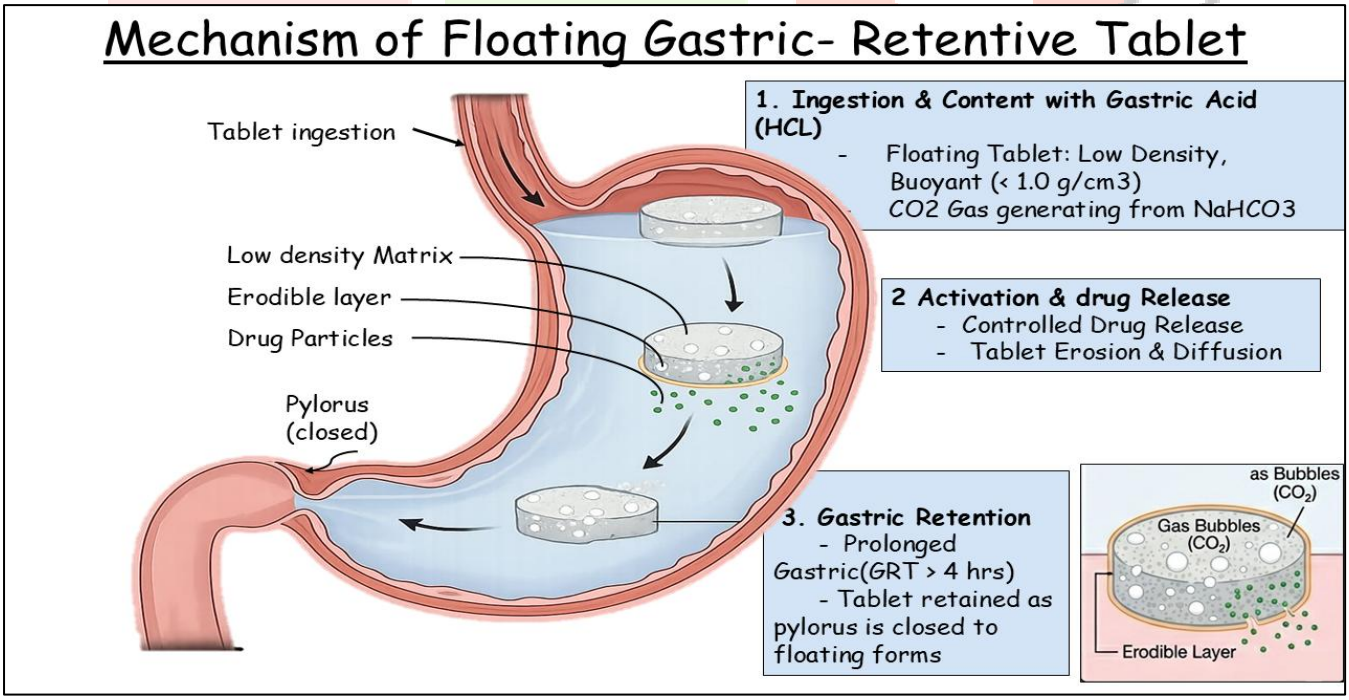

Figure 2: Mechanistic Insights of Floating

Non-effervescent systems use gel-forming polymers or derivatives of cellulose that are highly swellable. By mixing the drug with a gel-forming polymer, non-effervescent systems are created. Non-effervescent systems include single- and double-layer floating tablets, hydrodynamically balanced systems (HBS), and micro balloons/hollow microspheres. It is composed of one or more hydrophilic polymers that gel into a single unit dosage. HPMC, hydroxy propyl cellulose (HPC), hydroxyethyl cellulose, sodium carboxymethylcellulose, carrageenan, agar, and alginic acid are only a few of the polymers used in the

construction of the HBS system. Using this technique, a combination of the drug and polymer is put inside the gelatin capsule. The drug and gel-forming hydrophilic polymer that expands and hydrates upon contact with stomach fluid and keeps the tablet's bulk density at less than 1 g/cm3, can be uniformly mixed to create the floating tablet.**[13]** These mechanisms form the basic foundation for development of floating tablet by optimal combination of excipients and polymers for desired buoyancy and drug release.**[14]**

FORMULATION APPROACHES OF FLOATING TABLET:

Effective formulation strategies involve the integration of gel-forming polymers, gas-generating agents, and other excipients to achieve optimized buoyancy and drug release profiles.

- **Polymers-** Polymers has a substantial impact in the foundation of floating tablet by acting as matrix formers, providing buoyancy, controlling drug release, facilitating swelling and promoting gelation. Hydrophilic polymers come into contact with water; they can expand and create a gel layer thereby facilitating drug release and buoyancy. Carbopol 934P, HPMC K4M, HPMC K15M, and HPMC K100M are common examples. Other classifications based on origin include natural polymers, such as chitosan and sodium alginate, and semi-synthetic polymers, like cellulose derivatives like HPMC and HPC. The polymers are divided into three categories based on their place of origin: natural polymers such as sodium alginate and chitosan polymers that are semi-synthetic, such as EC and HPMC. Synthetic polymers such as derivatives of lactic acid and acrylic acid, among others.
- **Gas Generators:** Gas-generating agents are a crucial component of effervescent systems. Sodium bicarbonate, citric acid, and calcium salts are commonly employed in the floating system; they provide buoyancy by producing carbon dioxide when in contact with gastric acid. This gets incorporated in the polymer matrix thus, causing the dosage form to float and ensure regulated medication release over an extended time period. **[15]**

Other excipients in floating technology include binders like PVP K 30, starch that ensures tablet integrity, magnesium stearate, and talc act as lubricant that help during ejection. Diluents like microcrystalline cellulose and mannitol act as bulking agents.

Excipients	Role
Hydrophilic polymers (Matrix formers) Hypromellose (HPMC K100M, K15M)	Swelling and gel Formulation
Gas-generating agents (Sodium bicarbonate, Citric acid)	CO_2 generation
Fillers (Microcrystalline cellulose)	Bulking agent
Binder (PVPK30)	Enhances cohesion
Lubricants (Magnesium stearate)	Reduces friction during compression
Glidants (talc)	Improve flow properties

Table 2: Excipients with Roles

OPTIMIZATION IN FDDS:

In many fields of study, optimization techniques are used to find solutions that either maximize or minimize certain research characteristics, such as minimizing pricing in the manufacture of a good or service, maximizing profits, minimizing material in the advancement of a good, or maximizing production. The process of finding the best potential combinations is called optimization. It has a vital function in analyzing process in addition to formulation variables. Conventional optimization techniques, such the one-factor-at-a-time (OFAT) method, have limitations because they necessitate numerous experimental trials and do not assess the interaction effects between factors. Modern pharmaceutical research uses statistical optimization methods based on Design of Experiments (DoE) to get beyond these restrictions.**[16]**

DoE in FDDS:

DoE is a mathematical and statistical tool that helps in systematically designing as well as performing various sets of experiments. It helps to assess the consequence of multiple factors simultaneously and to ascertain the interaction between them. In FDDS, formulation is influenced by several independent variables like concentration of polymer, gas- generating agents, type of excipients, and various compression parameters. These variables directly impact responses like floating lag time (FLT), total floating time (TFT), drug release profile in addition to tablet integrity. Therefore, the DoE-based method provides a framework to analyse variables. FDDS formulation frequently uses a variety of experimental designs, including:

1. **Factorial Design:** A type of analysis methodology known as factorial design may allow for the examination of the most significant interaction effects between two or more independent variables and on one or more outcome variables.
2. **Central Composite Design:** An improved design for optimising formulations and constructing quadratic models.
3. **Box-Behnken design:** Response surface designs without embedded factorials or fractional factorials are known as Box-Behnken designs. Box-Behnken designs are typically less expensive to operate with the same number of factors since they have fewer design points than central composite designs. They can effectively estimate the first and second-order coefficients, but they are unable to incorporate runs from a factorial experiment. Unlike central composite designs, which may have up to five layers per factor, box-Behnken designs always have three.**[17]**

To ensure objective conclusions, the data should be assessed using statistical techniques after it has been gathered in accordance with the selected design.

Numerous software programs are available to aid, ranging from those that assist users in selecting a design to those that carry out statistical analysis, present findings, and create mathematical models. The ANOVA, a statistical technique according to the F test to assess the importance of model terms, is one such model.**[18]**

Independent Variables (Factors)	Polymer concentration (HPMC), Gas-generating agent ($NaHCO_3$), Binder concentration, Tablet hardness
Dependent Variables (Responses)	Floating lag time (FLT), Total floating time (TFT), Drug release (%), Swelling index
Experimental Design	Factorial Design, Central Composite Design (CCD), Box–Behnken Design (BBD)
Statistical Tools	ANOVA, Regression analysis, Response surface plots
Software Used	Design-Expert, Minitab.
Outcome	Optimized formulation with desired buoyancy and controlled drug release

Table 3: Generalized DoE model for FDDS

FLOATING TABLET IN VITRO EVALUATION:

Following the successful formulation of a floating tablet, a comprehensive evaluation is carried out. These parameters primarily involve physical characterization, buoyancy studies, in vitro drug release profiles.

Physical Evaluations:

1. Hardness: Hardness is a critical quality attribute of the tablet reflecting its mechanical strength. It ensures the tablet's resistance to mechanical shocks during the processing of the tablet. Tablet hardness is defined as the amount of force needed to shatter it. It is tested using the Monsanto or Pfizer hardness tester. It is expressed as 4-8 kg/cm2.
2. Friability: Friability assures resilience of the tablet to chipping or crumbling during handling and transport. Excessive friability leads to dose variability. Friability can be determined using the Roche Friablator. It should be under 1% limit.
3. Weight variation: Both coated and uncoated tablets can be tested using this method, which weighs 20 tablets individually and calculates the average mass. The standards for weight variation are met if the weight of no tablet's changes more than twice as much that percentage, and if the weight of no tablets deviates from the mean weight by a greater percentage than specified.**[19]**

Buoyancy Studies:

The success of a floating tablet relies on its ability to keep buoyant in the gastric environment for a sufficient time to ensure sustained release and prolonged absorption. This is assessed by the two key parameters, i.e., Floating lag time (FLT), Total floating time (TFT).

a) **Floating Lag Time (FLT):** The time required by tablets to move upward to the surface of dissolution media and initiate float. The tablets are placed in 0.1 N HCl in a 1000 mL beaker, and the time is recorded using a stopwatch.

b) **Total floating time (TFT):** The duration of tablets' continuous presence at the dissolving medium's surface is defined as total floating time. After the determination of FLT, TFT is measured in the same beaker for about 12 hours, during which tablet disintegrate or sank is determined in hours as TFT. A longer TFT ensures long-term, consistent release of the medication.

c) **In Vitro drug release studies:** To evaluate the medication's release pattern in a controlled and predictable way, in vitro drug release studies are carried out. These investigations are conducted at 37 °C ± 0.5 °C in a USP Type II dissolution apparatus with simulated gastric fluid conditions, i.e., 0.1 N HCl. The samples are periodically removed, and the concentration is calculated using UV spectrophotometry. **[20]**

THERAPEUTIC APPLICATIONS OF FLOATING SYSTEM:

Floating medication delivery method have gained importance due to their capacity to provide prolong gastric retention as well as site specific delivery. These systems have been applied in the following areas.

- Management of PUD and other Gastric disorders: Floating systems are widely used in treating disorders like gastritis, GERD, and peptic ulcer disease. They remain buoyant in the stomach, providing extended release of the medication and maintaining effective concentration, thus providing site-specific delivery. For example, a floating tablet of misoprostol, a drug known for its cytoprotective and mucosal-protective actions, is useful in preventing NSAIDs-induced peptic ulcers.
- Medications with a limited absorption window: Certain Medication is absorbed within the upper gastrointestinal tract; floating tablets remain intact for an extended length of time at this location, thus enhancing bioavailability. Example L-dopa, furosemide.
- Drugs unstable in acidic environment: Some drugs get degraded in the intestinal environment. A floating system allows them to remain in the acidic environment, thus providing stability.**[21]**

LATEST ADVANCEMENTS:

Floating Systems have shown significant advances over time, some of the important advances are:

Development of a 3D printing-based floating tablet: The technology helps to fabricate a floating system with precise control over geometry as well as dose. It also helps to fabricate customised delivery systems. Floating tablet of theophylline was successfully developed using a combination of Hot-Melt Extrusion (HME) and Fused Deposition Modeling (FDM) 3D printing. **[22]**

Formulation using sublimation technique: In a recent study, a floating tablet was formulated using the sublimation technique. Sublimation agents were combined with a gel-forming agent, as well as the active ingredient, anhydrous theophylline. The sublimation agents, such as ammonium chloride and menthol, had efficiency in forming a porous structure and lowering the density of tablets and causing flotation.**[23]**

Solid dispersion based floating tablet: The study involved the construction of a floating tablet of poorly soluble curcumin to overcome its poor solubility and bioavailability problem. Long-term stomach retention and controlled release were features of the tablets.**[24]**

Many studies also focused on utilizing combination GRDDS like mucoadhesive and floating tablet, use of gas-generating agents, some studies also utilized raft-forming system as well as bilayer floating tablet.

CURRENT CHALLENGES AND FUTURE DIRECTIONS:

Drug delivery methods that float have become popular as a promising approach to achieve gastric retention and prolonged release of the drug, which helps in enhancing the bioavailability of narrow absorption window drugs. Numerous studies have concluded use of polymers such as HPMC high

viscosity grades, gas-generating agents, and gelling agents significantly influenced buoyancy as well as drug release behavior of drugs. However, challenges like formulation variability, stability issues, and a lack of evaluation methods persist. These can be overcome by proper optimisation using software in addition to the development of robust methods. Future studies should focus on solving stability-related issues, performing in vivo evaluations, combination of technology along with AI in the creation of formulations of a floating tablet. Therefore, with appropriate optimization and design, a floating tablet offers valuable potential in improving therapeutic efficacy.

CONCLUSION:

Among gastrointestinal diseases, peptic ulcer disease is the most common. NSAIDs, being the most commonly prescribed medication, have emerged as one of the leading causes due to their mechanism of action; it leads to a deficiency of prostaglandin hormones that are essential for the protective action of the mucosa. The traditional drug delivery system lacks prolonged delivery; they show rapid transit from the stomach. For the sake of this, a gastroretentive drug delivery system would be one of the promising approaches. Of these systems, one promising one is floating tablets, which are formulated using various polymers and excipients like sodium bicarbonate (gas generating), HPMC (gel forming), the working principle behind them is that, on contact with simulated gastric fluid, the tablet starts floating and remains buoyant for a prolonged time, thus releasing the drug slowly. For successful development as well as economic development of such formulations, design expert software-based optimization would be ideal. By optimizing the formulations using various designs, an economical and robust process can be developed.

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