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Recent Innovations in Floating Bilayer Tablet Technology: Formulation Strategies, Release Modulation, and Clinical Relevance

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Abstract

Floating bilayer tablets (FBT's) comprise a complex gastroretentive drug delivery system, which counteracts the several shortcomings associated with conventional oral dosage forms. These deficiencies include gastric transit time variability, absorptive window constraint and pH dependence of solubility. By making use of the gastric retention capability of buoyancy in combination with the architecture of a two layer system, FBTs enable the biphasic release of drugs, an immediate release system for therapeutic onset followed by a floating paradigm designed for a prolonged drug release in the proximal gastrointestinal tract. This manuscript provides a comprehensive and analytical presentation of the FBT technology, including the basic principles underlying the use of gastroretention and the underlying mechanism details for buoyancy, relevant material science issues, and modern manufacturing techniques. Recent technological breakthroughs such as nanostructured bilayer systems, stimuli responsive polymers, ultra low density matrices, 3D printing and supported formulation modelling are critically reviewed in terms of their contribution to formulation robustness, predictability of release of clinical efficacy. The preclinical and clinical relevance as well as safety, stability, regulatory issues and future research initiatives are also discussed. Overall, floating bilayer tablets show great promise as a patient centric, next generation oral delivery system, which shows great potential for personalized and controlled drug release.

Keywords: Floating Bilayer Tablet; Gastro retentive delivery; Biphasic Tablet; New formulation technology

Introduction

Oral drug administration is the most commonly used and convenient method of administration of systemic drug delivery, however, it is not without significant problems with consistent therapeutic delivery of drugs with narrow absorption windows, pH dependent solubility, rapid intestinal transit, or limited intestinal permeability. Conventional oral dosage forms frequently cannot achieve predictable bioavailability because they are subject to a significant amount of intraday control from gastric emptying kinetics and intersubject physiological variability. To overcome these limitations, gastroretentive drug delivery systems (GRDDS) were developed to increase gastric residence time and controlled release to increase drug absorption. Among the different modalities of GRDDS such as swelling matrices, mucoadhesive devices, high density formulations, and raft forming systems, floating bilayer tablets (FBTs) have become an advanced and highly versatile modality which can deliver both immediate and sustained therapeutic effects in one dosage form [1].

FBTs combine the buoyancy properties with bilayer technology in order to ensure retention in the upper GI tract combined with independent bilayer, that controlling the release kinetics. Historically, the idea behind using monolayer tablets was for compatibility with incompatible active pharmaceutical ingredients (APIs), sequential release or to create fixed dose combinations. The addition of floating mechanisms to bilayer constructs led to a new paradigm, biphasic release with gastric retention [2]. Typically, immediate release (IR) layers are designed to have rapid onset of therapeutic effect, meanwhile sustained release (SR) floating layers are designed to control release by the gel formation mechanism, matrix erosion mechanism or diffusion mechanism. Floating is possible through effervescent agents, such as sodium bicarbonate and citric acid, or non effervescent hydrophilic polymers, such as hydroxypropyl methylcellulose (HPMC), carbomers and alginates, which swell when mixed with water to decrease the density of the tablet [3].

Over the past decade, the development of materials science and pharmaceutical engineering has significantly improved the range of designs of FBTs. Modern formulations take advantage of the use of multifunctional excipients, high viscosity hydrogels, gas entrapping polymers, and novel low density carriers such as aerogels and hollow microspheres. The arrival of new technologies hot melt extrusion, twin screw processing and additive manufacturing (3D printing) have enabled even more precision tailoring of tablet shape, tablet porosity and tablet release behaviour. These innovations are accompanied by computational modelling approaches and Quality by Design (QbD) methodologies, and predictive algorithms of artificial intelligence (AI) that can optimize the formulation parameters whilst enhancing the adhesion between the layers and the mechanical strength. Clinically, the importance of FBTs has grown considerably. Drugs used in the treatment of diabetes (such as metformin), bacterial infections (such as ciprofloxacin, clarithromycin), hypertension (such as propranolol) and gastric disorders (such as ranitidine, famotidine) have shown an increase in bioavailability and dosage reduction when prepared by floating bilayer platforms [4]. That FBTs are able to maintain steady levels of plasma concentration reduces peak to trough variability, which reduces adverse effects, and improves patient adherence especially in chronic therapeutic regimens.

Despite these advances, these hurdles remain, including separation between layers, complexity of manufacturing, polymer incompatibility, sensitivity to moisture and gastric physiological variation [5, 6]. Nonetheless, the development of next generation of technology (nano enabled bilayer systems, smart responsive polymers, ultra low density matrices and patient specific floating tablets) represents a transformative shift to more robust, predictable and personalized gastroretentive solutions. The present manuscript provides a global perspective of the conventional and modern formulation approaches as well as mechanistic understanding, industrial challenges, regulatory concerns and future innovations that contribute to the direction of floating bilayer tablet technology development.

Floating Bilayer Tablets

Floating bilayer tablet technology incorporates the concept of gastroretentive design linked with dual layer release modulation and therefore addresses the limitations of conventional oral delivery. By the combination of buoyancy driven retention with biphasic drug release, these systems can increase absorption, control the therapy and increase clinical effectiveness [7]. This section describes the

basic principles that have governed the structure and function of the gas retention, bilayer structure, and buoyancy mechanisms that allow the use of floating bilayer platforms.

Principles of Gastroretention

Floating bilayer tablet technology is based on some of the core principles of gastroretention technology, where a dosage form is designed to remain in the stomach area for extended periods of time through different routes of manipulating its density and swelling qualities and structural strength [8, 9]. By having a density below the gastric fluids or forcefully increasing their volume through hydration induced polymer swelling, these systems are endurance to gastric emptying and are likely to stay buoyant even under dynamic motility. This extended gastric time in transit provides for improved therapeutic efficacy of drugs that have narrow absorption presuppositions, a local gastric effect or a pH dependent solubility. Advanced hydrogels, mucoadhesive polymers and aerogel based constructs further provide retention reinforcement by providing mechanical stability to the matrix that can resist peristaltic forces and ensure controlled hydration and radial expansion [10].

Justification for Bilayer Configuration

The introduction of the bilayer configuration is a sophisticated advancement of the oral dosage design and allows the precise modulation of the release of the drug through spatial separation of the functional layers. Typically, the immediate release (IR) layer provides a fast onset of action whereas the sustained release (SR) floating layer delivers a prolonged course of action which would give a biphasic therapeutic profile that may mimic physiological rhythms or treatment needs [11, 12]. This architecture also enables incompatible APIs or excipients to be added in different layers, allows better formulation flexibility and results in better mechanical stability by independent optimization of compressional forces [13]. The use of a dual layer platform not only supports the pharmacokinetic optimization but also the formulation design space for fixed dose combinations, chronotherapeutic regimens or patient centric delivery.

Mechanisms of Buoyancy

The floating bilayer tablets, the hallmark of the product's floating characteristic, is achieved by effervescent and non-effervescent means, which reduces the density of the tablets when compared to the density of gastric fluids. Effervescent systems make use of gas generation agents such as sodium bicarbonate that interact with gastric acid to liberate CO2 that becomes trapped in a fast forming gel matrix [14, 15]. Non effervescent systems are based on the use of highly swelling polymers (such as HPMC, carbomers and alginates) which give rise to a cohesive hydrogel of low density able to keep floatation during extended periods of time. Emerging innovations integrate these mechanisms with porous scaffolds, aerogels or 3D printed hollow cavities that provide for fast buoyancy, greater stability and long floating time that are essential for good gastroretentive performance.

Material Science & Excipients in FBTs

Material science plays a pivotal role to define structural integrity, release behaviour and buoyancy performance of floating bilayer tablets [16, 17]. The strategic choice and engineering of polymers, fillers and functional excipients options allows for the precise modulation swelling, gel strength and dissolution kinetics. This section provides the key categories of materials in which FBT formulations are based collectively determining the efficiency, stability, and clinical reliability of FBT formulations.

Polymer for Sustained Release

Polymers used for the sustained releasing (SR) layer control the diffusion of drugs, their swelling behaviour and the integrity of the matrix, which leads to lasting therapeutic release. Hydrophilic polymers like HPMC, carbomers and xanthan gum create strong gel layers which govern the release through hydration gelation. Their viscosity grades allow for fine tuning of erosion, diffusional paths and gastric shear forces mechanical stability. Hydrophobic polymers such as ethyl cellulose complement hydrophilic matrices by designing semi consistently impermeable obstacles that further increase the release time. Polymer blends are being used increasingly to obtain the hybrid release mechanism by combining diffusion and erosion with osmotic modulation. Together, those polymers determine the precision of the pharmacokinetic and structural endurance of the floating sustained release layer [18].

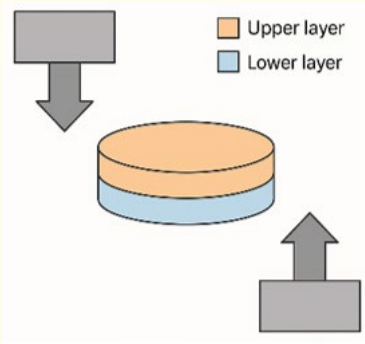

Figure 1: Floating Bilayer Tablet.

Floating Layer Excipients

Floating layer excipients decrease density of the tablet and create buoyancy necessary for the gastroretention. Effervescent agents such as sodium bicarbonate and citric acid liberate carbon dioxide (CO2) which becomes entrapped in a gel swollen matrix to preserve floatation. Non effervescent excipients, which include HPMC, alginate, and chitosan, expand by hydration to form low density, cohesive hydrogels. Low density fillers, aerogels, and porous microcarriers help to increase buoyancy but with improved matrix stability [19]. The floating agent and ratio determine floating lag time and the total floating duration and resistance to gastric motility. Together, these excipients are responsible to ensure reliable and sustained floatation to be critical for prolonged gastric residence.

Components of Immediate Release Layer

Immediate release (IR) layer excipients provide rapid disintegration of tablets and dissolve rapidly with a drug to achieve a fast onset of action. Super disintegrants like crospovidone and croscarmellose sodium are responsible for breaking the matrix instantaneously by wicking, and swelling mechanism. Solubilizers such as PVP and PEG increase drug wettability and dissolution rate especially in the case of poorly soluble drugs [20]. Wetting agents also help to further accelerate the drug release by decreasing interfacial tension in the gastric fluids. The functional design of the IR layer ensures immediate absorption with the preparation of the patient for the sustained release phase. This is a fine tuned interplay leading to functionality in biphasic drug delivery in the same dosage form.

Novel Excipients

Novel excipients give an advanced functionality, exceeding the scope of normal release control and buoyancy. Smart polymers have pH, enzyme, or temperature responsive behaviour, which allows for the release of the drug triggered by the environment. Nanofillers like silica nanoparticles or graphene derivatives have the ability to improve the strength of matrix mechanics and increase the barrier properties [21, 22]. Ultra-light materials such as aerogels and 3D printed porous scaffolds that can drastically decrease the tablet density and raise floatation stability. Mucoadhesive polymers help to contribute another attachment mechanism to increase the time of gastric retention under a changing physiological environment. These innovative materials are changing the design of FBT as they allow highly adaptive, intelligent and personalized drug delivery systems.

Manufacturing Approaches

Manufacturing floating bilayer tablets involves engineering factors to develop strong adherence between layers, density modulation and the reproducible biphasic release of the drug. The combination of more traditional compression technologies with modern thermal processing, continuous manufacturing, and additive fabrication has increased design capability immensely. Each manufacturing pathway affects the powder flow, interlayer strength, polymer hydration behaviour and floating efficiency [23]. Modern pharmaceuti-

cal engineering also includes the use of real time monitoring tools, which allows better controlling of the process and makes the batch more predictable. This section presents important manufacturing strategies and new technologies that are driving the development of advanced floating bilayer formulations.

Conventional Bilayer Compression

Conventional bilayer compression is still the most widely used because of its simplicity, scalability and compatibility with existing tablet presses. The process consists of successive compaction of two layers of powder under controlled forces of compression so that the powder is distributed uniformly and the integrity of each layer is reliable [24]. However, mechanical problems such as interlayer separation, inadequate adhesion and stress concentration in the interface are common problems that may complicate the production process. Powder and the flow consistencies and the compressibility of IR and SR layers further affect the robustness of tablets. Optimizing dwell time, pre compression parameters and tooling design is key to developing the same consistency in the bilayer performance. In spite of drawbacks there have been continuous improvements in the reliability of this method due to the advancements in press technology and die engineering.

Hot melt Granulation & Melt Extrusion

Hot melt granulation and melt extrusion offer the advantages of solvent free processing coupled with improved polymer dispersion, matrix strength and floating layer uniformity. These thermal techniques increase solubility of drugs, especially for Class BCS 2 drug molecules, by forming amorphous solid dispersions. Melt processing helps increase cohesion in the floating layer and minimize the friction as the product is less prone to friability and is also more stable in buoyancy under gastric condition. Figure.2 shows the Hot melt extrusion process. The ability to customize the polymer viscosity and melt rheology allows the control of the release kinetics as well as the density of the matrix. Hot melt methods also lend themselves to continuous manufacturing, which means that there is improved uniformity in the batch and less variability in the processing. With the increasing knowledge of polymer sciences taken together, melt extrusion has become a pathway of choice for high performing floating bilayer systems [25].

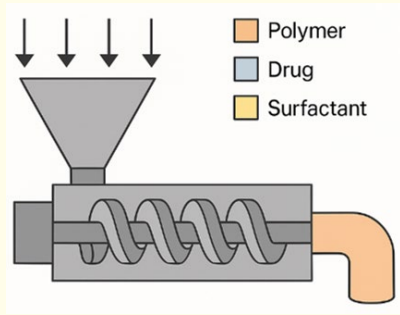

Figure 2: Hot Melt Extrusion.

3D Printing (Fused Deposition Modelling, Binder Jetting)

3D printing brings in geometrical freedom that hasn't occurred before, thus allowing them to create personalized bilayer architectures with tunable densities and release characteristics. Fused deposition modelling (FDM) enables polymeric filaments to be deposited to form hollow, porous or compartmentalised geometries, which will increase buoyancy. Binder jetting provides low on the density powder based matrices that can additionally consist of complex release channels and internal floatation chambers. These additive methods allow for on demand customization of patient specific dose and release profiles and anatomical aspects. Multi material printing also allows exact partitioning of the IR and SR functionality in one structure. As regulatory processes for printed pharmaceuticals

develop, 3D printed floating bilayer tablets are becoming a game changing manufacturing process [26, 27].

Quality Control & PAT

Quality control (QC) and process analytical technology (PAT) are used to ensure consistency, safety and performance of floating bilayer tablets from one batch of manufacture to another. Real time solutions like the near infrared (NIR) spectroscopy, Raman mapping, and laser induced breakdown spectroscopy allow for non destructively assessment layer uniformity and API distribution. PAT systems are used to monitor important process parameters like compression force, powder flow, moisture levels and to minimise the variability in the production process. Mechanical tests are used to determine hardness, friability, interlayer adhesion and functional tests to give information on floating lag time, total floating duration, and biphasic release profiles. Advanced modelling and use of digital twins for predictive quality assurance to reduce development cycles. Together, QC and PAT provide a platform of data driven FBT manufacturing that results in reliable and high quality production [28].

Mechanisms of Modulation of Drug Release

The drug release modulation of floating bilayer tablets (FBTs) is controlled by a confluence of physicochemical, polymeric and hydrodynamic determinants that equally control the active moiety's dissolution kinetics. A thorough insight into these mechanisms is invaluable to the rational design of matrices which will have an immediate onset of action whilst simultaneously ensuring an extended release over a more prolonged gastric stay. Release dynamics are dependent on polymer hydration, gel formation, erosion and the diffusion gradients that are established throughout the swollen matrix [29]. The engineers can appropriately design the absorption properties by carefully formulating these mechanisms to meet specific therapeutic goals. The major release pathways are subsequently described, and the synergy between them in the controlled delivery of drugs in FBT systems is explained below.

Diffusion Controlled release

Diffusion controlled release occurs when diffusion of the drug takes place due to concentration gradients within a hydrated polymeric network. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) swell on hydration and thereby set up gel layers that control the path length as well as the tortuosity [30]. This rate of release is modulated by polymer viscosity, molecular weight, gel strength and hydration kinetics. Poorly soluble drugs may have a non-linear diffusion because of localized dissolution in the gel matrix. By an optimal choice of polymer composition, the transition between Fickian, anomalous and non-Fickian diffusion behavior can be attained.

Erosion Controlled Release

Erosion controlled releasing is controlled by the progressive dissolution or mechanical breakdown of the polymer matrix. Some of the polymers like carbomers, polyethylene oxide and hydrophobic matrices degrade at a rates affected by gastric fluid and polymer solubility [31]. Erosion becomes strong when the polymer does not maintain the integrity of the gels in the presence of hydrodynamic stress. This mechanism is suitable for drugs that require zero order release profiles since controlled polymer degradation releases the agent at a steady rate. Both erosion and swelling index allows the fine tuning of release kinetics. Tablet shape, polymer cross linking and environmental pH further modulate the erosion behavior.

Swelling Controlled Release

It is based on hydration of swelling of polymers that leads to an increase in volume of the matrix and the formation of a gel. Hydrophilic excipients such as HPMC, xanthan gum and sodium alginate, take up gastric fluids, changing from the moisture state to the rubbery state. The conjunctional swollen gel controls the mobility of the drug and controls the drug interaction with gastric fluid [32]. The swelling capacity affects the floating of the tablet due to its density and buoyancy. A good balance between the amount of swelling and erosion is critical to preserving matrix integrity during a long gastric residence time. This mechanism is for the long term release functionality of floating layer sustained release.

Biphasic Release Engineering

Biphasic release engineering combines high rate drug delivery and long term maintenance of drug therapy through a dual layer architecture. The immediate release layer provides rapid absorption and onset of action that is ideal for drugs that require rapid plasma concentrations. Simultaneously the floating sustained release layer guarantees prolonged drug availability (by diffusion, swelling or erosion pathways). This combination minimizes the number of doses and peak and trough fluctuations in plasma levels [33]. Biphasic design can be adjusted for chronotherapeutic purposes, being combined with the circadian rhythms. Advanced polymers and computational modeling learn more about biphasic profiles for precision therapy.

Multi Mechanistic Release Models

Multi mechanistic, the complexity of diffusion, swelling, erosion and polymer relaxation processes in FBT matrices is captured by this type of release model. Mathematical frameworks such as Higuchi, Korsmeyer-peppas and zero order kinetics helps in characterizing the combination of these mechanisms [34]. Formulations may be changing between mechanisms depending on hydration, polymer interactions and solubility of the drug during a period of time. Hybrid matrices that are designed using polymer blends can be designed to intentionally utilize multiple mechanisms to achieve better control. Multi mechanistic approaches give improved robustness because of variability of gastric conditions and where consistent release is to take place. These models are necessary to predict *in vivo* performance and create an *in vitro* and *in vivo* correlation (IVIVC) [35].

Recent Innovations and Technological Advancements

Recent advances in FBT technology are the result of the fusion of material science, computational design and nanotechnology and are bringing down long existing limitations of conventional systems. Modern strategies are aimed at better buoyancy long term, precision release capabilities and personalization, as well as manufacturing [36]. These innovations allow for an expansion of the applicability of FBTs to a greater range of drugs, especially those with poor solubility, narrow windows of absorption, or chronotherapeutic needs. The combination of smart polymers, nano enhanced matrices, ultra light weight structural elements and digital formulation tools are redefining the next generation of this platform. This section offers an overview of the transformative innovations changing the way FBT is conducted in terms of performance, reliability and clinical relevance.

Nano Enabled Bilayer Systems

Nano enabled bilayer systems contain nanosuspensions, nanocrystals, or polymeric nanoparticles either in the immediate release or sustained release layer in order to impart solubility and bioavailability [37]. These nanocarriers enhance wettability, raise surface area and allow faster dissolution of poorly soluble drugs. In case of the sustained release, nanoparticles can be encapsulated in polymer layers to obtain more predictable diffusion release kinetics. Nano-encapsulation on the floating layer for further reinforcement of the mechanical integrity and for mucoadhesive properties of prolonged retention. Hybrid bilayer structures that combine nanotechnology with classical hydrogel structure allow us to have better control over the interlayer interactions. Overall, nano enabled FBTs significantly improve the efficiency of therapeutic and pharmacokinetic consistency [37].

Smart Floating Bilayer Platforms

Smart FBTs use stimuli responsive polymers which change properties in response to pH, temperature, enzymes or gastric motility. These platforms allow on demand environment triggered *in vivo* drug release that coincides with physiology. pH responsive polymers can expand or contract, or alter permeability in response to gastric acidity. Enzyme sensitive matrices remove selectively in diseases associated with gastric environments resulting in better targeting and improved therapeutic accuracy. Such systems guarantee increased adaptability and robustness of function to changing gastric physiology. Smart platforms can be seen as a paradigm shift towards an autonomous drug delivery system with greater and more precise and patient responsiveness.

Ultra Low Density Systems

Ultra Low Density floating composite - Ultra low density FBTs use aerogels, hollow microspheres, foam granules and porous polymer scaffolds to deliver extremely low bulk density for superior floatation. These structures preserve buoyancy even with intense gastric agitation, lag time of floating is greatly decreased. The high porosity of such excipients makes it possible to ensure fast hydration and stable gel formation in the floating layer. Ultra light carriers allow the use of higher drug loads without the accompanying decrease in density and structural integrity. They increase mechanical resistance to compression and resistance to delamination of the layers. These systems represent a breakthrough in accomplishing a long duration gastric retention with minimal failure of buoyancy.

3D Printed Intelligent FBTs

3D printing provides superior level of control of the spatial design, porosity, and layer geometry of floating bilayer tablet. Techniques such as Fused Deposition Modeling (FDM) and Binder Jetting, allow to build hollow structures or structures with multiple compartments or gradients integrated into the density, which would improve the buoyancy and allow tuning the release. Complex internal channels can be designed, which can generate programmable diffusion channels. Multimaterial printing can achieve an exact separation and customization to immediate release and sustained release layers into the same architecture. Personalized dosing, patient specific tablet geometry and on demand manufacturing is made possible with digital fabrication. These 3D printed intelligent FBTs are the future of precision gastroretentive delivery.

AI Assisted Formulation Modeling

AI assisted formulation modeling involves the use of machine learning and predictive algorithms on some aspects like optimizing the ratio of polymers, floating agents, and release kinematics. These are models used to analyze the complex formulation-performance relationships which are difficult to represent using conventional statistical approaches. The neural networks are capable of simulating the release of drugs under different physiological conditions and for the optimal design parameters with minimal experimental effort. Digital twins of the gastrointestinal tract enable the prediction of the floating behavior, the swelling dynamics as well as the *in vivo* release. AI tools are also an indicator of Quality by Design (QbD) approaches, increasing the robustness of a process and saving on development time [38].

Innovation Category	***Key Features***	***Advantages***	***Application/Impact***
Nano Enabled Bilayer Systems	Introduction of nanoparticles, nanocrystals and nanosuspensions in the IR/SR layers	Improves solubility, manages the diffusion process and strengthens the overall matrix	Improved bioavailability and produces more consistent pharmacokinetic profiles for poorly soluble drugs.
Smart Floating Bilayer Platforms	Stimuli responsive polymers, polymers sensitive to pH, enzymes, or temperatures, in adaptive matrices	On demand drug finer precision and gastrointestinal adaptability.	An intelligent system of delivery suited to deal in the gastric environment.
Ultra Low Density Systems	aerogels, hollow microspheres, foam granules and porous polymers	excellent buoyancy and rapid floatation and gastric retention	Suitable for high dose and long retention formulations
3D Printed Intelligent FBTs	Utilizing FDM, binder jetting, multi-material printing, and programmable porosity	personalized geometry with a tunable release profile and complicated internal channels to print personalized devices	precision medicine and patient specific therapy.
AI Assisted Formulation Modeling	Machine learning, digital twins, predictive algorithms	minimize the number of necessary and increase its robustness	Development process becomes more efficient, predictability of *in vitro in vivo* correlation

Table 1: Recent Innovations in Floating Bilayer Tablet Technology.

Preclinical and Clinical Relevance

Floating bilayer tablets show great translational relevance with enhanced drug absorption, bioavailability and therapeutic consistency by prolonged gastric retention and biphasic release profiles. Preclinical studies show predictable release kinetics, increased mucosal interaction and less variability in the absorption of the drug, which is dependent on gastric emptying. Clinically, FBTs are useful for drugs with narrow windows of absorption, short half life or pH dependent solubility as they ensure that the drug maintains dose availability at the optimal absorption site. Their Dual layer architecture provides rapid onset followed by sustained maintenance thus giving smoother pharmacokinetic profiles. Collectively, these benefits help highlight the increasing use of FBTs in the clinic for therapeutics that need to be exposed to drugs in a controlled fashion for extended periods of time [39].

Safety, Stability and Regulatory Considerations

Safety, stability and regulatory compliance are the top deciding factors in the successful development and commercialization of floating bilayer tablets. The complex design (buoyancy mechanisms coupled with dual layer release controlling) requires careful consideration of material compatibility, robustness of manufacturing, as well as long term performance. Stability issues such as moisture sensitivity, polymer degradation and gas generating components need to be addressed in an effort to maintain the reliability of treatment. Regulatory frameworks now focus more and more on patient safety, Quality by Design (QbD) principles and good *in vitro-in vivo* correlations (IVIVC). This section takes stock of such important considerations to ensure that FBTs comply with high global pharmaceutical standards.

Stability Concerns

Stability issues with FBTs are mostly caused due to moisture sensitivity for effervescent materials and polymers, depending on hydration, which will affect floating behavior and release kinetics. Sodium bicarbonate and citric acid might prematurely react under humid conditions and affect the buoyancy efficiency. Hydrophilic polymers like HPMC may occur in viscosity shift influencing gel strength and sustained release functioning. Temperature changes might give rise to recrystallization of amorphous drugs or to change polymer relaxation profiles [40]. Packaging strategies, such as aluminum-aluminum (blisters), desiccant containing containers, etc., are necessary to allow integrity of matrix. Stability studies need to be done to evaluate floating lag time, total floating time, and release profiles under storage conditions.

Challenges and Limitations

Floating bilayer tablets face challenges to develop high interlayer adhesion because of the differences in compressibility between the immediate release and sustained release layers. Physiological variability e.g. gastric motility, pH and fed fasted conditions are affecting buoyancy and release consistency. High dose drugs lead to higher matrix density, which makes it hard to maintain floatation and matrix structure. Moisture sensitivity of effervescent agents and hydrophilic polymers leads to compromising the stability and requires protective packaging. Manufacturing scale up is a complicated process with challenges regarding powder flow, die fill and compression uniformity. Advanced materials consisting of nanoparticles or smart polymers have led to additional aspects in terms of regulations and toxicity. Achieving strong correlation of *in vitro* support to *in vivo* remains quite challenging for gastroretentive systems. Mechanical stress along the ways of gastric transit may induce inconsistency of layer separation or erosions. Long gastric retention may not be appropriate for patients with motility disorders and anomalies. Collectively, such challenges identify the need for novel materials and design tools and optimization of manufacturing approaches.

Future Perspectives

Floating bilayer tablets will be developed based on smart and stimuli responsive polymers which allow adaptive release under different gastric conditions. 3D printing will allow creating personalized and programmable bilayer architectures with well defined control of density and release kinetics. Nanotechnology will increase solubility, absorption and drug retention of poorly soluble or complexed drugs. AI based formulation modeling will speed up the optimization process and minimize trial error experimentation.

Ultra low density materials such as aerogels will increase buoyancy efficiency and increase gastric retention. Hybrid systems with combination of floatation, mucoadhesion, and trigger release will lead to increased precision of therapy. Continuous and solvent free manufacturing technologies will increase scalability and sustainability. Advanced biorelevant dissolution models will be used to enhance IVIVC and regulatory acceptability. Collectively these innovations make FBTs next generation, high performing, gastroretentive platforms.

Conclusion

Floating bilayer tablet technology represents a major breakthrough in gastroretentive oral drug delivery and represents a sophisticated delivery system where the buoyancy and the biphasic control of the release are combined. The combination of immediate therapeutic action and maintenance of plasma levels overcomes the disadvantages of conventional dosage forms, especially for drugs having a narrow absorption window, for drugs with pH dependent solubility, or for drugs with a short half life. Recent innovations such as those that use nano enabled matrices, smart polymers, ultra low density scaffold, 3D printed architecture and AI assisted formulation modeling have given FBTs greater design capabilities and clinical relevancy. Despite challenges such as stability issues, interlayer adhesion, physiological variations, and complex scale up, the development of emerging technologies and better predictive tools still gives greater formulation robustness and regulatory acceptance. As material science, digital modelling and personalized manufacturing change, floating bilayer tablets are set to be highly adaptable, patient centric and therapeutically optimized systems. Collectively, these advancements make FBTs a next generation solution to improved oral drug delivery.

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