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A Review On Antiviral Drugs On Floating Drug Delivery System

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Abstract

Floating drug delivery systems (FDDS) have emerged as an innovative approach for enhancing the pharmacokinetics and bioavailability of drugs. Floating drug-delivery system (FDDS) is a gastro retentive pharmaceutical preparation that could delay the gastric residence time to obtain adequate bioavailability of a drug. The system is floating in the gastric fluid for a low substance density than the aqueous medium. Antiviral drugs, which play a crucial role in the management of viral infections, can benefit from the use of floating drug delivery systems, as they often exhibit poor solubility, limited bioavailability, and susceptibility to degradation in the gastrointestinal tract. This review focuses on the application of FDDS in the delivery of antiviral drugs, highlighting their advantages, formulation strategies, types of floating systems, and challenges associated with their development and implementation.

Keywords – *Floating Drug Delivery, Acyclovir, Bioavailability , gastro retentive*

INTRODUCTION

For dosage forms that stay in the stomach longer than traditional dosage forms, the ability to extend and regulate the emptying time is advantageous. The process of the stomach emptying dosage forms is very changeable. Creating controlled release systems to improve absorption and boost bioavailability is a challenging task. The difficulty to limit the dose form in the intended region of the gastrointestinal tract is one of these challenges.(Chandel et.al, 2012) The process of absorbing drugs from the gastrointestinal tract is intricate and diverse. It is commonly known that contact time with the small intestinal mucosa affects how much a medicine is absorbed through the gastrointestinal tract. Thus, for medications that are not fully absorbed, small intestinal transit time is a crucial factor. A summary of basic human physiology is provided, including information on gastrointestinal retention, motility patterns, and physiological and formulation factors that affect the emptying of the stomach. (Hirtz, 1985)

Structural Organization and Physiology of GIT

The stomach is a key component of the gastrointestinal tract, serving as a reservoir for ingested food and playing a crucial role in the digestion process. The human stomach is an “J”-shaped organ which is positioned in the left upper part of the abdomen, behind the liver, part of the diaphragm, and the anterior abdominal wall. The pancreas, the left kidney, the left adrenal, the spleen, and the colon are situated behind it. Though, the position, the shape, and the size of the stomach may vary depending on the extent of the gastric contents. The empty stomach has a volume of approx. 50 mL, in the filled state, the stomach volume increases up to a maximum of 1500 mL. It is divided into four main regions: the cardia, fundus, body, and pylorus. The stomach's muscular walls and acidic environment help break down food, initiating the digestive process before the food moves into the small intestine for further absorption. (Functional Anatomy of the Stomach, 2022)

The stomach is composed of three main regions: the fundus, the body, and the antrum (pylorus) as shown in **Figure** 1. The fundus and body of the proximal portion serve as a repository for undigested material,

while the antrum is the primary location for mixing motions and propels actions that function as a pump to empty the stomach. (Arora et al., 2005)

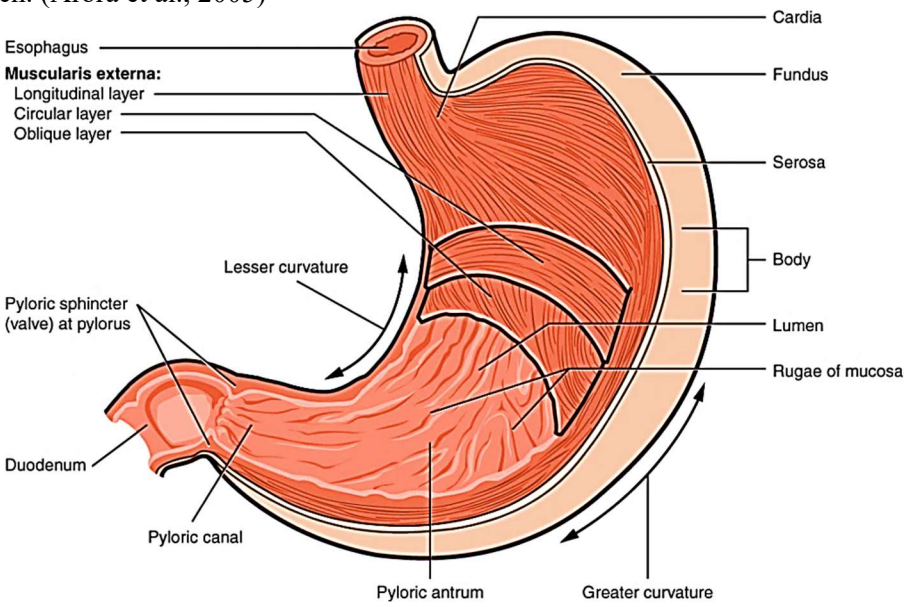

Figure 1 Structural organisation of Human Stomach

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours.8 This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington.(Vantrappen et al., 1979)

- *Phase I* (Basal phase) lasts from 40 to 60 minutes with rare contractions.
- *Phase II* (Pre-burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.
- *Phase III* (Burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- *Phase IV*Lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

The stomach has three layers of muscular a circular inside layer, a mid-longitudinal layer, and an outside but incomplete oblique layer. Motor functions in the stomach are isolated by region. The fundus relaxes as fluids and solids enter the oesophagus, a response known as accessible relaxation, and further, as food enters the fundus, a process is known as adaptive relaxation (Jahnberg et al., 1977 and Arakawa et al., 1997).

This response permits the liquid to pool in the fundus bag while the solid components of the meal remain in the mainstream of the flow to the pylorus. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.(Desai & Bolton, 1993)

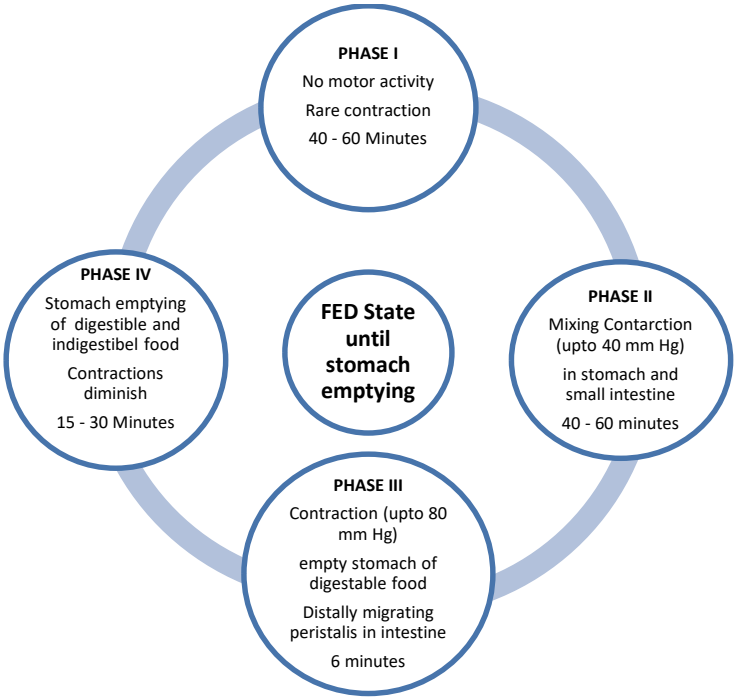

Figure 2. Overview of the phases of GIT Motility. (1977 by Vantrappen et al.)

Gastrointestinal Retention Time - Drugs' digestion time can be greatly extended by using gastro retentive, which can stay in the stomach area for several hours. Extended stomach retention increases the solubility of medications that are less soluble in high pH environments, decreases medication waste, and increases bioavailability. (Narang, N. 2011).

It can also be used to provide medications locally to the stomach and the first segment of the small intestine. Improved accessibility to novel products with novel therapeutic potential and significant patient benefits is made possible via gastro retention.(Chaudhary, 2014)

To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system for maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT. (Chaudhary, 2014)

Gastroretentive systems, such as mucoadhesive, high-density, expandable, and floating systems, have been developed to overcome the limitations of traditional oral drug delivery and maximize the absorption of drugs with narrow windows of absorption or those that act locally in the stomach. (Kotreka& Adeyeye, 2011) Floating drug delivery systems have shown the ability to adapt to various physiological and biological factors that can affect the gastric residence time and drug-delivery behavior. (Jain et al., 2005) The key mechanism underlying the functionality of floating drug delivery systems is their ability to maintain a density lower than that of the gastric fluid, enabling them to float on the surface and remain in the stomach for prolonged durations. (Sungthongjeen et al., 2006).

Approaches for Gastroretentive Drug Delivery System – Following the approaches for GRDDS (Figure 3) -

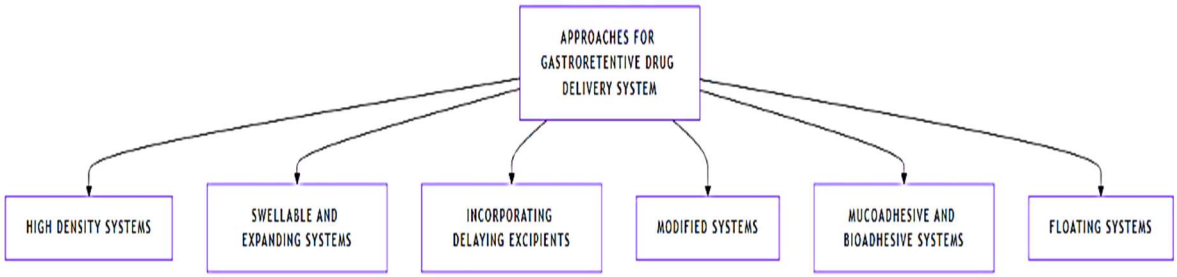

Figure 3. Different approaches of Gastroretentive drug delivery system. (Patil et al., 2015)

Factors affecting gastric retention time of the preparation -

1. Density-should be lower than that of the gastric fluidal contents (1.004 g/ml) (Jassal M, et.al, 2015).
2. Size-the diameter of more than 7.5 mm (Jassal M, et.al, 2015).
3. Incidence of feeding-GRT can rise by more than 400 min when consecutive foods are dispense compared to a single meal due to low-frequency MMC. (Jassal M, et.al, 2015).
4. Caloric content can be increased by 4-10 with foods high in protein and fat.(Arakawa et al., 1997)
5. Gender-average outpatient GRT in men (3.4 h) less than age and race matching with women (4.6 h) regardless of height, body weight and surface.(Arakawa et al., 1997)

The development of effective and reliable drug delivery systems has been a crucial aspect of modern pharmaceutical research. Floating drug delivery systems have emerged as a promising approach to address the challenges associated with conventional oral drug administration. (Kharvi et al., 2019) These systems are designed to maintain a low density, allowing them to float on the gastric fluid and remain buoyant for an extended period without affecting the gastric emptying rate. This unique characteristic of floating drug delivery systems offers the potential to improve the bioavailability and therapeutic efficacy of drugs, particularly those with narrow absorption windows or those that require local action in the stomach.(Strusi et al., 2008)

Definition of floating Drug Delivery system

Floating systems are low-density systems that have sufficientresistance to float on the stomach and stay afloat in the gastricwithout create? an effect on the gastric emptying rate for a longperiod time. While the system floats on the gastric contents, thedrug will be released slowly at the desired concentration in thesystem. Thus, the residue will be cleared from the stomach. Theseresults will conduct to GRT elevation and be better control of fluxin plasma drug concentrations. Even so, furthermore, to thecontent of the stomach minimally required to enable theachievement of the right of retention of the principle of buoyancy,floating style minimal level (F) also required to give a reliabledosage form floats on the surface of foods. (Desai, S 1993) It also useful forproximal gastrointestinal (GI) tracts local drugs, for example,antibiotics for Helicobacter pylori on the manage for a peptic ulcerand for drugs that difficult to dissolve or not stable inintestinal fluids (Umamaheshwari et al., 2003).

Advantage of Floating Drug Delivery System - Floating drug delivery systems offer several advantages over conventional oral dosage forms:

1. Improved bioavailability: By prolonging the gastric residence time, FDDS can enhance the absorption of drugs that are primarily absorbed in the stomach or upper small intestine. (Chandel et al., 2012)
2. Reduced dosing frequency: The extended gastric residence time of FDDS can lead to a reduction in the frequency of drug administration, thereby improving patient compliance. (Niharika et al., 2018)
3. Site-specific drug delivery: FDDS can be designed to deliver drugs locally in the stomach, making them particularly useful for the treatment of gastric ulcers, H.pylori infections, and other stomach-related disorders.(Chandel et al., 2012)

4. Controlled release: The floating nature of these systems allows for a more controlled and sustained release of the drug, leading to improved therapeutic efficacy. (Patil et al., 2015)
5. Stability enhancement: FDDS can help protect acid-labile drugs from the acidic environment of the stomach, thereby improving their stability. (Niharika et al., 2018)
6. Versatility: Floating systems can be designed to accommodate a wide range of drug properties and release profiles, making them a versatile platform for drug delivery. (Niharika et al., 2018)
7. Reduced side effects: By targeting the drug release to the desired location in the stomach, FDDS can help minimize the systemic exposure of the drug, potentially reducing associated side effects. (Chandel et al., 2012)

Disadvantage of FDDS

Despite the numerous advantages, floating drug delivery systems also have a few limitations:

1. Requirement of a sufficient amount of gastric fluid: FDDS rely on the presence of gastric fluid to achieve and maintain buoyancy. (Chandel et al., 2012)
2. Variability in gastric emptying process: The gastric emptying process is highly variable and can be affected by various physiological factors, which can impact the performance of FDDS. (Niharika et al., 2018)
3. Limited drug loading capacity: Depending on the design and composition of the floating system, the drug loading capacity may be limited. (Niharika et al., 2018)
4. Potential food effect: The presence of food in the stomach can affect the floating behaviour and drug release from FDDS, leading to variable bioavailability. (Kotreka& Adeyeye, 2011)
5. Requirement of special manufacturing process: The development of FDDS often requires a specialized manufacturing process, which can be more complex and costly compared to conventional oral dosage forms.(Kotreka& Adeyeye, 2011)

Types of Floating Drug Delivery System

Davis first introduced FDDS in 1968. These systems are known to have lower densities than the gastric fluid, remaining buoyant for a long time in the stomach. They are recognized as an important means of achieving adequate gastric retention and drug bioavailability (Badoni, et.al, 2012). Several types of floating drug delivery systems have been developed to address the limitations of conventional oral dosage forms and improve the therapeutic efficacy of drugs. These systems can be broadly classified into the following categories:

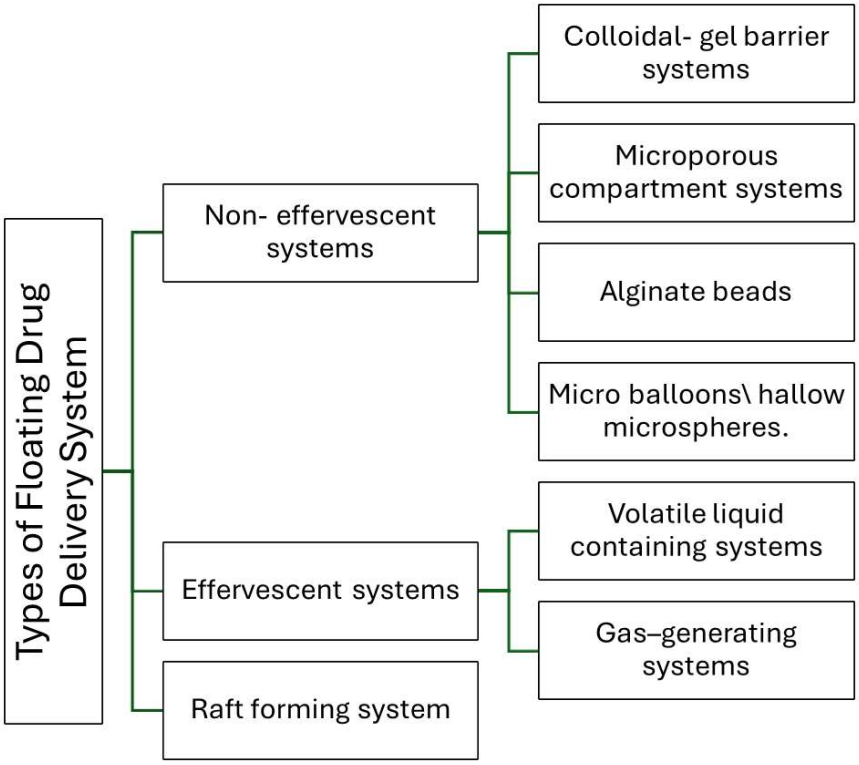

Figure 4 - Types of Floating Drug Delivery System

A) Non- effervescent systems

Viscous fluid inhibitions cause this system to bulge uncontrollably upon swallowing, blocking their exit from the belly. These systems may also stay near the stomach valve due to the plug-type mechanism. The first of such arbitrary number of formulations mixes the medication with a gel that expands when taken orally and with viscus fluid to maintain bulk and form integrity within the jelly-like barrier. The larger complex blocks air, giving the current buoyancy forever. (Jayswal, B. D et.al, 2012)

a. **Colloidal- gel barrier systems** – (Balanced hydrodynamic system) -This technique extends stomach retention time and maximizes drug absorption in solution form. The gel-forming hydrocolloids in the medication help it stay afloat in the stomach. Examples include polycarbophil, polystyrene, and polyacrylate. Hydrocolloid in the system hydrates to form a colloid gel barrier when in contact with gastrointestinal fluid. (Burns et al., 1998)
b. **Microporous compartment systems** - This method encapsulates a drug reservoir in a microporous compartment with top and bottom pore walls. The delivery system floats over the stomach content due to the entrapped air in the flotation chamber.(Burns et al., 1998)
c. **Alginate beads** - multi-unit floating dosage forms are made from 2.5 mm calcium alginate spherical beads by adding sodium alginate solution to a calcium chloride aqueous solution. The beads are then precipitated, separated, snap-frozen in liquid nitrogen, and freeze-dried at 400˚C for 24 hours to create a porous system. This device can maintain a floating force for almost 12 hours, with floating beads lasting over 5.5 hours.(Burns et al., 1998)
d. **Micro balloons\ hallow microspheres -** Hollow microspheres, or micro balloons, are the most effective buoyant device. It has a core hollow region within the microsphere. Hollow

microspheres with drug-loaded exterior polymer shelves are created using a unique solvent diffusion process for emulsion. (Burns et al., 1998)

B) Effervescent systems

Gas producing agents, carbonates (such as sodium bicarbonate) and alternative organic acids (such as acid and salt acid) are used in effervescent systems to deliver CO2 gas, lowering the system's density and causing it to float over the stomach fluid. An alternative is to add a matrix with a liquid component that produces gas that evaporates at body temperature. (Janhavi et al., 2015)

a. **Volatile liquid containing systems** - Because of the floating chamber, which can be empty, filled with air, or filled with a safe gas, the device is designed to float inside the belly, and the medication reservoir is enclosed in a microporous compartment. (Janhavi et al., 2015)
b. **Gas–generating systems** - These are made by carefully combining the medication and the CO2 producing substances inside the matrix tablet. These float in the stomach, slowing down the rate at which the stomach empties, because their bulk density is lower than that of gastric fluids. (Dongare, P. S, 2013).

C) Raft forming system - Raft-forming systems are being studied for delivering antacids and drugs for gastrointestinal infections and illnesses. Gastric fluid causes a gel-forming solution to swell and create a viscous substance, allowing for gradual medication release in the stomach as shown in Figure 5.

Table 1 Summarised Some drugs are explored in Floating Dosage forms (Kamalakkannan, et.al, 2011)

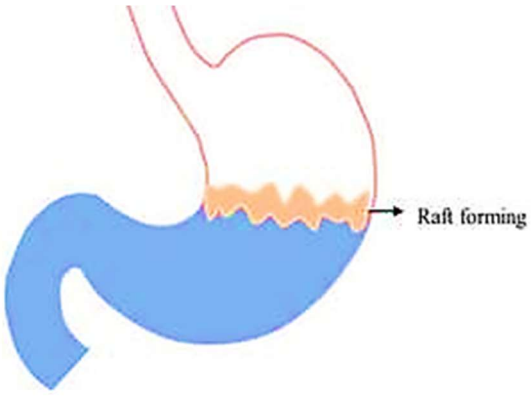

Figure 5. Raft forming System

Table 1 Drugs explored in FDDS

Types of Dosage Forms	Drugs explored in FDDS
Microsphere Granules	Aspirin, Griseofulvin, Ibuprofen, Ketoprofen, Terfendine, Tranilast, Diclofenac Sodium. Indomethcin, Predinsolone
Films	Cinnarizine
Capsules	Chlorodiazopoxide HCl, Diazepam, Furosemide, L-DOPA, Benserazide, Misoprostol, Nicardipine, Propoanalol,
Tablets/Pills	Acetaminophen, Aspirin, Amoxycillin trihydrate, Ampicillin, Atenolol, Captopril, Chlorphenarmine, Furosemide, 5-Flurouracil, Dotalol, Verapami, Prednisolone.

Mechanism of Floating Drug Delivery Systems

Floating drug delivery systems are designed to have a lower density than the gastric fluids, allowing them to float on the surface of the stomach contents. This prolonged gastric residence time enhances the

absorption of the encapsulated drug, particularly for drugs that are primarily absorbed in the stomach or have a narrow window of absorption. (Garg & Gupta, 2008).

The mechanism of floatation is achieved through the incorporation of low-density materials, such as gas-generating agents or low-density polymers, within the formulation (**Figure 6**). This provides buoyancy to the system, resulting in its prolonged stay in the gastric region without affecting the gastric emptying rate. (Kharvi et al., 2019)

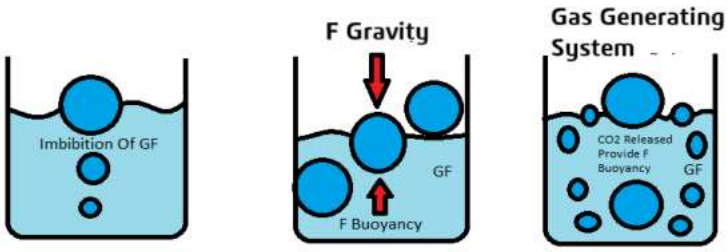

Figure 6 – Mechanism of FDDS.

The advantages of using floating drug delivery systems for antiviral drugs include improved bioavailability, reduced drug waste, enhanced solubility in the gastric environment, and the potential for local drug delivery to the stomach and proximal small intestines. (Sathish et al., 2011).

Available Market Products for FDDS

In Table 2, Some commonly available marketed FDDS formulation (Ichikawa et al., 1991)

Table 2. Marketed FDDS Formulation (Ichikawa et al., 1991)

Product	Content	Manufacturer	Type of Formulation
Madopar ℗	Levodopa 100mg, Benserazide 25 mg,	Roche Products, USA	Floating, CR Capsule.
Valrelease	Diazepam 15 mg	Hofmann -LaRoche USA	Floating Capsule
Liquid Gaviscon	Aluminium Hydroxide 95 mg, Magnesium carbonate 358 mg	GlaxoSmithkline, India	Effervscent floating liquid alginate.
Topalkan	Aluminium -Magnesium Antacid	Pierre Fabre Drug, France	Floating liquid alginate.
Almagate Flot Coat	Aluminium -Magnesium Antacid	-	Floating Dosage Form
Conviron	Ferrous Sulphate	Ranbaxy, India	Colloidal gel forming FDDS
Oflin O D	Ofloxacin	Ranbaxy, India	FDDS Tablet
Cytotech	Misoprostol	Pharmacia USA	FDDS Capsule
Glumetza	Metformin HCl	Roche, India	FDDS Tablet

Antiviral Drugs in Floating Drug Delivery Systems

Antiviral drugs, which play a crucial role in the management of viral infections, can benefit from the use of floating drug delivery systems, as they often exhibit poor solubility, limited bioavailability, and

susceptibility to degradation in the gastrointestinal tract. (Chandel et al., 2012)

Classification of Antiviral Drugs

Antiviral drugs are a class of medications that are specifically designed to target and inhibit the replication of viruses, thereby reducing the severity and duration of viral infections. These drugs can be classified into different categories based on their mechanism of action, target virus, and therapeutic indications. (Clercq, 2004) Antiviral drugs are classified based on their mechanisms of action, which can be broadly divided into several categories:

1. Viral Entry Inhibitors

- **Fusion inhibitors:** Prevent the virus from entering the host cell by blocking the fusion of the viral envelope with the host cell membrane. (Antiviral Agents, 2022)
  - Example: Enfuvirtide (used for HIV) (Antiviral Agents, 2022)
- **Attachment inhibitors:** Prevent the virus from attaching to the host cell surface.
  - Example: Maraviroc (used for HIV) (Antiviral Agents, 2022)

2. Nucleic Acid Inhibitors

- **Nucleoside Reverse Transcriptase Inhibitors (NRTIs):** Compete with natural nucleotides for incorporation into the viral DNA, leading to chain termination.
  - Examples: Zidovudine, Lamivudine (used for HIV) (Antiviral Agents, 2022)
- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):** Bind directly to the reverse transcriptase enzyme, inhibiting its function.
  - Examples: Nevirapine, Efavirenz (used for HIV) (Antiviral Agents, 2022)
- **Integrase Inhibitors:** Prevent the integration of the viral DNA into the host cell's genome.
  - Examples: Raltegravir, Dolutegravir (used for HIV) (Antiviral Agents, 2022)
- **Polymerase Inhibitors:** Inhibit the viral polymerase enzyme, preventing viral replication.
  - Examples: Oseltamivir, Zanamivir (used for influenza) (Antiviral Agents, 2022)

3. Protease Inhibitors

- Inhibit viral proteases, preventing the cleavage of viral proteins into their mature forms.
  - Examples: Ritonavir, Lopinavir (used for HIV) (Antiviral Agents, 2022)

4. Neuraminidase Inhibitors

- Inhibit the viral enzyme neuraminidase, preventing the release of new virus particles from infected cells.
  - Examples: Oseltamivir, Zanamivir (used for influenza) (Antiviral Agents, 2022)

5. Interferons

- Naturally occurring proteins produced by the body in response to viral infection. They can inhibit viral replication and enhance the immune response.
  - Examples: Peginterferon alfa (used for hepatitis B and C) (Usach et al., 2013)

6. Other Antiviral Agents

- **Amantadine and rimantadine:** Block the uncoating of influenza A virus, preventing viral replication. (Usach et al., 2013)
- **Cidofovir:** Inhibits viral DNA polymerase, used for cytomegalovirus (CMV) and smallpox. (Usach et al., 2013)
- **Acyclovir:** Inhibits viral DNA polymerase, used for herpes simplex virus (HSV) and varicella-zoster virus (VZV). (Usach et al., 2013)

Formulation Strategies for Antiviral Drugs in Floating Drug Delivery Systems

Various formulation strategies have been explored for the development of antiviral drugs in floating drug delivery systems.

These include the incorporation of gas-generating agents, such as sodium bicarbonate or citric acid, to produce carbon dioxide and create a buoyant effect. Additionally, the use of low-density polymers, such as hydroxypropyl methylcellulose or ethyl cellulose, has been investigated to achieve a floating matrix. (Cotugno et al., 2005)

Researchers have also explored the use of calcium silicate-based microspheres for the delivery of antiviral drugs, such as repaglinide, as these systems have demonstrated effective floating capabilities and prolonged gastric residence time as summarised in Table 4 (Floating Microsphere, 2020).

Table 3.Summary of Formulation Strategies for Antiviral Drugs in Floating Drug Delivery Systems.

Formulation Type	Mechanism of Action	Examples
Gas-Generating Systems	Generation of carbon dioxide or nitrogen gas to create buoyancy	Sodium bicarbonate/citric acid, sodium nitrite/ascorbic acid
Hydrogel-Based Systems	Swelling and floating of hydrogel matrices	Carbopol, chitosan
Lipid-Based Systems	Low density of lipid-based carriers	Liposomes, solid lipid nanoparticles
Matrix Systems	Erosion or swelling of polymeric matrices	Eudragit, cellulose derivatives

Challenges in FDDS for Antiviral Drugs

Various formulation strategies have been explored for the development of antiviral drugs in floating drug delivery systems. These include the incorporation of gas-generating agents, such as sodium bicarbonate or citric acid, to produce carbon dioxide and create a buoyant effect. Additionally, the use of low-density polymers, such as hydroxypropyl methylcellulose or ethyl cellulose, has been investigated to achieve a floating matrix. (Cotugno et al., 2005)

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Literature related to FDDS on antiviral drugs

Several studies have explored the application of floating drug delivery systems for antiviral drugs. For instance, a review article discussed the various technological approaches utilized in the prolongation of gastric residence time, including floating drug delivery systems, and highlighted their advantages for oral controlled drug delivery. (Sopyan et al., 2020)

Another study investigated the development of a gastroretentive floating microsphere formulation for the delivery of the antiviral drug acyclovir, demonstrating improved in vitro and in vivo performance compared to a conventional tablet formulation. The floating microsphere formulation exhibited prolonged gastric residence time and enhanced drug absorption, which are key advantages for improving the oral delivery of antiviral drugs that often face challenges related to poor solubility and limited bioavailability. This highlights the potential of floating drug delivery systems to overcome the limitations associated with the conventional administration of antiviral medications. (Raghuvanshi & Pathak, 2014).

Furthermore, a research group reported the successful development of a floating tablet formulation of the antiviral drug lamivudine. The researchers demonstrated that the floating tablet formulation exhibited superior floating ability, drug release, and pharmacokinetic profiles compared to a conventional tablet formulation. Specifically, the floating tablet maintained its buoyancy for an extended period, allowing for prolonged gastric residence time and enhanced absorption of the antiviral drug. The improved drug release characteristics of the floating system led to higher bioavailability and more favorable pharmacokinetic parameters, such as increased peak plasma concentration and extended drug half-life, when compared to the

conventional tablet. These findings suggest that the floating drug delivery approach can be effectively applied to improve the delivery and therapeutic efficacy of antiviral drugs like lamivudine, which often exhibit challenges related to poor solubility and limited bioavailability. (Astuti et al., 2020)

Several studies have explored the application of floating drug delivery systems for antiviral drugs. For instance, a review article discussed the various technological approaches utilized in the prolongation of gastric residence time, including floating drug delivery systems, and highlighted their advantages for oral controlled drug delivery. The review emphasized that floating systems can improve the bioavailability, reduce drug waste, enhance solubility, and enable potential for local drug delivery to the stomach and proximal small intestines, which are particularly beneficial for antiviral drugs that often exhibit poor solubility, limited bioavailability, and susceptibility to degradation in the gastrointestinal tract.(Merisko-Liversidge & Liversidge, 2008)

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Furthermore, a research group reported the successful development of a floating tablet formulation of the antiviral drug lamivudine. The floating tablet formulation exhibited superior floating ability, drug release, and pharmacokinetic profiles compared to a conventional tablet formulation. The improved drug release characteristics of the floating system led to higher bioavailability and more favourable pharmacokinetic parameters, such as increased peak plasma concentration and extended drug half-life, when compared to the conventional tablet. (Wei et al., 2001)

These findings suggest that the floating drug delivery approach can be effectively applied to improve the delivery and therapeutic efficacy of antiviral drugs, which often face challenges related to poor solubility and limited bioavailability. (Choi et al., 2016)

Furthermore, a research group reported the successful development of a floating tablet formulation of the antiviral drug lamivudine. The floating tablet formulation exhibited superior floating ability, drug release, and pharmacokinetic profiles compared to a conventional tablet, suggesting that the floating drug delivery approach can be effectively applied to improve the delivery and therapeutic efficacy of antiviral drugs. The research in this field continues to evolve, future perspectives may include the development of multi-unit floating systems, the incorporation of novel antiviral agents, and the exploration of different formulation strategies to address the unique challenges associated with antiviral drug delivery.

Author studied that to evaluate the potential of floating alginate beads as a drug carrier for acyclovir to prolong gastric residence time of drug in its absorption window. The prepared beads were evaluated for percentage drug loading, entrapment efficiency, surface morphology and in vitro release characteristics to know the effect of addition of these polymers to alginate solution and the addition of Pectin to cross linking solution. Pectin treated beads prepared with Xanthan gum & Pectin not only showed improved percentage drug loading but also exhibited sustained drug release in the pH 1.2. So, these floating alginate beads may act as a promising carrier for acyclovir to improve its oral bioavailability. (Muvattupuzha et al., 2023)

Khariya AA(2010) studied design and optimize floating drug delivery systems of acyclovir using psyllium husk and hydroxypropylmethylcellulose (HPMC) as the polymers and sodium bicarbonate as a gas generating agent. The tablets were prepared by wet granulation method. These studies indicated that the proper balance between psyllium husk and HPMC can produce a drug dissolution profile like the predicted dissolution profile. The optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix.

This review focuses on advances in antiviral drug delivery systems based on chitosan (CS) and derivatized CS carriers. CS and its derivatives are evaluated concerning methods of their preparation, their basic characteristics and properties, approaches to the incorporation of an antiviral drug in the CS polymer as well as CS nanoparticulate systems, and their recent biomedical applications in the context of actual antiviral therapy.

The degree of development (i.e., research study, in vitro/ex vivo/in vivo preclinical testing), as well as benefits and limitations of CS polymer and CS nanoparticulate drug delivery systems, are reported for viral diseases and corresponding antivirotics.(Žigrayová et al., 2023)

Table 3 – Summary of Floating Drug Delivery system for Antiviral Drugs

Drug	Work Done	Reference
Acyclovir	They established GR system is applicable to multiple pharmaceuticals and holds significant potential in the design and development of innovative controlled-release formulations.	(Shin et al., 2019)
Acyclovir	The dimensions of the microspheres synthesized from various ratios of acyclovir and ethyl cellulose ranged from 1.1 to 2.7 µm. As the drug-to-polymer ratio was elevated, both the size and percentage of drug content rose.	(Bhosale et al., 2012)
Acyclovir	Acyclovir was the first herpes-specific antiviral medication commonly used to treat HSV types I and II and Varicella Zoster. This study used Acyclovir floating beads to sustain medication release in the GIT absorption window. HPMC K4m, Eudragit rl 100, and xanthan gum have been tested for Acyclovir release retardancy in vitro. Each polymer was concentrated at 0.5%, 1%, and 1.5%. Sodium alginate beads with xanthan gum and pectin had increased drug loading and prolonged drug release at pH 1.2. Thus, floating alginate beads may boost oral acyclovir bioavailability.	(Mohan et al., 2023)
Ritonavir	The research work aimed to design a floating ritonavir (RN) medication delivery device to boost gastric residence duration and bioavailability. Direct compression was used to make RN floating tablets from HPMC, Metliocel E15LV, E50LV, K100LV, and K4M, and polyvinyl pyrrolidone. Sodium bicarbonate released gas. The formulations were optimized for matrix integrity, floating time, swelling, and in vitro drug release.	(Biswas, M et.al, 2013)
Acyclovir	The study demonstrates a floating drug delivery system for Acyclovir, enhancing gastric residence time and improving oral bioavailability, crucial for effective antiviral treatment against Herpes Simplex Virus.Developed floating capsule for controlled Acyclovir delivery. Prolonged gastric residence enhances therapeutic efficacy against HSV.	(Patel et al., 2017)
Acyclovir	They Developed floating matrix tablets for acyclovir delivery and improved gastric retention and controlled drug release.	(Naveen, N. R et al., 2013)
Ritonavir	They Formulated Ritonavir floating micro balloons for controlled release. And Evaluated for yield, efficiency, size, and drug release. FM1 formulation showed highest drug release and stability. Ritonavir effectively delivered via floating microballoons.	(Uroko, 2017)
Stavudine	They Developed gastroretentive tablets for Stavudine using various polymers and Evaluated drug release, buoyancy, and physical characteristics of tablets.	(S. Verma et al., 2011)

Stavudine	This study aims to prepare and evaluate floating microballoons of Stavudine, an antiviral agent for HIV treatment, to enhance its gastric residence time. They prepared Eight formulations of floating microballoons were created using various polymers (Eudragit S100, Ethyl Cellulose, and PVP K30) through an emulsion solvent diffusion method. Results indicated that the mean particle diameter ranged from 230.23 to 238.33 µm, with a cumulative drug release of 53.62% to 87.45% after 24 hours.	(Yusuf, 2016)
Antiviral drug	Antiviral drug development is crucial due to COVID-19 pandemic. Biosafety nanomaterials enhance drug delivery and efficacy in antiviral therapy.	(Wang et al., 2022)
Acyclovir	They Developed chitosan floating formulations for acyclovir delivery. They determined Swelling and dissolution influenced by pH and formulation ratios. They achieved Effective floating systems achieved through freeze-drying process and Optimized ratios can control acyclovir release timing.	(Ruiz-Caro & Veiga, 2010)
Acyclovir	The research focuses on the formulation and in-vitro evaluation of floating acyclovir tablets using a direct compression method. Key ingredients included HPMC K100 LV, Psyllium Husk, and Sodium Bicarbonate, with Psyllium Husk treated to enhance its compression properties.The optimized batch demonstrated a non-Fickian, anomalous diffusion release mechanism, and stability studies indicated promising results for gastroretentive drug delivery.	(Aatish, T. et al. 2014)
Lamivudine	They prepared Gastroretentive microspheres enhance Lamivudine absorption in GIT. And Formulated microspheres show extended release and stable properties.	(Karosiya et al., 2022)
Acyclovir	The prepared and evaluated Floating tablets enhance drug release and bioavailability for Acyclovir and Formulated using various polymers, showing zero lag time and prolonged buoyancy.	(Rawat et al., 2018)
Valacyclovir	The study demonstrates a floating in situ gelling system for Valacyclovir, enhancing gastric retention and controlled release, which is beneficial for antiviral drug delivery.	(Patel et al., 2017)
Acyclovir	Ayclovir's gastric floating drug delivery system enhances bioavailability by prolonging gastric retention, utilizing swellable polymers and effervescent agents to sustain drug release effectively. They Developed floating tablets to enhance drug retention and absorption.	(Kumar et al., 2009)
Zidovudine	The research aimed to develop a multiparticulate floating gastroretentive system for the modified release of zidovudine (AZT), an antiretroviral drug. The system was created by polymer coating calcium silicate-adsorbed AZT and evaluated for various parameters including drug loading capacity and release kinetics.	(Yoshida, 2013)

Antiviral drugs	Antiviral drugs face challenges like low bioavailability and drug resistance. Nanosystems enhance metabolism and pharmacokinetics of antiviral drugs.	(Chen et al., 2021)
Stavudine	They Developed floating microspheres of stavudine for prolonged gastric retention. And achieved 88% encapsulation efficiency and good buoyancy for over 12 hours	(Mehul, et al., 2011)
Acyclovir.	They prepared positive sustained release floating tablets of acyclovir were produced using an effervescent technique and analysed for floating behaviour and drug release. Tablets with 20-30% HPMC K4M, 30% Na CMC (and/or 20% PVP or 20% Na alginate), and 12-15% gas producing agent demonstrated satisfactory in vitro results.	(Tavakoli et al., 2012)
Zanamivir	They developed self-double emulsifying system for zanamivir oral delivery and enhanced intestinal permeability and bioavailability compared to traditional methods.	(Ifrah et al., 2023)
Antiviral drugs	This paper outlines the challenges of treating viral infections and presents several innovative strategies, including combination therapies, advanced drug delivery systems, hybrid molecules, and metal-based nanoparticles, as potential solutions to enhance antiviral efficacy.	(Khwaza et al., 2022)
Ritonavir	They Developed floating tablets of ritonavir for improved bioavailability and exhibited prolonged release up to 12 hours.	(Chukka, 2017)
Zidovudine	The purpose of this study was to develop a Gastroretentive tablet of Zidovudine to enhance its bioavailability and sustained action. In 32 factorial designs, amount of HPMC K4M (X1) and gas generating agents (X2) were selected as independent variable. The time required for 50% drug release t50% (Y1) was selected as dependent variable. The results of factorial design showed thatfactor X1 and X2 significantly affect the studied dependent variables. The formulationwith good floating time (24hrs) and the percent drug release (98.05) emerged as optimal.	(Dalavi & Patil, 2009).
Acyclovir	The objective of the research was, formulation and characterization of low-density gastro-retentive microspheres of Acyclovir (ACV) using hydroxyl propyl methyl cellulose to enhanced retention time and bioavailability.	(Mishra & Khatri, 2015)
Oseltamivir	The study was aimed for preparation of gastroretentive tablets of oseltamivir using xanthan gum, sodium bicarbonate and ethyl cellulose as matrixing agent, gas generating agent and floating enhancer respectively.Results of the multiple regression analysis indicated that the Formulation S6 was selected as a promising formulation and was found stable at 40oC temperature and 75% RH for 3 months.	(Teen, Y. T et al., 2013)
Zanamivir	The objective of the present study is to develop gastro retentive drug delivery system of Zanamivir .Floating tablets of Zanamivir	(Kumar et al., 2019)

	were developed with a gas generating agent NaHCO3 and in combination of different hydrophobic and hydrophilic polymers like xanthan gum, guar gum, HPMC and methyl cellulose .	
Famciclovir.	This study develops a gastro retentive floating drug delivery system (GRDDS) for Famciclovir, an antiviral medicine with a 75% oral bioavailability, to enhance therapeutic efficacy, stomach residence time, and reduce administration frequency.	(Vasudeva M. S. 2014).
Acyclovir	This study focused on enhancing the oral bioavailability of acyclovir (ACV) by incorporating it into a gastroretentive dosage form utilizing floating hollow chitosan beads. Hollow chitosan beads were synthesized through a solvent-free, ionotropic gelation technique. The formulations containing the drug exhibited yields greater than 70.5 ± 0.31%.	(Svirskis et al., 2013)
Anti-viral drugs	In recent decades, viral infections have constituted a global health problem. The conventional administration of antiviral medications with inadequate pharmacodynamic parameters is the primary cause of suboptimal treatment outcomes and the development of multidrug resistance. The nano dimensional shape, characterised by greater permeability and retention effect, increased surface-area-to-volume ratio, and capacity for surface functionalisation, constitutes the advantageous features that render it an excellent drug delivery system for administering antiviral therapies. Despite the extensive comprehension of the numerous advantages of nanotechnology-based drug delivery systems, their repeatability, in vivo stability, and toxicity remain significant concerns about clinical safety and efficacy.	(Pradhan et al., 2021)
Acyclovir	This research aimed to create a gastroretentive acyclovir dose form that can float on gastric content. The polymer was sodium alginate, while the floating agent was calcium carbonate. Drug release, floating lag time, and viscosity were dramatically affected by sodium alginate and CaCO3 concentrations. To determine the appropriate release pattern, dissolving was done in 0.1 N HCl at 50 rpm. The suspension showed shear-thinning behavior, immediate gelation, 99.2% drug release at 12 h, and floating ability over 12 h in 0.1 N HCl. Thus, a 12-hour sustained-release floating acyclovir dose form was designed.	(Chiprikar& Ranpise, 2023)
Valacyclovir	This research aimed to create a Valacyclovir hydrochloride drug delivery system that prolongs stomach residence time and achieves the appropriate release profile in vitro. Valacyclovir hydrochloride is a highly soluble anti-viral medication in stomach pH. Valacyclovir hydrochloride floating tablets were manufactured employing effervescence and sodium bicarbonate/citric acid as gas-generating agents in this study.	(Rajani T et al., 2021)
Ritonavir	The purpose of this study was to formulate Ritonavir floating matrix tablets by melt granulation technique to prolong its gastric	(Velivela, S et al., 2016)

	residence time thereby increasing its bioavailability.	
Acyclovir	The goal of this study is to create and assess acyclovir floating tablets using natural polymers through direct compression. Acyclovir floating tablets were made using direct compression, Hibiscus rosa sinensis (HRS) leaf mucilage, and xanthum gum as natural rate-controlling agents. Sodium alginate controls semi-synthetic rate. Different excipients are used to make tablets.	(Gudigennavar, A. S et al., 2020)
Atazanavir	BCS class II medication atazanavir sulfate has poor oral bioavailability because to fast first-pass metabolism and P-GP efflux. The in situ floating gel with the complexed medication was generated by ion gelation and optimized using 32 full factorial design. The improved formulation had an 18-s floating lag time and a medication release rate of 94.18 ± 0.18 % after 16 hours. Drug release and floating lag time depend on gelling polymer concentration.	(Masareddy et al., 2023)
Famciclovir	A famciclovir floating drug delivery system was created to extend gastric residence time, target stomach mucosa, and boost drug bioavailability employing various polymers, including HPMC E15, Xanthan gum, methyl cellulose, and compritol 888 ATO, with varying concentration Famciclovir that floats in the stomach was developed and tested. Wet granulation was used to create gel bits using sodium bicarbonate and citric acid as effervescence agents. reduced floating lag time for medication release up to 12 hours.	(Lateef Amrohi et al., 2021)
Acyclovir	This study aimed to create and assess sustained release hydrodynamic balanced acyclovir systems employing hydrocolloid polymers like HPMC and EC. Floating was produced by introducing an effervescent mixture of sodium bicarbonate and anhydrous citric acid. In vitro properties determined the optimal formulation, and in vivo experiments on Sprague Dawley rats assessed drug bioavailability. Area under the curve (AUC) was nearly twice as high as the drug solution. The acyclovir formulation-maintained plasma concentration during 24 hours, unlike the drug solution, which only maintained it for 4 hours.	(Khatri et al., 2015)
Nevirapine	This study indicates that maltose and SCMC polymers can limit medication release in nevirapine tablets. The strong mucoadhesive strength of this formulation may enhance its gastrointestinal tract residence duration, leading to increased bioavailability. Proper release and mucoadhesion require a balance between individual amounts of the two polymers.	(Mahajan et al., 2015)
Atazanavir	Swelling polymers like Pullulan gum, PEO WSR Coagulant, and HPMC K 100 M can effectively create controlled release floating tablets of Atazanavir. The formulation was successful without a gas-generating agent. Using a polymer combination can yield better results. The work offered valuable insights for formulators developing controlled drug delivery systems for Atazanavir	(Rajkumar, J et al., 2019)

	employing hydrophilic polymers. Commercialization of produced formulations is possible after ensuring safety and efficacy in healthy human volunteers.	
Rilpivirine	The introduction of long-acting antiretroviral (ARV) medications might help prevent and treat HIV. Rilpivirine is an antiviral drug. However, medication bioavailability needs improvement, hence floating microspheres were examined. Methods: Ethyl cellulose and carbopol polymers are used to make Rilpivirine floating microspheres by emulsion-solvent diffusion.	(Ponnaganti et al., 2021)
Stavudine	Due to its short half-life of 0.8-1.5 hours, stavudine requires frequent dosing to maintain steady plasma levels. To maintain stable stavudine levels throughout the day, gastroretentive systems may effectively release the drug content from matrix tablet reservoirs for several hours.	(Gangane et al., 2021)
Oseltamivir Phosphate	Oseltamivir phosphate (OP), which may compete with new generations, was the most effective influenza molecule. OP's low solubility, low absorption rate, short effectiveness, and large dosage requirements have led researchers to develop modified-release dosages to address its physical and chemical limitations and how it is metabolised in the body. This work created a gastro-retentive in-situ gelling technology for OP to improve oral bioavailability and duration of action. Sodium alginate and HPMC K 100 M were coupled with a pH-sensitive in-situgel employing a simple gelation technique in the central composite statistical design formulation.	(Thirugnanasambandham et al., 2023)
Favipiravir	Favipiravir, was prepared by using solvent diffusion method by using 3^2 factorial design with using polymer eudragit S 100, Using Design of Experiments (DoE) software coupled with response surface methodology (RSM), graphical and numerical optimization techniques were applied to identify the optimal composition based on various responses. Findings for formulations FES 1 through 9 revealed that drug release percentages ranged between 0.192 and 0.277 µm, with entrapment efficiencies from 68.65 ± 1.9% to 76.25 ± 3.2%, and particle sizes also spanning 0.192 to 0.277 µm.	(Naga C Pallam et al 2024)
Patent		
WO2001058424A1	Drug-containing coated particles, which consist of a drug-containing core coated with an enteric polymer that prevents significant drug release in an acidic environment but permits drug	(Watts et al., n.d.)

WIPO (PCT)	release in a more alkaline environment, are part of a multiparticulate drug delivery composition that has been adapted for the delivery of a pharmacological agent to a mammal's small intestine. The particles float when suspended in water.	
US20230115025A1 United States	The invention addresses issues with floating drug delivery systems (FDDS) in the art. The systems' weakness, especially damage to the gas-filled chamber, makes it susceptible to water, reducing buoyancy and stomach residence duration. The innovation provides a self-repairing FDDS that maintains floating capacity after damage. The invention's floating medicine delivery systems can also carry significant amounts of active chemicals. Floating medication delivery devices can release active component independent of fluid pH. The invention's floating medicine delivery mechanism is easy to make, making it economically viable.	(Meijerink et al., n.d.)
RU2693491C2 Russia	Pharmaceutical delivery system production is the subject of this invention. Calcium carbonate with a reaction-modified surface is formed by reacting natural ground or precipitated calcium carbonate with carbon dioxide and one or more acids in an aqueous medium, where carbon dioxide is formed in-situ during acid treatment or supplied externally. Calcium carbonate is mixed with pharmaceutically active agent and auxiliary additive, compacted by roller compactor at 4 to 20 bar, and pressed to make a tablet, mini-tablet, capsule, or granule.	(Атрия et al., 2014)
WO2007106957A1 WIPO (PCT)	An oral pharmaceutical multiple-unit controlled release floating composition with at least one drug containing system containing at least one active drug, one fusible binder, and one gas generating agent, and either a coating layer or a swelling agent.	(Vanderbist et al., n.d.)

CONCLUSION

In conclusion, the review article has highlighted the significant potential of floating drug delivery systems for the administration of antiviral drugs. The key advantages of this approach include improved bioavailability, enhanced solubility, and extended gastric residence time, which can ultimately lead to enhanced therapeutic efficacy, reduced dosing frequency, and improved patient compliance. Floating drug delivery systems have shown promising results in enhancing the delivery and effectiveness of various antiviral agents, particularly those with poor solubility and limited bioavailability. As research in this field continues to evolve, future advancements may involve the development of more sophisticated floating systems, the incorporation of novel antiviral drugs, and the exploration of innovative formulation strategies to further optimize the delivery and therapeutic outcomes of antiviral medications.

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