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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET OF LOVASTATIN BY USING NATURAL POLYMERS

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ABSTRACT

The present study focuses on the formulation and evaluation of gastroretentive floating tablets of Lovastatin with the objective of improving its solubility, enhancing gastric retention time, and achieving sustained drug release. Lovastatin, a lipid-lowering agent categorized under BCS Class II, suffers from poor aqueous solubility and limited oral bioavailability due to its narrow absorption window in the upper gastrointestinal tract. To overcome these limitations, nine formulations (F1–F9) were prepared using the direct compression method by varying the concentrations of natural and synthetic polymers such as guar gum, HPMC, and carbopol, along with sodium bicarbonate as a gas-generating agent.

Preformulation studies including organoleptic characteristics, melting point analysis, solubility testing, UV spectroscopy, and FTIR confirmed the purity and compatibility of Lovastatin with selected excipients. The pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose revealed good to acceptable flow characteristics. Post-compression evaluations showed uniform weight, adequate hardness, low friability, and consistent drug content across all batches.

In vitro buoyancy studies indicated rapid floating within 60 seconds and prolonged floatation for over 12 hours. Drug release studies in 0.1N HCl demonstrated sustained drug release, with formulation F6 showing the highest cumulative drug release (~96%) over 12 hours. Drug release kinetics revealed that most formulations followed Higuchi and Korsmeyer–Peppas models, suggesting that the drug release was governed by a combination of diffusion and erosion mechanisms.

In conclusion, the developed gastroretentive floating tablets of Lovastatin offer a promising approach to improve its bioavailability and therapeutic efficiency. The optimized batch (F6) showed potential for further in vivo and clinical studies for effective management of hyperlipidaemia.

Keywords:
Lovastatin, Gastroretentive tablet, Floating drug delivery, Sustained release, Hyperlipidaemia, BCS Class II, Guar gum, In vitro buoyancy, Bioavailability enhancement, Release kinetics.

1. INTRODUCTION

Oral medication administration might be challenging and reduce therapeutic effectiveness[1]. Short stomach emptying durations can reduce the efficiency of orally delivered medicines, resulting in inadequate drug release and uneven bioavailability[1]. Optimizing solubility and presence in the stomach is critical for improved treatment effects, as they are mostly absorbed in the upper gastrointestinal tract[1]. Gastro-retentive drug delivery systems (GRDDS) optimize medication administration to the absorption site by extending gastric residency and reducing waste[2].

GRDDS are especially useful for ulcer therapy and other situations when a medicine has a restricted absorption window in the upper small intestine, extending the duration between required dosages[2]. Developing floating gastro-retentive devices can increase drug administration time proportionally to stomach residency time[2]. Floating drug delivery systems (FDDS) can boost therapeutic effectiveness by deliberately keeping the dose form at the primary absorption site, even for medicines with limited bioavailability[2].

Sustained release drug delivery methods guarantee stable drug concentrations in the bloodstream by distributing medication gradually over time[3]. These technologies are especially suitable for medicines with short biological half-lives[3]. Matrix tablets are a cost-effective option for extended-release medication therapy, providing prolonged and regulated release in solid oral dose forms[3]. A matrix tablet is an oral solid dosage form that contains homogeneously dispersed or dissolved drugs within hydrophilic or hydrophobic polymeric matrices[3]. A sustained-release dosage form should release the drug through a zero-order mechanism to maintain plasma levels comparable to continuous intravenous infusion[3].

1.1 Anatomy and physiology of human stomach

The stomach processes and transports food while also serving as a temporary storage area for larger meals. It stimulates enzymatic digestion, particularly of proteins, by strong contractions of its smooth muscles.[4]. The stomach has three main sections: fundus, body, and antrum (pylorus). The fundus and body store in process the gastric contents, while the antrum regulates stomach emptying with vigorous peristaltic pumps.

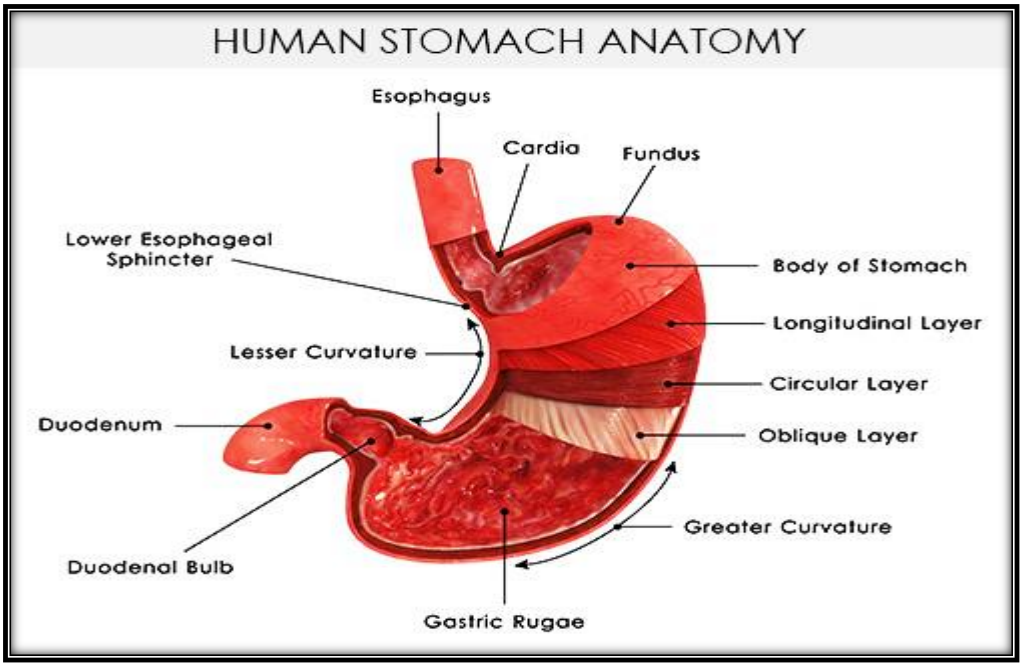


Figure 1.1 Human stomach anatomy.

Source:https://www.alamy.com/stockphotostomachlayers77386314.html?imageid=CECDE0961A194FF59F38882366EFD9FF&p=234500&pn=1&searchId=4080e3e7abc8a3a2bb17fce26d728fc0&searchtype=0

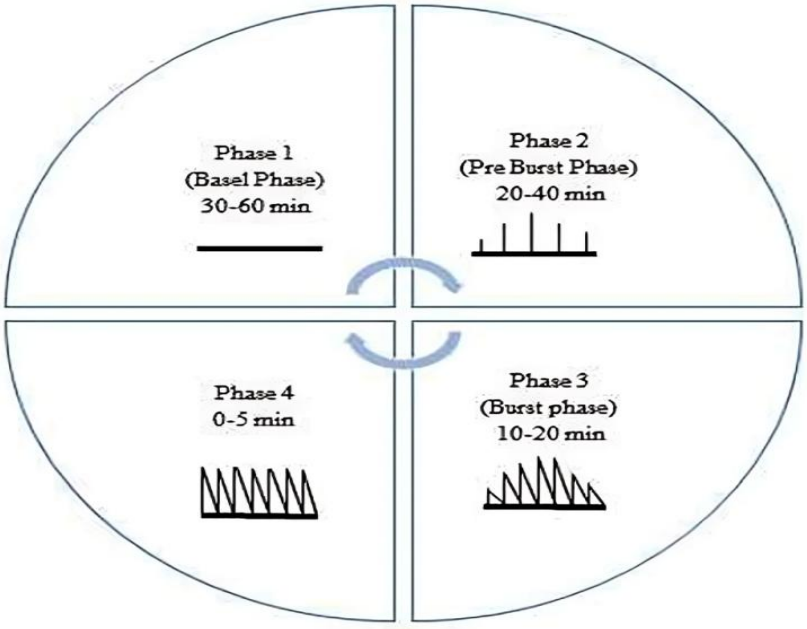


Figure 1.2 Motility pattern in gastrointestinal tract.[126]

Source: http://dx.doi.org/10.4274/tjps.galenos.2021.44959

Table 1. 1 Anatomy and Physiology of GITSS.

Section	Average length (cm)	pH	Major constituents	Transient Time of food (hr)
Oral cavity	15-20	5.2-6.8	Amylase, maltase, ptyalin, mucins	short
Esophagus	25	5-6	-	Very short
Stomach	20	1.2-3.5	HCl, pepsin, rennin, lipase, intrinsic	0.25-3.00
Duodenum	25	4.6-6.0	Bile, trypsin, chymotripsin, amylase, maltase, lipase, nuclease, CYP3A5	1-2
Jejunum	300	6.3-7.3	Amylase, maltase, lactase, sucrase, CYP3A5	-
Colon	150	7.9-8.0	-	4-20
Rectum	15-19	7.5-8.0	-	Variable

1.2 Need for gastro retentive drug delivery system

The continuous and controlled release of drugs within the stomach offers significant therapeutic advantages due to the extended contact duration with the absorption site[5]. This approach is particularly beneficial for medications that are difficult to digest or have limited absorption in the upper GI tract, where absorption primarily occurs[1]. By prolonging the agent's interaction in the stomach or upper small intestine, the need for repeated dosing frequencies is eliminated.[5] In general, Controlled Release Gastro-Retentive Drug Formulations (CRGRDFs) are an excellent fit for drugs that exhibit acceptable upper GI tract (GIT) absorption characteristics but poor colonic absorption.[5]

Specifically, GRDDS are needed for:

- I. Materials that are poorly soluble in alkaline pH: For instance, Verapamil.[5]
- II. Medications that the GIT processes rapidly: Such as Metronidazole with Tetracycline.[5]
- III. Medication with a localized effect on the stomach: Examples include Antacids, Misoprostol, and H. pylori eradication drugs.[5]
- IV. Medicines that break down in the gut: For example, Ranitidine with Metformin HCl.[5]
- V. Prescription drugs which mostly absorb in the stomach: Like Amoxicillin.

- VI. Medication which alters the colon's normal microbiome: Such as medications to treat H. pylori.[5]
- VII. Medication which shows a short window of absorption: For example, Levodopa.[5]

1.3 Gastro-retentive drug delivery system

Oral controlled-release medicine delivery is gaining popularity in the pharmaceutical industry due to its versatility, convenience of dosing, and improved patient compliance. These formulations attempt to extend the duration of an effective medication concentration in the systemic circulation by overcoming the short half-lives of easily absorbed medicines in the gastrointestinal tract. One important feature is that the medication, when administered orally, is kept in the stomach and gradually released, ensuring a continuous supply of the drug to the GIT absorption sites. However, typical controlled-release techniques frequently have disadvantages, such as short and unpredictable stomach retention durations, which can lead to insufficient drug release and reduced dosage effectiveness.[6]

To create an effective and site-specific oral controlled-release dosage form, it is highly desirable for the drug administration to prolong the stomach residence duration. Extended stomach retention enhances medication solubility, decreases drug waste, increases the drug's bioavailability, and prolongs its release period.[6] These include systems based on high density, super porous hydrogels, low density (floating), mucoadhesion, unfoldable designs, magnetic systems, and extendible forms.[7]

1.4 Factors controlling gastric retention of dosage forms

The pyloric sphincter and other stomach physiological variables play crucial roles in the development of gastro-retentive dose forms. Several factors determine the size of particles that can cross the sphincter and enter the small intestine, including the amount of food consumed, the frequency with which it is consumed, the size of the dose form, and patient-specific factors such as age, gender, and general health. Certain medications, such as prokinetics and anticholinergics, also have an effect on gastrointestinal transit time.

A. Density of dosage

The density of the dosage form significantly impacts its delivery mechanism within the stomach, which, in turn, influences the rate of stomach emptying[5]. Density is one of the most crucial factors affecting the performance and stability of various GRDDS. For floating systems to effectively remain buoyant on the stomach contents, their bulk density must be maintained below 1 g/cm^3.[9]

B. Shape and size of the dosage form

When creating indigestible single-unit dosage forms, size and shape are important considerations for stomach retention. The size of a non-floating dosage form influences its mean stomach residence time, resulting in a longer GRT. Dosage forms larger than 7.5 mm have higher GRT compared to those with a 9.9 mm diameter[6]. Furthermore, particular geometries such as rings have been demonstrated to have superior GRT.[10]

C. Food intake and its nature

Several parameters related to food, including viscosity, amount of food intake, calorie content, and frequency of feeding, can profoundly affect gastric retention, or GRT. If gastric emptying time (GET) is slowed by increased stomach acid and calorie content, the gastric retention of the delivery mechanism may further increase[7]. Therefore, GRT is greatly influenced by factors such as caloric value, viscosity, and the nature of food consumption.[11]

D. Effect of gender, posture and age

Gastric emptying, and consequently GRT, is a physiological process that varies significantly among individuals and in different situations. Generally speaking, females tend to exhibit a slower pace of gastric emptying than males. Furthermore, gastric emptying may be noticeably delayed in older individuals compared to younger populations[8]. Patient posture can also influence GRT.[12]

1.5 Approaches to achieve gastric retention

In the last three decades, many ways have been used to improve the stomach retention of oral dose forms.[13]

1. Hydrodynamically balanced systems
2. Raft – forming systems
3. Bio adhesive or mucoadhesive systems
4. Modified-shape systems
5. High-density systems
6. Swelling and expanding systems
7. Magnetic systems

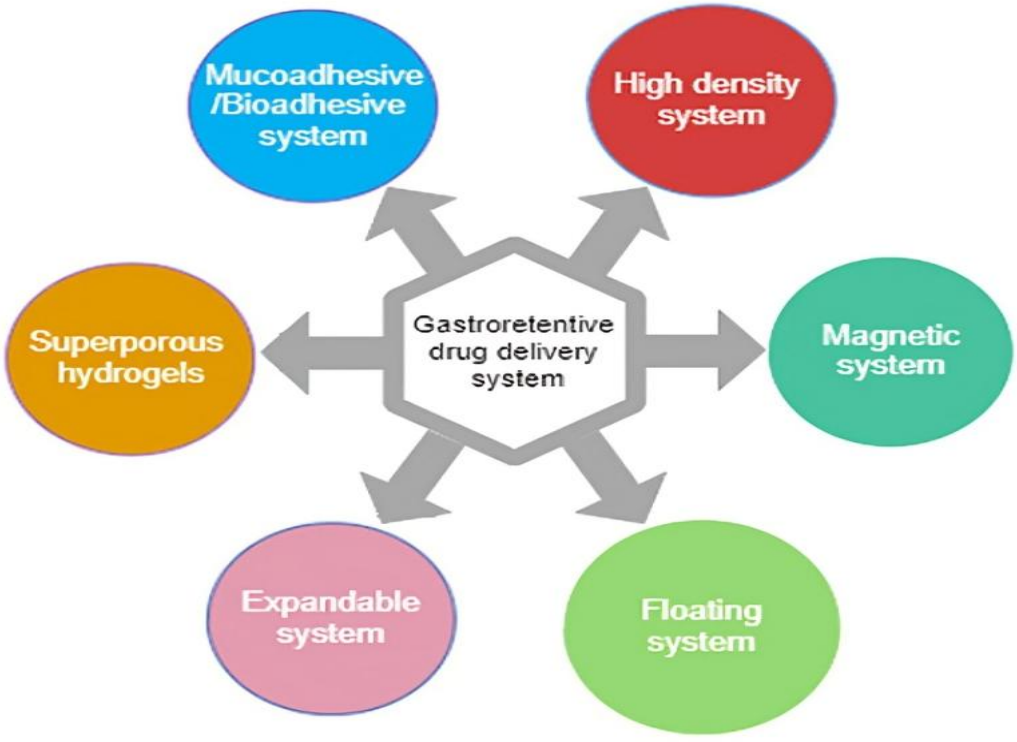


Figure 1.3 Approaches of gastro-retentive drug delivery system.[127]

1. Hydrodynamically balanced systems (hbs):

Sheth and Tossounian pioneered the concept of hydrodynamically balanced drug release systems for medications that form gels in the presence of hydrocolloids, specifically designed to prevent rapid absorption into the stomach. These systems incorporate one or more water-loving polymers, such as sodium carboxymethyl cellulose, HPMC, and hydroxyethyl cellulose. Typically, the polymer is encased in a capsule alongside the medication, forming a hydrodynamically stable structure that provides long-term buoyancy in gastric juice. Low-density fatty excipients in these formulations also offer protection against erosion. *Madopar LP®*, launched in the 1980s, was an early commercial example of a system based on this principle. The drug release profile is significantly impacted by the polymer-to-drug loading ratio, where the interplay between polymer properties and drug loading determines the release kinetics. To enhance the performance and increase the GRT of hydrodynamically stable floating devices, several strategies have been studied, including optimizing polymer shelf life. Drug release and floatation are influenced by critical variables such as solvent choice, plasticizer content, polymer ratio, and the total amount of polymers used[1]. Among the most promising buoyant systems are microballoons, which have demonstrated the ability to continually float for over 12 hours in an acidic dissolving liquid containing a surfactant.[14]

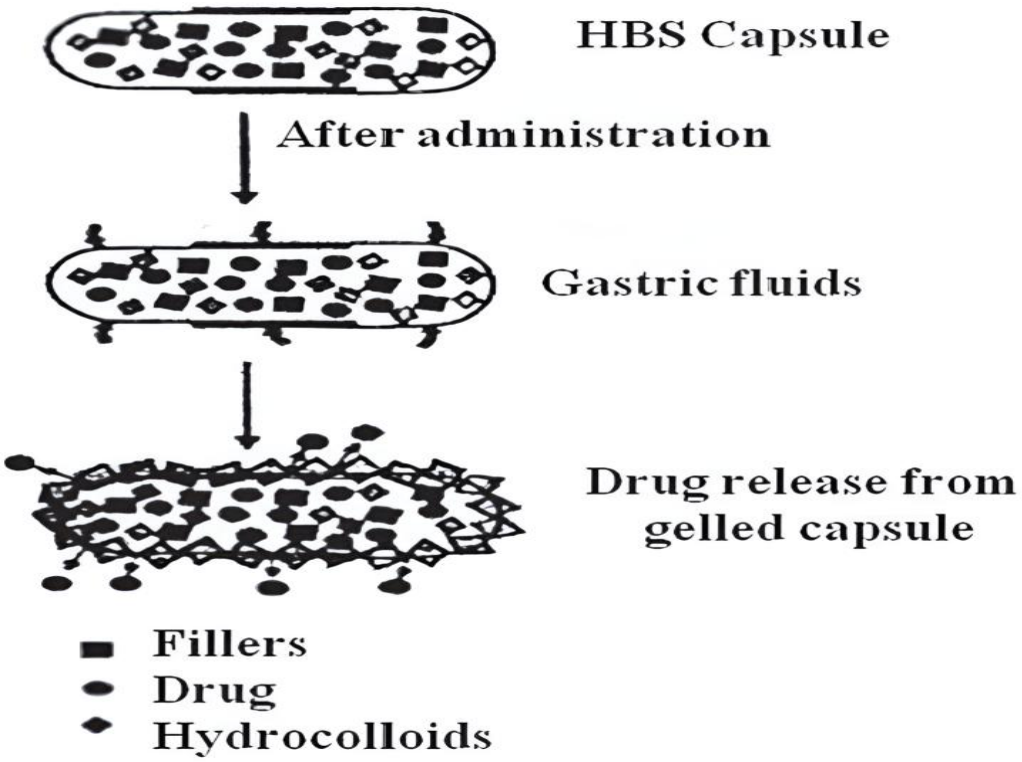


Figure 1.4 Hydrodynamically balanced system.[128]

Source: https://www.pharmamirror.com/pharmacy/pharmaceutics-floating-drug-delivery-systems/

2. Raft-forming systems

When raft-forming processes come into contact with stomach juices, a cohesive gel quickly forms, resulting in a viscous "raft". The raft, supported by CO_2, floats atop gastrointestinal contents and serves as a physical barrier[17]. This barrier is intended to keep stomach contents, such as enzymes and hydrochloric acid, from

refluxing into the esophagus. The gel-forming chemicals paired with alkaline bicarbonates or carbonates contribute to the system's low density, allowing it to float effectively on the gastrointestinal juices.[15]

3. Bioadhesive or mucoadhesive systems

Bioadhesive drug delivery methods utilize bioadhesive polymers to enhance the site-specific absorption of medications. By adhering to the stomach's epithelial surface, these polymers prolong gastric retention. The process of adhesion ensures that dosage forms remain attached to the mucosal surface, thereby extending the period during which the medication is absorbed.[16] Several theories explain bioadhesion:

A. The wetting hypothesis: Proposes that polymers with bioadhesive qualities can intimately contact and disperse across mucosal layers, enhancing their utility.[16]

B. The diffusion theory: Suggests that mucin strands (from the mucosal layer) can physically entangle with and interpenetrate the porous structure of the polymer substrate.[16]

C. The absorption theory: States that secondary forces, such as Van der Waals forces and hydrogen bonding, significantly influence bioadhesion.[16]

D. The electron theory: Posits that bioadhesive materials engage in attractive electrostatic interactions with the glycoprotein mucin network.[16]

While bioadhesion is a promising strategy, frequently achieved by using various polymers, the rapid mucus turnover within the gastrointestinal tract makes it challenging to achieve consistently efficient retention of these components.[16]

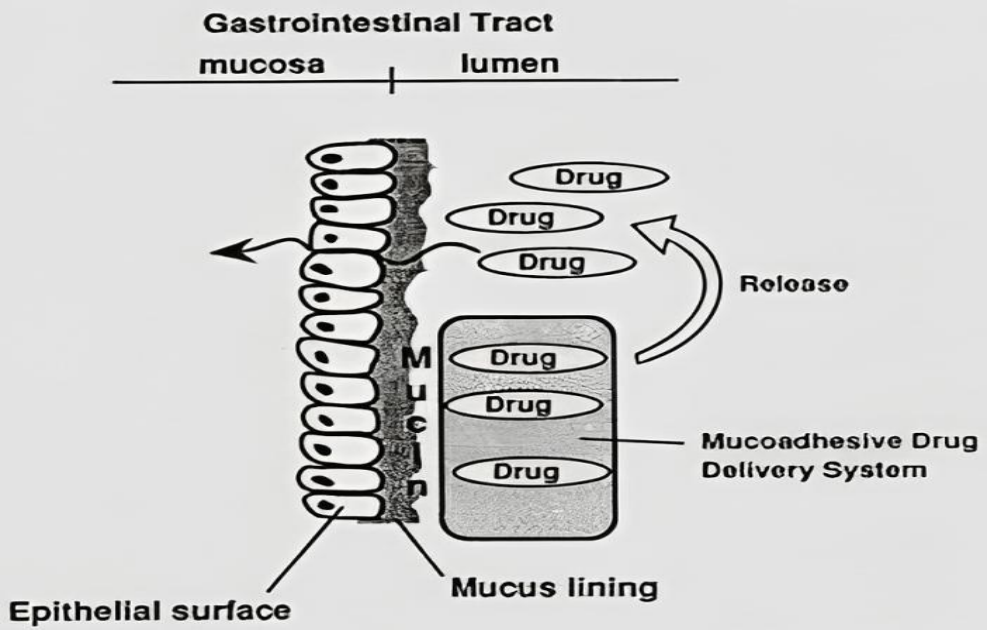


Figure 1.5 Mucoadhesive drug delivery system.[129]

Source: http://dx.doi.org/10.1016/j.jconrel.2009.07.016

A. The wetting hypothesis: Because of their bioadhesive characteristics, mucosal layers can be closely touched and disseminated by polymers, making them valuable in a range of applications.[17]

B. The diffusion theory: According to the study, mucin strands may physically entangle themselves and may interpenetrate the polymer substrate's porous structure.[18]

C. The absorption theory: According to the study, secondary forces, such as Vander Waals forces and hydrogen bonding, have an impact on bioadhesion.[19]

D. The electron theory: According to the electron theory, the bioadhesive materials have enticing electrostatic interactions with the glycoprotein mucin network.[20]

Bioadhesion is frequently achieved by using polymers. The gastrointestinal tract's (GIT) rapid mucus turnover makes it difficult to retain these components efficiently.[21]

4. Modified shape systems

The flexural modulus of silastic elastomer, a material made from polyethylene blends, has a substantial impact on how long it takes for a drug delivery device to break down. Furthermore, the shapes and sizes of the elastomer influence the time required for the drug to reach the mucoepithelial surface. Modified-shape systems are designed to prevent transit through the pylorus based on their geometry, not density.[22]

5. High-density systems

High-density pellets, typically comprised of mostly inert substances like zinc oxide and barium sulphate, are designed with a composition that critically depends on the stomach's contents. Because these dense pellets settle in the lower section of the antrum (pylorus), it is anticipated that they will remain in the stomach for a longer duration, resisting the emptying forces.[23]

6. Swelling systems

Swelling and expanding dosage forms are engineered to enlarge to a point where the pylorus cannot release them, thereby retaining them in the stomach for an extended period. These devices, often referred to as plug-type devices, are activated upon contact with stomach contents, which causes the polymer to absorb water and expand significantly. The substantial swelling is attributed to the physicochemical crosslinks within the hydrophilic polymer network, which helps maintain the stomach in a "fed" condition and reduces the effect of the housekeeper wave (MMC Phase III). Examples of such distribution techniques include hydrogel balloons that swell and modified polymer sheets[8]. To maximize therapeutic benefit and prevent adverse consequences, it is crucial to meticulously balance the rate and degree of erosion and swelling.[24]

7. Magnetic systems

In magnetic systems, where dosage forms carry an internal magnet, the proper positioning of an external magnet on the patient's belly is critical for achieving and maintaining gastric retention. The external magnetic field holds the internally magnetized dosage form within the stomach.[25]

1.6 Floating drug delivery systems (fdds)

Floating Drug Delivery Systems are specifically intended to address the issue of medications having a narrow window of absorption in the stomach and small intestine, preventing premature transit. Because

FDDS are less dense than gastric fluid, drugs can be progressively given at the appropriate rate by floating over the stomach contents without hastening stomach emptying. Unlike standard controlled-release dosage forms, which sink, floating drug delivery increases bioavailability and absorption by keeping the dosage form at the absorption site. Floating drug delivery is used for both continuous medication administration and targeted site delivery in the upper GI tract.[26]

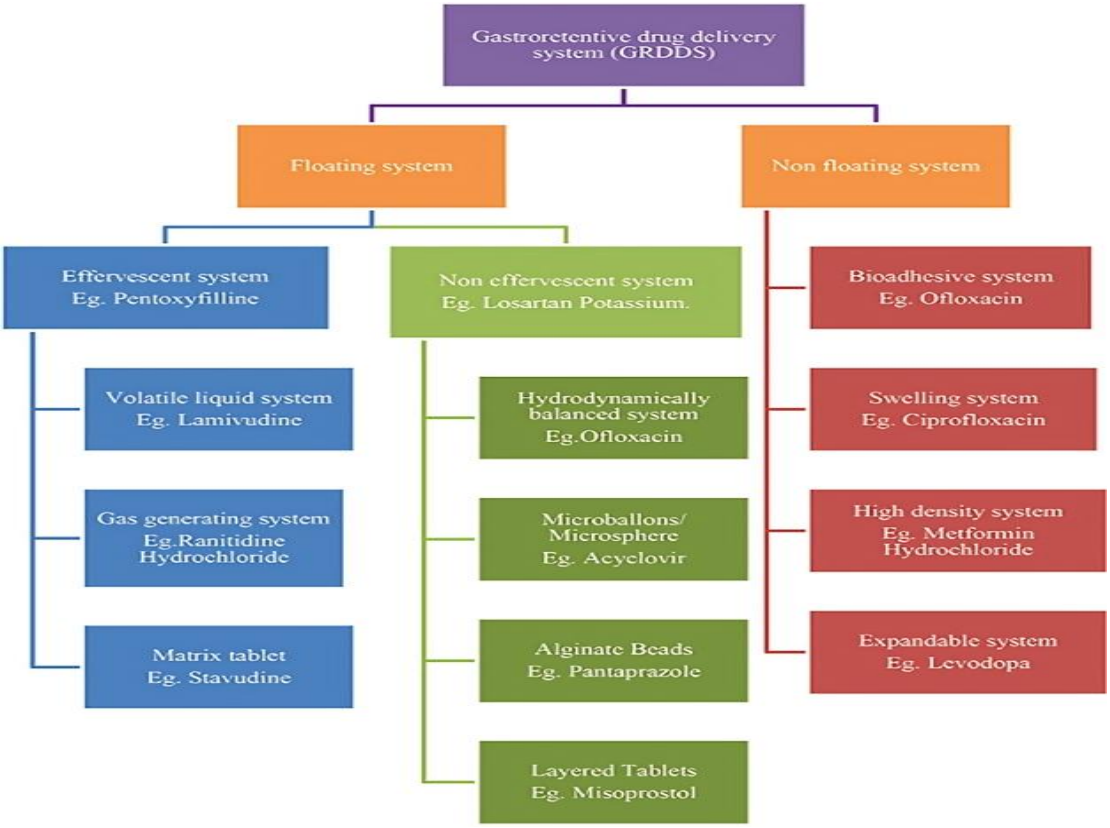


Figure 1.6 Classification of gastro-retentive drug delivery system.[130]

Source: http://dx.doi.org/10.4274/tjps.galenos.2021.44959

1.7 Non-effervescent systems

Non-effervescent floating drug delivery methods are largely made up of gel-forming or highly swellable cellulose hydrocolloids, polysaccharides, and other matrix-forming polymers. HPMC (Hydroxypropyl Methylcellulose) and polyacrylates are common examples. These devices maintain a constant shape and bulk density in the gastrointestinal environment, buoyed by air trapped within the expanding polymer matrix[1]. Polyacrylates, polyvinyl acetate, and HPMC are examples of common excipients.[27]

A. Colloidal gel barrier system: Sheth and Tossounian developed this hydrodynamically balanced method for medication absorption in the stomach contents. This method utilizes gel-forming hydrocolloids such as HPC (Hydroxypropyl Cellulose), HEC (Hydroxyethyl Cellulose), and HPMC to maintain buoyancy and optimize medication absorption.[28]

B. Microporous compartment system: In this technique, a medicine reservoir is enclosed in a microporous compartment that prevents the drug from coming into direct touch with the stomach surface. The reservoir's outer edge is sealed to avoid quick medication discharge into the stomach cavity. The dissolved drug can then pass through the porous hole and into the gut for absorption.[29]

C. Alginate beads: Recent research has investigated the creation of multiple-unit floating systems utilizing cross-linked beads, often made from sodium alginate and low methoxylated pectin. Following their formation, these beads are separated and dried using techniques like air convection and freeze-drying, which creates a porous structure. This porous structure enhances their buoyancy, allowing them to float for greater than 12 hours and potentially raising the GRT by more than 5.5 hours.[30]

D. Hollow microspheres / microballoons: Hollow microspheres or microballoons are drug-filled, spherical polymeric shells. These are considered promising buoyant systems due to their excellent floating qualities and their multiple-unit structure, offering a large surface area for drug release and a low density for buoyancy.[31]

1.8 Effervescent systems

Effervescent systems make use of gas-generating ingredients like tartaric acid and sodium bicarbonate. When they interact with stomach contents, they produce CO_2, which is subsequently enclosed within a swollen hydrocolloid matrix. This approach, commonly used in a swellable asymmetric triple-layer tablet, provides efficient drug administration by creating buoyancy.[32]

A. Volatile liquid-containing systems

These devices are designed as deformable hollow units that contain a volatile liquid, becoming floating systems after a period of time. Such systems are capable of expanding and contracting, and eventually, they will revert to their collapsed condition. The drug is typically contained in a first chamber, while volatile liquids, such as ether, are housed in a second chamber. The device continually releases medication into the stomach fluid.[33]

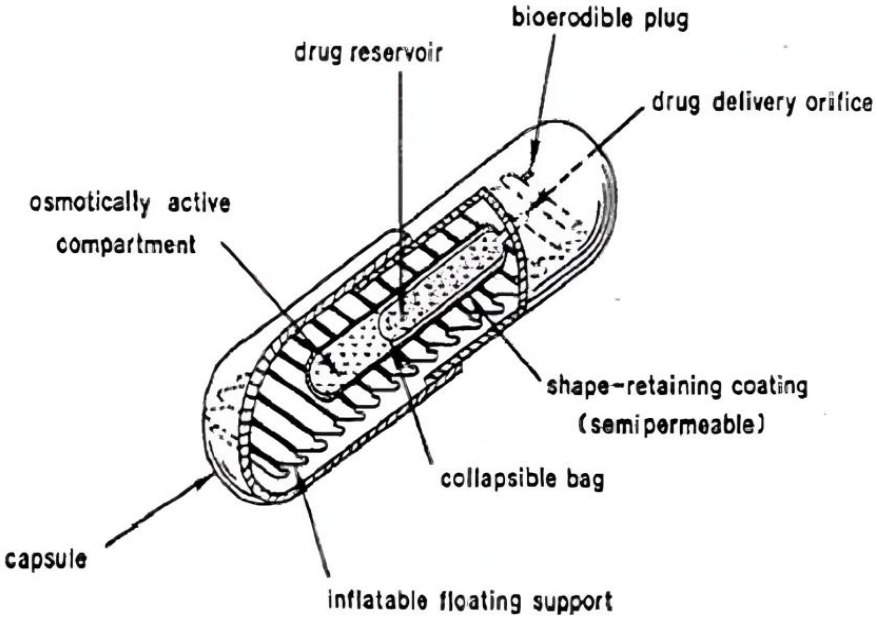


Figure 1.7 Volatile liquid containing systems.[131]

Source: http://dx.doi.org/10.5897/ajpp2015.4307

B. Gas-generating systems:

Buoyant systems known as gas-generating systems are specifically made to float in the stomach by utilizing effervescent substances like sodium bicarbonate in conjunction with swellable polymers. When consumed, these systems release carbon dioxide, which causes the formulation to float.[34] Several strategies exist, including floating tablets composed of lactose, polyvinylpyrrolidone, and sodium bicarbonate covered with HPMC,[35] as well as floating systems employing ion exchange resin technology[2]. Some capsules consist of a covering and a central core, with the drug (e.g., pepstatin) covered by an HPMC layer[3]. Because CO_2 is released into the gastric fluid, the system either floats immediately or remains inside the stomach for a long duration.[36]

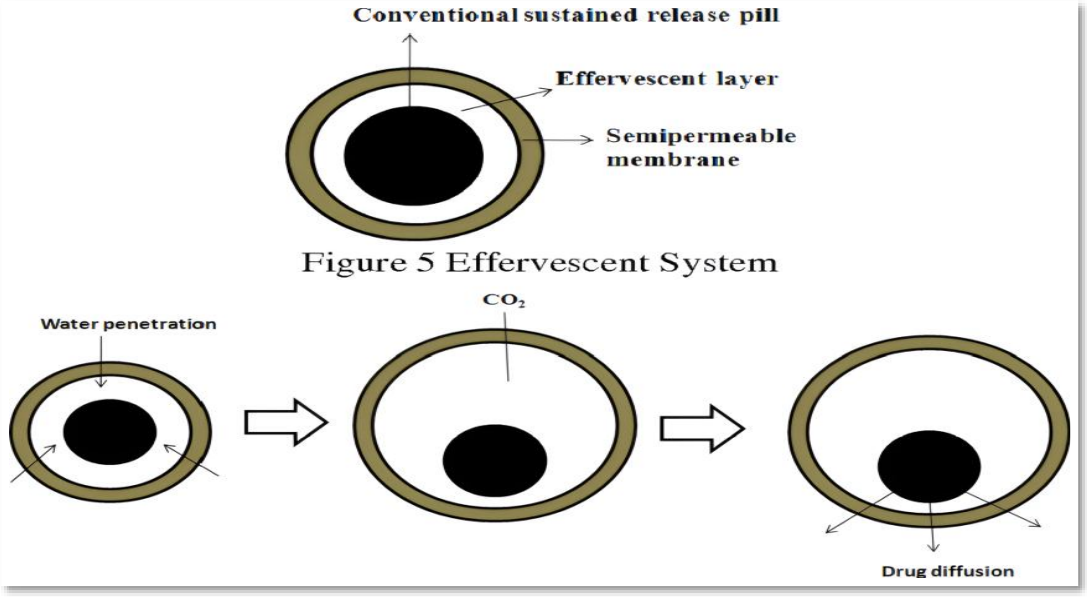


Figure 1.8 Effervescent (gas generating) system.[125]

Source: https://www.researchgate.net/figure/Drug-release-from-effervescent-gas-generating-systems_fig2_202883617

1.9 Advantages of gastroretentive drug delivery system (grdds):

Floating dosage devices represent a notable technological advancement in drug administration, exhibiting gastric retentive behavior and offering a myriad of advantages.

A. **Reduced adverse activity at the colon:** GRDF formulations, particularly those pharmacodynamic in nature, can lessen the likelihood of gastrointestinal adverse effects by reducing the drug's entry into the colon, an environment that can be challenging for microbial interactions.[37]

B. **Sustained drug delivery / reduced frequency of dosing:** GRDDS enable slower pharmacokinetic changes throughout therapy, improving patient compliance and treatment success by mitigating the pharmacokinetic flip-flop often associated with conventional frequent dosing. This translates to reduced dosing frequency.[37]

C. **Site-specific drug delivery:** In the small intestine, it is possible to control and slow down This strategy prolongs stomach availability and lessens detrimental effects on blood flow, allowing for less frequent dosing.[37]

D. **Enhanced bioavailability:** Compared to non-GRDF controlled-release polymeric formulations, GRDDS, such as a Riboflavin CR-GRDF, demonstrate superior bioavailability by optimizing the processes of drug absorption and transit within the gastrointestinal tract.[37]

E. **Extended time over critical (effective) concentration:** For certain drugs, such as beta-lactam antibiotics, therapeutic effectiveness is more closely linked to the duration of time spent above a critical therapeutic concentration rather than merely peak concentration[1]. Even for non-concentration-dependent pharmacodynamics, prolonged periods of maintaining blood levels above a threshold concentration can enhance pharmacological effects and overall therapeutic outcomes[37].

F. **Improved selectivity in receptor activation:** By reducing concentration variations that can activate different receptor types at varying dosages, the drug's pharmacological activity can be significantly increased and made more selective.[37]

G. **Reduced counteractivity of the body:** Slowing a drug's absorption into the body can increase its therapeutic efficacy because the body's physiological response to rapid drug disruption might trigger a rebound activity, which GRDDS can mitigate, thereby lowering the chance of side effects.[37]

H. **Target therapy for local ailments in the upper GIT:** Achieving a consistent release of therapeutic medicine from the GRDF, even with low systemic absorption and distribution of the drug, can significantly enhance therapy for localized stomach and intestinal conditions (e.g., gastritis, ulcers).[37]

I. **Reduced fluctuations of drug concentration:** Especially crucial for medications with a narrow therapeutic window, GRDDS treatment with CRGRDF ensures constant drug effects and minimizes unwanted effects from peak concentrations by producing blood drug concentrations within a tighter, more desirable range.[37]

J. **Enhanced first-pass biotransformation:** Studies suggest that extended drug input to metabolic enzymes, particularly CYP3A4, can significantly improve a substance's pre-systemic metabolism for certain drugs.[37]

1.10 Limitations of gastroretentive drug delivery systems (grdds)

Despite their numerous advantages, GRDDS also certain limitations:

A. **Solubility:** GRDDS are not practical for drugs that have inherent solubility issues throughout the GI tract, especially if they are poorly soluble in gastric fluid.[38]
B. **High level of fluid:** The gastrointestinal tract requires a significant amount of fluid for the floating system to transport medication efficiently. For optimal performance, FDDS should typically be consumed with 200–250 cc of water.[39]
C. **First-pass metabolism:** Drugs undergoing extensive first-pass metabolism may not be ideal candidates for systems that primarily retain food in the stomach, as this could lead to prolonged exposure to metabolizing enzymes without achieving desired systemic levels.[40]
D. **Gastro-irritant drugs:** Medications that irritate the stomach mucosa are generally undesirable for GRDDS, as prolonged contact could exacerbate irritation.[41]
E. **Stability:** GRDDS are not recommended for drugs that break down or are unstable in the stomach's acidic pH.[42]
F. **Absorption throughout the GIT:** Medications that are absorbed uniformly throughout the digestive tract are not ideal candidates for GRDDS. The medication should ideally have a restricted window of absorption within the GIT.[43]

1.11 Factors affecting floating drug delivery systems

Several factors can influence the performance of a floating drug delivery system:

A. **Rate of dissolution of drug:** If the formulation fails to retain a medicine that dissolves fast in water, it will soon pass through the pylorus.[44]
B. **Density:** As previously stated, low-density systems float on top of the gastric fluid, and high-density systems sink to the stomach's bottom.[45]
C. **Disease state:** The presence of certain illnesses can alter a person's GRT, affecting the performance of GRDDS.[46]
D. **Shape of dosage form:** It is stated that devices with ring and tetrahedron geometries have greater GRT than devices of other forms.[47]
E. **Posture:** Patient posture can significantly change GRT.[48]

F. **Meal type:** Eating indigestible polymers or fatty salts can shift the motility pattern of the stomach to a fed state, delaying the pace of gastric emptying and extending the period that medicine is released from the stomach..[49]

G. **Gender:** For the same age group, the male GRT (3.4 ± 0.6 hours) is typically less than the female GRT (4.6 ± 1.2 hours).[50]

H. **Concomitant drug administration:** Co-administration of other medications can influence GRT. For example, prokinetic drugs (like metoclopramide and cisapride) can accelerate emptying, while anticholinergic drugs (like atropine and propantheline) can delay it.[51]

I. **Caloric content:** GRT can be significantly elevated (e.g., four to ten hours) after consuming a high-protein meal.[52]

J. **Nature of drug:** When taken with food, water-soluble pharmaceuticals often leave the stomach with water, whereas fat-soluble drugs leave the stomach with lipids and are eventually eliminated.[53]

K. **Age:** The GRT is notably longer in older patient groups compared to younger groups.[54]

L. **Fed or unfed state:** During a fast, MMC occurs every 1.5 to 2 hours, increasing stomach motility and decreasing the gastric motility threshold. However, in the federal state, GRT is substantially longer, and MMC is postponed.[55]

M. **Frequency of feed:** The consumption of multiple small meals versus a single large meal can result in a significant GRT increase (e.g., more than 400 minutes) due to a lesser influence of the MMC.[56]

N. **Size:** Dosage form units with larger diameters and capacities are generally associated with a greater GRT. As volume increases, density will decrease, which facilitates floating. Devices with a larger diameter are said to have a greater GRT than those with a smaller one.[57]

O. **Time of drug administration:** When ingesting a single-unit system, strong peristaltic impulses during Phase III of the MMC can dramatically increase the likelihood of the drug being prematurely expelled into the duodenum.[58]

1.12 Advantages of floating drug delivery systems

Floating dosage devices represent a notable technological development in drug administration systems, showing gastric retentive behavior and providing several significant advantages.[59]

A. **Delivery of medication to designated areas:** FDDS allows for targeted delivery to the upper GI tract, optimizing absorption where it's most effective.[60]

B. **Useful in diarrhoea/frequent bowel movements:** FDDS are helpful because they keep the medication floating inside the belly, providing a somewhat improved response even when there is diarrhoea or frequent bowel movements that would otherwise rapidly clear the GI-tract.[61]

C. **Long-term buoyancy in liquids:** Dosage forms like tablets and capsules can float in liquids for a long time, especially at acidic gastric pH levels, ensuring extended residence.[62]

D. **Enhanced patient compliance and ease of administration:** By potentially reducing dosing frequency, FDDS contribute to improved patient compliance and simpler administration-regimens.[63]

E. **Primary focus on treating gastrointestinal diseases:** These systems are particularly beneficial for treating GI conditions, especially reflux illness, by providing sustained localized drug action.[64]

F. **Reduced gastric irritation:** For medications like aspirin that might irritate the stomach wall upon contact, FDDS formulation can be useful by maintaining the drug at the surface of gastric fluid, thereby minimizing direct contact with the mucosa.[65]

G. **Controlled and gradual drug release:** Medication distribution involves giving the medicine gradually and at a controlled rate, which minimizes pain and maintains control over the medication's effects on the mucosal system.[66]

H. **Beneficial for locally active drugs:** FDDS are beneficial for medications intended to work locally within the GIT, providing sustained presence at the site of action.[67]

1.13 Disadvantages of floating drug delivery systems

Despite their benefits, Floating Drug Delivery Systems (FDDS) also come with certain limitations:

A. **Supine emptying variability**: The stomach emptying of floating forms in supine individuals may vary significantly depending on the size and diameter of the form. As a result, giving patients floating dosage forms before bed is not recommended, as the dosage form might not remain buoyant effectively.[68]

B. **Dependence on gastric fluid volume**: The operation of floating systems depends on the availability of sufficient gastric fluid for optimal buoyancy. In conditions with limited gastric fluid, their function may be impaired.[69]

C. **Difficulty in predicting gastric retention**: Gastric retention is influenced by various factors such as gastric motility and pH, making it difficult to precisely predict the residence time of the dosage form.[70]

D. **Incompatibility with unstable/soluble drugs**: FDDS are not suitable for drugs that are unstable in acidic conditions or have high solubility in gastric fluids, as this may lead to premature release or degradation.[71]

E. **Requirement for food**: The effectiveness of floating systems often requires the presence of food in the stomach to prolong gastric retention by maintaining the fed state.[72]

F. **Bioavailability reduction for extensive absorption**: If a drug is absorbed predominantly in the small intestine, FDDS might reduce its systemic bioavailability due to delayed transit to the absorption site.[73]

G. **Irritant drugs**: Drugs that cause irritation to the gastric mucosa are not suitable for floating systems because of their prolonged contact with the gastric lining.[74]

1.14 Application of floating drug delivery system

Floating Drug administration Systems are critical for improving drug administration to the upper GI tract and increasing the bioavailability of medicines with narrow absorption windows.[75]

A. **Reduced fluctuations of drug concentration**: Continuous release Gastroretentive formulations (CRGRDFs) minimize drug level fluctuations and reduce side effects caused by peak plasma levels.[76]
B. **Absorption enhancement**: Floating devices improve the absorption of drugs with poor solubility or stability in the distal GIT.[77]
C. **Pharmacotherapy of the stomach**: GRDFs deliver drugs directly to the gastric mucosa to treat gastric ulcers, esophagitis, and gastritis, and are used in antacid formulations like calcium-carbonate.[78]
D. **Minimized adverse activity at the colon**: Floating systems help in avoiding premature drug delivery to the colon, reducing colonic side effects and microbial resistance, especially in antibiotic therapy.[79]
E. **Sustained release drug delivery**: HBS formulations provide prolonged drug release by remaining buoyant in the stomach for extended periods, overcoming the limitations of conventional controlled-release forms.[80]
F. **Site-specific drug delivery**: Drugs absorbed in the stomach or proximal small intestine, such as riboflavin and furosemide, benefit significantly from FDDS due to optimized exposure.[81]
G. **Delivery of sparingly soluble and insoluble drugs**: FDDS enhance the gastric residence of sparingly soluble drugs, allowing better dissolution and absorption by overcoming rapid GIT transit.[82]

1.15 Criteria for selection of drug candidate for fdds.

Drugs suitable for floating systems meet at least one of the following criteria:

A. **Local action in the stomach**: Drugs like Misoprostol, 5-Fluorouracil, antacids are meant to act locally in the stomach.[83]
B. **Site-specific absorption**: Drugs like Atenolol, Furosemide, Levodopa, and Salbutamol are absorbed in the stomach or proximal small intestine.[84]
C. **Unstable in lower GI tract**: Examples include Captopril, which degrades in the distal GIT.[85]
D. **Acid-soluble basic drugs**: These drugs, such as Diazepam, Diltiazem, and Chlordiazepoxide, dissolve well in acidic pH but poorly in the intestine.[86]
E. **Narrow absorption window**: Drugs such as L-DOPA, furosemide, and riboflavin have a short GIT absorption window requiring prolonged gastric retention.[87]
F. **Locally active in the stomach**: e.g., Misoprostol and antacids used for treating peptic ulcers and reflux disorders.[88]

G. **Instability in intestine/colon**: Drugs like Metronidazole and Ranitidine HCl are unstable in the intestinal environment and need protection.[89]

H. **Disturbance to colonic microbes**: Antibiotics such as Amoxicillin and Clarithromycin used for H. pylori treatment benefit from stomach-targeted delivery to avoid colonic disruption.[90]

I. **Low solubility at high pH**: e.g., Diazepam and Verapamil, whose solubility decreases at intestinal pH.[91]

Because of its simplicity, patient compliance, and cost-effectiveness, oral medication delivery is the most popular and convenient method of administration.[92] However, certain medications have problems, such as low bioavailability due to limited absorption windows or gastrointestinal instability.[93] Gastroretentive drug delivery systems (GRDDS) provide a strategic strategy for increasing the therapeutic efficacy of such medications by extending their stomach residence period.[94] These systems are meant to keep the dosage form in the stomach for an extended amount of time before releasing the medicine in a regulated manner.[95]

GRDDS can take numerous forms, including floating systems, mucoadhesive systems, expandable systems, high-density systems, and superporous hydrogels.[96] Floating medication delivery devices are the most commonly used because they are simple and effective.[97] Because of their lower density than gastric content, floating systems remain buoyant on gastric fluid and distribute drugs to the stomach and upper small intestine at particular locations.[98]

1.16 Lovastatin

Lovastatin is a lipid-lowering medication that belongs to the class of HMG-CoA reductase inhibitors (statins). It is commonly used to treat hypercholesterolemia and prevent cardiovascular disease.[100] This lactone prodrug inhibits HMG-CoA reductase, the rate-limiting enzyme in cholesterol manufacture, by hydrolyzing in vivo to its active β-hydroxy acid form.[101] Despite its therapeutic effectiveness, lovastatin has a bioavailability of just around 5% due to substantial first-pass metabolism and low water solubility.[102]

Moreover, lovastatin has a short biological half-life of about 2.2 hours, necessitating frequent administration to maintain therapeutic plasma concentrations.[103] To overcome these limitations, the development of a gastroretentive floating drug delivery system for lovastatin can be a promising approach.[104] Such a system can enhance drug solubility, prolong gastric retention, and sustain drug release, leading to improved bioavailability and reduced dosing frequency.[105]

Natural polymers have gained immense attention in pharmaceutical formulations due to their biodegradability, biocompatibility, low cost, and non-toxic nature.[106] These polymers can be used as matrix formers, swelling agents, and release retardants in floating tablet formulations.[107] Commonly employed natural polymers include guar gum, xanthan gum, pectin, tamarind seed powder, and sodium alginate .[108]

Guar gum is a non-ionic polysaccharide obtained from Cyamopsis tetragon Loba seeds and is known for its high viscosity and swelling properties, making it suitable for controlled drug delivery systems.[109] Xanthan gum is another microbial polysaccharide with excellent swelling and mucoadhesive characteristics, which help in prolonging gastric residence time.[110] Pectin, a natural polymer derived from the cell walls of fruits, especially citrus fruits, is an anionic polysaccharide capable of forming gel-like structures in acidic environments.[111] Tamarind seed polysaccharide, extracted from Tamarindus indica seeds, is a hydrophilic polymer that swells in the presence of gastric fluid and contributes to sustained drug release.[112]

Floating drug delivery systems require the presence of gas-generating chemicals such as sodium bicarbonate or citric acid, which react with gastric acid to produce carbon dioxide that is trapped inside the polymer matrix, lowering the dosage form's density and allowing it to float.[113] The polymer content and type have a substantial impact on the floating lag time, total floating time, swelling index, and drug release kinetics.[114]

Several investigations have shown that natural polymers have potential for use in the development of gastroretentive floating devices. Patil et al., for example, used tamarind seed powder to create a floating matrix tablet of metformin that released the medicine continuously for 12 hours.[115] Similarly, Sreenivas et al. created floating ciprofloxacin pills with xanthan gum and demonstrated enhanced bioavailability and an extended-release profile.[116] These findings support the use of natural polymers in the production of floating tablets for medications such as lovastatin.[117]

In addition to polymers, excipients such microcrystalline cellulose (MCC), magnesium stearate, and lactose are utilized to improve tablet compressibility, lubrication, and flowability.[118] The measures used to evaluate floating tablets are hardness, friability, weight fluctuation, drug content uniformity, in vitro buoyancy studies, swelling index, and in vitro drug release studies.[119] To replicate physiological circumstances, in vitro drug release is often carried out in simulated stomach fluid (pH 1.2).[120]

Furthermore, kinetic modeling of the drug release profile aids in comprehending the mechanism of drug release from the matrix system. To get the best match, the release data is fitted into models such as zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas equations.[121] Stability studies following ICH recommendations are required to assess the formulation's physical and chemical stability under accelerated settings.[122]

Thus, the formulation and evaluation of a lovastatin gastroretentive floating tablet based on natural polymers aims to solve its pharmacokinetic constraints, improve stomach retention, improve therapeutic efficacy, and assure greater patient compliance.[123] The successful creation of such a formulation may provide a unique strategy to the effective control of hypercholesterolemia utilizing natural and safe polymeric excipients.[124]

2. LITERATURE REVIEW

Meenakshi et al. (2023): The study's purpose was to develop a floating matrix tablet of mitiglinide that would absorb more efficiently after spending more time in the stomach. Sodium bicarbonate, sodium alginate, and HPMC K15M were utilized as gas-forming and matrix-forming polymers. Using a full factorial design of 32 improved medication release and flotation qualities. The drug's 50%, 90%, and foamy lag times were all dependent variables. The drug and excipient compatibility were determined using FTIR. The medication content, frying time, stability, hardness, friability, and in vitro dissolution of the tablets were all evaluated. The analysis of dissolution data using kinetic models revealed a drug release mechanism. To determine how long the body would retain the optimal feeding matrix tablets containing mitiglinide, a radiographic examination was eventually done. The results show that the physical parameters of the developed formulations are all within normal norms. Because M3 has the most independent variables, it was chosen as the best formulation. A radiographic study revealed that the pills float in the rabbit is stomach contents for up to 12 hours.[132]

Jagan et al. (2022): Tinidazole floating tablets are intended to improve absorption and bioavailability by extending the drug's stay in the stomach. The goal of these pills is to increase stomach residence, which improves the drug's therapeutic efficacy. They are made up of a range of polymers, including guar gum, sodium alginate, eudragit, and carbopol. The tablets produced good post-compression assessment findings in terms of content homogeneity, hardness, weight fluctuation, thickness, floating lag time, and total floating time. In contrast to the other formulations, formulation f2 provided better controlled drug release and floating properties.[133]

Nawaf et al. (2022): The QbD method was used to design and optimize the lomoxicam dispersion tablet product. Content homogeneity, friability, filler ratio, dispersion length, dissolving efficiency, disintegrant concentration, and mixing time were all evaluated. FTIR and DSC were utilized to study the drug-excipient interaction and seek for accelerated stability. FTIR analysis demonstrated that there was no detectable chemical interaction in the solid state, emphasizing the importance of design in achieving consistency. The LX endothermic peak showed a line reduction due to the diluting action, as evidenced by the DSC thermogram. The friability of the LXDT formulations ranged between 0.9% and 0.2. The dissolving efficiencies of the LXDT formulations ranged between 72.21 and 93.63%. The findings of the entire experiment revealed that the best concentrations of independent components were 6.23%, an 11-minute mixing time, and a 3:1 MCC/Mannitol ratio. Using the QbD technique can help gain a full understanding of how CMAs and CPPs influence CQAs in the LXDT outcome.[134]

Chanam et al. (2019): The study investigates the use of floating medication delivery devices to increase gastric retention and produce a dose form that is less thick than stomach fluid. The device floats above the stomach contents without affecting how quickly it empties. Sodium bicarbonate was employed as a gas

generator, while microcrystalline and hydroxypropyl methylcellulose were used to control the drug's release throughout the dry granulation process. Five different formulations with differing amounts of MCC and HPMC were produced. With a floating lag time of 40 seconds, the enhanced formulation FS had a medication release percentage of 33.17% after 12 hours. According to the study, gas-generating agents and HPMC can be employed to generate gastro-retentive floating tablets, ensuring regulated medicine release over time.[135]

Raghavendra et al (2019): The study aims to create a gastro-retentive roxifloxacin by combining multiple drug release modifiers. Moxifloxacin is a brand-new synthetic fluoroquinolone antibiotic. Methods: To make SR granules, loxifloxacin gastro-retentive pills were used. HCI was created using a wet granulation process with varying amounts of Lannea coromandelica gum (LCG) and HPMCK100M. Precompression studies and drug release properties were investigated in ten distinct SR granule formulations. Based on the results, polymer concentrations are chosen and used in tablet formulations. Six different tablet formulations were created and tested for use in various pharmacopeial assays. The results reveal that when polymer viscosity falls, so does the retention time. F16 manufactured with LCG demonstrated the highest swelling property. The formulation's longer Gl residency time is most likely owing to its strong bioadhesive qualities.[136]

Saddam et al. (2018): The goal of the study was to develop gastro-retentive floating tablets that would allow Ibuprofen to remain in the upper gastrointestinal tract or stomach for an extended period of time due to the low bulk density of stomach gastric fluids. Ibuprofen is an anti-inflammatory medication. Design formulation was attained by trial and error. Four batches of ibuprofen floating tablets were produced utilizing xanthan gum, sodium bicarbonate, HPMC, and citric acid as gas-producing agents. The research looked at the drug content, buoyancy tests, weight variation, and 13-hour drug release of the improved formulation F4. It demonstrated a considerable divergence in the releasing procedure by demonstrating expected features and floating behavior within the permissible range.[137]

Raghavendra et al. (2017): The two most advanced drug delivery systems that have advanced greatly over time are in vitro and in vivo. These strategies seek to increase GRT by concentrating on specific difficulties with medicinal components and formulations. GRFDDS, polymeric bioadhesive systems, high density systems, and expanding and swelling systems are examples of such systems. Most of the polymers employed in these systems are derived from natural sources. Because floating medicine delivery devices have lower viscosity than stomach juices. The review paper gives an overview of the most recent technical breakthroughs in floating drug delivery systems, including their primary Dotation mechanism, the results, and potential applications of in vitro and in vivo research.[138]

Swati et al. (2016): This study sought to address the issue of unequal and restricted bioavailability in oral drugs by creating a gastro-retentive pharmaceutical delivery system capable of administering propranolol hydrochloride. It was determined whether polymers such as xanthan gum and sodium alginate could form gels. Propranolol's high first-pass metabolism means that only 25% of it enters the bloodstream. Propranolol is more accessible after meals, and the P-glycoprotein (P-gp) efflux transporter aids in its absorption in the distal gastrointestinal system. Propranolol floating pills were designed to keep the medicine in the upper gastrointestinal tract for longer periods of time. Preliminary studies revealed that formulations including sodium alginate, HPC, and HPMC E 15 LV had poor floating properties, however formulations containing xanthan gum had superior drug retention capacities. Finally, HPMC K4 M and HPC were employed in the floating tablet formulation.[139]

Shammy et al. (2016): This study investigates how excipients affect the buoyancy and medication release properties of floating tablets. Gastro-retentive tablets were produced with rate-controlling polymers such as HPMC K4M, carbopol 971P, carbopol 934P, and Crosspovidone. The effects of formulation parameters on tablet performance were measured by analyzing buoyant properties, swelling behavior, and drug release characteristics using mathematical models to investigate the drug release mechanism. Cross povidone and HPMC/carbopol matrices have been shown to reduce oedema while also improving medication release. The non-Fickian process of the drug release technique was demonstrated when paired with sodium bicarbonate, demonstrating a superior release pattern for up to 24 hours.[140]

Bhabani et al. (2015): The pharmaceutical industry is investigating potential uses for the gastro-retentive oral medication delivery device known as the Floating medication Delivery device (FDDS). The goal of this research is to learn more about FDDS, namely its current and future developments. By prolonging the stomach residence time, FDDS.[141]

Hesham et al. (2014): The goals were to increase the solubility of lornovicam (LOR) and produce small tablets utilizing an enhanced technique that would offer a multi-particulate formulation with quick release. LOR systems were created via co-adsorption onto Neusilink USZalone or Pluronic RF-68 (PLU) in the presence of different polysorbate 80 concentrations. All systems were evaluated using FT-IR, differential scanning calorimetry, and flowability. Mini tablets were produced with technology that provided the best dissolving rate and flowability. The impact of excipient settings and storage on the properties of tiny tablets were studied, with an emphasis on content uniformity and tensile strength. The rapid-release LOR-optimized mini-tablet formulation displayed increased flowability and faster dissolving. It was consequently chosen for additional in vivo testing. The pharmacokinetic profile indicated the fast release and higher absorption of LOR given by the mini tabs.[142]

Ghorpade et al. (2014): This review of recent research on gastro-retentive floating medication delivery devices focuses on the basic mechanism of stomach retention while floating. High blood pressure is one of the most common disorders worldwide. It currently affects an estimated 143 million individuals globally, and this figure is growing rapidly. The goal of the study is to find a short gastric residence time (GRT). These will be extremely useful in the administration of medications with a "narrow absorption window". Four technologies have been applied in various human therapeutic studies: expansion, mucoadhesion, floating, and density modification. The floating drug distribution method increases the time that medication spends in the stomach by enabling it to float on the stomach's contents and surrounding tissue for several hours. Scientific and technical breakthroughs have allowed for novel routes to pharmaceutical delivery, such as the oral route, which addresses physiological concerns such as irregular gastric emptying intervals and short stomach residence times. This paper discusses recent improvements in stomach-specific antihypertensive medicines created as floating drug delivery systems.[143]

Kodalkar et al. (2014): In this study, lornoxicam tablets with sustained release are created using the direct compression approach. The hydrophilic polymer concentrations used in Lonoxicam long-lasting release tablets differ depending on the viscosity class. Micromeritic characteristics were investigated as part of the initial formulation studies for excipient-based medication combinations. The tablet underwent several tests, including physicochemical, kinetic, and in vitro drug release experiments. FTIR analysis revealed no interaction between the polymers and the medication. The pills' physicochemical properties were confirmed to be within permissible limits. Rheumatoid arthritis is one of the most common conditions treated with first-generation analgesics, such as lornoxicam.[144]

Parmar et al. (2014): This review focused on Floating Drug Delivery Systems (FDDS) as a novel strategy to improving stomach retention and bioavailability of medications that absorb at particular sites in the upper gastrointestinal tract. The article divided FDDS into effervescent and non-effervescent systems, highlighting their processes, formulation methodologies, and types (e.g., single- and multiple-unit systems). Factors influencing stomach retention were reviewed, including dose form size, density, fed/fasting state, and illness status. The review also discussed several polymers utilized in floating dosage forms, including HPMC, Carbopol, and natural gums, as well as evaluation measures such as floating lag time, swelling index, in vitro drug release, and in vivo radiography examinations. FDDS uses include sustained drug release, better bioavailability, less drug waste, and local gastric therapy. Despite the benefits, issues such as irregular stomach emptying and gastric physiology variability were discovered. The authors concluded that FDDS offer a viable route for efficient and regulated oral medication delivery for specific therapeutic purposes.[145]

Uttam et al. (2013): GRDDS's popularity has grown dramatically. This strategy, which is frequently employed to resolve difficulties with traditional oral administration, entails retaining the recommended dosage in the gastrointestinal tract for an extended period of time before gradually releasing the medication. GRDDS are being developed employing a range of cutting-edge approaches, including as plug-type swelling

systems, floating systems with or without effervescence, mucoadhesion techniques, and magnetic field-assisted gastroretention. In addition to in vitro testing, a well-planned in vivo study is required for the successful development of GRDDS in order to demonstrate improved gastro-retention and longer drug release. The duration of in-vivo stomach occupancy can be determined using two commonly utilized methods: MRI and gamma scintigraphy. It remains challenging to assess the overall in vivo efficacy of this sort of dose form in animals such as mice and rats. Although there are numerous effective in vitro outcomes, there are few published in vivo trials including humans, rabbits, or beagle dogs. Despite all of the advantages, the market supply of GRDDS is limited by variables such as meal effects. This review study describes the existing GRDDS in vivo initiatives, as well as their limitations and outstanding difficulties that require immediate attention.[146]

Spandana et al. (2014): This study aimed to create bilayer floating tablets that combined an instant release layer of lovastatin with a sustained release layer of simvastatin to successfully manage hyperlipidaemia. The immediate release layer was created utilizing super disintegrants such as sodium starch glycolate, croscarmellose sodium, and L-HPC, whereas the sustained release layer was created using HPMC K100M, sodium alginate, and Polyox WSR 303. Sodium bicarbonate was utilized as a gas-generating agent to add buoyancy. The floating tablets released 90% of the lovastatin within 30 minutes, while simvastatin was released over a 12-hour period. Simvastatin drug release was controlled, as evidenced by zero-order, Korsmeyer-Peppas, and Hixson-Crowell kinetics. Based on dissolving characteristics, S4 (for simvastatin) and SL9 (for lovastatin) were shown to be the most optimal formulations. FTIR investigations demonstrated drug compatibility with excipients, and stability testing done in accordance with ICH guidelines revealed no significant changes in drug content or physical appearance over a three-month period. This bilayer pill achieved biphasic release and shown the potential for effective and prolonged therapy of lipid diseases.[147]

Khosro et al. (2013): This technique enhances drug absorption by manipulating stomach emptying. As a result, medication release time is greatly lengthened, dosage intervals are extended, and drug bioavailability is raised. As a result, patient adherence and medication effectiveness have improved. This article covers the key concepts driving the development of pharmacological dosage forms with extended stomach residence periods. It also discusses the factors that affect stomach emptying, the benefits and drawbacks, formulation challenges, and the factors that influence gastro-retentive systems. The main focus is on the many GRDDS types and the classification as a whole. Finally, a summary of the evaluation methodologies employed by these systems has been provided.[148]

3. DRUG AND EXIPIENTS PROFILE

3.1 Drug profile:

3.1.1 Lovastatin[149-159]

1. **Name of drug:** Lovastatin
2. **Chemical structure:**

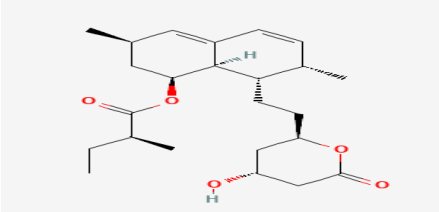


Figure 3.1 Lovastatin structure

3. **IUPAC name:** (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2-methylbutanoate.
4. **Molecular formula:** $C_{24}H_{36}O_5$.
5. **Molecular weight:** 404.55 g/mol.
6. **Category:** HMG-CoA reductase inhibitor.
7. **Appearance:** White to off-white crystalline powder.
8. **Odor:** Odourless.
9. **Functional category:** Cholesterol-lowering agent, Cardiovascular therapeutic.
10. **Storage guidelines:** Store at room temperature (15°C–30°C). Avoid high humidity and heat.
11. **Applications in pharmaceutical formulation:** Used as a lipid-lowering agent in hypercholesterolemia and related conditions.
12. **Description:** Lovastatin is a natural chemical formed during the fermentation of Aspergillus terreus or Monascus purpureus (red yeast rice).It operates by blocking HMG-CoA reductase, an enzyme involved in cholesterol production. This process efficiently reduces LDL cholesterol levels and is linked to a considerable reduction in cardiovascular disease risk. Lovastatin is a prodrug that must be converted to its beta-hydroxy acid form by the liver before it can be used pharmacologically.

3.2 Excipients profile

3.2.1 Hydroxypropyl methylcellulose k100 (HPMC K100)[160]

1. **Name of drug:** Hydroxypropyl Methylcellulose K100 (HPMC K100)
2. **Chemical structure:**

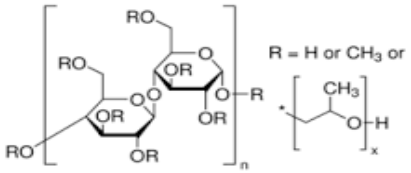


Figure 3.2 HPMC K100 structure

3. **IUPAC name:** 2-Hydroxypropyl methylcellulose.
4. **Molecular formula:** C10H18O6.
5. **Molecular weight:** Approx. 86,000 to 1,200,000 g/mol, depending on the polymer grade and viscosity.
6. **Category:** Controlled release polymer, Film-former.
7. **Appearance:** White to off-white, fibrous or granular powder.
8. **Odor:** Odorless.
9. **Functional category:** Binder, Film-coating agent, Thickener, Controlled-release agent, Suspending agent.
10. **Storage guidelines:** Store in a cool, dry place, keep container tightly closed, Protect from moisture and high temperatures, Store below 25°C.
11. **Applications in pharmaceutical formulation:** Used in controlled release formulation, Binder in wet granulation, Film-coating agent for tablets, Thickener in oral and topical formulations, Suspending agent in liquid formulations.
12. **Description:** HPMC K100 is a non-ionic cellulose ether produced through chemical modification of natural cellulose. It is commonly utilized in pharmaceutical formulations as a hydrophilic matrix forming in sustained release systems. The "K100" grade refers to a high-viscosity substance that is appropriate for creating strong, stable gel barriers in tablets that limit medication release by diffusion.

3.2.2 Hydroxypropyl methylcellulose k4m (HPMC K4M) [160]

1. **Name of drug:** Hydroxypropyl Methylcellulose K4M (HPMC K4M)
2. **Chemical structure:**

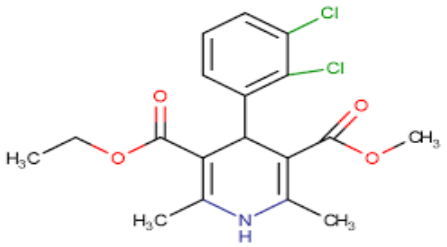


Figure 3.3 HPMC K4M structure

3. **IUPAC name:** 2-Hydroxypropyl methylcellulose
4. **Molecular formula:** C10H18O6
5. **Molecular weight:** Ranges from ~10,000 to 1,000,000+ g/mol depending on grade. For **K4M**, average molecular weight is typically around **86,000 to 150,000 g/mol**.
6. **Category:** Pharmaceutical excipient modified cellulose polymer, Controlled-release matrix former.
7. **Appearance:** White to off-white, fibrous or granular powder
8. **Odor:** Odourless.
9. **Functional category:** Hydrophilic matrix former for sustained release, Binder in tablets, Film-former, thickening agent, Suspending agent.
10. **Storage guidelines:** Store in a cool, dry place, keep container tightly closed, Protect from heat, moisture, and direct sunlight, Ideal storage temperature: below 25°C.
11. **Applications in pharmaceutical formulation:** Used in sustained-release matrix tablets, improves tablet integrity and control of drug release, Film-coating for tablets and capsules, Thickening and stabilizing agent in suspensions and topical gels.
12. **Description:** HPMC K4M is a high-performance cellulose ether polymer that is commonly utilized in pharmaceutical formulations as controlled-release oral dosage forms. The "K4M" implies a viscosity of around 4,000 mPa·s, ideal for creating moderate gel strength matrices.

3.2.3 Guar gum[160]

1. **Name of drug:** Guar Gum
2. **Chemical structure:**

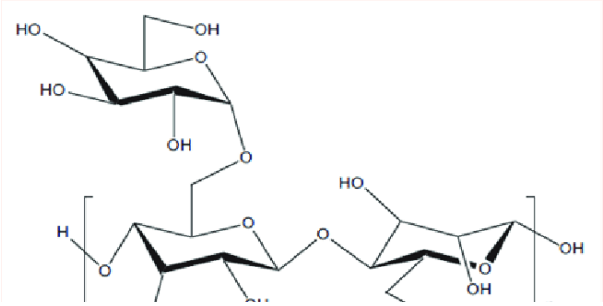


Figure 3.4 Guar gum structure

3. **IUPAC name:** (1→4)-β-D-Mannopyranan, with α-D-galactopyranose side chains
4. **Molecular formula**: C10H18O9
5. **Molecular weight:** 50,000–8,00,000 g/mol
6. **Category:** Natural polymer
7. **Appearance:** Off-white to yellowish-white powder
8. **Odor:** Odorless
9. **Functional category:** Forms a gel matrix for sustained release and Promotes tablet disintegration.
10. **Storage guidelines:** Store in a tightly closed container in a cool, dry place, Recommended storage temperature: **15–25°C**.
11. **Applications in pharmaceutical formulation:** It acts as a stabilizer and thickener and also forms a gel-like matrix, aiding buoyancy.
12. **Description:** Guar gum is a naturally occurring, water-soluble polymer derived from guar plant seeds (Cyamopsis Tetragonoloba). It is commonly employed in pharmaceutical formulations because of its outstanding thickening, stabilizing, and gelling qualities. Guar gum quickly hydrates in the presence of water, forming a highly viscous solution or gel, making it ideal for controlled release and floating drug delivery systems. It is non-toxic, biodegradable, and biocompatible, making it a useful excipient for oral, topical, and liquid dosage forms.

3.2.4 Citric acid[160]

1. **Name of drug:** Citric acid
2. **Chemical structure:**

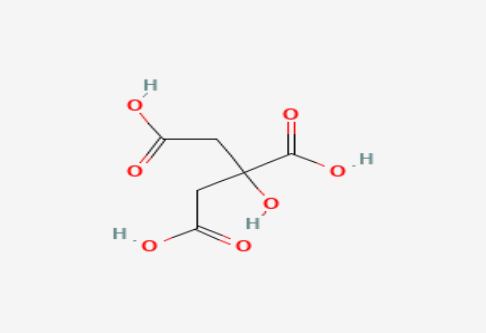


Figure 3.5 Citric acid structure

3. **IUPAC name:** 2-Hydroxy-1,2,3-propane-tricarboxylic acid
4. **Molecular formula**: $C_6H_8O_7$.
5. **Molecular Weight:** 192.12 g/mol.
6. **Category:** Chelating agent
7. **Appearance:** White or colorless crystalline powder or granules
8. **Odor:** Odorless
9. **Functional category:** It reacts with sodium bicarbonate to produce effervescence in floating and effervescent tablet formulations.
10. **Storage guidelines:** Store in a tightly closed container in a cool, dry place, Recommended storage temperature: **15–30°C**.
11. **Applications in pharmaceutical formulation:** It combined with sodium bicarbonate in effervescent tablets and powders and also maintain pH.
12. **Description:** Citric acid is a naturally occurring organic acid found in citrus fruits that is commonly employed in medicine, food, and cosmetic goods. It is a weak organic acid that is very soluble in water and can be used as an acidulant, buffer, or chelating agent in a variety of formulations. Citric acid is often utilized in pharmaceutical applications such as effervescent tablets, syrups, and suspensions to improve stability, pH, and flavor. Its role in effervescence makes it an important component in gastroretentive floating formulations, which assure quick pill buoyancy.

3.2.5 Sodium bicarbonate($nahco_3$) [160]

1. **Name of drug:** Sodium Bicarbonate
2. **Chemical structure:**

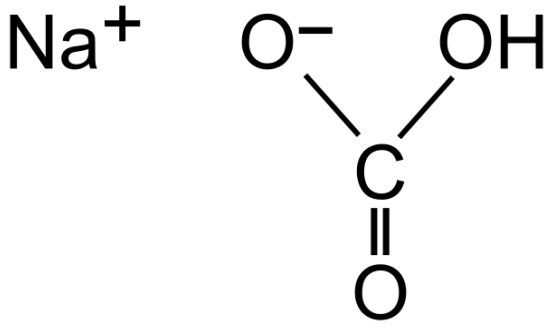


Figure 3.6 Sodium bicarbonate structure

3. **IUPAC name:** Sodium hydrogen carbonate.
4. **Molecular formula**: $NaHCO_3$.
5. **Molecular weight:** 84.01 g/mol.
6. **Category:** Effervescent agent.
7. **Appearance:** White crystalline powder or granules.
8. **Odor:** Odorless
9. **Functional category:** It Used in formulations to produce carbon dioxide, aiding buoyancy in floating drug delivery systems.
10. **Storage guidelines:** Store in a tightly closed container in a cool, dry place, Recommended storage temperature: **15–30°C**.
11. **Applications in pharmaceutical formulation:** It Combined with citric acid to produce carbon dioxide.
12. **Description:** Sodium bicarbonate, usually known as baking soda, is an inorganic salt that is commonly employed in pharmaceutical, food, and industrial settings. In pharmaceutical compositions, it acts as an effervescent, antacid, and pH adjuster. When dissolved in water, it reacts with acids to produce carbon dioxide gas, which can improve buoyancy in floating medicine delivery devices. Its non-toxic, affordable, and easily accessible character makes it a valuable component in a number of dosage forms, such as effervescent and gastroretentive tablets, antacid preparations, and oral electrolyte solutions.

3.2.6 Magnesium stearate[160]

1. **Name of drug:** Magnesium Stearate.
2. **Chemical structure:**

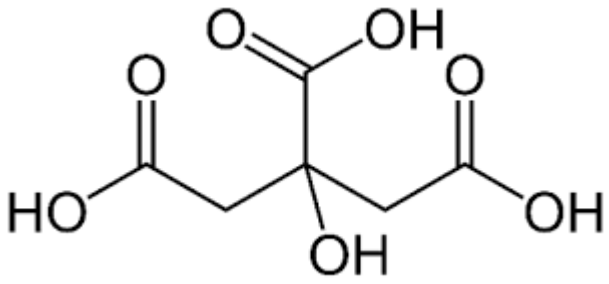


Figure 3.7 Magnesium stearate structure

3. **IUPAC name:** Magnesium octadecenoate.
4. **Molecular formula**: C36H70MgO4.
5. **Molecular weight:** 591.24 g/mol.
6. **Category:** Lubricant.
7. **Appearance:** Fine, white, or almost white powder.
8. **Odor:** Odorless
9. **Functional category:** It Used to reduce friction during tablet compression.
10. **Storage guidelines:** Store in a tightly closed container in a cool, dry place, Recommended storage temperature: **15–30°C**.
11. **Applications in pharmaceutical formulation:** It is used as a lubricant to improve the flow of powders and prevent sticking during compression and also for used as an anti-caking agent in the food industry.
12. **Description:** Magnesium Stearate is a popular pharmaceutical excipient renowned for its hydrophobic and lubricating qualities. It improves the manufacturing process by preventing powder combinations from sticking to the machinery, resulting in consistent tablet output. Its non-reactive nature makes it compatible with a wide range of medications and formulations. However, it is utilized in tiny doses (usually 0.25-5% w/w) since large concentrations can impair tablet breakdown. Magnesium Stearate is also employed in cosmetics and food goods, making it a versatile component in many industries.

3.2.7 Talc[160]

1. **Name of drug:** Talc
2. **Chemical structure:**

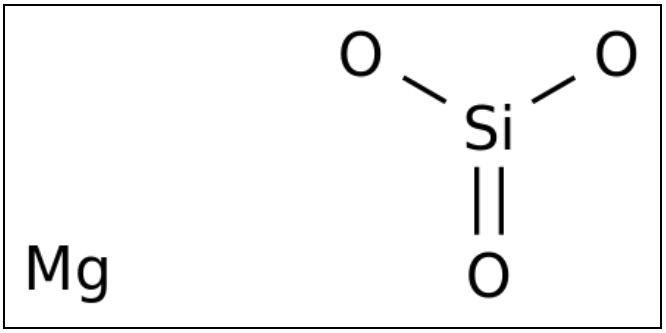


Figure 3.8 Talc structure

3. **IUPAC name:** Magnesium silicate hydroxide.
4. **Molecular formula**: $Mg_3Si_4O_{10}(OH)_2$.
5. **Molecular weight:** 379.27 g/mol.
6. **Category:** Glidant.
7. **Appearance:** Fine, white to grayish-white, unctuous crystalline powder**.**
8. **Odor:** Odorless.
9. **Functional category:** It Used to reduce friction during tablet compression.
10. **Storage guidelines:** Store in a tightly closed container in a cool, dry place and keep away from acids, alkalis, and other reactive substances.
11. **Applications in pharmaceutical formulation:** It acts as a lubricant and glidant to improve flowability and prevent sticking.
12. **Description:** Talc is a naturally occurring mineral made up of hydrated magnesium silicate. It is commonly employed in pharmaceutical formulations because of its excellent lubrication, anti-caking, and glidant qualities. It is chemically inert, non-toxic, and hydrophobic, making it an ideal excipient in a range of dosage forms. Talc has good flowability, which allows for homogeneous powder mixing and makes manufacturing operations easier. Its delicate texture and smooth feel make it ideal for use in topical applications such as dusting powder.

3.2.8 Lactose[160]

1. **Name of drug:** Lactose
2. **Chemical structure:**

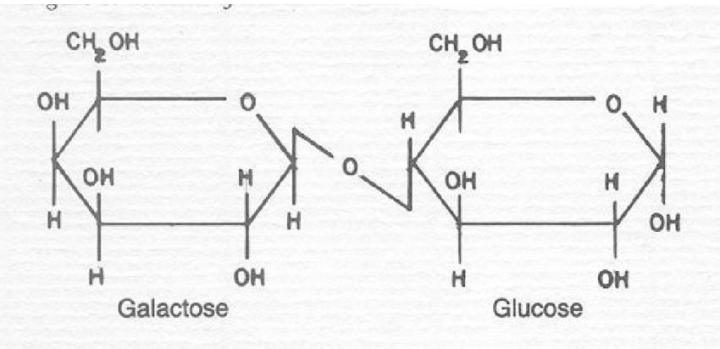


Figure 3.9 Lactose structure

3. **IUPAC name:** β-D-galactopyranosyl-(1→4)-D-glucose.
4. **Molecular formula**: $C_{12}H_{22}O_{11}$.
5. **Molecular weight:** 342.30 g/mol.
6. **Category:** Sweetening agent, filler
7. **Appearance:** White or off-white crystalline powder**.**
8. **Odor:** Odorless.
9. **Functional category:** It Provides cohesion in direct compression formulations, and most commonly used in tablet and capsule formulations.
10. **Storage guidelines:** Store in a tightly closed container in a cool, dry place and keep away from acids, alkalis, and other reactive substances, storage temperature: **15–30°C**.
11. **Applications in pharmaceutical formulation:** It Used as a filler in both direct compression and wet granulation processes.
12. **Description:** Lactose is a disaccharide sugar generated from milk that contains one molecule of glucose and one molecule of galactose. It is a well-known, chemically inert excipient utilized as a diluent in oral solid dosage forms due to its outstanding compressibility and mixing properties. Its mildly sweet flavor and low hygroscopicity make it ideal for direct compression, wet granulation, and dry granulation operations. Furthermore, lactose is commonly employed in dry powder inhalation products as a carrier for micronized medication particle.

4. AIM, NEED AND OBJECTIVES

4.1 Aim

Formulation, Development and Evaluation of Gastroretentive Floating Tablet of *Lovastatin* Using Natural Polymer.

4.2 Rationale

The development of gastroretentive drug delivery systems (GRDDS) is a critical technique for overcoming the limitations of traditional oral drug administration, especially for medicines with low solubility, limited stability in the intestinal environment, or a narrow absorption window. Lovastatin, a BCS Class II drug, has limited water solubility, resulting in unequal absorption and variable bioavailability when administered orally. Because it absorbs best in the stomach and upper region of the small intestine, it is a great candidate for a gastroretentive formulation.

Natural polymers including xanthan gum, guar gum, and pectin have considerable advantages for GRDDS. These polymers are biodegradable and non-toxic, forming a viscous gel matrix that allows for controlled medication release while keeping the tablet buoyant for extended periods of time. Using these attributes, the formulation is intended to increase gastric retention time, allowing the medicine to remain in the stomach for a longer period of time, improving dissolving and absorption characteristics.

4.3 Need of work

The main goal of the oral controlled medication delivery system's design was to increase and stabilize bioavailability. The optimal system should administer a single dose for the length of therapy, delivering the active medication directly to the designated spot and releasing it in a controlled manner. However, a variety of physiological issues, including variations in the stomach emptying process, make this challenging.

By changing the physiological condition and producing formulations that prolong the gastric emptying activity from a few minutes to twelve hours, this can be avoided. Extended stomach retention reduces medication waste and boosts bioavailability. The best possible bioavailability is being ensured by these systems. The purpose of the floating medication delivery system is to extend the duration of a medicine's stomach occupancy. Retained in the stomach, G.R.D.D.S. helps to improve oral sustained medication delivery. A third-generation cephalosporin antibiotic with bactericidal properties is cefixime. Cefixime, a weak acid with a pka value of 2.5, enhances absorption in the stomach area because it will remain unionized at an acidic pH.

4.4 Objectives

1. The purpose of this study is to develop a floating tablet that extends stomach retention time for an effective medication delivery system using a variety of polymers and combinations.
2. To enhance the flotation and controlled release properties of the dosage form.
3. To increase the therapeutic efficacy of lovastatin.

5. PLAN OF WORK

1. Literature review.
2. Selection of drug and excipients.
3. Preformulation studies.
   a) Determination of Organoleptic properties.
   b) U.V. Spectroscopy study.
      i. Determination $\lambda_{max.}$
      ii. Determination of standard calibration curve.
   c) Determination of Solubility studies.
   d) Determination of Melting point.
   e) Compatibility studies.
      i. FTIR studies.
4. Pre-compression studies of the sustained release powder or granule.
   a) Angel of Repose.
   b) Bulk density.
   c) Tapped density.
   d) Carr's index.
   e) Hausner's ratio.
5. Preparation of gastro-retentive floating tablet of lovastatin.
6. Evaluation of gastro-retentive floating tablet of lovastatin.
   a) Physical appearance.
   b) Tablet thickness.
   c) Tablet hardness.
   d) Weight variation test.
   e) Friability.
   f) In vitro buoyancy studies.
   g) Determination of drug content by simultaneous equation method.

h) Evaluation of in-vitro dissolution study of floating tablets by simultaneous method.

i) Evaluation of release kinetics of optimized floating formulation

6. MATERIALS & METHODS

6.1 Materials:

The following firms and suppliers provided the pharma grade and laboratory grade lovastatin, pharmaceutical excipients and other compounds that were used. The list of chemicals used with their names and suppliers is shown in table 6.1.

Table 6.1 List of chemicals.

Sr. No	Ingredients	Application	Suppliers
1	**Lovastatin**	API	Balaji agency
2	HPMC K15	Matrix forming polymer	Vishal chem
3	HPMC K 4	Matrix forming polymer	Vishal chem
4	Gaur gum	Matrix forming polymer	Vishal chem
5	Citric acid	Taste masking	Vishal chem
6	Sodium bicarbonate	Effervescent agent	Research lab fine chem industries
7	Magnesium stearate	Lubricant and glidant	Vishal chem
8	Talc	Lubricant and glidant	Research lab fine chem industries
9	Lactose	Binder	Vishal chem

The list of equipment, instruments and machines used is shown in table 6.2.

Table 6.2 List of equipment, instruments, makers and models.

Sr. No.	Equipment	Company
1	Digital balance	Wenser weighing balance PGB620
2	UV visible spectrophotometer	Jasco v730
3	Ultrasonic cleaner	Remi instrument
4	FTIR	Jasco FT/IR
5	Digital PH meter	Digisum electronics

6.2 Methodology:

6.2.1 Characterization of raw materials.

A. Melting point determination

The melting points of the drug samples were determined using the Thiel's tube method.[161]

B. Determination of λ_{max}

10 mg of Lovastatin were dissolved in one 100 ml of distilled water to create a stock solution of the medication (100 µg/mL). To find the drug's λmax, this solution was then diluted and subjected to spectroscopic analysis.[162]

6.2.2 Preparation of calibration curve for Lovastatin in acetonitrile

To create a stock solution with a concentration of 100 µg/mL, 10 mg of precisely weighed lovastatin was added to a 100 mL volumetric flask, and the volume was adjusted with acetonitrile. Aliquots of 1 mL to 5 mL were extracted from this stock solution and put into different 10 mL volumetric flasks. After that, acetonitrile was used to modify the quantities to create working solutions with 10–50 µg/mL of lovastatin.[163]

6.3 Compatibility studies

A. FTIR spectroscopy

The drug's purity and compatibility with the excipients were evaluated using FTIR spectroscopy.[164] The analysis was performed using a Jasco FTIR-4600 spectrophotometer, which generated spectra in the range of 400–4000 cm^{-1}. The same instrument was used to prepare and analyze drug-excipient combinations, pure drug samples, and individual excipient samples. The resulting spectra, obtained within the 400–4000 cm^{-1} range, were evaluated for any possible interactions or impurities.[165]

6.4 Evaluation of granules

The following tests were done on all types of polymers and pharmaceutical ingredients.[166]

A. Bulk density

The powder sample under test was filtered via sieve no.18, and the equivalent of 25 gm was carefully measured and put in a 100 ml graduated cylinder. The powder was leveled, and the unsettled volume, V_0, was recorded. The bulk density in gm/cm3 was estimated using the following formula.[167]

$$\text{Bulk density} = M/V_o$$

Where,

M = Mass of powder and

V_o = Apparent unstirred volume

B. Tapped density

The powder sample under examination was screened via sieve no.18, and a 25-gram sample was placed in a 100-ml graduated cylinder. The cylinder was tapped from a height of 2 inches until a steady volume was achieved, and the tapped volume V_0 was recorded.[68]

$$\text{Tapped density} = M/V_f$$

Where,

M = Weight of sample powder

V_f = Tapped volume

C. Compressibility index

The bulk and tapped density were determined, and the compressibility index was derived using the following formula.[169]

$$\text{Compressibility Index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

D. Hausner ratio

Tapped and bulk density were measured, and the Hausner ratio was determined using the following formula.[170]

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

6.5 Formulation design

Formulation of Gastroretentive floating tablet of lovastatin shown in table 6.3.

Table 6.3 Composition of floating table.

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lovastatin	20	20	20	20	20	20	20	20	20
HPMC K4M	40	30	25	45	50	55	-	-	-
HPMC K100	30	30	25	45	50	45	20	25	30
Gaur gum	15	15	15	-	-	10	20	25	30

Citric acid	5	5	5	10	10	10	10	10	10
NaHCO3	60	70	80	50	40	30	80	70	60
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	20	20	20	20	20	20	40	40	40
Total Weight(mg)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

6.8 Floating tablet of Lovastatin

A. Preparation for floating tablet

The direct compression technique was used to manufacture several tablet formulations F1-F9.[171] All powders were processed through an 18 mesh sieve.[172] The needed amounts of medication, matrix polymer, and low-density powder were carefully combined.[173] To lubricate, magnesium stearate was added.[174] The mix was crushed (10 mm diameter, concave punches) with a rotating tablet compression machine.[175] Each pill included 20 mg of Lovastatin and additional excipients.[176]

B. Evaluation of floating tablet

I. Hardness

Tablets' hardness determines their resistance to shipment or breakage under normal storage, transportation, and handling conditions prior to use. The tablet us hardness was tested using a Monsanto hardness tester (Nevtex). The hardness was assessed in terms of kg/cm 2.[177]

II. Thickness

The thickness and width of tablets were critical for uniform tablet size. Thickness and diameter were measured with a Vernier caliper.[178]

III. Friability

Friability is a measurement of tablet strength. A Roche friabilator was used to test the friability. 20 tablets were carefully weighed and placed in a tumbling mechanism that rotated at 25 rpm, falling the tablets 6 inches with each revolution. After 4 minutes, the tablets were weighed to establish the percentage decrease in tablet weight.[179]

IV. Uniformity of weight

Weigh 20 tablets at random and find their average weights. Only two of the individual weights differ from the average weight by more than the percentage given, and none by more than twice that amount.[180]

V. Determination of drug content

For medication content, precisely weighed tablets were selected and crushed to a fine powder. A quantity equal to 50 mg of medication was dissolved in acetonitrile and filtered through filter paper. The filtered solutions of suitable dilutions were analyzed at 239 nm using a UV spectrophotometer. The quantity of Lovastatin was calculated by measuring the absorbance at 239 nm.[181]

VI. Floating lag time

The time required for a dosage form to emerge on the surface of a medium is known as Floating Lag Time (FLT) or Buoyancy Lag Time (BLT), and the amount of time required for the dosage form to emerge on the surface of a medium is known as Total Floating Time (TFT).[182]

VII. In-vitro release study

The release of Lovastatin in different floating tablet formulations was measured using a USP dissolving test device (type II). The dissolving media was 900 cc of 0.1N HCl at 37±0.2 °C and 50 rpm stirring speed. Aliquots of 10 mL were removed at 1-hour intervals, filtered, and replaced with an equivalent volume of new dissolving medium. The test sample was filtered via a 0.45 µm membrane filter, and the concentration of drug release was measured using a UV-visible spectrophotometer at λmax 239 nm.[183]

6.9 Mathematical modelling of drug release profiles.

A. Zero order equation

The following equation would predict a zero-order release

$$Q_t - Q_0 = K_0 t$$

Where,

Q_t = Amount of drug release dissolved in time t'

Q_0 = Initial amount of drug concentration in solution.

$K_0 t$ = Zero order rate constant

If the data follows zero order kinetics with a slope of K_0 and is displayed as cumulative percent drug release versus time, the plot will be linear. The release profile demonstrated by this model is appropriate for delivering the necessary prolonged pharmacological action.[184]

B. First order equation

The following is the kinetic equation for the first order release.

$$\text{Log } Q_t = \log Q_0 + K_1 t/2.303$$

Where

Q_0 = the drug's starting concentration in the solution is

Qt = the quantity released in time t

K = the first order release constant

This will result in a linear chart showing the decimal logarithm of the drug's release quantity Vs time. The amount of medication released per unit time decreases in pharmaceutical dosage forms that follow this dissolving profile, such as those containing water-soluble medicines in porous matrices. These dosage forms release the medicine in a proportional manner to the amount of drug left in their interior.[185]

C. Higuchi kinetics

The Higuchi release model is analyzed by fitting the release rate data to the following equation.

$$F\text{-}K.t1/2$$

Where,

"K" is the release rate constant, while

"F" is the percentage of drug release.

As a result, the drug release rate and the reciprocal of the square root of time are commensurate.[186]

D. Korsmeyer-peppas equation:

A basic, semi-empirical model was created by Korsmeyer that establishes an exponential relationship between the drug delivery and the elapsed time.[187]

The equation might be as follows:

$$Q/Q_0=K$$

Where,

n =the diffusion exponent which is contingent upon the mode of release.

K = a constant containing the geometric characteristics of the structure.

Q/Qo = the percentage of drug released at time t.

7. RESULTS & DISCUSSION

7.1 Preformulation Studies:

7.1.1 Organoleptic properties:

The organoleptic and physical evaluation revealed that the drug is a slightly white, crystalline solid, confirming its purity and characteristic appearance. It was odourless and tasteless or slightly bitter, which

is acceptable for oral formulations. These properties indicate good stability and no signs of contamination. These tests were performed as per procedure. The results were illustrated on the table.7.1.

Table 7.1 Observation of Organoleptic properties.

Sr. No.	Properties	Observation
1	Colour	Slightly White
2	Oduor	Odourless
3	Taste	Tasteless or Slightly Bitter
4	Appearance	Crystalline Solid

7.1.2 Melting point of drug.

The melting point of the drug was found to be 173–174.8 °C, indicating a shasrp range and confirming its purity. This value is consistent with reported literature standards. A narrow melting point range suggests the absence of impurities and good thermal stability.

Table 7.2 Observation of Melting Point.

Sr. No.	Test	Observation
1	Melting point	173-174.8ºC

7.1.3 Solubility analysis.

According to the solubility study, the drug is insoluble in distilled water but soluble in methanol, ethanol, and acetonitrile. This suggests a lipophilic character and low aqueous solubility, which may impact bioavailability. The high solubility in organic solvents is important in analytical and formulation applications.

Table 7.3 Solubility analysis of Lovastatin.

Sr. No.	Solvent	Solubility
1	Distilled Water	Insoluble
2	Methanol	Freely soluble
3	Ethanol	Freely soluble
4	Acetonitrile	Freely soluble

7.1.4 U.V Spectroscopy

A. Determination of λ_{max}:

The UV spectroscopic study in acetonitrile showed a λmax at 239 nm, showing the wavelength of maximum absorption for the medication. This shows significant electronic transitions, which are important for quantitative estimate. Figure 7.1 shows that the results validate acetonitrile's usefulness as a solvent for analytical research.

Table 7.4 Determination of λ_{max} values of Lovastatin in Acetonitrile.

Sr. No	Solvent	λ_{max} in nm
1.	Acetonitrile	239

B. Determination of standard calibration curve of Lovastatin:

Lovastatin's calibration curve revealed a linear rise in absorbance with concentration between 10 and 50 ppm. The statistics show a strong connection between concentration and absorbance, demonstrating that Beer-Lambert's rule is being followed. This verifies the method's appropriateness for accurate quantitative analysis, as seen in table 7.3 and Figure 7.1.

Figure 7.1 UV spectrum of Lovastatin.

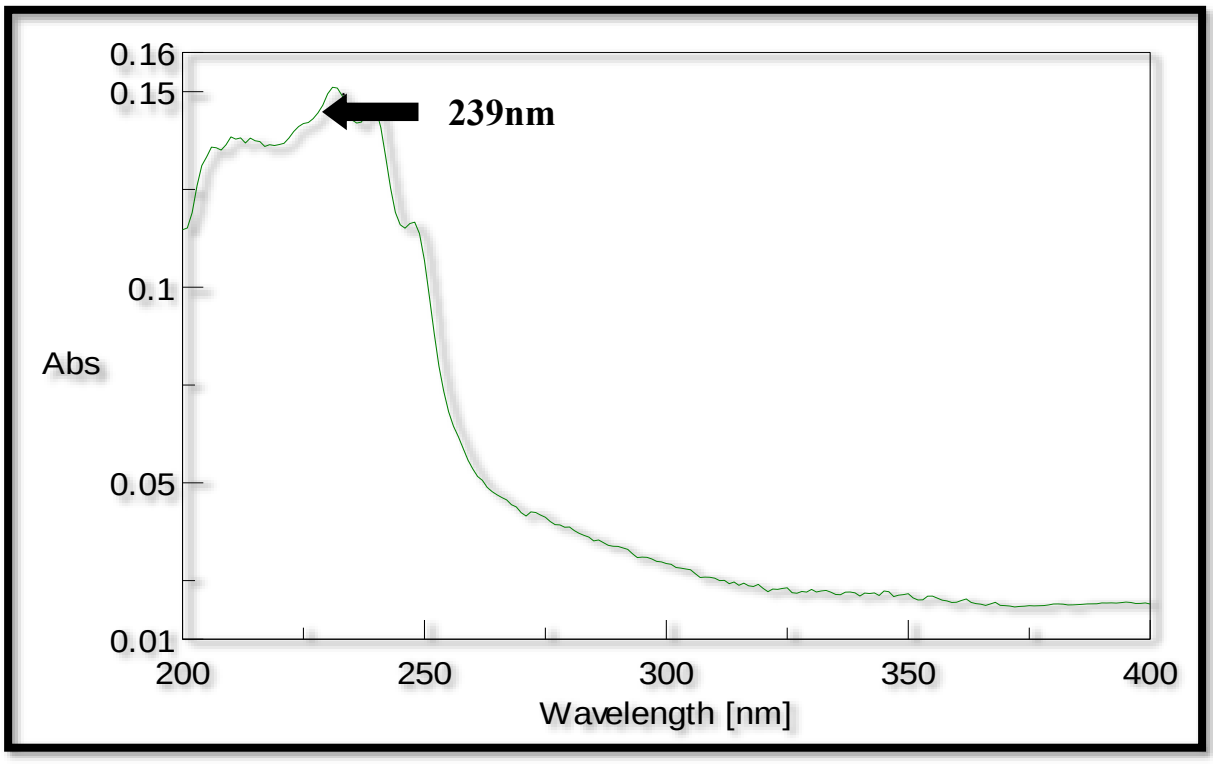


Table 7.5 Standard calibration on curve of Lovastatin.

Concentration of Lovastatin (ppm)	Absorbance (nm)
0	0
10	0.1245
20	0.2467
30	0.3789
40	0.4996
50	0.6352

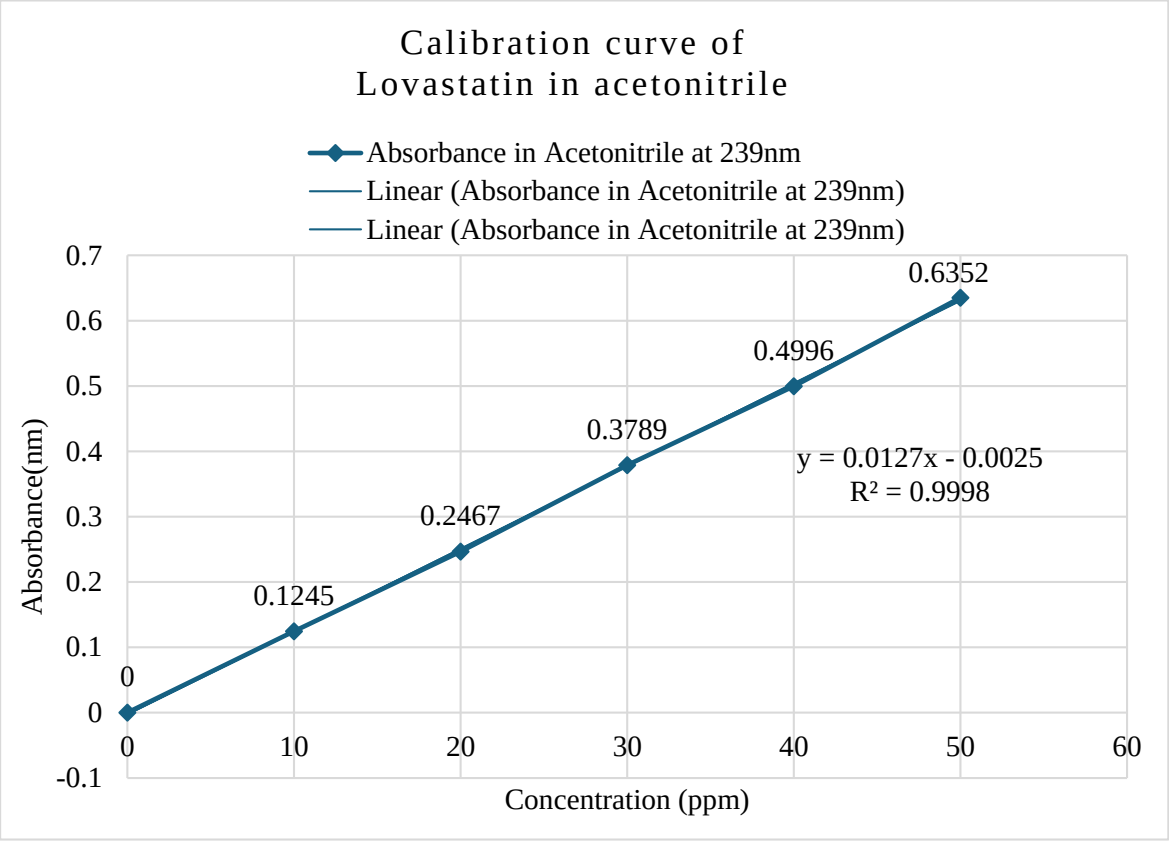


Figure 7.2 Standard calibration curve of Lovastatin in Acetonitrile.

The calibration curve followed Beer's Law within the concentration range of 10-50 µg/ml. The regression coefficient (0.998) indicates a linear connection between concentration and absorbance, as seen in Figure 7.2.

$$\mathbf{Y = mx \pm c}$$

Where,

Y = Absorbance
m = Slope
x = Concentration

7.1.5 Drug-excipient compatibility studies.

A. Infrared absorption spectrophotometry of Lovastatin.

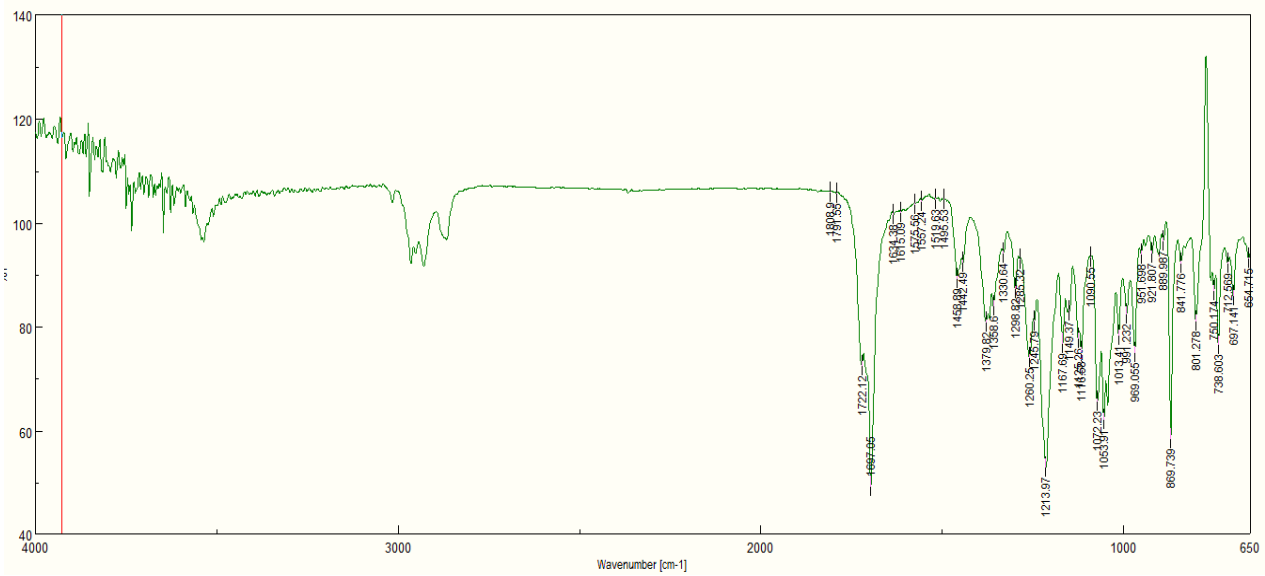


Figure 7.3 FTIR Spectra of Lovastatin.

The FTIR analysis revealed typical peaks, confirming the drug's essential functional groups. A prominent C=O stretching band was discovered at 1722 cm^{-1}, accompanied with O-H stretching at 3544 cm^{-1}. Peaks at 2957-2872 cm^{-1} relate to C-H stretching, whereas bands at 1276 cm^{-1} suggest C-O stretching. These results indicate the presence of ester and alcohol groups consistent with the drug's composition.'s structure.

Table 7.6 Characteristic Peak of Lovastatin.

Observed Peak (cm^{-1})	Reported Peak (cm^{-1})	Interpretation
3544.85	3500–3200	O–H stretching
2957.03	2950–2850	C–H stretching
2872.29	2950–2850	C–H stretching
1722.14	1750–1720	C=O stretching
1644.85	1680–1600	C=C or conjugated C=O
1458.29	1470–1450	C–H bending

1385.85	1380–1370	C–H bending
1276.70	1300–1200	C–O stretching

B. Infrared absorption spectrophotometry of Lovastatin + Excipients.

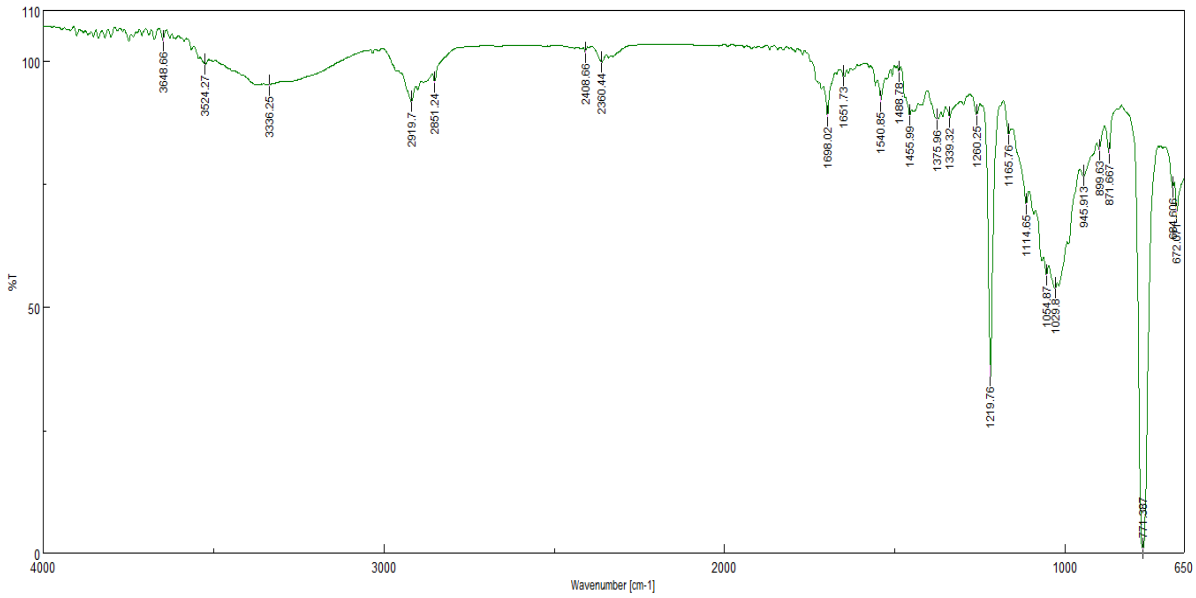


Figure 7.4 FTIR Spectra of Lovastatin+ Excipients.

The FTIR spectrum showed crucial peaks that confirmed the drug's functional groups. The broad band at 3524 cm^{-1} indicates N-H or O-H stretching, while the peaks at 2919 and 2851 cm^{-1} represent C-H stretching vibrations. A prominent C=O stretching band occurred at 1688 cm^{-1}, while C=C stretching was seen at 1631 cm^{-1}, verifying the compound's structural integrity.

Table 7.7 Characteristic Peak of mixture.

Observed Peak (cm^{-1})	**Reported Peak Range (cm^{-1})**	**Interpretation (Bond/Group)**
3524.27	3700–3200	N–H or O–H stretching
2919.17	2950–2850	C–H stretching
2851.24	2950–2850	C–H stretching
1688.02	1750–1650	C=O stretching
1631.73	1650–1600	C=C stretching

7.2 Pre-compression studies of the sustained release powder or granules.

A. Angle of repose.

Table 7.8 shows the results for all the. The value was determined to be in the range of 26 to 28.44 for all exhibit angles of repose below 30°. This shows that the tablet blend has good flow qualities.

B. Bulk density and tapped density.

The bulk and tapped density of the tablet blend were measured. Table 7.8 displays the results. The bulk density and tapped density ranged from 0.40 to 0.87 gm/ml, respectively.

C. Carr's compressibility index.

The % compressibility of a powder blend was calculated by Carr's compressibility index. Carr's index ranges from 12.23 to 19.71 percent. All have good flow properties. The results are reported in Table 7.8.

D. Hausner's ratio.

The Hausner ratio was determined to be between 1.11 to 1.25, as mentioned in Table 7.8.

Table 7.8 Pre-compression parameters of the tablet blend.

Formulations	Bulk density (gm/mL)	Tapped density (gm/mL)	Angle of repose	Carr's compressibility index (%)	Hausner's ratio	Flowability
F1	0.720 ± 0.043	0.87 ± 0.01	26.62 ± 0.21	17.126 ± 0.6	1.206 ± 0.06	Fair
F2	0.719 ± 0.042	0.873 ± 0.04	27.46±0.11	19.714 ± 0.7	1.251 ± 0.04	Fair
F3	0.409 ± 0.046	0.483 ± 0.5	28.32 ±0.31	15.113 ± 0.8	1.178 ± 0.08	Good
F4	0.45 ± 0.045	0.52 ± 0.09	28.06 ±0.31	15.160 ± 0.2	1.15 ± 0.02	Good
F5	0.44 ± 0.046	0.49 ± 0.06	27.58 ±0.15	12.23 ± 0.6	1.12 ± 0.04	Good
F6	0.42 ± 0.041	0.51 ± 0.08	28.44 ±0.11	12.58 ± 0.8	1.13 ± 0.08	Good
F7	0.41 ± 0.049	0.483 ± 0.49	28.32 ±0.33	15.113 ± 0.9	1.178 ± 0.07	Good
F8	0.710 ± 0.032	0.873 ± 0.036	27.46 ±0.15	19.714 ± 0.6	1.24 ± 0.05	Fair

F9	0.43 ± 0.042	0.49 ± 0.06	28.03 ± 0.04	12.32 ± 0.8	1.17 ± 0.03	Good

Mean, ± S.D., n=3

7.3 Evaluation of formulated tablet.

A. Hardness test.

Table 7.9 shows the average tablet hardness value. All have hardnesses of 4 to 5 kg/cm². The standard deviation number indicates that all of the formulations had nearly uniform hardness and good mechanical strength with sufficient hardness.

B. Thickness.

The thickness of the formulated tablet was determined using a Vernier calliper, and the results are reported in Table 7.9. The mean thickness of tablets was virtually consistent, with values ranging from 4.66 to 5.2 mm.

C. Friability test.

The friability value of produced tablets is shown in table 7.9. they values are less than 1%, indicating that they have good compactness and sufficient resilience to mechanical shock and abrasion.

D. Drug content.

Table 7.9 shows the results of the content uniformity tests performed on all formulations. The tablet us drug content ranged from 98.40 to 99.70% Lovastatin.

E. Weight variation test.

20 tablets have been selected at random from every batch and tested. The average weight of each was calculated and displayed in Table 7.9. The value was fairly uniform and met the USP criteria. All of the tables passed the weight variation test since the variation was less than 75% w/w, as specified by the pharmacopeia.

Table 7.9 Evaluation of formulated tablets.

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	201.56±0.69	5.02±0.03	4.23±0.27	0.20	99.54±0.30
F2	204.18±0.86	4.93±0.11	4.67±0.26	0.10	99.76±0.41

F3	207.03±0.75	5.03±0.05	5.33±0.55	0.12	98.63±0.85
F4	202.24±0.65	4.93±0.37	5.20±0.50	0.08	99.08±0.30
F5	204.09±0.58	5.2±0.2	4.83±0.29	0.30	99.41±0.20
F6	201.13±0.56	4.66±0.15	5.17±0.29	0.08	98.50±0.30
F7	205.04±0.59	4.76±0.23	5.0±0.50	0.06	97.91±0.30
F8	202.29±0.63	5.2±0.26	4.5±0.50	0.24	98.56±0.49
F9	204.73±0.79	5.26±0.25	4.00±0.50	0.08	98.76±0.49

Mean, ± S.D., n=3

All formulations met pharmacopeial standards for weight fluctuation, thickness, and hardness, showing consistency and mechanical strength. Friability values were less than 1%, indicating superior abrasion resistance in tablets. Drug content varied from 97.91 to 99.76%, indicating remarkable content homogeneity. Overall, the tablets demonstrated acceptable physical and chemical quality qualities that are suitable for further investigation.

F. Swelling index.

To determine the swelling index of the floating tablet, all tablets were immersed in 100 mL of 0.1N HCl and the swelling behavior of tablets after 1 hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, and 6 hrs was observed. Table 7.10 Shows the results.

Table 7.10 Results of swelling study of tablets (F1-F3).

Time (hrs)	**F1 (%)**	**F2 (%)**	**F3 (%)**
1 hr	22.15 ±1.02	25.84 ±1.18	29.52 ±1.25
2 hrs	35.42 ±1.25	40.58 ±1.42	48.20 ±1.52
3 hrs	44.85 ±1.42	52.12 ±1.58	61.40 ±1.70
4 hrs	53.72 ±1.58	62.35 ±1.72	72.85 ±1.85

5 hrs	59.85 ±1.68	70.05 ±1.80	82.52 ±1.92
6 hrs	65.20 ±1.75	77.85 ±1.85	92.10 ±1.95

Mean, ± S.D., n=3

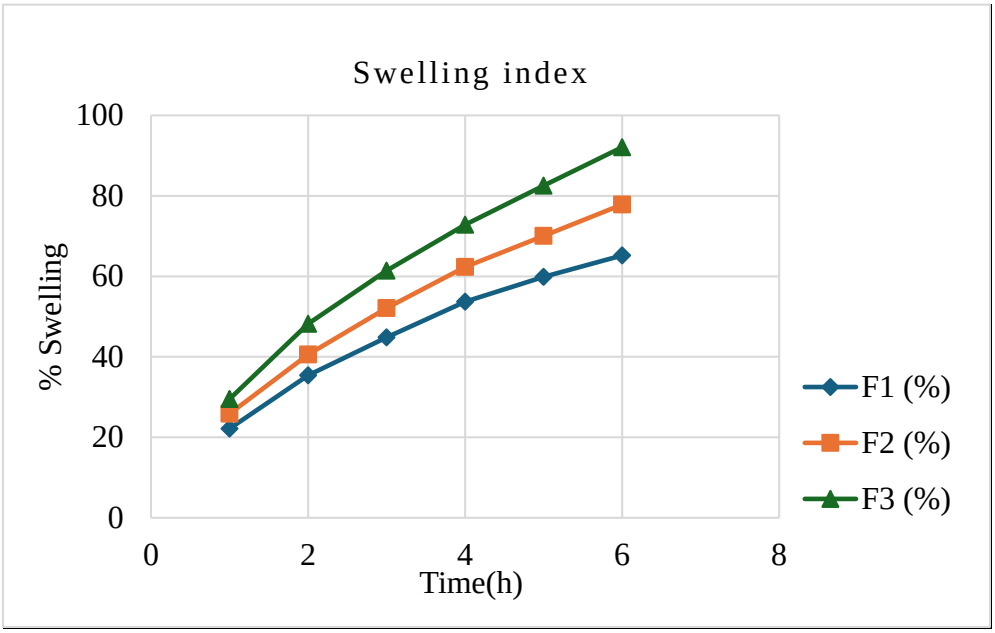


Figure 7.5 Swelling index of (F1-F3 batch).

Table 7.11 Results of swelling study of tablets (F4-F6).

Time (hrs)	F4 (%)	F5 (%)	F6 (%)
1 hr	23.76 ±1.05	27.95 ±1.35	33.48 ±1.42
2 hrs	36.35 ±1.15	43.85 ±1.68	53.72 ±1.78
3 hrs	46.85 ±1.28	55.72 ±1.80	68.95 ±1.85
4 hrs	56.40 ±1.32	65.85 ±1.88	81.28 ±1.78
5 hrs	63.12 ±1.38	74.25 ±1.92	91.85 ±1.80
6 hrs	70.25 ±1.45	81.40 ±1.95	99.48 ±1.85

Mean, ± S.D., n=3

Figure 7.6 Swelling index of (F4-F6 batch)

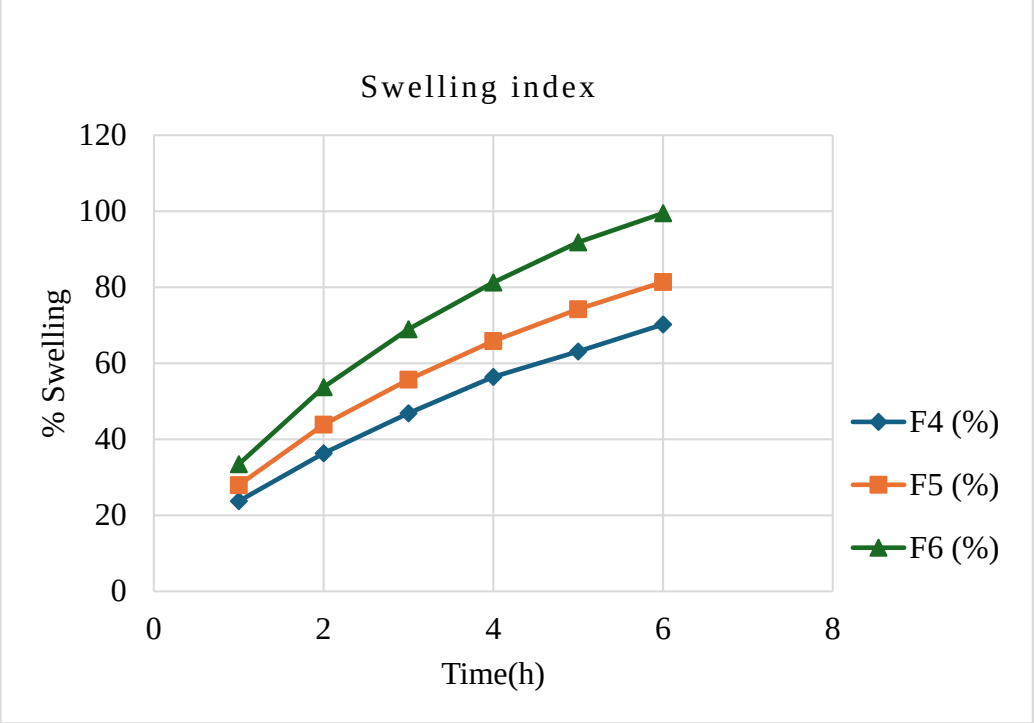


Table 7.12 Results of swelling study of tablets (F7-F9).

Time (hrs)	F7 (%)	F8 (%)	F9 (%)
1 hr	20.68 ±1.08	24.12 ±1.00	26.05 ±1.28
2 hrs	31.50 ±1.32	38.84 ±1.12	43.55 ±1.55
3 hrs	40.42 ±1.42	49.05 ±1.20	57.28 ±1.70
4 hrs	48.12 ±1.52	58.70 ±1.25	68.85 ±1.78
5 hrs	54.78 ±1.58	66.28 ±1.30	78.42 ±1.82
6 hrs	62.15 ±1.62	73.15 ±1.38	88.25 ±1.85

Mean, ± S.D., n=3

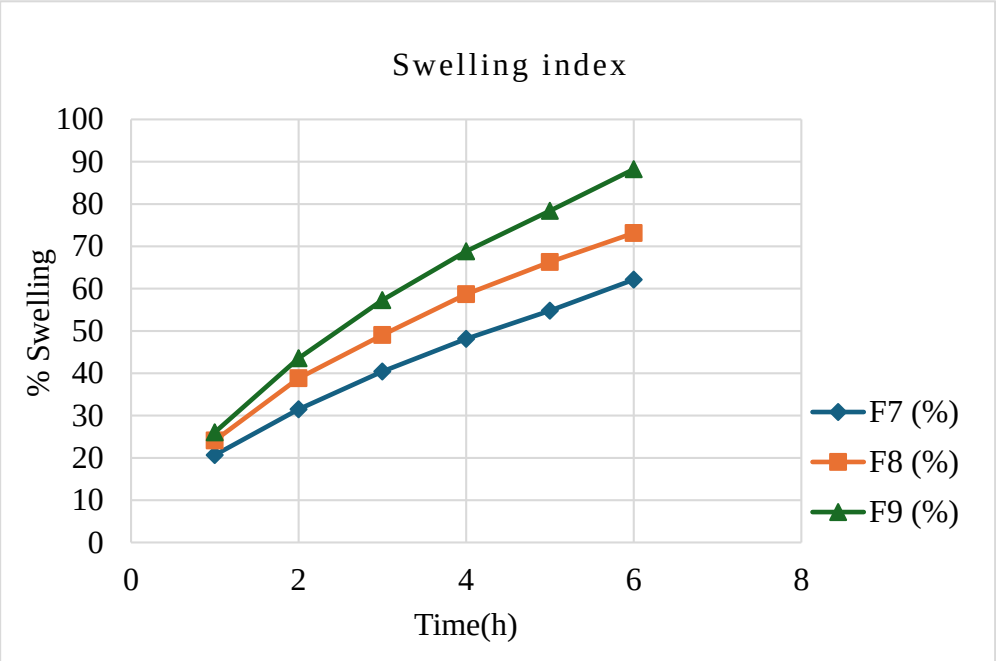


Figure 7.7 Swelling index of (F7-F9 batch)

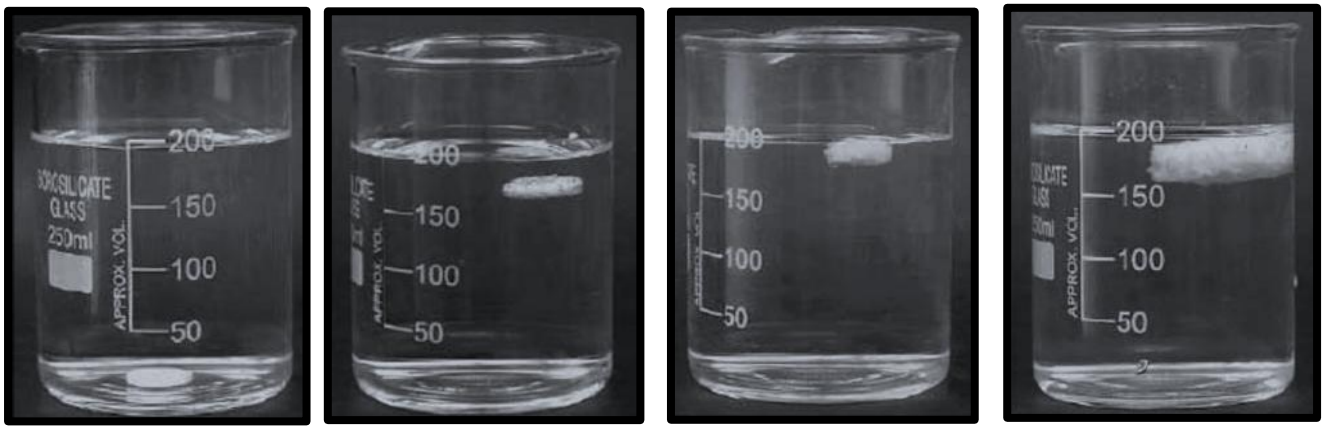
The swelling behaviour of the manufactured floating tablets (batches F1-F9) in 0.1N HCl was tested during a 6-hour period. The results are shown in Tables 7.10, 7.11, and 7.12, with graphic illustrations in Figures 7.4, 7.5, and 7.6. It was discovered that the swelling index increased steadily over time for all formulations. With a swelling index of 92.10% at 6 hours, F3 had the highest of the F1-F3 batches, indicating a greater ability to absorb water. Similarly, formulation F6 had the greatest swelling index of 99.48% after 6 hours in batches F4–F6, indicating higher polymer hydration and swelling. At the end of the testing period, the F9 batch had the highest swelling index of the F7-F9 batches at 88.25 percent. The swelling index decreased proportionally with time and polymer content, following a pattern seen in all formulations. A thicker gel layer formed around the tablet as a result of the greater polymer content, which may have prolonged drug release and produced persistent swelling. Furthermore, the study found that formulations with lower polymer ratios exhibited reduced swelling, which could affect medication release patterns and buoyancy. The results show that formulation mix and exposure time to dissolving medium have a substantial impact on swelling index. This swelling action is critical for keeping tablets floating and using medications safely over time.

7.4 Buoyancy/floating test.

When immersed in 0.1 N HCL solution pH (1.2) at 37°C, the tablets floated and did not disintegrate. Table 7.10 displays the findings of the buoyancy investigation as well as the buoyancy characteristics of the manufactured tablets.

Table 7.13 Results of floating time of different formulations F1-F9.

Sr. No.	Batch no.	Lag time (Sec)	Total floating time
1	F1	132	>12hrs
2	F2	140	>12hrs
3	F3	129	>12hrs
4	F4	135	>12hrs
5	F5	152	>12hrs
6	F6	122	>12hrs
7	F7	136	>12hrs
8	F8	142	>12hrs
9	F9	137	>12hrs



At initial time after 2 mins after 08 hrs. after 12 hrs.

Figure 7.8 Buoyancy/floating study of Lovastatin tablet**.**

In the dissolution media (0.1N HCl), $NaHCO_3$ generates CO_2 gas. The generated gas is trapped in the gel formed by the polymer's hydration, reducing the tablet its density to less than 1 gm/ml and making it buoyant. The effect of NaHCO3 on floating lag time and floating time was investigated broadly, and it was determined that the more NaHCO3 there was, the shorter the floating lag time. This was done at 37ºC with 0.1N HCl as the dissolving medium. The buoyancy time was defined as the time required for the tablet to rise to the surface and float. They displayed an impressive floating time of more than 12 hours.

7.6 In Vitro dissolution studies of tablets.

Using the dissolving test apparatus USP XXIII with paddles, in vitro drug release tests were conducted for two hours in 900ml of 0.1 N HCL and for the remaining twelve hours in phosphate buffer (pH 6.8). As the proportion of polymers increased, the drug's release rate from the matrix tablets dropped. The technique was followed for conducting the dissolution study. Figure 7.5 displayed the results, while Table 7.11 provided the F1–F9 data.

Table 7.14 In Vitro dissolution study.

Time hr	% CDR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15.4	16.2	17.1	25.9	26.3	16.5	35.8	36.4	34.9
2	22.8	24.1	25.3	30.4	31.8	26.4	42.2	43.7	41.6
3	30.3	31.9	33.7	36.8	38.2	38.2	49.3	50.9	48.2
4	39.1	40.4	42.2	45.3	46.6	50.7	56.1	58.3	55.0
5	48.5	49.7	51.3	53.6	54.9	61.0	63.2	65.7	62.5
6	56.3	57.8	59.6	61.8	63.1	70.4	70.5	72.9	69.7
7	63.9	65.2	67.4	68.9	70.7	77.5	76.8	78.6	75.2
8	71.1	72.6	74.8	76.0	77.9	84.3	82.9	84.2	80.5
9	77.3	78.9	80.2	82.2	84.0	90.5	88.3	89.6	86.0
10	83.0	84.7	85.6	87.4	89.1	94.2	92.7	93.8	90.4
11	88.2	89.9	90.4	91.8	93.3	97.5	95.9	96.3	93.7
12	92.5	93.7	94.2	95.7	96.8	99.3	98.4	98.9	97.5

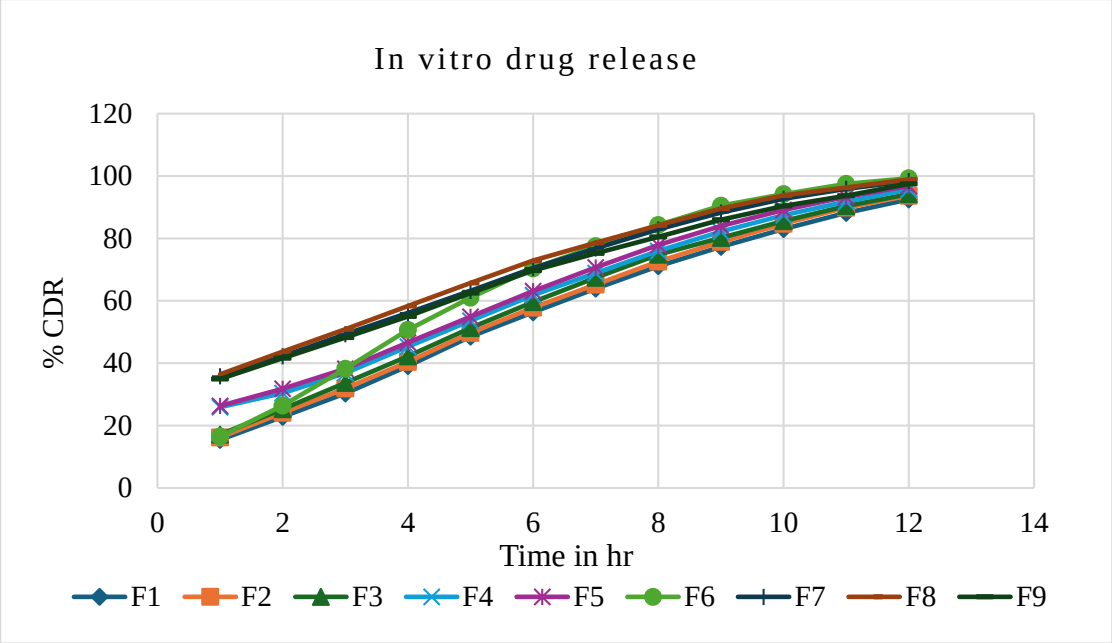


Figure 7.9 In Vitro drug release.

For all formulations, the in vitro drug release profiles demonstrated a sustained release pattern lasting 12 hours. F6 had the largest cumulative drug release, approaching approximately 100%, suggesting optimal release characteristics. Other batches had somewhat slower but constant release rates. The findings imply that polymer concentration and formulation composition have a substantial impact on drug release behavior.

7.7 Kinetic Studies of Gastro-retentive floating tablet of Lovastatin.

Drug Release Kinetics. The optimized dissolution data was fitted to different mathematical models (zero-order, first order, Higuchi, and Peppas) to determine drug release kinetics. The greater the regression coefficient (R^2), the more suitable model was chosen. Table 7.12 demonstrates that the dissolution data fit well into first-order release kinetics.

Table 7.15 Regression analysis data of floating tablets.

Formulations	R2			
	Zero order	First order	Peppas	Higuchi
F1	0.9911	0.9526	0.9946	0.9900
F2	0.9907	0.9466	0.9954	0.9907
F3	0.9867	0.9515	0.9958	0.9925
F4	0.9909	0.9287	0.9710	0.9824
F5	0.9895	0.9198	0.9754	0.9842

F6	0.9545	0.8985	0.9893	0.9900
F7	0.9857	0.9038	0.9797	0.9908
F8	0.9795	0.8942	0.9860	0.9936
F9	0.9878	0.9130	0.9819	0.9926

7.8 Kinetic study of optimized formulation (F6).

A. Zero order kinetics

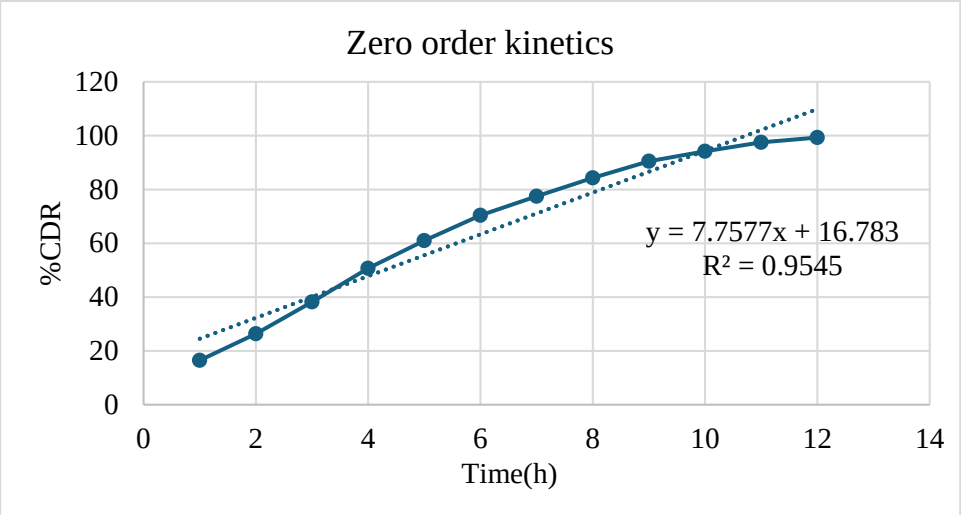


Figure 7.10 Zero-order kinetics of optimized formulation (F6).

B. First order kinetics

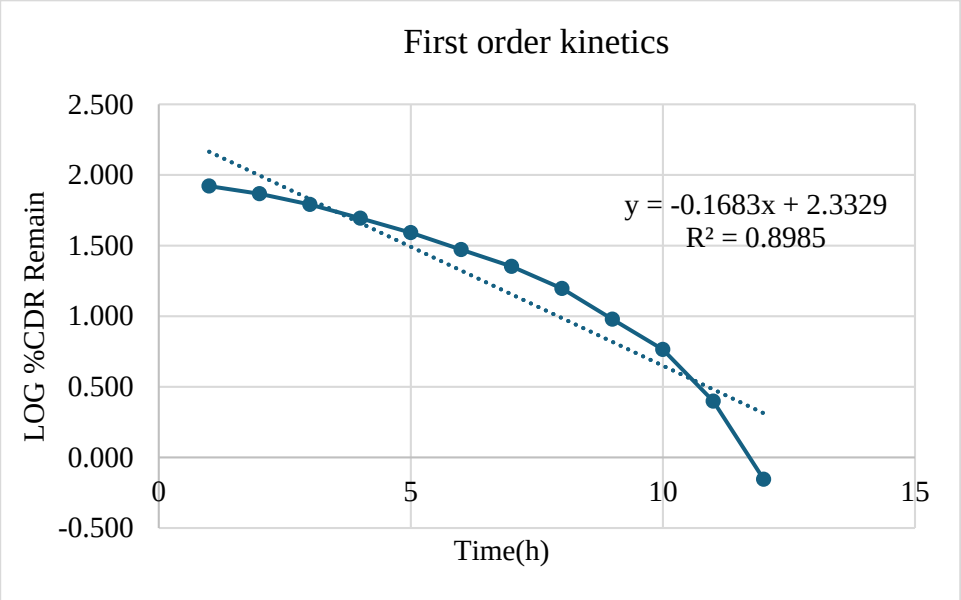


Figure 7.11 First Order kinetics of optimized formulation (F6).

C. Higuchi model

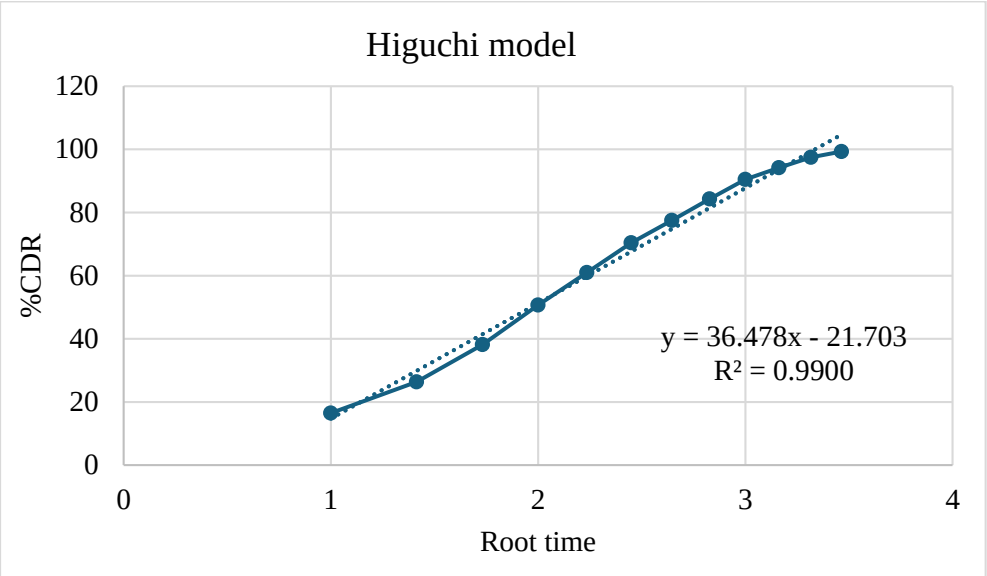


Figure 7.12 Higuchi kinetics of optimized formulation (F6).

D. Korsmeyer-peppas model.

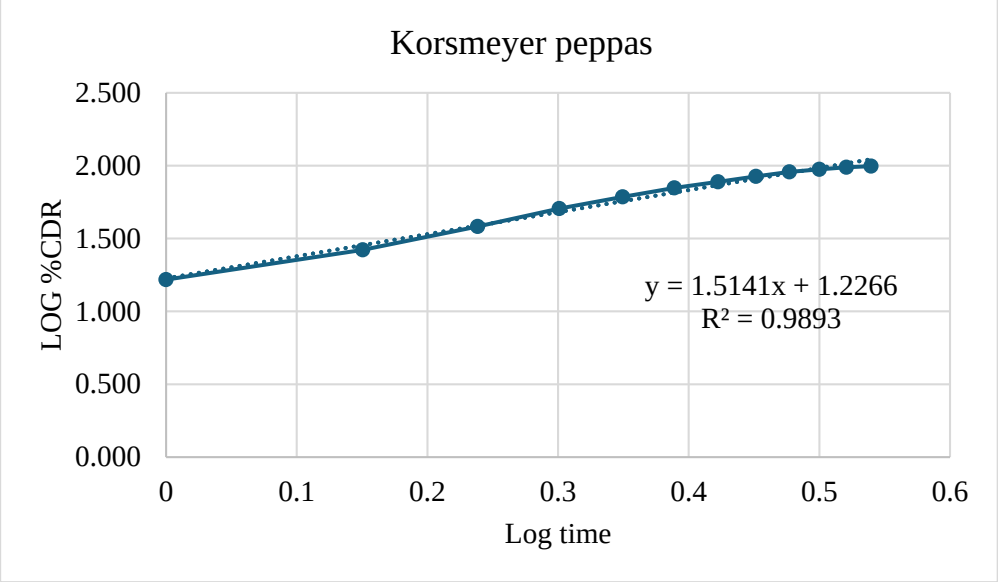


Figure 7.13 Korsmeyer-peppas kinetics of optimized formulation (F6).

7.9 Stability studies.

For 30 days, the improved formulation was stored at ambient temperature and 75% relative humidity. Following that, those tablets' physical properties and dissolution tests were evaluated.The findings are presented in Table 7.16.

Table 7.16 Results of stability study.

Parameters	Results
Hardness (kg/cm^2)	5.17±0.29
Thickness (mm)	4.66±0.15
% Friability (%w/w)	0.08
Weight variation (mg)	20.1.12±0.56
Drug Content (%w/w)	98.50±0.30

The hardness, % friability, weight variation, and content uniformity of formulation F6 did not alter significantly, as per the stability research.

8. SUMMARY & CONCLUSION

The current study was conducted to create Gastroretentive floating tablets of Lovastatin with the goal of improving solubility and maintaining drug release. As a BCS Class II medication, lovastatin's therapeutic efficacy is limited by its poor water solubility and mostly upper gastrointestinal absorption. Several formulations were created and assessed using thorough Preformulation, pre-compression, and post-compression experiments in order to address these difficulties. The drug's distinctive melting point, organoleptic characteristics, and FTIR spectra demonstrating the presence of functional groups commensurate with its structure all supported the conclusion that it was of excellent purity. According to solubility experiments, lovastatin is easily soluble in methanol, ethanol, and acetonitrile but insoluble in water. This suggests that a delivery mechanism that can keep the medication soluble in the stomach is necessary. Excellent linearity was shown in calibration investigations, guaranteeing accurate analytical estimate during the trials. Acceptable flow characteristics and compressibility were demonstrated by all created formulations, enabling consistent tablet manufacture with minimal friability, weight, hardness, and thickness. The consistent distribution of the medication content across batches was confirmed by the fact that it was within pharmacopeial limitations. The floating tablets effectively maintained the release of lovastatin for 12 hours, according to in vitro release experiments; formulation F6 had the greatest and most regulated release profile. According to drug release kinetics, the majority of formulations adhered to the Korsmeyer–Peppas and Higuchi models, indicating that the release was governed by a mix of diffusion and erosion processes. Long-term maintenance of therapeutic levels is facilitated by this steady and consistent resistance. Overall, the study finds that it is possible to manufacture Gastroretentive floating tablets of lovastatin in a way that will result in sustained drug release and prolonged stomach retention. Because of its excellent release behavior and advantageous physicochemical characteristics, F6 stood out as the batch that was optimized out of all the formulations. These results show that this strategy has the potential to increase

Lovastatin's bioavailability and boost patient adherence to hyperlipidemia treatment. It is advised that more in vivo research be done to confirm the new formulation's safety and effectiveness.

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