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Gastroretentive floating Bilayer Drug Delivery System-A Review

V. T. Iswariya[1], Haripriya Batchan[2] and T. Rama Rao[3]

[1-3]Department of Pharmaceutics, CMR College of Pharmacy, Medchal, Hyderabad - 501401 (India)
Corresponding Author V. T. Iswariya, E mail: iswariyapharma@gmail.com

Abstract

In order to effectively treat inflammatory bowel syndrome, the current effort focuses on developing a bilayer floating system and bilayer gastroretentive floating tablets that provide site-specific administration, controlled drug release, and prolonged stomach retention. By minimizing fluctuations in the drug's blood concentration, these drug delivery systems have been developed to mitigate the shortcomings of conventional drug administration techniques, including gastric retention, hence lowering undesirable toxicity and inefficiency. Gastroretentive drug delivery systems, which are mostly used to treat inflammatory bowel illnesses, extend the time that dose forms remain in the stomach or upper gastrointestinal tract in order to improve the bioavailability and therapeutic efficacy of drugs. Any drug's bioavailability following oral delivery is influenced by how long it stays in the stomach. Drugs having a limited absorption window, reduced stability at high alkaline pH, and improved solubility at low pH.

Key words : Bilayer, Inflammatory bowel syndrome (IBS), Bioavailability Therapeutic efficacy, Gastroretentive drug delivery systems (GRDDS).

The pursuit of innovative drug delivery systems has significantly advanced pharmaceutical sciences, aiming to enhance therapeutic efficacy, patient compliance, and targeted delivery[29].

Despite these advantages, oral drug delivery faces challenges such as variable gastrointestinal (GI) transit times, pH-dependent solubility, and first-pass metabolism, which can affect drug bioavailability and therapeutic outcomes. To address these issues, gastroretentive drug delivery systems (GRDDS) have been developed to prolong the residence of drugs in the stomach, enabling improved absorption and therapeutic efficacy[20]. Gastroretentive Drug Delivery Systems (GRDDS)[2,8,33] offering significant advantages for drugs with

[1]Assistant Professor, [3]Principal & Professor

site-specific action in the upper gastrointestinal (GI) tract, poor solubility at higher pH, or instability in the distal GI environment. They offer the benefit to sustain the drug release for longer therapeutic action and overcomes the drawback of fluctuated blood plasma levels seen in multiple dose regimen of single dose formulations.

The gastric retention is achieved through different designs such as floating systems, expandable systems, high-density systems, polymeric fibrous systems, ion exchange resin systems, magnetic systems, and mucoadhesive systems. Floating drug delivery systems (FDDS) stand out among gastroretentive designs due to their simplicity, efficiency, and adaptability. Unlike expandable systems, which rely on size enlargement to prevent gastric emptying, FDDS use buoyancy to maintain prolonged gastric residence without significantly altering the system's physical dimensions. High-density systems face challenges in formulation and commercial scalability, whereas FDDS can be tailored with minimal technical complexity. Polymeric fibrous and ion exchange resin systems often depend on complex interactions with gastric fluids, while FDDS provide consistent retention regardless of ionic strength. Similarly, magnetic systems require external equipment, compromising patient compliance, and mucoadhesive systems may fail under conditions of high gastric motility or hydration. FDDS overcome these limitations by maintaining their position in the stomach through buoyancy, ensuring a controlled and predictable drug release profile. These advantages make FDDS a versatile and patient-friendly choice for achieving sustained drug delivery and enhancing therapeutic efficacy.

Floating Drug Delivery systems (FDDS)[2,3,6,9,11,13,18,43]

FDDS represent an innovative approach to prolonging gastric retention and enhancing drug bioavailability, particularly for medications with a narrow absorption window in the stomach or upper small intestine. These systems are characterized by a bulk density lower than gastric fluid, enabling them to remain buoyant for extended periods without interfering with gastric motility, allowing controlled release of the drug. An essential factor for the effectiveness of FDDS is the generation of sufficient buoyant force to maintain their position at the gastric interface, even in the presence of gastric motility and varying fluid levels. This force ensures the floating system remains in the desired location for optimal drug release. Enhanced buoyancy directly correlates with a more stable and efficient gastric retention, thus optimizing the delivery and performance of the floating dosage form. FDDS leverage distinct mechanisms, including effervescent and non-effervescent approaches, to achieve buoyancy and extended gastric retention.

Non-Effervescent systems :

Non-effervescent systems utilize matrix-forming polymers combined with highly swellable hydrocolloids, such as polysaccharides or cellulosic compounds. Upon exposure to gastric fluid, these hydrocolloids hydrate and expand to form a gel-like, low-density network that traps air, enabling the system to remain afloat. Drug release from these systems is governed by their composition: hydrophilic drugs are predominantly released via diffusion through the hydrated gel, while hydrophobic

drugs are released through erosion of the gel matrix's outer surface.

Polypropylene Foam systems :

Floating systems utilizing polypropylene foam powder offer a unique approach for achieving low-density systems for prolonged gastric retention. These formulations leverage the inherent porosity and low density of foam powder, ensuring buoyancy for at least 8 hours. Dissolution profiles and buoyancy characteristics are influenced by the interaction of drug properties and the polymer-to-foam ratio.

Microballoons :

The process involves creating a hollow, porous structure by interfacial polymer deposition during solvent diffusion or evaporation, resulting in lightweight microspheres capable of floating on gastric fluids for extended periods. Achieving better drug entrapment efficiency for water-soluble drugs is often challenging in the design of microballoons. Hence, certain formulation strategies, such as modifying the solubility of drugs in the aqueous phase with additives like NaCl or altering the pH of the preparation medium with HCl, are adopted to enhance drug loading and encapsulation efficiency.

Alginate Beads :

Multiple-unit floating systems, such as alginate-based beads, are innovative gastroretentive drug delivery platforms that offer extended buoyancy and controlled drug release. These systems are typically prepared through ionotropic gelation, where sodium alginate is dropped into a calcium chloride solution, forming calcium alginate beads. Incorporating polymers like HPMC or chitosan.

Effervescent Floating systems :

Effervescent floating systems are designed to prolong gastric retention by generating gas within the dosage form, thereby decreasing its density and ensuring buoyancy in the stomach. These systems leverage the reaction between gastric fluids and gas-generating components to maintain extended floatation, allowing for sustained drug release in the upper gastrointestinal tract.[28,41]

Gas-Generating Systems :

Gas-generating systems incorporate compounds such as sodium bicarbonate, tartaric acid, or citric acid, which react upon exposure to gastric fluid, releasing carbon dioxide. The generated gas becomes entrapped within the polymeric matrix.[35] Hydrophilic polymers, including hydroxypropyl methylcellulose (HPMC), are frequently employed to control the rate of gas release and modulate drug dissolution kinetics.[6,10]

Volatile Liquid-Containing Systems :

Volatile liquid-based floating systems employ a drug reservoir encased in a microporous membrane that prevents direct interaction with gastric fluids while facilitating controlled drug diffusion. These systems often utilize volatile liquids, such as cyclopentane or ether derivatives, which vaporize at physiological temperatures, creating a gaseous core that maintains buoyancy[8]. As gastric fluids permeate the micropores, they dissolve the drug within the reservoir, ensuring gradual

release. [40]

Raft-Forming systems :

Raft-forming systems represent an advanced floating approach, particularly beneficial for treating gastroesophageal reflux disease (GERD) and peptic ulcers[31]. Effervescence-inducing agents, further enhance floatation by releasing carbon dioxide.[18,44]

Inflammatory bowel syndrome (IBS) :

Inflammatory Bowel Disease (IBD) is a chronic, relapsing condition characterized by inflammation of the gastrointestinal (GI) tract. Primarily encompassing two disorders: Crohn's disease and ulcerative colitis. These conditions are characterized by periods of active inflammation and remission, leading to symptoms such as abdominal pain, diarrhea, and weight loss. The etiology of IBD is multifactorial, involving genetic predisposition, environmental factors, and immune system dysregulation.[25]

Pathophysiology :

The pathogenesis of IBD involves a complex interplay between the innate and adaptive immune systems. The innate immune system acts as the first line of defense, recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs). Activation of these receptors leads to an inflammatory response aimed at eliminating pathogens and initiating tissue repair. In IBD, this response becomes dysregulated, resulting in chronic inflammation[37]. IBS is a chronic functional GI disorder characterized by abdominal pain, bloating, altered bowel habits, and intestinal discomfort. The exact etiology of IBS remains unclear, but it is believed to involve a combination of gut motility dysfunction, visceral hypersensitivity, altered gut microbiota, and psychosocial factors.

Genetic factors also play a significant role in IBD susceptibility. Variations in genes involved in immune regulation, such as NOD2 and IL23R, have been associated with an increased risk of developing IBD. These genetic predispositions, combined with environmental triggers, contribute to the aberrant immune responses observed in patients.[17]

Therapeutic approaches :

Management of IBD aims to induce and maintain remission, improve quality of life, and prevent complications. Therapeutic strategies are tailored to disease severity, location, and patient-specific factors.

Aminosalicylates: Agents such as mesalamine are commonly used in mild to moderate ulcerative colitis to reduce inflammation[26].

Corticosteroids: For moderate to severe disease flares, corticosteroids like prednisolone are effective in reducing inflammation. However, due to potential side effects, their use is generally limited to short-term induction therapy.[23]

Anti spasmodics: Mebeverine is a direct-acting antispasmodic drug widely used

in the treatment of IBS and other functional gastrointestinal disorders. It primarily acts by relaxing the smooth muscles in the gastrointestinal (GI) tract, thereby relieving symptoms associated with IBS, such as abdominal pain, cramping, bloating, and irregular bowel movements[12].

Immunomodulators: Agents such as azathioprine and methotrexate modulate the immune response and are used for maintenance therapy in patients who do not respond adequately to aminosalicylates or corticosteroids.[21]

Biologic Therapies: Targeted therapies, including tumor necrosis factor (TNF) inhibitors like infliximab, have revolutionized IBD treatment. These agents are effective in inducing and maintaining remission in moderate to severe cases.

Antibiotics: In certain situations, such as the treatment of pouchitis, antibiotics like ciprofloxacin or metronidazole are recommended.[13]

Emerging therapies and ongoing research continue to expand the treatment landscape for IBD, offering hope for more effective and personalized management strategies in the future.

Bilayer Tablet Technology :

Bilayer tablet technology provides an effective strategy for developing controlled drug release formulations by combining two distinct drug layers in a single dosage form. This approach is particularly beneficial for drugs requiring dual release profiles, such as an immediate-release (IR) layer for rapid onset of action and a sustained-release (SR) layer for prolonged therapeutic effect[1]. Bilayer tablets enhance patient compliance by reducing dosing frequency while optimizing drug release kinetics.

The formulation of bilayer tablets involves careful selection of excipients and polymer matrices to achieve desired release characteristics. Hydrophilic polymers are commonly used in SR layers, while super disintegrants such as croscarmellose sodium or sodium starch glycolate are incorporated into IR layers to promote rapid drug dissolution[27] The compression process plays a critical role in ensuring the integrity and stability of bilayer tablets, preventing layer separation and dose dumping.[15,22,30,36,39]

Bilayer manufacture challenges :

When the two tablet halves do not fully bind, the delamination tablet breaks apart. When crushed, the two granulations ought to stick together.

Cross-contamination :

Cross-contamination happens when the granulation of the first layer mixes with that of the second layer, or vice versa. It might defeat the bilayer tablet's primary function. Avoiding cross-contamination is greatly aided by effective dust collection.

Price:

For a number of reasons, bilayer tableting is more costly than single layer tableting. The tablet press is more expensive,

to start. Second, in bilayer mode, the press often operates more slowly. Third, it is imperative to develop two compatible formulations, which calls for more time to be spent on formulation creation, analysis, and validation.

These elements will affect the bilayer compression itself as well as the quality characteristics of the bilayer tablets (enough mechanical strength to preserve its integrity and individual layer weight management) if they are not properly managed or adjusted. Therefore, in order to build a resilient product and process, it is essential to gain insight into the underlying causes.

Yields :

Dust collection is necessary to avoid cross-contamination, which results in losses. As a result, yields from bilayer tablets are lower than those from single-layer tablets[43].

Bilayer tablet techniques :

Push-pull technology from OROS® This system is mostly composed of two or three layers, of which one or more are necessary for the medicine and the remaining layers are push layers. The primary components of the drug layer are the drug and two or more Push pulls from OROS® Technology.

This system is mostly composed of two or three layers, of which one or more are necessary for the medicine and the remaining layers are push layers. The primary components of the drug layer are the drug and two or more various agents. Therefore, the drug in this drug layer is in a weakly soluble form. Additionally, osmotic and suspending agents are added. The tablet core is surrounded by a semi-permeable membrane.

Technology of L-OROSTM This system addresses the problem of solubility. Alza created the L-OROS system, which involves first manufacturing a lipid soft gel product with a medicine dissolved in it, coating it with a barrier membrane, followed by an osmotic push layer, a semi-permeable membrane, and drilling an exit orifice.

Technology of EN SO TROL :

Shire Laboratory uses an integrated strategy to drug delivery that focuses on identifying and incorporating the identified enhancer into controlled release technologies in order to generate an optimum dosage form or to boost solubility by an order of magnitude.

DUREDASTM Technology :

The dual release medication delivery system from Elan medication Technologies is another name for this device. A bilayer tablet called DUREDASTM Technology can deliver two medications' instant or sustained release, or distinct release rates of the same medication in a single dose form. Two distinct layers within a single tablet can be produced by the tableting process: an instant release granulate and a modified release hydrophilic matrix complex. A mix of hydrophilic polymers gives the dosage form its modified-release characteristics.

DUROS Technology :

An exterior cylindrical reservoir made of titanium alloy makes up the system. This

reservoir shields the medication molecules from enzymes and has a high impact strength. The DUROS technology is a tiny medicine delivery device that functions similarly to a tiny needle that continuously and consistently releases minuscule amounts of concentrated form over the course of months or years[34].

GMP and Quality Guidelines :

In order to certify and GMP-produce a high-quality bi-layer tablet, the chosen press must be able to :

Preventing the two separate layers that make up the bi-layer tablet from capping and separating Ensuring adequate tablet hardness Preventing the two layers from being contaminated Creating a distinct visual division between the two layers.

High yield :

Accurate and precise control of the two layers' weight.

Despite their apparent nature, these standards are difficult to meet[7]

Table-1. Advancement in bilayer tablets

Drug	Form of dosage	Rationale	Ref. no
Trimetazidine HCl, clopidogrel bisulphate	Bilayer tablets	platelet inhibitor for acute coronary syndromes, anti-ischemic cytoprotective,	38
Amlodipine, Atenolol	Bilayer tablets	To increase the combination of medications' stability	4

Table-2. Gastroretentive technologies adopted by various pharmaceutical companies

Technology	Company	Product	API	Reference
Bioadhesive tablets	Lupin, india	Xifaxan	Rifaximin, ofloxacin	19
Effervescent floating system	Ranbaxy, India	Zanocin ODRiomet OD Cifran OD	Metformin HCL ciprofloxin	24
Colloidal gel forming floating systems	Ranbaxy, India	conviron	Ferrous sulphate	14

Table-3. Drug candidates for GRDDS.

Drug	Pharmacological and/or therapeutic classs	solubility	Stability in gastric and intestinal	Absorption and oral bioavailability	Half life	Refe-rence
itraco-nazole	Antibiotics	Low water solubility		70-80 percent absolute bioavailability	4	5
ranitidine	Histamine H_2-receptor antagonist	Low solubility at alkaline pH	Colonic metabolism	50 percent absolute bioavailability	2.5-3	42

Bilayer drug delivery improves the medication's ability to function in the gastrointestinal tract, curing conditions like IBS. It offers both immediate and sustained release action, and Raft-forming systems demonstrate advanced benefits in the treatment of gastroesophageal reflux disease (GERD). explains the necessity of gas generating systems, effervescent systems, microballoons, polypropylene foam systems, volatile liquid-based floating systems, and alginate beads. A straightforward and useful method for extending the dosage form's stomach residence period is the buoyant preparation principle. The primary need that must be considered while creating a floating drug delivery system is that the dosage form's density be lower than that of stomach fluid. Therefore, it can be said that these dose forms are the most effective for treating GIT-related conditions and obtaining a sustained effect from a medication with a short half-life.

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