Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 4305-4318 | ISSN:2251-6727

Gastroretentive Bilayer Tablets: A Comprehensive Review on *In-Vitro*, *Ex-Vivo*, and *In-Vivo* Evaluation Parameters

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(Received: 16 February 2026 Revised: 14 March 2026 Accepted: 25 April 2026)

KEYWORDS

Gastroretentive drug delivery, bilayer tablets, floating tablets, *In-Vitro* evaluation, *Ex-Vivo* studies, *In-Vivo* evaluation

ABSTRACT:

Gastroretentive drug delivery systems (GRDDS) are used to enhance the bioavailability of drugs like narrow absorption window, drug with pH dependent solubility, and drugs with local gastric action having most efficient absorption in stomach or upper gastrointestinal tract. Bilayered tablets are a good choice where one layer is designed to release immediate dose and the other is for sustained release. This method enhances the absorption of medications and reduces the frequency of doses administered to the patient. On the other hand, just making these tablets is the first step, so they must go through stringent testing to verify their mechanical strength, cure adhesion, buoyancy or swelling, drug release profile, *in-vivo* studies, etc. This study reviews the prominent evaluation methods of gastroretentive bi-layer tablets. *In-Vitro* testing is performed to check the inherent properties like hardness, weight uniformity and floating lag time. Moreover, the total floating duration, swelling behaviour and the complete dissolution kinetics are also evaluated. The employed animal gastric mucosa in *Ex-Vivo* studies assesses swelling and mucoadhesion on actual tissues and residence time. *In-vivo* methods like X-ray, gamma scintigraphy, and pharmacokinetic studies can clearly indicate gastric retention time and improvement of drug bioavailability and clinical efficacy. The integration of these methods works the best. It does provide reproducible preliminary data. *Ex-vivo* does give us more relevant and physiological data. *In-vivo* tests do check if it's working or not in the proper organism. Bringing these formulations to patients successfully relies on an effective evaluation strategy that complies with regulatory standards.

1. Introduction

1.1. Gastroretentive Drug Delivery System

Oral administration has always been the most preferred route of treatment for local and systemic gastrointestinal diseases [1]. The oral drug delivery is the preferred route for drug administration due to its ease of use, cost-effective nature, patient compliance and capacity for large-scale manufacturing. However, these forms give rise to lack of reproducible excretion timing (i.e. gastric acid emptying time), poor drug bioavailability with narrow therapeutic absorption window and low therapeutic efficacy for the drugs which are unstable or sparingly soluble in intestinal fluid. Gastroretentive drug delivery systems (GRDDS) have been designed for a prolonged gastric retention of a dosage form and to enhance drug absorption [2].

Gastroretentive formulations are best for drugs which act locally in the stomach, are absorb primarily from stomach or upper part of GIT, have pH-dependent solubility profile and get destabilized in the small bowel environment. Different systems have been developed for gastric retention such as floating systems, mucoadhesive systems, expandable system and high-density system. Floating drug delivery systems are one of the most studied ones due to their simplicity and effectivity [3-6].

Through the advantage of having the two different layers with their own unique release profile or functionality combined in a single dosage form, bilayer tablet technology is gaining prominence in gastroretentive drug delivery. Such a design enhances the odds that patients will comply with their medication regime, reduces the frequency of doses, and maximizes therapeutic efficacy [7].

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JCHR (2026) 16(2), 4305-4318 | ISSN:2251-6727

The formulation and design of gastro retentive bilayer tablet is well advanced, but thorough and systematic evaluation is essential for success. Evaluation is done to check the physical integrity, inter layer adhesion, floating behaviour, swelling characteristics, drug release kinetics and gastric retention of dosage form. The *in-vitro* evaluation parameters used so far for the gastrointestinal retentive bilayer tablets are hardness, friability, weight variation, floating lag time, total floating duration, swelling index and dissolution studies [7–9]. Nonetheless, using *in-vitro* testing alone may not be a reliable predictor of *in-vivo* gastric retention and drug absorption behaviour.

Isolated gastric mucosa was used in various ex-vivo studies to assess the mucoadhesive strength, swelling behaviour and drug release in conditions which mimic closely the physiological condition to overcome these limitations [10,11]. Also, the in vivo assessment techniques such as radiography, gamma scintigraphy, and pharmacokinetic investigations are needed to confirm the gastric residence time, bioavailability enhancement and overall therapeutic efficacy with gastroretentive bilayer system [6,8]. Thus, an integrated evaluation using *in-vitro, ex-vivo*, and *in-vivo* methods is essential for sensible development, optimization, and regulatory approval of gastroretentive bilayer tablets.

Although numerous studies have reported formulation strategies and therapeutic applications of bilayer tablets, a consolidated review focusing specifically on the evaluation parameters and methodologies employed for gastroretentive bilayer tablets remains limited. Hence, the present review aims to comprehensively compile and critically analyse the *in-vitro, ex-vivo*, and *in-vivo* evaluation techniques used for gastroretentive bilayer tablets, thereby providing a structured reference framework for researchers and formulation scientists.

1.2. Bilayer Tablets:

The administration of drugs the employ of has improved. Bilayer tablets. Compared to single layer tablets, bilayer tablets The offer many advantages. Gives dual release of two different medications in alter either separately or in combination, to reduce inconsistency. The tablet is made of two layers: Gives one immediate release, And another gives. Sustained release. Provides rapid release. A rapid onset of action And gets faster a high serum concentration. Second A team made of a hydrophilic matrix with controlled release which maintains effective plasma level over a prolonged time. This formation can be done physically separate incompatible drugs And the goal different diseases [12].

1.3. Gastroretentive Bilayer Tablets: Review of concept and design

Gastroretentive drug delivery systems There are oral dosage forms prepared with the objective Increase in the duration For which a drug live in the stomach. These systems are primarily for drugs that act locally. The gastric region is preferentially absorbed from or the upper GIT.

In conventional oral dosage forms, the rate of gastric emptying is highly variable and depends on several physiological factors. Rapid gastric transit can result in incomplete drug release and reduced absorption, especially for drugs with a narrow absorption window. Gastroretentive systems are developed to overcome these limitations by ensuring retention and controlled drug release, thereby minimizing fluctuations in plasma drug concentration [4,5].

To achieve gastric retention, a number of formulation strategies have been investigated, such as high-density systems, expandable or swelling systems, mucoadhesive systems, and floating systems [3,6]. To keep gastric fluid buoyant, floating systems usually use low density, gas generation, or swelling polymers [4,11].

Gastroretentive drug delivery systems have certain drawbacks despite their benefits, including inter-individual variations in gastric motility, variability between fed and fasted states, and reliance on gastric fluid volume. Therefore, to guarantee consistent performance and predictable therapeutic results, careful formulation design and thorough evaluation using *in-vitro, ex-vivo*, and *in-vivo* methods are crucial [6,8].

2. Bilayer Tablet Technology

A highly advanced oral dosage form design known as "bilayer tablet technology" enables the integration of two separate layers—each with a unique composition, release characteristics, or functionalities—into a single tablet [7,12].

Bilayer tablets are commonly designed with one layer providing an immediate or loading dose of the drug to achieve rapid onset of action, while the second layer is

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JCHR (2026) 16(2), 4305-4318 | ISSN:2251-6727

formulated to deliver the drug in a sustained or controlled manner over an extended period. These designs are especially helpful when combination therapy is needed or when maintaining a steady plasma drug concentration is crucial [13-16]. By allowing one layer to promote gastric retention while the other layer regulates drug release, bilayer tablets provide additional benefits in gastroretentive drug delivery [17-19].

Bilayer tablet technology has been widely explored in gastroretentive drug delivery systems to enhance gastric residence time and improve bioavailability of drugs with narrow absorption windows. By combining gastroretentive mechanisms such as floating or swelling in one layer with sustained drug release in the other, bilayer tablets provide a flexible and effective platform for controlled oral drug delivery [8,20].

2.2. Rationale for Gastroretentive Bilayer Tablets

The development of these gastroretentive bilayer tablets is necessitated by limitations of oral dosage forms. This is especially true for drugs with narrow absorption window or short half-live. Moreover, drugs also show poor bioavailability due to fast gastric emptying. The combination of gastroretentive drug delivery principles with bilayer tablet technology is a rational means to enhance drug absorption and therapeutic performance [3,4].

By keeping the functionalities separate, a bilayer design helps to'introduce differentiated release profiles. Usually, a first layer is made in form of an immediate or loading dose for rapid action and the second layer is made to provide sustained or controlled drug delivery with gastric retention. This design aims to ensure an initial therapeutic concentration of the drug followed by a prolonged release of the drug in the stomach to achieve a constant plasma concentration of the drug and to reduce the dosing frequency [7, 8, 19].

Another essential reason for gastroretentive bilayer tablets is that one layer can incorporate gastric retention mechanisms, such as floating, swelling, or mucoadhesion. The other layer may exclusively deal with drug release [18,21]. Medicinal products that are instable in the intestinal environment or require prolonged gastric residence can benefity with the help of such systems [5,6].

The gastroretentive bilayer tablet can reduce dosing frequency and plasma drug concentration fluctuation and thus offer a lot from patient compliance point of view. Also, bilayer gastroretentive systems may reduce dose-related side effects by avoiding peak plasma concentrations with the immediate release formulations.

Overall, the rationale for gastroretentive tablets is based on their ability to combine controlled drug release, prolonged gastric retention, and improved bioavailability with a single oral dosage form. This makes them a promising platform for the effective delivery of drugs with challenging pharmacokinetic and absorption characteristics, thereby justifying continued research and development in this area [6,11].

2.3. Mechanisms of gastric Retention in Bilayer tablets

Gastric retention of oral dosage forms is a key factor in enhancing the bioavailability of drugs that are preferentially absorbed in the upper gastrointestinal tract or require prolonged gastric residence for optimal gastroretentive bilayer tablets employ various mechanisms to resist gastric emptying and maintain their positions in the stomach for extended periods [3,4]. Gastroretentive bilayer tablets employ multiple retention strategies, including floating, swelling, mucoadhesive, and high-density mechanisms, as summarized in **Figure 2.**

2.3.1 Floating (Low-Density) Mechanism

Floating bilayer tablets are designed to remain buoyant in gastric fluid by maintaining a density lower than that of gastric contents. This is commonly achieved using gas-generating agents such as sodium bicarbonate or calcium carbonate in combination with hydrophilic polymers. Upon contact with gastric fluid, carbon dioxide is generated and entrapped within the polymeric matrix, allowing the tablet to float on the gastric contents [4,18] (**Figure 1**).

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JCHR (2026) 16(2), 4305-4318 | ISSN:2251-6727

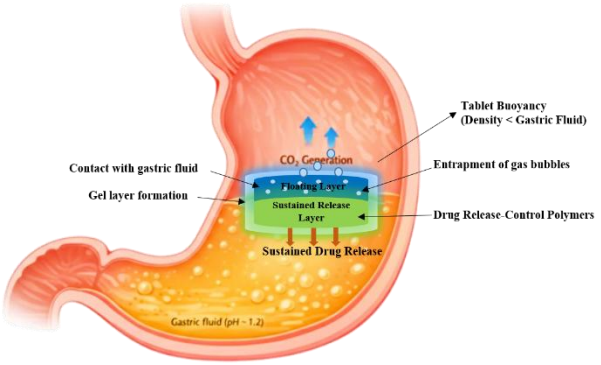

Figure 1. Schematic representation of floating gastroretentive bilayer tablet showing gas generation and buoyancy mechanism

2.3.2 Swelling and Expandable Mechanism

Swelling-based gastrointestinal bilayer tablets utilize polymers that rapidly hydrate and expand upon contact with gastric fluid, resulting in an increase in tablet size. The enlarged dosage form resists passage through the pyloric sphincter, thereby prolonging gastric residence time. Polymers such as hydroxypropyl methyl cellulose (HPMC), polyethylene oxide, and Carbopol are commonly used for this purpose [6,23-26] (**Table 1**).

In bilayer tablets, the swelling layer often functions as the gastroretentive component, while the second layer ensures sustained drug release. This design allows the tablet to retain its integrity while gradually releasing the drug over an extended period [11,19].

2.3.3 Mucoadhesive Mechanism

Mucoadhesive gastrointestinal systems rely on the addition of the dosage form to the gastric mucosal lining through physicochemical interactions such as hydrogen bonding and electrostatic attraction. Polymers like Carbopol, chitosan, and sodium alginate are widely used to impart mucoadhesive properties [3,6].

In bilayer formulations, the mucoadhesive polymer is typically incorporated into one layer to promote adhesion to the gastric mucosa, while the other layer regulates drug release. Although effective, the performance of mucoadhesive systems may be influenced by mucous turnover and gastric motility [15].

2.3.4 High-Density Mechanism

High-density gastroretentive mechanisms are formulated with densities greater than that of gastric fluid, enabling them to settle in the lower part of the stomach and resist peristaltic movement. Materials such as barium sulphate, zinc oxide, or iron powder are used to increase tablet density [3].

Due to formulation complexity and limited clinical success, high-density systems are less commonly employed in bilayer tablets compared to floating and swelling mechanisms. However, they remain an important conceptual approach in gastroretentive drug delivery research [6].

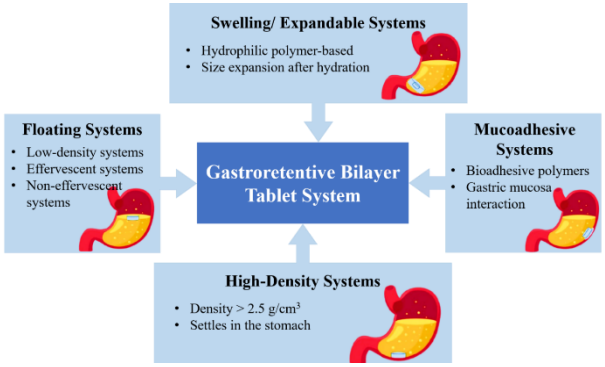

Figure 2. Classification of gastroretentive mechanisms employed in bilayer tablet systems

3. Evaluation of Gastroretentive Bilayer Tablets

3.1 *In-Vitro* Evaluation Parameters and Methods

In-vitro evaluation plays a critical role in the development and optimization of gastroretentive bilayer tablets, as it provides essential information regarding the physicochemical properties, mechanical strength, buoyancy behaviour, swelling characteristics, and drug release performance of the dosage form. Comprehensive *in-vitro* testing ensures formulation consistency, predicts

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JCHR (2026) 16(2), 4305-4318 | ISSN:2251-6727

Table 1

Common polymers used for swelling-based gastroretentive bilayer tablets

Polymer	Type	Swelling mechanism	Functional role in bilayer tablets	References
Hydroxypropyl Methyl cellulose (HPM C K4M, K15M, K100M)	Hydrophilic cellulose ether	Rapid hydration and gel layer formation	Provides swelling, matrix integrity, and sustained drug release	[4,6,11]
Polyethylene oxide (PEO)	Hydrophilic polymer	High water uptake and chain relaxation	Enhances swelling capacity and prolongs gastric retention	[6,26]
Carbopol (Carbomer 934P, 940)	Cross-linked polyacrylic acid	pH-independent swelling	Improves swelling and mucoadhesive properties	[3,15]
Sodium alginate	Natural anionic polysaccharide	Ionic gel formation in acidic medium	Promotes swelling and contributes to matrix stability	[6,18]
Xanthan Gum	Natural polysaccharide	Viscosity enhancement and hydration	Supports controlled release and tablet integrity	[27,30]
Guar Gum	Natural galactomannan	Water absorption and swelling	Acts as a swellable matrix former	[27,31]
Chitosan	Cationic natural polymer	pH-dependent swelling	Add swelling and muco-adhesive characteristics	[3,6]
Hydroxypropyl Cellulose (HPC)	Semi-synthetic polymer	Hydration-induced swelling	Assist in controlled release and mechanical strength	[15,28]

in vivo behaviour, and supports regulatory acceptance before animal or clinical studies [6,11].

The *in-vitro* evaluation of gastroretentive bilayer tablets can be broadly classified into pre-compression parameters, post-compression parameters, and functional gastroretentive performance tests, each addressing specific quality attributes of the formulation [7,15].

3.1.1 Pre-Compression Evaluation Parameters

Pre-compression studies are performed to assess the flow and compressibility characteristics of the powder or granule blends intended for bilayer tablet compression. These parameters are crucial to ensure uniform die filling, layer integrity, and reproducible tablet weight.

Commonly evaluated pre-compression parameters include bulk density, tapped density, angle of repose, Carr's compressibility index, and Hausner ratio (**Table 2**). Adequate flow properties are particularly important in bilayer tablet manufacturing to prevent layer weight variation and interlayer mixing during compression [15, 27, 28].

3.1.2 Post-Compression Evaluation Parameters

Post-compression evaluation is conducted to assess the physical integrity and quality of the compressed bilayer tablets. These tests ensure that the tables possess sufficient mechanical strength to withstand handling, packing, and transportation without compromising performance.

Key post-compression parameters include tablet thickness, diameter, hardness, friability, weight variation, and drug content uniformity. In bilayer tablets, additional attention is given to layer adhesion and absence of layer separation, as poor interfacial bonding may lead to delamination or dose dumping [7, 15]. Friability values below 1% and acceptable hardness are generally considered indicative of good tablet integrity [28].

3.1.3 Floating Lag Time and Total Floating Time

Floating behaviour is a critical functional parameter for floating gastroretentive bilayer tablets. Floating lag time (FLT) refers to the time required for the tablet to rise to

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Table 2

Pre-compression evaluation parameters for gastroretentive bilayer tablets

Parameter	Equation oblique method	Acceptable range	Significance	References
Bulk density (g/cm³)	Mass / Bulk volume	Formulation dependent	Indicates the packing ability of powder	[15, 28]
Tapped density (g/cm³)	Mass / Tapped volume	Formulation dependent	Reflects powder compressibility	[15]
Angle of repose (θ)	Tan θ = h / r	≤ 30° (good flow)	Assesses flow properties	[28]
Carr's Index (%)	(TD – BD) / TD × 100	≤ 15% (good flow)	Indicates compressibility	[15, 27]
Hausner Ratio	TD / BD	≤ 1.25	Predicts flow behaviour	[15, 28]

Table 3

In-vitro buoyancy and swelling evaluation parameters of gastroretentive bilayer tablets

Parameter	Method	Desired Outcome	Significance	References
Floating lag time (sec / min)	Simulated Gastric Fluid (SGF)	< 2min	Rapid buoyancy	[4,18]
Total floating time (h)	Visual observation	>12 h	Prolonged gastric retention	[4]
Swelling index (%)	(Wt – W0) /W0 × 100	Controlled swelling	Maintains tablet integrity	[6,26]
Matrix integrity	Visual inspection	No erosion	Sustained release support	[11]

the surface of the dissolution medium after contact with gastric fluid, whereas total floating time (TFT) indicates the duration for which the tablet remains buoyant (**Table 3**).

These parameters are typically evaluated using simulated gastric fluid (pH 1.2) without enzymes at 37 ± 0.5°C. Short floating lag time and prolonged total floating time are desirable characteristics, as they indicate rapid buoyancy and sustained gastric retention capability [4, 18].

3.1.4. Swelling Index

Swelling behaviour significantly influences gastric retention and drug release from gastroretentive bilayer tablets. The swelling index is determined by measuring the weight gain of the tablet after immersion in gastric fluid at predetermined time intervals.

A controlled and uniform swelling profile (**Table 3**) is essential to maintain tablet integrity and prevent premature erosion of disintegration. Excessive swelling may lead to structural weakness, whereas insufficient swelling may reduce gastric retention efficiency [6,26].

3.1.5. *In-Vitro* Drug Release Studies

In-vitro drug release studies are conducted to evaluate the release kinetics and mechanism of drug release from gastroretentive bilayer tablets. Dissolution testing is commonly performed using USP apparatus I or II with simulated gastric fluid, followed by buffer media when required.

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Table 4

Kinetic models used for the analysis of drug release from gastroretentive bilayer tablets

Kinetic Model	Mathematic Equation	Release Mechanism	Application in Gastroretentive Bilayer Tablets	References
Zero-order model	$Q_t = Q_0 + k_0t$	Drug release is independent of concentration	Describes ideal controlled release from sustained-release layer	[27, 38, 50, 99]
First-order model	Log Q_t = log Q_0 – $\frac{kt}{2.303}$	Concentration-dependent release	Commonly applied to immediate-release layer	[27, 38]
Higuchi model	$Q_t = k_H\sqrt{t}$	Diffusion-controlled release	Suitable for matrix-based gastroretentive tablets	[27, 62]
Korsmeyer-Peppas model	$\frac{Qt}{Q\infty} = ktn$	Diffusion, erosion, or combined mechanism	Widely used to interpret bilayer tablet release behaviour	[27, 64, 78]
Interpretation of Korsmeyer-Peppas release exponent (n) • n ≤ 0.45 → Fickian diffusion • 0.45 < n < 0.89 → Non-Fickian (anomalous) transport • n = 0.89 → Case-II transport • n > 0.89 → Super Case-II trasport				
Hixon-Crowell model	$Q_0^{1/3} - Q_t^{1/3} = k_{HC}t$	Release with change in surface area	Applicable when tablet erosion occurs	[38, 99]

Bilayer tablets typically exhibit biphasic release profiles, where the immediate-release layer provides an initial burst release, followed by sustained drug release from the controlled-release layer. Drug release data are further analyzed using kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models (**Table 4**) to elucidate the release mechanism [8,19,27].

3.2 *Ex-Vivo* Evaluation of Gastroretentive Bilayer Tablets

Ex-vivo evaluation serves as an important intermediate step between *in-vitro* testing and *in-vivo* studies, as it allows assessment of gastroretentive bilayer tablets under conditions that more closely resemble the physiological gastric environment. These studies are generally performed using excised gastric tissue obtained from suitable animal models such as rats, rabbits or pigs. *Ex-vivo* methods help in understanding the interaction of the dosage form with gastric mucosa, swelling behaviour and retention characteristics without the ethical and technical constraints associated with *in-vivo* experiments [12, 16, 18].

One of the most widely employed *ex-vivo* evaluation techniques for gastroretentive bilayer tablets is the mucoadhesion study. This method is particularly relevant for formulations containing mucoadhesive or swelling polymers intended to prolong gastric residence time. In such studies, the tablet or polymeric layer is placed in contact with freshly excised gastric mucosa, and the adhesive strength or detachment force is measured using modified balance assemblies or texture analyzers. Strong muco-adhesive interactions contribute to prolonged gastric retention and improved drug absorption, especially for drugs with a narrow absorption window in the upper gastrointestinal tract [24, 25, 29].

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Table 5

Summary of *ex-vivo* evaluation methods for gastroretentive bilayer tablets

***Ex-vivo* evaluation method**	**Experimental setup**	**Parameters evaluated**	**Key outcomes significance**	**References**
Muco-adhesive strength study	Bilayer tablet or polymeric layer attached to excised gastric mucosa using a modified balance or texture analyzer	Detachment force (g or N), residence time	Determines adhesive interaction between tablet polymers and gastric mucus, predicting prolonged gastric retention	[24, 25, 29]
Gastric retention study	Excised stomach mounted within a dissolution or perfusion chamber containing simulated gastric fluid (pH 1.2)	Retention time, tablet position, and floating stability	Predicts the ability of gastroretentive bilayer tablets to remain in the stomach under physiological conditions	[12, 16, 23, 33]
Swelling behaviour on gastric tissue	Tablet placed on excised gastric tissue immersed in simulated gastric fluid	Swelling index, dimensional change, matrix integrity	Helps optimise polymer concentration to ensure adequate expansion without premature erosion	[20, 23, 26, 30]
Dimensional stability study	Periodic measurement of tablet size and shape during *ex-vivo* exposure	Thickness, diameter, erosion pattern	Ensures mechanical integrity of bilayer tablets during prolonged gastric residence	[6, 11, 26]
Floating behaviour assessment	Tablet introduced into excised stomach field with gastric medium	Floating lag time, floating duration	Confirms buoyancy and density reduction essential for floating gastroretentive systems	[13, 17, 31]

Ex-vivo gastric retention and positioning studies are also performed to evaluate the ability of bilayer tablets to remain in the stomach under simulated gastric conditions. In these experiments, the excised stomach is mounted in a dissolution or perfusion setup containing simulated gastric fluid, and the dosage form is introduced to observe its retention, floating behaviour, and positional stability. These studies are useful in predicting the *in-vivo* gastric residence time of floating and expandable gastroretentive systems [13, 16, 23, 30].

Another important aspect of *ex-vivo* evaluation is the assessment of swelling behaviour and dimensional stability of gastroretentive bilayer tablets on gastric tissue. Swelling studies help determine the extent and rate of tablet expansion, which are critical parameters influencing gastric retention. Excessive swelling may lead to dose dumping or discomfort, whereas insufficient swelling can result in premature gastric emptying. Therefore, *ex-vivo* swelling studies provide valuable guidance for optimising polymer concentration and bilayer design [20, 23, 26, 31].

Overall, *ex-vivo* evaluation methods (**Table 5**) provide meaningful insights into the gastric interaction, retention potential, and mechanical behaviour of gastroretentive bilayer tablets. When used alongside *in-vitro* studies, these methods strengthen formulation optimization and

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improve the predictability of *in-vivo* performance, thereby supporting the rational development of effective gastroretentive drug delivery systems [3, 6, 11, 32].

3.3 *In-Vivo* Evaluation and Imaging Techniques

In-vivo evaluation is an important criterion to ensure gastric retention, drug release behaviour, and therapeutic performance of gastroretentive bilayer tablets. Research is often conducted on suitable animal models, which provide direct evidence of performance that cannot be obtained from *in-vitro* or *ex-vivo* model methods alone [3, 6, 16].

Table 6

In-vivo evaluation techniques for gastroretentive bilayer tablets

Technique	Purpose	Key outcome	References
X-ray imaging	Visualise gastric location and retention	Confirms gastric residence time	[22, 32]
Gamma scintigraphy	Real-time tracking of tablet movement	Quantitative gastric retention data	[22, 37]
Pharmacokinetic study	Evaluate drug absorption and bioavailability	C_{max}, T_{max}, AUC enhancement	[15, 38, 50]
IVIVC analysis	Correlate *in-vitro* and *in-vivo* data	Predicts in vivo performance	[21, 38, 51]

The inclusion of radio-opaque markers in the formulation has made it possible to widely use radiographic imaging techniques (X-ray studies) to visualize the location and retention time of bilayer tablets in the stomach. Gamma scintigraphy is a non-invasive imaging technique that allows real-time tracking of dosage forms in the gastrointestinal tract and provides quantitative data on gastric residence time [22,33-37]. The *in-vivo* evaluation of gastroretentive bilayer tablets using gamma scintigraphy principle (as shown in **Figure 3**) is carried-out Pharmacokinetics studies (**Figure 3**) to assess the effect of gastroretentive bilayer tablets on the drug absorption and bioavailability through the determination of Cmax, Tmax and AUC. Prolonged presence of drug in plasma due to better availability indicates successful gastric retention. *In-vivo-in-vitro* correlation (IVIVC) helps to predict the *in-vivo* behaviour of the formulation through its *in-vitro* dissolution data and assists to optimise the formulation intermediate or final stages as well as supporting regulatory acceptance by the authority [21, 38, 51].

In-vivo evaluation provides definitive confirmation of the effectiveness of gastroretentive bilayer tablet systems and complements other assessments like *in-vitro and ex-vivo* studies for formulation assessment [6, 11, 32]. As reported in **Table 6**, there are several *in-vivo* evaluation techniques of gastroretentive bilayer tablets **Table 6**.

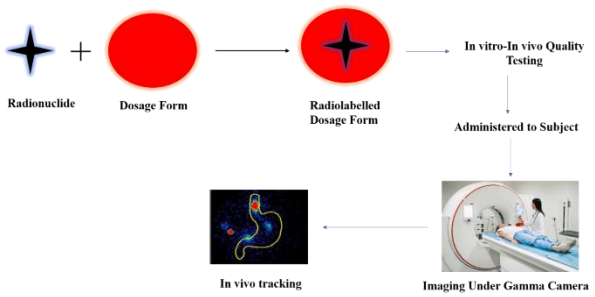

Figure. 3 Principle of Gamma Scintigraphy

4. Conclusion

Gastroretentive bilayer tablet systems offer a powerful strategy for oral drug delivery, improving gastric residence time, enabling controlled drug release and boosting therapeutic efficacy, especially for drugs with narrow absorption windows or targeted gastric effects. The bilayer design supports simultaneous immediate and sustained release profiles, improving bioavailability and less frequent dosing [3, 6, 11].

Thorough evaluation of gastroretentive bilayer tablets via *in-vitro, ex-vivo*, and *in-vivo* methods proves

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essential for validating performance and predicting chemical behaviour. In-vitro studies yield initial data on buoyancy, swelling, and release kinetics, while *ex-vivo* techniques reveal gastric mucoadhesion and retention dynamics. *In-vivo* imaging and pharmacokinetics studies deliver conclusive proof of gastric retention and therapeutic effectiveness [22, 32, 38].

A systematic, multi method evaluation strategy strengthens formulation refinement and facilitates regulatory approval for gastroretentive bilayer tablets. Ongoing research focusing on novel polymers, refined evaluation protocols and robust *in-vitro-in-vivo* correlation promises to further enhance the clinical potential of gastroretentive bilayer drug delivery systems [6, 11, 39].

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