DOI: 10.55522/jmpas.V13I6.6679 **ISSN NO. 2320 – 7418**

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Review article

Exploring the journey of (revolutionizing) gastro retentive drug delivery system from conception to its profitable achievement–A comprehensive review

Shivam Pratap Singh, Jatin Kumar, Peeush Singhal*

Department of Pharmaceutical Sciences, Gurukula Kangri Deemed to be University, Haridwar, Uttarakhand, India

Corresponding author: Peeush Singhal, ✉ peeushpharma@gmail.com, **Orcid Id**: https://orcid.org/0000-0002-0008-1272

Department of Pharmaceutical Sciences, Gurukula Kangri Deemed to be University, Haridwar, Uttarakhand, India

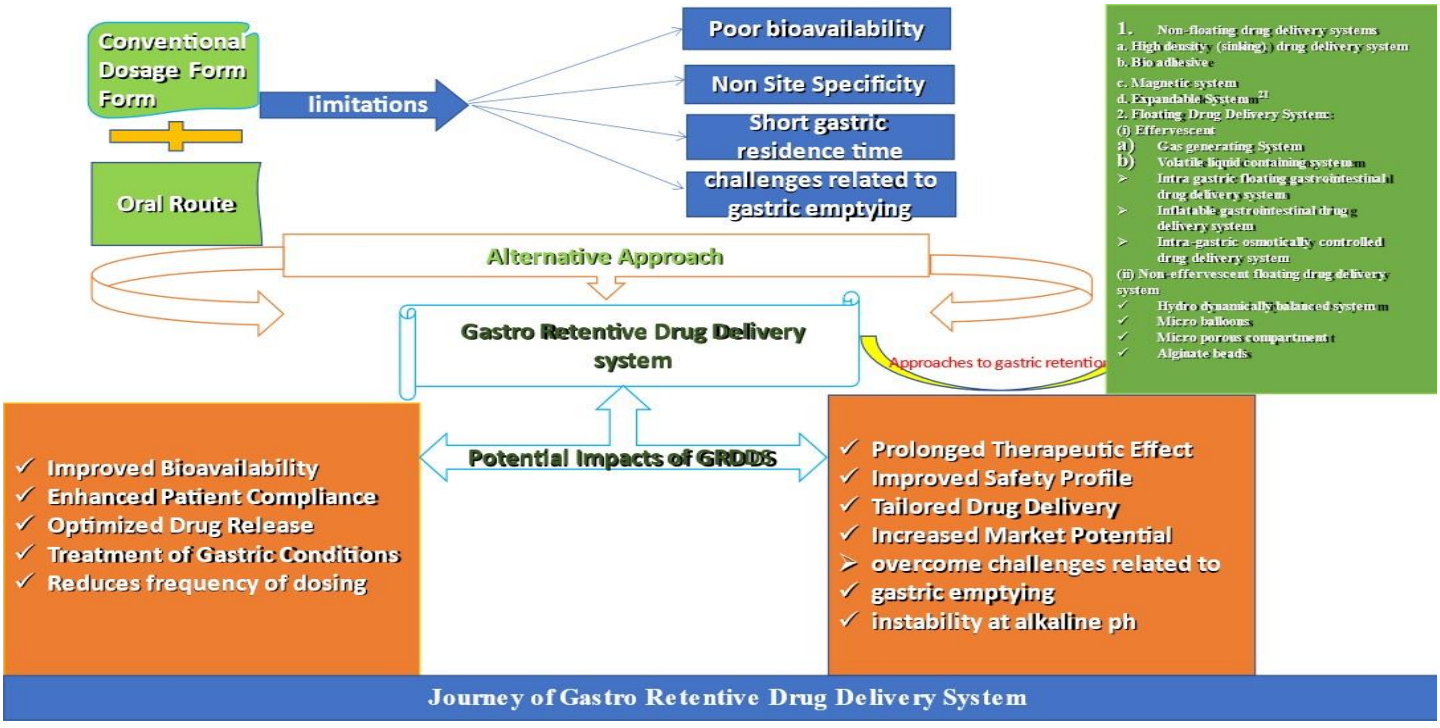
Received - 03-09-2024**, Revised** - 27-11-2024, **Accepted** - 09-12-2024 **(DD-MM-YYYY)**

Refer This Article

Shivam Pratap Singh, Jatin Kumar, Peeush Singhal, 2024. Exploring the journey of (revolutionizing) gastro retentive drug delivery system from conception to its profitable achievement–A comprehensive review. Journal of medical pharmaceutical and allied sciences, V 13 - I 6, Pages - 6883 – 6891. Doi: https://doi.org/10.55522/jmpas.V13I6.6679.

ABSTRACT

In today fast-paced world, the demand for efficient and effective medication delivery system is on rise, with the advancement of new technologies. In the field of contemporary medicine, drug delivery system plays a critical role, one of them system which gain widespread attention and recognition in the world is gastro retentive drug delivery system.[1] But the question is how did this idea become a profitable reality? In this article we will explore the journey of Gastro retentive drug delivery system from conception to its success in the market, potential impact and upcoming possibilities (future prospective) of Gastro retentive drug delivery system and we discuss the physiological state of stomach, recently applied gastro retentive drug delivery system technologies, along with their merits and demerits. Overall, this review may inform whole concept about gastro retentive drug delivery system from beginning to conclusion.



Keywords: Gastro Retentive Drug Delivery System, Narrow Absorption Window, Future Prospective, Gastric Emptying.

INTRODUCTION

Firstly, we have to understand what exactly gastro retentive drug delivery system is and how it works? In simple words it is a drug delivery system designed to lengthen the gastric residence time of medications, thereby ensuring controlled and sustained release [1]. This system is specifically designed to improve the delivery and effectiveness of certain medications. Example-Imagine we have a stomachache and need to take a painkiller. Instead of taking a regular pill that quickly passes through our stomach and into our intestine Imagine a special pill that stays in our stomach for a longer time and slowly release the medication to provide relief over an extended period [2,3]. This is how gastro retentive drug delivery system works. This system is designed to improve the absorption and therapeutic effect of medications by managing them in the stomach for a longer period, allowing for better control and targeted release of drug [1-4]. Drugs with minimal absorption in the bottom half of the gastrointestinal tract, instability, poor solubility at alkaline pH, short half-lives, and local activity in the upper section of the intestine for H. Pylori eradication are likely to be delivered by a gastro-retentive drug delivery system[4-6]. Several formulation strategies and designs have been employed in the development of effective control-release gastroretentive drug delivery systems. This paper covers the history, background, and prospects of the gastroretentive drug delivery system (GRDDS), as well as its inception [1, 8, 10].

An Impressive Evolution of The Gastro-Retentive Drug Delivery System

The development of modern gastroretentive drug delivery systems can be traced back to the 1960s when researchers first explored the concept of extending the gastric residence time of a drug. In the 1980s the first gastro retentive drug delivery system developed known as the floating system. This system consists of a floating tablet or capsule made of polymer that would remain in the stomach for a prolonged time [11, 12]. This significant achievement opens a new gate for future innovations in the field. Since then, there has been significant advancement in gastro retentive drug delivery technology, with various types of systems being developed and tested [5]. Early efforts focused on buoyant systems, leading to the development of floating dosage forms. Over time various approaches like muco-adhesive system and expandable system emerged to increase gastric retention and optimize drug release. The next step was to conduct clinical trials to test the safety and efficacy of gastro retentive drug delivery system in humans. These trials showed promising result with improve drug absorption and less side effects [6]. Overall, we see that, to make effective gastro-retentive drug delivery system, we have to explore more effective ways to prolong and control the release of medication in the stomach, but we are limited by the natural process such as gastric emptying. This meant that medications would often pass through the stomach too quickly, leading to incomplete absorption and reduced effectiveness [7]. To address this issue, we have to look at the basic anatomy and physiology of the gastrointestinal tract and stomach.

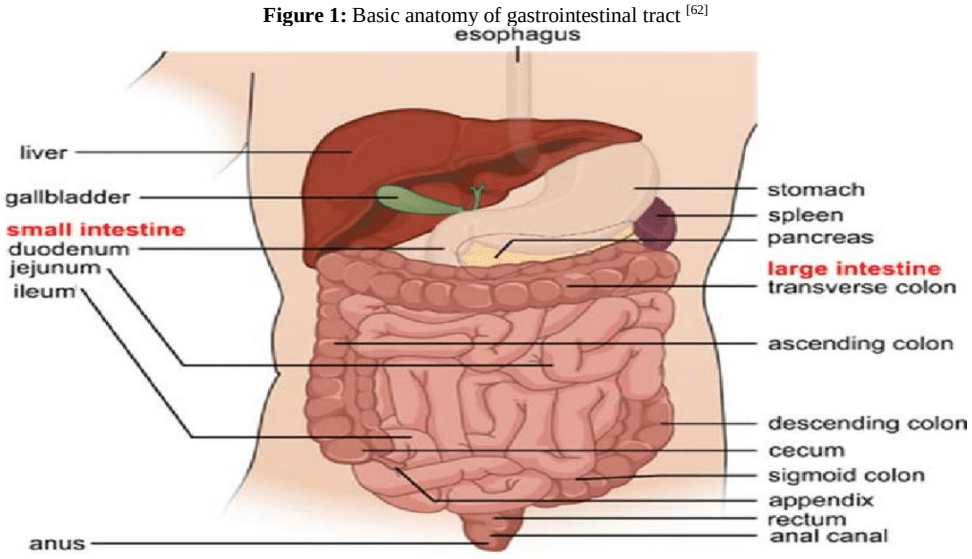
Basic Anatomy and Physiology of Gastrointestinal Track, Stomach [8]

Basically, G.I.T is divided into three main regions they are- Stomach (I) Proximal stomach- Fundus, Body (II) Distal stomach- Antrum, (Pylorus).

Small intestine.

Large intestine

Figure 1: Basic anatomy of gastrointestinal tract [62]



Tomach Functions & Mechanism

A thorough understanding of the architecture and physiology of the stomach is essential for the successful development of an effective dosage form since the stomach plays a significant role in the gastro retentive drug delivery system. The stomach is split into two sections anatomically [9]. The distal stomach is composed of the pylorus and the antrum, whereas the proximal portion is composed of

the fundus and body. The stomach's primary function is to process food, store it for a while, and then**s** gradually release it into the duodenum. The Antrum functions as a pump to aid in gastric emptying by moving food, while the Fundus and body serve as storage areas for undigested food [10]. A series of contractions known as the migrating myoelectric cycle cyclically passes through the stomach and intestine every 120–180 minutes, causing gastric emptying in both the fed and fasted states [11]. It is separated into four further phases (Table 1). The term "digestive motility pattern" refers to the pattern of contraction alterations in a fed condition. Phases 1 (base phase), 2 (preburst phase), 3 (burst phase), and 4 make up this pattern [12].

Table 1: Four phases of migrating motor complex (MMC).

PHASES	NAMES	COMMENTS	DURATION
Phase 1	Basal Phase	Quiescent period with rare contractions.	30-60 min
Phase 2	Pre-burst Phase	contraction and sporadic action potentials that progressively increase in frequency and intensity as the phase goes on	20-40 min
Phase 3	Burst Phase	Brief intervals of strong, frequent, and severe contractions. Because it allows all undigested debris to be swept out of the stomach and down to the small intestine, this phase is known as the "housekeeper wave."	10-20 min
Phase 4	Last Phase	Occurs in a brief transitional phase that sits between phases 3 and 1 of two successive cycles.	0-5 min

Figure 2: Schematic view on the anatomy of stomach

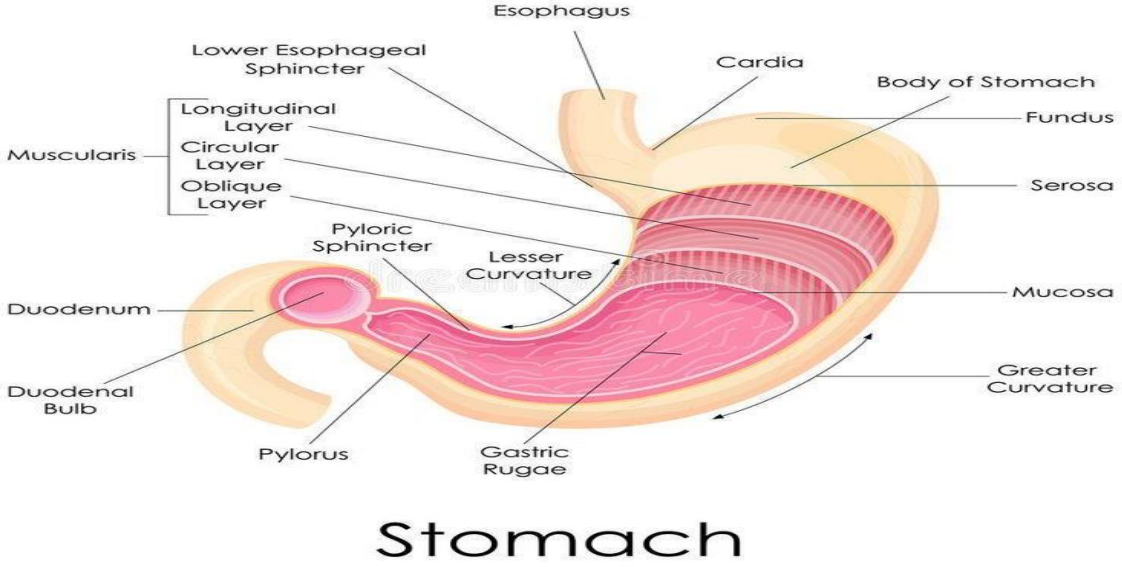
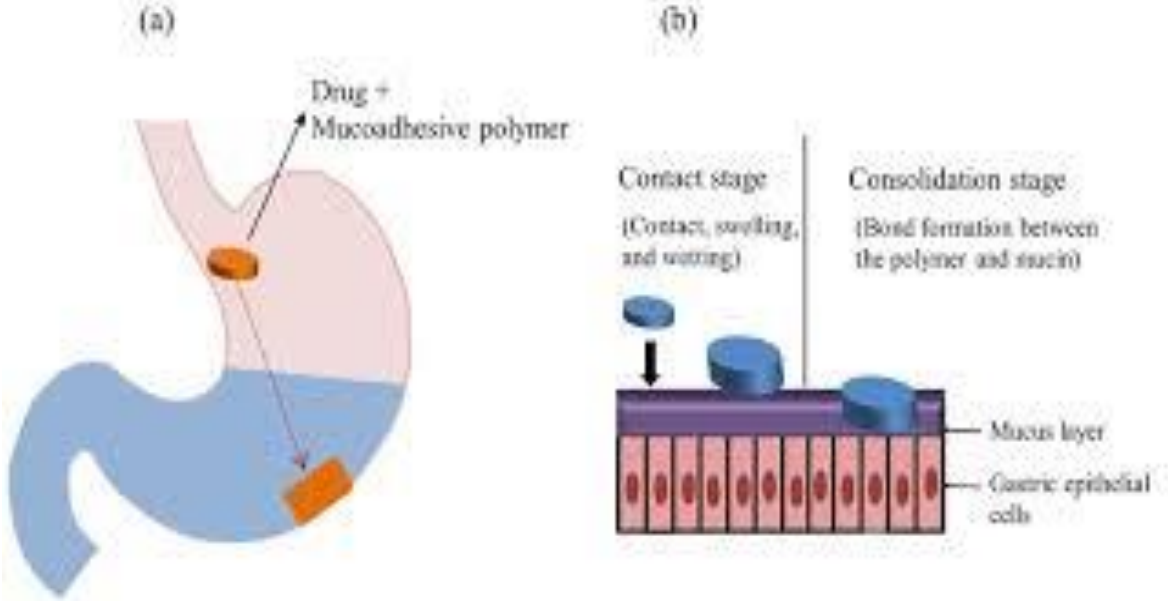


Figure 3: Mucoadhesive GRDDS (a) general representation of mucoadhesive systems and (b) mechanism of mucoadhesive system



Current Pharmaceutical Technologies of GRDDS

Non-floating Drug Delivery Systems

High Density (sinking) Drug Delivery System

An administration of a formulation intended to sink quickly to the bottom of the gastrointestinal tract is known as a high-density (sinking) drug delivery system. This property is especially helpful for medications that need to work locally in the lower gastrointestinal (GI) tract or that target certain GI tract regions. The following are some salient features of high-density medication delivery systems:

Purpose

High-density formulations are mostly used to make sure the medication stays in the targeted area of the GI system for a longer amount of time. This is particularly helpful for medications that target diseases like colonic infections, IBD, or locally advanced colorectal cancer.

Formulation

Since the materials used to construct high-density drug delivery devices are often denser than intestinal and stomach fluids, they sink quickly in the GI tract. Zinc oxide, heavy metal salts, or barium Sulphate are often utilized materials. Benefits Localized Drug activity: The medication has a greater localized drug activity and fewer systemic adverse effects since it sinks to the bottom of the GI tract and stays close to the target spot.

Prolonged Residence Time

Longer residence durations in the lower gastrointestinal system are characteristic of high-density formulations, which enable sustained drug release and better therapeutic results. Increased Patient Compliance: Lower dosage frequency and increased patient compliance may result from targeted administration to the precise place of action.

Applications

Treatment of Colonic Diseases

When treating colonic conditions like ulcerative colitis, Crohn's disease, and colorectal cancer, high-density medication delivery devices are especially helpful.

Colon Targeting

Additionally, these formulations can be utilized for colon-targeted drug administration, in which the medication is intended to be delivered only to the colon and does not need to transit via the upper GI tract.

Formulation Considerations

When designing high-density drug delivery systems, stability, release kinetics, drug compatibility, and material biocompatibility must all be carefully taken into account.

Drug Release Mechanisms

Drug release from high-density systems can be regulated by mechanisms such pH-dependent release, erosion, or diffusion, depending on the particular formulation.

For the treatment of a variety of GI illnesses, high-density drug delivery systems provide an inventive method of targeted drug delivery in the gastrointestinal tract. These systems have advantages over other methods in terms of localized drug activity, prolonged residence time, and enhanced patient compliance [15-20].

Bio Adhesive or Mucoadhesive Drug Delivery System

The bio adhesive technology for the stomach mucous membrane has prolonged the gastric retention period [16]. The delivery system's attachment to the stomach wall lengthens the residence period, which boosts bioavailability. Among the substances used to promote mucoadhesion are gliadin, polycarbophil, lecithin, chitosan, carboxy methylcellulose, and Carbopol [23]. There have also been attempts to attach novel adhesive materials to the gut that are generated from bacterial fimbriae or their synthetic equivalents. Nevertheless, the stomach wall's propulsion power is typically too great for the gastric mucoadhesive force to withstand [17]. Another drawback for this kind of system is the constant generation of mucus and dilution of the stomach content. Numerous researchers have experimented with a floating and bio adhesion system synergistic approach. mucoadhesive medication delivery mechanism [18, 24].

Magnetic System

With this approach, a small magnet is contained in the dose form, and a second magnet is applied to the abdomen above the stomach. The degree of precision with which the external magnet is positioned should potentially reduce patient compliance [19]. Drug absorption may continue for a while. Using bio adhesive granules containing ultrafine ferrite, a rabbit was used in the initial technological trial. Almost all of the granules that had been transferred to the esophagus using an external magnet of 1700 G for the first two minutes (at intervals of two minutes) remained in the area after two to ten hours [20].

Expandable System [21]

These systems have the capacity to enlarge and stay in the stomach for extended periods of time. These are often made in the shape of folded, compressed capsules that hold the dosage. The dose form expands and the capsule shell disintegrates in the stomach's environment, preventing the capsule from exiting the stomach. Drug distribution that is regulated and sustained can be accomplished by utilizing the right polymer.

Floating Drug Delivery System

Because floating medication delivery systems have a lower bulk density than gastric fluids, they float in the stomach for an extended amount of time without slowing down the rate at which the stomach empties [22]. The medicine is gradually removed from the system at the desired pace while it is floating on the contents of the stomach. The leftover system is then expelled from the stomach [23]. As a result, the oscillations in plasma drug concentration are better controlled and the stomach retention period is extended. Drug delivery systems that float can be categorized in to [24]:

Effervescent Floating Drug Delivery System

These systems were further classified into

Gas Generating System

The primary process in this system is the reaction between sodium bicarbonate, citric acid, and tartaric acid, which produces CO_2 gas. The gas generated causes the system's density to decrease, causing it to float on the stomach fluids. The release of CO_2 by salts and citric/tartaric acid traps it in the system's

hydrocolloid layer, lowering its specific gravity and causing it to float [26]. A sustain-release tablet that is encased in two layers makes up the mechanism. The effervescent inner layer contains tartaric acid and sodium bicarbonate [26].

Volatile liquid-containing System

These feature an inflatable chamber filled with a liquid (such as ether or cyclopentane) that gasifies at body temperature, causing the stomach chamber to expand [27]. These systems have a hollow defined unit that is controlled osmotically and are floating systems. The medicine is contained in the first of the system's two chambers, while the volatile system is contained in the second. These systems have again been classified into the following [28].

Intragastric Floating Gastrointestinal Drug Delivery System

This system has a microporous compartment that encloses a drug reservoir and a flotation chamber that is filled with either vacuum or an inert, harmless gas [28, 30].

Inflatable Gastrointestinal Drug Delivery System

These devices have an inflatable chamber that fills with liquid ether that gasifies to expand the stomach when it reaches body temperature. The bio-erodible polymer filament (such as a copolymer of polyvinyl alcohol and polyethylene) found in the inflatable chamber eventually dissolves in the stomach contents, causing the chamber to collapse and release gas [29].

Intra-gastric Osmotically Controlled Drug Delivery System

It consists of an inflatable floating capsule and a drug delivery system regulated by osmotic pressure. The two parts of the osmotically regulated medication delivery system—the drug reservoir compartment and the osmotically active compartment—are released when the inflated capsule breaks down in the stomach [30]. Super porous hydro gels are a great illustration of this strategy in action. When the dosage form comes into contact with gastric fluid, it swells dramatically to several times its original volume. The dosage form is then pushed to the pylorus by the gastric contraction, but because of its larger size, the contractions slide over the system's surface and the dosage form pushes back into the stomach [30-32].

Non-effervescent Systems

Alginate beads, Microbaloons, Microporous compartments, and hydro-dynamically balanced systems are further categories for non-effervescent systems [33].

Hydro-dynamically Balanced System

This medication formulation uses gel-forming hydrocolloids to stay afloat in the stomach contents. Drug Delivery Systems stay afloat in the stomach for an extended amount of time without slowing down the process of gastric emptying because their bulk density is lower than that of gastric fluids [34]. After the drug is removed from the system at a desired rate, the system floats on the contents of the stomach, allowing the drug to emerge gradually. The stomach is cleared of the drug's leftover system following its release. This leads to a rise in the GRT and improved management of variations in the plasma medication concentrations [35].

Micro Balloons

In the strictest sense, micro balloons, also known as hollow microspheres, are spherically shaped, empty particles devoid of a core. These microspheres, which are essentially free-flowing powders made of artificial polymers or proteins, should preferably be less than 200 micrometers. Solvent evaporation is one of the innovative techniques used to manufacture the hollow inner core of micro balloons that are loaded with drugs and have an outside polymer shell [36, 37]. The medication and a mixture of enteric acrylic polymers are dissolved in an ethanol/dichloromethane solution and then added to an agitated Poly Vinyl Alcohol (PVA) solution that is heated to 40°C under thermal control [38]. Once a stable emulsion has formed, the organic solvent is removed from the emulsion by stirring continuously or by raising the temperature while applying pressure. The gas phase is generated in the droplet of dispersed polymer by the evaporation of dichloromethane and thus formed the hollow internal cavity in the microsphere of the polymer with drugs [39].

Micro Porous Compartment

The medication reservoir in this system is housed inside a microporous chamber with pores along the length of its top and bottom walls [40].The medicine is dissolved and transported to the stomach and the proximal portion of the small intestine for absorption via the delivery system, which floats over the gastric fluid due to the entrapped air in the flotation chamber [41].

Alginate Beads

Multi-unit floating dose forms have been developed using freeze-dried calcium alginates [26]. Aqueous calcium chloride solution can be used to create spherical beads with a diameter of roughly 2.5 mm by dropping sodium alginate solution into it [42]. After being separated, these beads are air-dried. As a result, the stomach develops a porous system that stays buoyant [43].

Countless Merits/ Benefits [43]

Minimizes mucosal irritation and offers a more comfortable and effective treatmentprocess.

Site-specific drug delivery for stomach and small intestine disorders.

Reduces frequency of dosing.

Targeted drug delivery to the upper GI tract for more effective treatment.

More effective than traditional methods of drug administration.

Sustained release in the stomach and small intestine is ideal for treating related disorders.

Prolong the release of medication for a longer residence time and avoid first-pass metabolism.

High accessibility due to good blood supply and rapid absorption.

Minimizes body counter activity for higher drug efficiency.

Proven to enhance the bioavailability of therapeutic agents metabolized in the upper digestivetract.

The Downsides [45]**-**

Risk of gastric irritation.

The challenge of maintaining consistent drug release.

Careful consideration of these factors is crucial when developing such drug deliverysystem.

Variability in gastric emptying rates among individuals.

Design and implementation of these systems may increase production costs andcomplexity.

The Success of GRDDS in the Market

The key factor of the success of the gastroretentive drug delivery system in the market is its ability to overcome various physiological and patient-related challenges. The unique features make it especially useful for drugs with a narrow therapeutic index [46]. This system also helps a solution for those drugs that are unstable in the acidic environment on stomach or also beneficial for ph. sensitive drugs, Such as antibiotic and proton pump inhibitor. The success of gastro retentive drug delivery system is not limited only for treatment but also have great impact on pharmaceutical industry [47]. According to a report by Grand View Research, the GRDDS market size was valued at 10.75 billion in 2020 and may be reach 28 million in 2028. It grows about 12.2% during the period (2021-2028). There is no doubtto say that it is a vast and profitable area [48].

Several Potential Impacts of Grdds [49, 50]

A gastro-retentive drug delivery system can have several potential impacts, including:

Improved Bioavailability

Enhances the absorption of drugs, ensuring a sustained and controlled release, leading to better bioavailability and therapeutic efficacy [50].

Enhanced Patient Compliance

Reduces the frequency of dosing, promoting better patient adherence to medication regimens [50].

Optimized Drug Release

Allows for controlled release of drugs in the stomach, preventing variations in drug levels and minimizing side effects [51].

Treatment of Gastric Conditions

Suitable for drugs targeting gastric conditions, such as localized infections or disorders, optimizing therapeutic outcomes [52].

Prolonged Therapeutic Effect

Offers a prolonged therapeutic effect by maintaining therapeutic drug concentrations over an extended period, reducing the need for frequent dosing [53].

Improved Safety Profile

Minimizes fluctuations in drug levels, potentially reducing the risk of adverse effects associated with peak drug concentrations [54].

Tailored Drug Delivery

Enables the design of dosage forms specific to the drug's pharmacokinetics and the patient's needs [55].

Increased Market Potential

Expands the market potential for drugs that may otherwise be limited by poor solubility or rapid gastrointestinal transit [56].

However, challenges such as formulation complexity, variability in gastric emptying times among individuals, and potential device-related issues need to be addressed for the successful implementation of gastro retentive drug delivery systems [57].

Opportunities or Future Prospective of GRDDS

The Gastroretentive drug delivery system (GRDDS) offers several opportunities and prospects in the pharmaceutical field:

Improved Drug Bioavailability

GRDDS can enhance the bioavailability of drugs, especially those with poor solubility or permeability, by maintaining a sustained release profile and prolonging residence time in the stomach.

Enhanced Therapeutic Efficacy

By ensuring prolonged drug release at the desired site of action, GRDDS can improve therapeutic outcomes, especially for drugs targeting conditions in the upper gastrointestinal tract [59].

Targeted Drug Delivery

GRDDS can be designed to release drugs specifically in the stomach, allowing targeted delivery to treat gastric diseases or conditions.

Reduced Dosage Frequency

The sustained release profile of GRDDS can reduce the frequency of dosing, improving patient compliance and convenience.

Minimized Side Effects

Controlled release of drugs with GRDDS can help minimize fluctuations in drug levels, reducing side effects associated with peak plasma concentrations.

Potential for Combination Therapy

GRDDS can facilitate the delivery of multiple drugs simultaneously, allowing for combination therapy tailored to specific patient needs.

Application in Geriatric and Pediatric Patients

GRDDS can be particularly beneficial for geriatric and pediatric patients who may have difficulty swallowing conventional dosage forms or require controlled drug release.

Versatility in Drug Formulation

GRDDS can accommodate various drug types, including both hydrophilic and hydrophobic compounds, expanding its applicability across different therapeutic areas [60].

Extended Patent Protection

Developing novel GRDDS formulations can provide opportunities for pharmaceutical companies to extend patent protection for existing drugs through formulation modifications.

Customization and Personalization

Advances in formulation technologies enable the customization of GRDDS to suit individual patient requirements, promoting personalized medicine approaches.

Overall, the continued research & development in GRDDS hold promise for addressing challenge in drug delivery and improving patient outcomes across a range of therapeutic areas [61].

CONCLUSION

The journey of gastro retentive drug delivery system from idea to its profitable reality has been remarkable. This system opens new door for new drugs to enter in the market. This revolutionized system has played a significant role and provides numerous advantages with its ability to improve patient compliance and reduce side effects. This system help overcome challenges related to gastric emptying, ensuring sustained drug level in the body and instability at alkaline pH. Even through various gastro retentive drug delivery systems such as magnetic, nanomaterial based GRDDS have been reported in this review, there clinical significance still needs to be studied. As the field continues to evolve and expand, gastro retentive drug delivery system is set to make an even greater impact in the pharmaceutical industry, offering hope for a better future in healthcare. A thorough understanding of the anatomy and physiology state of the stomach, and process variables on dosage form quality is a prerequisite for the successful design of GRDDS. Moreover, a QbD approach can be used to a better understand the effect of formulation and process variable on product performance.

REFERENCE

1. Tripathi J, Thapa P, Maharjan R, et al, 2019. Current state and future perspectives on Gastroretentive drug delivery systems. Pharmaceutics. 11(4), Pages 193. Doi: 10.3390/ pharmaceutics11040193.

2. Deshpande AA, Shah NH, Rhodes CT, et al, 1997. Development of a novel controlled-release system for gastric retention. Pharmaceutical research. 14, Pages 815-819. Doi: 10.1023/a: 1012171010492.

3. Streubel A, Siepmann J, Bodmeier R, 2006. Gastroretentive drug delivery systems. Expert opinion on drug delivery. 3(2), Pages 217-233. Doi: 10.1517/17425247.3.2.217.

4. Fateh MV, Kumar V, Chaudhary R, et al, 2018. Gastro-retentive drug delivery system for treatment of Ulcer. International Journal of Agricultural Invention. 3(2), Pages 203-210. Doi: 10.46492/IJAI/2018.3.2.18.

5. Arora S, Ali J, Ahuja A, et al, 2005. Floating drug delivery systems: a review. Aaps PharmSciTech. 6, Pages E372-390. Doi: org/10.1208/pt060347.

6. Singh RP, Rathore DS, 2012. Gastroretention: a means to address local targeting in the gastric region. Pharmacophore. 3(6), Pages 287-300.

7. Pant S, Badola A, Kothiyal P, 2016. A review on Gastroretentive drug delivery system. Indian Journal of Pharmaceutical and Biological Research. 4(2), Pages 1. Doi: 10.30750/ijpbr.4.2.1.

8. Wilson RL, Stevenson CE, 2019. Anatomy and physiology of the stomach. Shackelford's Surgery of the Alimentary Tract, 2 Volume Set (Eighth Edition). Pages 634-646. Doi: https://doi.org/10.1016/B978-0-323-40232-3.00056-X.

9. Szurszewski JH, 1969. A migrating electric complex of canine small intestine. American Journal of Physiology-Legacy Content. 217(6), Pages 1757-1763. Doi: 10.1152/ajplegacy.1969.217.6.1757.

10. Rouge N, Leroux JC, Cole ET, et al, 1997. Prevention of the sticking tendency of floating minitablets filled into hard gelatin capsules. European journal of pharmaceutics and biopharmaceutics. 43(2), Pages 165-171. Doi: https://doi.org/10.1016/S0939-6411(96)00003-3.

11. Shivram S, Imran T, Sadhana S, 2011. Gastro retentive Drug Delivery System: A Review. Int. Journal of Pharmaceutical Research & Allied Sciences. 1(1), Pages 01-13.

12. El-Zahaby SA, Kassem AA, El-Kamel AH, 2014. Design and evaluation of Gastroretentive levofloxacin floating mini-tablets-in-capsule system for eradication of Helicobacter pylori. Saudi Pharmaceutical Journal. 22(6), Pages 570-579. Doi: https://doi.org/10.1016/j.jsps.2014.02.009.

13. Jiménez-MI, Quirino-BT, Villafuerte-RL, 2008. Sustained delivery of captopril from floating matrix tablets. International journal of pharmaceutics. 362(1-2), Pages 37-43. Doi: https://doi.org/10.1016/j.ijpharm.2008.05.040.

14. Sethi S, Mangla B, Kamboj S, et al, 2018. A QbD approach for the fabrication of immediate and prolong buoyant cinnarizine tablet using polyacrylamide-g-corn fiber gum. International journal of biological macromolecules. 117, Pages 350-361. Doi: https://doi.org/ 10.1016/ j .ijbiomac.2018.05.178.

15. Awasthi R, Kulkarni GT, 2016. Decades of research in drug targeting to the upper gastrointestinal tract using Gastroretention technologies: where do we stand? Drug delivery. 23(2), Pages 378-394. Doi: ttps://doi.org/ 10.3109/10717544.2014.936535.

16. Prajapati VD, Jani GK, Khutliwala TA, et al, 2013. Raft forming system—an upcoming approach of Gastroretentive drug delivery system. Journal of controlled release. 168(2), Pages 151-165. Doi: https://doi.org/ 10.1016/ j.jconrel.2013.02.028.

17. Mandal UK, Chatterjee B, Senjoti FG, 2016. Gastro-retentive drug delivery systems and their in vivo success: A recent update. Asian journal of pharmaceutical sciences. 11(5), Pages 575-584. Doi: https://doi.org/ 10.1016/ j.ajps.2016.04.007.

18. Prinderre P, Sauzet C, Fuxen C, 2011. Advances in gastro

retentive drug-delivery systems. Expert opinion on drug delivery. 8(9), Pages 1189-1203. Doi: https://doi.org/ 10.1517/17425247.2011.592828.

19. Hwang SJ, Park H, Park K, 1998. Gastric retentive drug-delivery systems. Critical Reviews™ in Therapeutic Drug Carrier Systems. 15(3), Pages 243-284. Doi: 10.1615/CritRevTherDrugCarrierSyst.v15.i3.20.

20. Cvijic S, Ibric S, Parojcic J, et al, 2018. An in vitro-in silico approach for the formulation and characterization of ranitidine Gastroretentive delivery systems. Journal of Drug Delivery Science and Technology. 45, Pages 1-35. Doi: https://doi.org/10.1016/j.jddst.2018.02.013.

21. Hooda A, Nanda A, Jain M, et al, 2012. Optimization and evaluation of gastroretentive ranitidine HCl microspheres by using design expert software. International journal of biological macromolecules. 51(5), Pages 691-700. Doi: https://doi.org/10.1016/j.ijbiomac.2012.07.030.

22. Odeku OA, Aderogba AA, Ajala TO et al, 2017. Formulation of floating metronidazole microspheres using cassava starch (Manihot esculenta) as polymer. Journal of pharmaceutical investigation. 47, Pages 445-451. Doi: 10.1007/s40005-017-0319-7.

23. Diós P, Nagy S, Pál S, et al, 2015. Preformulation studies and optimization of sodium alginate based floating drug delivery system for eradication of Helicobacter pylori. European Journal of Pharmaceutics and Biopharmaceutics. 96, Pages 196-206. Doi: https://doi.org/10.1016/j.ejpb.2015.07.020.

24. Jain SK, Jangdey MS, 2009. Lectin conjugated Gastroretentive multiparticulate delivery system of clarithromycin for the effective treatment of Helicobacter pylori. Molecular pharmaceutics 6(1), Pages 295-304. Doi: https://doi.org/10.1021/mp800193n.

25. Hardikar S, Bhosale A, 2018. Formulation and evaluation of gastro retentive tablets of clarithromycin prepared by using novel polymer blend. Bulletin of Faculty of Pharmacy, Cairo University. 56(2), Pages 147-157. Doi: https://doi.org/ 10.1016 /j.bfopcu.2018.07.001.

26. Inukai K, Takiyama K, Noguchi S, et al, 2017. Effect of gel formation on the dissolution behavior of clarithromycin tablets. International Journal of Pharmaceutics. 521(1-2), Pages 33-39. Doi: https://doi.org/ 10.1016/ j.ijpharm.2017.01.065.

27. Mostafavi A, Emami J, Varshosaz J, et al, 2011. Development of a prolonged-release Gastroretentive tablet formulation of ciprofloxacin hydrochloride: Pharmacokinetic characterization in healthy human volunteers. International journal of pharmaceutics. 409 (1-2), Pages 128-136. Doi: https://doi.org/10.1016/j.ijpharm.2011.02.035.

28. Fu J, Yin H, Yu X, et al, 2018. Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems. International journal of pharmaceutics. 549(1-2), Pages 370-379. Doi: https://doi.org/10.1016/j.ijpharm.2018.08.011.

29. Kagan L, Lapidot N, Afargan M, et al, 2006. Gastroretentive accordion pill: enhancement of riboflavin bioavailability in humans. Journal of controlled release. 113(3), Pages 208-215. Doi: https://doi.org/10.1016/j.jconrel.2006.03.022.

30. Qin C, Wu M, Xu S, et al, 2018. Design and optimization of gastro-floating sustained-release tablet of pregabalin: In vitro and in vivo evaluation. International Journal of Pharmaceutics. 545(1-2), Pages 37-44. Doi: https://doi.org/ 10.1016 /j.ijpharm.2018.04.011.

31. Ngwuluka NC, Choonara YE, Kumar P, et al, 2015. An optimized Gastroretentive Nano system for the delivery of levodopa. International journal of pharmaceutics. 494(1), Pages 49-65. Doi: https://doi.org/ 10.1016/j.ijpharm.2015.08.014.

32. Oh TO, Kim JY, Ha JM, 2013.Preparation of highly porous Gastroretentive metformin tablets using a sublimation method. European Journal of Pharmaceutics and Biopharmaceutics. 83(3), Pages 460-467. Doi: https://doi.org/10.1016/j.ejpb.2012.11.009.

33. He W, Li Y, Zhang R, et al, 2014. Gastro-floating bilayer tablets for the sustained release of metformin and immediate release of pioglitazone: Preparation and in vitro/in vivo evaluation. International journal of pharmaceutics. 476(1-2), Pages 223-231. Doi: https://doi.org/ 10.1016/j.ijpharm.2014.09.056.

34. Patil S, Talele GS, 2015. Gastroretentive mucoadhesive tablet of lafutidine for controlled release and enhanced bioavailability. Drug delivery. 22(3), Pages 312-319. Doi: https://doi.org/10.3109/10717544.2013.877099.

35. Pawar VK, Kansal S, Garg G, et al, 2011. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. Drug delivery. 18(2), Pages 97-110. Doi: https://doi.org/10.3109/10717544.2010.520354.

36. Kotreka U, Adeyeye MC, 2011. Gastroretentive floating drug-delivery systems: a critical review. Critical Reviews™ in Therapeutic Drug Carrier Systems. 28(1), Pages 47-99. Doi: 10.1615/CritRevTherDrugCarrierSyst.v28.i1.20.

37. Talukder R, Fassihi R, 2004. Gastroretentive delivery systems: A mini-review. Drug development and industrial pharmacy. 30(10), Pages 1019-1028. Doi: https://doi.org/10.1081/DDC-200040239.

38. Garg S, Sharma S, 2003. Gastroretentive drug delivery systems. Business Briefing: Pharmatech. 5(2), Pages 160-162. Doi: 10.5958/0974-360X.2018.00398.0.

39. Timmermans J, Moës AJ, 1990. How well floating dosage do forms float? International journal of pharmaceutics. 62(2-3), Pages 207-216. Doi: https://doi.org/10.1016/0378-5173 (90)90234-U.

40. Chauhan MS, Kumar A, Pathak K, 2012. Osmotically regulated floating asymmetric membrane capsule for controlled site-specific delivery of ranitidine hydrochloride: Optimization by central composite design. AAPS PharmSciTech. Pages 1492-1501. Doi: 10.1208/s12249-012-9870-8.

41. Rajora A, Nagpal K, 2022. A critical review on floating tablets as a tool for achieving better gastric retention. Critical

Reviews™ in Therapeutic Drug Carrier Systems. 39(1), Pages 65-103. Doi: 10.1615/ CritRevTher DrugCarrierSyst.2021038568.

42. Clarke GM, Newton JM, Short MD, 1993. Gastrointestinal transit of pellets of differing size and density. International journal of pharmaceutics. 100 (1-3), Pages 81-92. Doi: https://doi.org/10.1016/0378-5173 (93)90078-T.

43. Streubel A, Siepmann J, Bodmeier R, 2006. Drug delivery to the upper small intestine window using Gastroretentive technologies. Current opinion in pharmacology. 6(5), Pages 501-518. Doi: https://doi.org/10.1016/j.coph.2006.04.007.

44. Arora S, Ali J, Ahuja A, et al, 2005. Floating drug delivery systems: a review. Aaps PharmSciTech. Pages E372-90. Doi: 10.1208/pt060347.

45. Shaha SH, Patel JK, Pundarikakshudu K, et al, 2009. An overview of a gastro-retentive floating drug delivery system. Asian journal of pharmaceutical sciences. 4(1), Pages 65-80.

46. Calbet JA, MacLean DA, 1997. Role of caloric content on gastric emptying in humans. The Journal of physiology. 498(2), Pages 553-559. Doi: org/10.1113/jphysiol.1997. sp021881.

47. Juvonen KR, Purhonen AK, Salmenkallio-MM, et al, 2009. Viscosity of oat bran-enriched beverages influences gastrointestinal hormonal responses in healthy humans. The Journal of nutrition. 139(3), Pages 461-466. Doi: https://doi.org/10.3945/jn.108.099945.

48. Vinchurkar K, Sainy J, Khan MA, et al, 2022. Features and facts of a Gastroretentive drug delivery system-a review. Turkish journal of pharmaceutical sciences. 19(4), Pages 476. Doi: 10.4274/tjps.galenos.2021.44959.

49. Murphy CS, Pillay V, Choonara YE, 2009. Gastroretentive drug delivery systems: current developments in novel system design and evaluation. Current drug delivery. 6(5), Pages 451-460. Doi: https://doi.org/ 10.2174/ 156720109789941687.

50. Ito R, Machida Y, Sannan T, et al, 1990. Magnetic granules: a novel system for specific drug delivery to esophageal mucosa in oral administration. International Journal of Pharmaceutics. 61(1-2), Pages 109-117. Doi: https://doi.org/ 10.1016/0378-5173(90)90049-A.

51. Gaur PK, Mishra S, Bhardwaj S, et al, 2014. Ion exchange resins in Gastroretentive drug delivery: characteristics, selection, formulation and applications. Journal of Pharmaceutical Sciences and Pharmacology, 1(4), Pages 304-312. Doi: https://doi.org/10.1166/jpsp.2014.1037.

52. Jeong SH, Park K, 2008. Drug loading and release properties of ion-exchange resin complexes as a drug delivery matrix. International journal of pharmaceutics. 361(1-2), Pages 26-32. Doi: https://doi.org/10.1016/j.ijpharm.2008.05.006.

53. Jeong SH, Berhane NH, Haghighi K, et al, 2007. Drug release properties of polymer coated ion-exchange resin complexes: experimental and theoretical evaluation. Journal of pharmaceutical sciences, 96(3), Pages 618-632. Doi: https://doi.org/10.1002/jps.20677.

54. Anand V, Kandarapu R, Garg S, 2001. Ion-exchange resins: carrying drug delivery forward. Drug Discovery Today. 6(17), Pages 905-914. Doi: https://doi.org/10.1016/S1359-6446 (01)01922-5.

55. Eisenächer F, Garbacz G, Mäder K, 2014. Physiological relevant in vitro evaluation of polymer coats for Gastroretentive floating tablets. European Journal of Pharmaceutics and Biopharmaceutics. 88(3), Pages 778-786. Doi: https://doi.org/10.1016/j.ejpb.2014.07.009.

56. Strübing S, Abboud T, Contri R.V, et al, 2008. New insights on poly (vinyl acetate)-based coated floating tablets: characterization of hydration and CO2 generation by benchtop MRI and its relation to drug release and floating strength. European Journal of Pharmaceutics and Biopharmaceutics. 69(2), Pages 708-717. Doi: https://doi.org/10.1016/j.ejpb.2007.12.009.

57. Chen J, Blevins WE, Park H, et al, 2000. Gastric retention properties of super porous hydrogel composites. Journal of controlled release. 64(1-3), Pages 39-51. Doi: https://doi.org/10.1016/S0168-3659 (99)00139-X.

58. Kashyap N, Viswanad B, Sharma G, et al, 2007. Design and evaluation of biodegradable, bio sensitive in situ gelling system for pulsatile delivery of insulin. Biomaterials. 28(11), Pages 2051-2060. Doi: https://doi.org/ 10.1016/j.biomaterials.2007.01.007.

59. Kim S, Hwang KM, Park YS, et al, 2018. Preparation and evaluation of non-effervescent Gastroretentive tablets containing pregabalin for once-daily administration and dose proportional pharmacokinetics. International journal of pharmaceutics. 550(1-2), Pages 160-169. Doi: https://doi.org/ 10.1016/j.ijpharm.2018.08.038.

60. Chamberlain J, 1991. Physiological Pharmaceutics. Biological Barriers to Drug Absorption; Clive G. Wilson and Neena. Journal of Pharmacy and Pharmacology. 43(4), Pages 296. Doi: https://doi.org/10.1111/j.2042-7158. 1991.tb06692.x.

61. Sarkar D, Nandi G, Changder A, et al, 2017. Sustained release Gastroretentive tablet of metformin hydrochloride based on poly (acrylic acid)-grafted-gellan. International journal of biological macromolecules. 1(96), Pages137-148. Doi: https://doi.org/10.1016/j.ijbiomac.2016.12.022.