



AN OVERVIEW OF FLOATING DRUG DELIVERY SYSTEMS FOR ORAL BIOAVAILABILITY ENHANCEMENT

¹Animesh Dadheech*, ²Anil Kumar Goyal,

³Rajesh Asija, ⁴Seema Yadav Trimukhe

¹Student, ²Associate Professor, ³Principal, ⁴Associate Professor

¹Department of Pharmaceutics,

¹Maharishi Arvind Institute of Pharmacy Mansarovar, Jaipur Rajasthan India

Abstract : Drug delivery systems play a crucial role in enhancing the therapeutic efficacy of drugs and maximizing patient compliance. Among various drug delivery systems, floating drug delivery systems have gained significant attention due to their ability to improve the oral bioavailability of poorly soluble drugs. This comprehensive review aims to provide an in-depth analysis of floating drug delivery systems and their potential in achieving good oral bioavailability. Floating drug delivery systems are designed to float on the gastric fluid for an extended period, thereby allowing sustained release of the drug and enhancing its absorption. Various approaches such as effervescent systems, hydrodynamically balanced systems, and raft-forming systems have been developed to achieve optimal floating properties. The holistic approach towards developing a successful floating drug delivery system involves a thorough understanding of factors affecting gastric emptying time, formulation parameters, and physicochemical properties of the drug. By considering these factors comprehensively, researchers can design a system that ensures maximum drug release at the desired site of action. Moreover, the use of novel polymers, excipients, and technologies has further enhanced the feasibility and effectiveness of floating drug delivery systems. These advancements offer promising opportunities for improving the oral bioavailability of a wide range of drugs with poor solubility and permeability. This review examines floating drug delivery systems, which are designed to improve oral bioavailability of poorly soluble drugs. These systems float on the gastric fluid for an extended period, allowing sustained drug release and enhanced absorption. Various approaches, including effervescent, hydrodynamically balanced, and raft-forming systems, have been developed to achieve optimal floating properties. A holistic approach to developing a successful system involves understanding factors affecting gastric emptying time, formulation parameters, and drug physicochemical properties. The use of novel polymers, excipients, and technologies has further enhanced the feasibility and effectiveness of floating drug delivery systems. This review emphasizes the potential of these systems to overcome challenges associated with poor solubility and absorption rates, ultimately improving therapeutic outcomes for patients.

Keywords

Floating drug delivery systems, effervescent systems, hydrodynamically, oral bioavailability

1.INTRODUCTION

For dosage forms that stay in the stomach for a longer period of time, the capacity to extend and regulate the emptying time is a useful feature. The gastric emptying of dosage forms is a highly variable process longer than with traditional dosing formulations. Creating controlled release systems for improved absorption and 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. 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 system [1].

Small intestinal transit time is therefore a crucial factor to consider when prescribing medications that are not fully absorbed. A summary of basic human physiology is provided, including information on the specifics of gastric emptying, motility patterns, and physiological and formulation factors that influence the gastric emptying. Drugs' gastric residence time can be further extended by gastroretentive mechanisms, 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 drug waste, and increases bioavailability. It can also be used to administer medications locally to the stomach and the first few inches of the small intestine [2].

Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Many attempts have been made to develop sustained release preparations with extended clinical effects and reduced dosing frequency. A problem frequently encountered with conventional sustained release dosage forms is the inability to increase their residence time in stomach and no control over drug delivery, leading to fluctuations in plasma drug level [3]. Better product availability with novel therapeutic potential and significant patient benefits is made possible by gastro retention. A detailed description of the classification of floating drug delivery systems (FDDS) has been provided based on these methods. Scientists have talked about evaluating FDDS in vivo and in vitro to determine the effectiveness and practicality of such systems [4]. A number of recent cases have been published demonstrating the effectiveness of these systems for medications with bioavailability issues.

2 BASIC GASTRO INTESTINAL TRACT (GIT) PHYSIOLOGY

The stomach is composed of three main regions: the fundus, the body, and the antrum (pylorus). The antrum is the primary location for mixing motions and functions as a pump for stomach emptying via thrusting actions, while the proximal portion, composed of the fundus and body, serves as a reservoir for undigested material [5]. Both when fed and while fasting, gastric emptying happens. But there are differences in the motility patterns between the two states. An inter-digestive sequence of electrical events occurs during the fasting state; these events occur every two to three hours in the stomach and intestine [6]. This is known as the inter-digestive myoelectric cycle, or migrating myoelectric cycle (MMC), and Wilson and Washington have further classified it into the following four phases. Since dosage forms stay in the stomach longer than conventional dosage forms, the ability to extend and regulate the emptying time is a crucial asset. Gastric emptying of dosage forms is a highly variable process. Both when fed and while fasting, gastric emptying happens [7]. But there are differences in the motility patterns between the two states.

An inter-digestive sequence of electrical events occurs during the fasting state; these events occur in the stomach and intestine every two to three hours. The 40–60 minute phase I, or basal phase, is punctuated by sporadic contractions. The pre-burst phase, or phase II, is characterised by sporadic contractions and action potentials that last 40 to 60 minutes. Both the intensity and frequency steadily rise as the phase goes on. Four to six minutes make up Phase III, or the blast phase. It involves brief, frequent, and strong contractions. All of the undigested material is carried out of the stomach and into the small intestine by means of this wave. Another name for it is the housekeeping wave. Phase IV of two consecutive cycles takes place in the interval between phases III and I and lasts for 0 to 5 minutes [8, 9].

The pattern of contractions shifts from the fasted to the fed condition after consuming a mixed meal. This pattern, sometimes referred to as the digestive motility pattern, consists of ongoing contractions similar to those in phase II of the fasting state. Food particles are reduced in size (to less than 1 mm) as a result of these contractions, and they are then transported in the form of suspension towards the pylorus. The delayed start of MMC during the fed state causes the rate of stomach emptying to slow down [10, 11].

3 FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems represent a crucial method for achieving stomach retention and obtaining adequate medication bioavailability. For medications with an absorption window in the belly or upper colon, these delivery methods are preferred [12]. This has a lower bulk density than stomach fluids, which allows it to remain buoyant in the abdomen and slow down the rate at which the stomach empties. The medicine is also removed from the body gradually at the proper rate. The residual system is emptied from the abdomen upon medication release, leading to an extended gastric retention time (GRT) and improved control of the variation in plasma drug concentration [13].

The intrinsic low density can be produced by adding low density materials (such as fatty materials or oils, or foam powder) or by trapping air (such as hollow chambers). For the design of floating dosage forms for single and multiple-unit systems, the following methods have been applied [14]. A floating system including polypropylene foam powder, matrix-forming polymers, medication, and filler was recently suggested. Accurate control of the resulting drug release patterns could be successfully paired with these systems' good floating behavior. Single-unit dosage forms can cause irritation in the gastrointestinal tract (GIT) due to issues like sticking together or being clogged [15].

On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping [16].

Various multiple-unit floating system like air compartment multiple-unit system, hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method, microparticles based on low density foam powder, beads prepared by emulsion gelatin method, etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs [17].

4 CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system [18].

4.1 Single Unit Floating Dosage Systems

4.1.1 Effervescent Systems (Gas-generating Systems)

These buoyant systems utilized matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1 [19]. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach [20]. Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates [21, 22].

4.1.2 Non-Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the abdomen. These systems could also be referred as “plug-type systems” since they need a bent to stay lodged close to the pyloric sphincter. One amongst the formulation ways of such indefinite quantity forms involves the blending of drug with a gel, that to bear with gastric fluid swells [23]. The air freed by the swollen chemical polymer confers buoyancy to those indefinite

quantity forms. Samples of this type of FDDS embody colloid barrier, micro porous compartment system, alginate beads, and hollow microspheres. Another type may be a Fluid filled floating chamber which has incorporation of a gas-filled floatation chamber into a small porous part that homes a drug reservoir. Apertures or openings are present at the highest and bottom walls through that the channel fluid enters to dissolve the drug. The other 2 walls to bear with the fluid are sealed so the undissolved drug remains in it [24, 25]. The fluid present could be air, below partial vacuum or the other appropriate gas, liquid, or solid having an applicable specific gravity and an inert behavior. The device is of swellable size, remains afloat inside the abdomen for a prolonged amount of your time and once the entire release the shell disintegrates, passes off to the viscous, and is eliminated [26]. A three-layer matrix is used in a more recent self-correcting floatable asymmetric configuration drug delivery device to control drug release. In order to modulate extent and achieve zero-order release dynamics, an asymmetric configuration drug delivery system was developed, initially maintaining a continuing space at the diffusing front with ulterior dissolution/erosion towards the completion of the release method [27]. This improved the three-layer principle. The system was engineered to float, extending the in-vivo gastric duration. This resulted in an extended overall transit time within the most absorbent channel environment, and subsequently, a higher bioavailability. This specific characteristic would be applicable to medicine that have pH-dependent solubility, a slender window of absorption, and are absorbed by transport from either the proximal or distal portion of the small intestine [28, 29].

4.2 Multiple Unit Floating Systems

Despite much research and improvement, the all-or-nothing character of hydrodynamically balanced systems and alternate floating tablets has a significant drawback: substantial variability in GI transit time after oral administration. Multiple unit floating systems were created to address this drawback by lowering the likelihood of dose-dumping and the intersubject variability in absorption [30]. Reports on both effervescent and non-effervescent multiple unit systems' events can be found. A great deal of research has been done on hollow microspheres, which have better gastric retention qualities and can float on stomach fluid. Scientists are still investigating this field [31].

4.2.1 Non-effervescent Systems

Not a lot of report was found within the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reportable the likelihood of developing such system containing indomethacin, using chitosan because the chemical polymer excipient [32]. A multiple unit HBS containing indomethacin as a model drug ready by the extrusion method is reportable. A combination of drug, chitosan and acetic acid is extruded through a needle, and also the extrudate is cut and dried. Chitosan hydrates and floats within the acidic media, & the specified drug release might be obtained by modifying the drug-polymer ratio [33].

4.2.2 Effervescent Systems (Gas-generating Systems)

There are reports of sustained release floating granules containing tetracycline hydrochloride [34]. The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of HPMC, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. 60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h. Floating minicapsules of pepstatin having a diameter of 0.1-0.2 mm has been reported by Umezawa [35]. These minicapsules contain a central core and a coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the CO₂ release in gastric fluid and the pepstatin resides in the stomach for prolonged period. Alginates have received much attention in the development of multiple unit systems [36]. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues. A multiple unit system was prepared comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system [37]. The freeze-drying technique is used to prepare floating calcium alginate beads. Sodium alginate solution is added to calcium chloride, causing instant gelation and forming calcium alginate. The beads are freeze-dried, resulting in a porous structure for floating. Researchers studied the behavior of radio-labeled floating beads in human volunteers using gamma scanning, finding a prolonged gastric residence time of over 5.5 hours for floating beads [38]. A new floating dosage system has been developed, consisting of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents, containing sodium bicarbonate and tartaric acid, is divided into two sublayers surrounded by a swellable polymer membrane. When immersed in a 37°C buffer, CO₂ is generated by the neutralization reaction, resulting in swollen pills with a density less than 1.0 g/ml [39, 40].

4.2.3 Hollow Microspheres

These are considered as one of the most promising buoyant systems, as they possess the distinctive benefits of multiple unit systems likewise as higher floating properties, due to the central cavity within the microsphere. The final techniques concerned in their preparation embody easy solvent evaporation methodology and solvent diffusion and evaporation methodology [41]. The drug release and higher floating properties chiefly depends upon the kind of polymer, softener and also the solvents utilized for the formulation. Polymers like Polycarbonate, Eudragit®, and cellulose ester were employed in the preparation of hollow microspheres, and also the drug release may be modulated by optimizing the polymer-plasticizer quantitative relation and also the polymer amount. Sustained release floating microspheres using polycarbonate were developed, using solvent evaporation technique [42].

4.2.4 Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for GI infections and disorders. The fundamental mechanism concerned within the raft formation includes the formation of viscous cohesive gel to bear with the gastric fluids, wherein every portion of the liquid swells forming endless layer known as a raft. The raft floats due to the buoyancy created by the formation of carbon dioxide and act as a barrier to stop the reflux of gastric contents like Hydrochloride and enzymes into the muscular structure [43]. Raft forming systems are used for antacid delivery and gastrointestinal infections. They create a viscous, cohesive gel in contact with gastric fluids, forming a continuous layer called a raft. This raft floats due to

CO₂ formation and acts as a barrier to prevent gastric contents from refluxing into the esophagus. The system typically contains a gel-forming agent and alkaline bicarbonates or carbonates [44].

5 MECHANISM OF FLOATING DRUG DELIVERY SYSTEMS

Various methods have been developed to increase the retention time of dosage forms in the stomach, including floating dosage forms, gas-generating systems, swelling or expanding systems, mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices, and co-administration of gastric-emptying delaying drugs [45]. Floating drug delivery systems (FDDS) have been the most commonly used due to their buoyancy in the stomach and ability to remain buoyant without affecting gastric emptying rates for extended periods. The drug is released slowly at the desired rate, and the residual system is emptied from the stomach, resulting in increased gastric emptying rate and better control of plasma drug concentration fluctuations [46]. However, a minimal gastric content and floating force level are required for the buoyancy retention principle. A novel apparatus has been developed to measure the floating force kinetics, allowing for optimization of FDDS stability and durability to prevent unforeseeable intragastric buoyancy capability variations [47].

6 EVALUATION PARAMETERS OF STOMACH SPECIFIC FDDS

Studies show that pharmaceutical dosage forms with in vitro floating behavior exhibit prolonged gastric residence in vivo. However, good in vitro floating behavior alone isn't enough for efficient gastric retention in vivo, as the effects of food and stomach motility are difficult to estimate. In vivo studies provide definitive proof.

6.1 Measurement of Buoyancy Capabilities of the FDDS

The floating behaviour was evaluated with resultant weight measurements. The experiment was carried out in two different media, deionised water in order to monitor possible difference. The apparatus and its mechanism are explained earlier in this article. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to deionized water [48].

6.2 Floating time and dissolution

The floating time measurement test is typically conducted in stimulated gastric fluid or 0.1 mole/lit HCl at 37°C using a USP dissolution apparatus. The time taken for the dosage form to float is called floating lag time, and the time for which the dosage form floats is called floating or flotation time. A more relevant in-vitro dissolution method was proposed to evaluate a floating drug delivery system for tablet dosage form [49]. A modified 100 ml glass beaker was modified to hold 70 ml of 0.1 mole/lit HCl dissolution medium and a burette was mounted to deliver the medium at a flow rate of 2 ml/min. The proposed method showed good in vitro-in vivo correlation, mimicking in vivo conditions such as gastric volume, gastric emptying, and gastric acid secretion rate [50].

6.3 Size and Shape Evaluation

The study reveals that particle size and shape significantly influence drug solubility and bioavailability, using various methods such as Sieve analysis, air elutriation, photo analysis, optical microscope, and various techniques [51].

6.4 In-vitro Release Studies

In vitro release studies were conducted using various dissolution apparatuses, including the USP Dissolution 2000, Franz diffusion cell system, and synthetic membrane, to determine drug release amount [52].

6.5 Fourier Transforms Infrared (FTIR) Analysis

Fourier transform infrared spectroscopy (FTIR) is a technique used to identify organic, polymeric, and inorganic materials and determine functional groups. It was used to measure pure drug, polymer, and drugloaded polymer formulations [53].

6.6 Differential Scanning Calorimetric (DSC) Analysis

The Shimadzu Model-DSC-60/DSC-50/Metler Telleo is used to characterize pharmaceutical water of hydration. Thermograms are obtained using an intercooler, calibrated using Indium/Zinc standards, and heated at 10°C/min [54].

6.7 Pharmacokinetic Studies

Pharmacokinetic studies are crucial in in vivo studies. Verapamil, a drug, was compared to conventional tablets using floating pellets filled into capsules. The t_{max} and AUC values were higher for floating pellets than conventional tablets. The C_{max} values showed no significant difference, suggesting improved bioavailability. Additionally, piroxicam in hollow polycarbonate microspheres showed 1.4 times more bioavailability and a three-times increased elimination half-life compared to the free drug [55].

7 POLYMERS USED IN FLOATING DRUG DELIVERY SYSTEM

Polymers play a crucial role in the development of floating drug delivery systems, which are designed to release drugs slowly and steadily in the stomach. These polymers are carefully selected based on their ability to float on gastric fluids and control the release of drugs. One commonly used polymer in floating drug delivery systems is ethyl cellulose, which has excellent film-forming properties and can be easily manipulated to achieve the desired drug release profile [56]. Another important polymer used in floating drug delivery systems is hydroxypropyl methylcellulose (HPMC), which forms a gel barrier that controls the release of drugs. HPMC is biocompatible and can be tailored to provide sustained drug release for extended periods of time [57]. Additionally, chitosan, a natural polymer derived from chitin, has been shown to enhance the bioavailability of drugs by improving their solubility and permeability. In conclusion, polymers are essential components of floating drug delivery systems as they enable controlled drug release and improve patient compliance. By selecting appropriate polymers with specific characteristics, researchers can develop effective floating drug delivery systems that optimize therapeutic outcomes [58].

8 APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

8.1 Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in-vivo [59, 60].

8.2 Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased [61, 62].

8.3 Absorption Enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption [63, 64].

9 CONCLUSIONS

This review examines floating drug delivery systems, which are designed to improve oral bioavailability of poorly soluble drugs. These systems float on the gastric fluid for an extended period, allowing sustained drug release and enhanced absorption. Various approaches, including effervescent, hydrodynamically balanced, and raft-forming systems, have been developed to achieve optimal floating properties. A holistic approach to developing a successful system involves understanding factors affecting gastric emptying time, formulation parameters, and drug physicochemical properties. The use of novel polymers, excipients, and technologies has further enhanced the feasibility and effectiveness of floating drug delivery systems. These advancements offer promising opportunities for improving the oral bioavailability of a wide range of drugs with poor solubility and permeability, ultimately improving therapeutic outcomes for patients.

10 CONFLICT OF INTEREST

None

11 REFERENCES

- [1]. Cohn J. N. 1996. The management of chronic heart failure. *New England Journal of Medicine*, 335(7), 490-498.
- [2]. Groenewegen A., Rutten, F. H., Mosterd, A., & Hoes, A. W. 2020. Epidemiology of heart failure. *European Journal of Heart Failure*, 22(8), 1342-1356.
- [3]. Kemp C. D., & Conte J. V. 2012. The pathophysiology of heart failure. *Cardiovascular Pathology*, 21(5), 365-371.
- [4]. Roger V. L. 2013. Epidemiology of heart failure. *Circulation Research*, 113(6), 646-659.
- [5]. Dixit N. 2011. Floating drug delivery system. *Journal of Current Pharmaceutical Research*, 7(1), 6-20.
- [6]. Sharma N., Agarwal D., Gupta M. K., & Khinchi M. 2011. A comprehensive review on floating drug delivery system. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2(2), 428-441.
- [7]. Shah S. H., Patel J. K., & Patel N. V. 2009. Stomach-specific floating drug delivery system: A review. *International Journal of Pharm Tech Research*, 1(3), 623-633.
- [8]. Yeole P. G., Khan S., & Patel V. F. 2005. Floating drug delivery systems: Need and development. *Indian Journal of Pharmaceutical Sciences*, 67(3), 265.
- [9]. Sanjay, S., Vaibhav, J. and Kumar, B.P., 2003. Gastro retentive drug delivery systems. In National Institute of Pharmaceutical Education and Research (NIPER), Pharmatech.
- [10]. Lenaerts, V.M. and Gurny, R., 1989. Bioadhesive drug delivery systems. CRC press.
- [11]. Bruschi, M.L. and de Freitas, O., 2005. Oral bioadhesive drug delivery systems. *Drug development and industrial pharmacy*, 31(3), pp.293-310.
- [12]. Dixit, N., 2011. Floating drug delivery system. *Journal of current pharmaceutical research*, 7(1), pp.6-20.
- [13]. Yeole, P.G., Khan, S. and Patel, V.F., 2005. Floating drug delivery systems: Need and development. *Indian journal of pharmaceutical sciences*, 67(3), p.265.
- [14]. Sharma, N., Agarwal, D., Gupta, M.K. and Khinchi, M., 2011. A comprehensive review on floating drug delivery system. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2(2), pp.428-441.
- [15]. Graffner, C., Johansson, M.E., Nicklasson, M. and Nyqvist, H., 1985. Preformulation studies in a drug development program for tablet formulations. *Journal of pharmaceutical sciences*, 74(1), pp.16-20.
- [16]. Lee, B.J., 2010. Pharmaceutical preformulation: Physicochemical properties of excipients and powders and tablet characterization. *Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing*, pp.1-54.
- BG, P. and Mishra, O., 2021. Concept, Manufacturing and Characterization of Effervescent Tablets: A Review.
- [17]. Parida, D.R., Kharia, A.A. and Choudhary, N.K., 2022. Recent Trends in Floating Drug Delivery System. *Research Journal of Pharmacy and Technology*, 15(1), pp.429-435.

- [18]. Sravya, V., Patro, J. and Ch, S., 2022. Formulate gastroretentive floating bioadhesive drug delivery system of nizatidine by direct compression technique: <https://doi.org/10.54037/WJPS.2022.100106>. World Journal of Pharmaceutical Sciences, pp.59-73.
- [19]. Kothule, S., Aher, S. and Bachhav, R., Formulation Development and Evaluation of Gastroretentive Floating Tablet of Vildagliptin.
- [20]. Özdoğan, A.I., Akca, G. and Şenel, S., 2021. Development and in vitro evaluation of gel formulation of atorvastatin solid dispersions. Journal of Drug Delivery Science and Technology, 61, p.102199.
- [21]. Kumar, A. and Srivastava, R., 2021. In vitro In Vivo Studies On Floating Microspheres ForGastroretentive Drug Delivery System: A Review. Asian Journal of Pharmaceutical and Clinical Research, pp.13-26.
- [22]. Rahamathulla, M., Hani, U., Alqahtani, A., HV, G., Begum, Y., Jaffer, M., Osmani, R.A.M., Chidambaram, K., Moin, A. and Shankar, S.J., 2021. 23 Factorial Design and Optimization of Effervescent Floating Matrix Tablet of Neratinib. Journal of Pharmaceutical Innovation, pp.1-12.
- [23]. Rashmitha, V., Madhusudan Rao, Y. and Pavani, S., 2021. Formulation and evaluation of fenoverine floating tablets. Asian J Pharm Clin Res, 14(4), pp.175-180.
- [24]. Krisanti, E.A., Budiadmadjaja, M.G. and Mulia, K., 2021, March. Formulation and characterization of gastro-retentive floating tablet contained curcuminoids from Curcuma Longa extracts for treatment of gastric ulcers. In AIP Conference Proceedings (Vol. 2344, No. 1, p. 040003). AIP Publishing LLC.
- [25]. Rathi, S., Vaghela, S., Shah, R. and Shah, S., 2021. Formulation and Evaluation of Gastroretentive Floating Tablets of Febuxostat. Research Journal of Pharmacy and Technology, 14(10), pp.5359-5365.
- [26]. Chandrakala, M., Narendranath, S.B., Ramana, N.V. and Shanmugam, V., Formulation And Evaluation of Effervescent Floating Tablets of The Model Drug Atorvastatin Calcium.
- [27]. Shah S. H., Patel J. K., Pundarikakshudu K., & Patel N. V. 2009. An overview of a gastro-retentive floating drug delivery system. Asian Journal of Pharmaceutical Sciences, 4(1), 65-80.
- [28]. Gupta P., Gnanarajan P. K., & Kothiyal P. 2015. Floating drug delivery system: A review. International Journal of Pharma Research & Review, 4(8), 37-44.
- [29]. Rajora A, Nagpal K. A Critical Review on Floating Tablets as a Tool for Achieving Better Gastric Retention. Crit Rev Ther Drug Carrier Syst. 2022;39(1).
- [30]. 31. Dhone PG, Sahu YP, Sabitri B, Khandelwal PN. Formulation and evaluation of floating tablet of levofloxacin.
- [31]. Israr M, Pugliese N, Farid A, Ghazanfar S, Di Cerbo A, Muzammal M, Alamri AS, Basheeruddin Asdaq SM, Ahmad A, Khan KA. Preparation and Characterization of Controlled-Release Floating Bilayer Tablets of Esomeprazole and Clarithromycin. Molecules. 2022;27(10):3242.
- [32]. Ashish D, Vibhu S. Formulation and Evaluation of Floating Tablet of Thiocolchicoside. Curr Res Pharm Sci. 2022;59-67.
- [33]. Ahirrao S, Bhambere D, Todkar K, Patil M, Khairnar P, Udavant P. Formulation Development and Evaluation of Floating Tablets of Zolmitriptan. Biosci Biotechnol Res Asia. 2022;19(2):395-405.
- [34]. Nijhu RS. Formulation and in vitro evaluation of bilayer floating tablet of Aceclofenac and esomeprazole by using natural and synthetic polymer.
- [35]. Desai D, Masareddy R, Patil A, Desai S, Matt VK. Formulation, optimization and validation of floating oral in situ gel of Ivabradine hydrochloride. Ther Deliv. 2022;May(0).
- [36]. Arshad MS, Kiran M, Mudassir J, Farhan M, Hussain A, Abbas N. Formulation, Optimization, in vitro and in-vivo evaluation of levofloxacin hemihydrate Floating Tablets. Brazilian Journal of Pharmaceutical Sciences. 2022 Mar 14;58.
- [37]. Kim B, Byun Y, Lee EH. DoE-Based Design of a Simple but Efficient Preparation Method for a Non-Effervescent Gastro-Retentive Floating Tablet Containing Metformin HCl. Pharmaceutics. 2021 Aug 8;13(8):1225.
- [38]. Albadry AA, Ali WK, Al-saady FA. Formulation and evaluation of prochlorperazine maleate sustained release floating tablet. Int J Pharm Pharm Sci. 2017;9(2):89-98.

- [39]. Rathore J, Parmar HK. Formulation and evaluation of floating tablet norfloxacin. *Int J Pharma Sci Res.* 2015;6(1):23-27.
- [40]. Reddy MY, Anjum M. Formulation and evaluation of gastro retentive effervescent floating matrix tablets of Cephalixin. *J Drug Deliv Ther.* 2014;4(1):22-30.
- [41]. Kukati L, Chittimalli K, Shaik NB. Formulation and evaluation of floating tablets of cefpodoxime proxetil. *J Sci Res.* 2014;6(3):563-579.
- [42]. Kumar L, Singh V, Meel RK. Formulation and evaluation of gastro retentive floating tablets of Terbutaline sulphate. *Int J PharmaSci Res.* 2014;5(10):639-645.
- [43]. Sirimamilla N. Formulation and Evaluation of Atorvastatin Calcium Immediate Release Tablets Using Super Disintegrants [PhD dissertation]. KK College of Pharmacy, Chennai, Tamil Nadu, India; 2013.
- [44]. Kesarla RS, Vora PA, Sridhar BK, Patel G, Omri A. Formulation and evaluation of floating tablet of H2-receptor antagonist. *Drug Dev Ind Pharm.* 2015;41(9):1499-1511.
- [45]. Khan R. Gastroretentive drug delivery system-a review. *Int J Pharm Bio Sci.* 2013;4(2):630-646.
- [46]. Rapolu K, Sanka K, Vemula PK, Aatipamula V, Mohd AB, Diwan PV. Optimization and characterization of gastroretentive floating drug delivery system using Box-Behnken design. *Drug Dev Ind Pharm.* 2013;39(12):1928-1935.
- [47]. Rajesh M. Formulation and Evaluation of Gastro Retentive Floating Tablets of Atorvastatin Calcium [PhD dissertation]. KM College of Pharmacy, Madurai; 2012.
- [48]. Shinde A.J., Prajapati K, Pathak AK, Mishra A. Formulation and evaluation of floating tablet of captopril. *Int J PharmTech Res.* 2011;3(1):333-341.
- [49]. Garg R, Gupta GD. Preparation and evaluation of gastroretentive floating tablets of silymarin. *Chem Pharm Bull.* 2009;57(6):545-549.
- [50]. National Center for Biotechnology Information. (2024) PubChem Compound Summary for CID Ivabradine Hydrochloride. [https://pubchem.ncbi.nlm.nih.gov/compound/Ivabradine Hydrochloride](https://pubchem.ncbi.nlm.nih.gov/compound/Ivabradine%20Hydrochloride). (Accessed 15 April 2024)
- [51]. National Center for Biotechnology Information. (2024) PubChem Compound Summary for CID Nebivolol. Available at <https://pubchem.ncbi.nlm.nih.gov/compound/Nebivolol>. (Accessed 15 April 2024)
- [52]. Katzbauer, B., 1998. Properties and applications of xanthan gum. *Polymer degradation and Stability*, 59(1-3), pp.81-84.
- [53]. Urlacher, B. and Noble, O., 1997. Xanthan gum. In *Thickening and gelling agents for food* (pp. 284-311). Springer, Boston, MA.
- [54]. Sworn, G., 2021. Xanthan gum. In *Handbook of hydrocolloids* (pp. 833-853). Woodhead Publishing.
- [55]. Koczur, K.M., Mourdikoudis, S., Polavarapu, L. and Skrabalak, S.E., 2015. Polyvinylpyrrolidone (PVP) in nanoparticle synthesis. *Dalton Transactions*, 44(41), pp.17883-17905.
- [56]. Robinson, B.V., Sullivan, F.M., Borzelleca, J.F. and Schwartz, S.L., 2018. PVP: a critical review of the kinetics and toxicology of polyvinylpyrrolidone (povidone). CRC Press.
- [57]. Siepman, J. and Peppas, N.A., 2012. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Advanced drug delivery reviews*, 64, pp.163-174.
- [58]. Battista, O.A. and Smith, P.A., 1962. Microcrystalline cellulose. *Industrial & Engineering Chemistry*, 54(9), pp.20-29.
- [59]. Araki, J., Wada, M., Kuga, S. and Okano, T., 1998. Flow properties of microcrystalline cellulose suspension prepared by acid treatment of native cellulose. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 142(1), pp.75-82.
- [60]. Crowley, P. and Martini, L.G., 2001. Drug-excipient interactions. *Pharm Technol*, 4, pp.7-12. 62. Ertel, K.D. and Carstensen, J.T., 1988. Chemical, physical, and lubricant properties of magnesium stearate. *Journal of pharmaceutical sciences*, 77(7), pp.625-629.
- [61]. Jadhav, N.R., Paradkar, A.R., Salunkhe, N.H., Karade, R.S. and Mane, G.G., 2013. Talc: A versatile pharmaceutical excipient. *World Journal of Pharmacy and Pharmaceutical Sciences*, 2, pp.4639-4660.
- [62]. Granberg, R.A. and Rasmuson, Å.C., 1999. Solubility of paracetamol in pure solvents. *Journal of Chemical & Engineering Data*, 44(6), pp.1391-1395.