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Original Research Article

Evaluation and Future Perspectives of Gastro Retentive Dosage Forms

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Abstract

In past years, technological advances have been achieved to improve the therapeutic efficacy and medication bioavailability of oral dosage forms. In this situation, a variety of gastro retentive drug delivery systems (GRDDS) have been employed to increase the therapeutic effectiveness of medications with a limited window of absorption, instability at alkaline pH, solubility in acidic circumstances, and local stomach activity. The physiological status of the stomach and numerous factors that have an impact on GRDDS are covered in this review. Expandable, ultra porous hydrogel, bio/mucoadhesive, magnetic, ion-exchange resin, low- and high-density systems, and other recently utilised gastrointestinal technologies have also been reviewed along with their benefits and drawbacks. The importance of the in vitro and in vivo evaluation parameters of the different GRDDS, as well as their applications, are outlined. Future prospects for this technology are also highlighted in order to reduce the rate of stomach emptying in both the fasting and fed stages. Overall, this review are designing the GRDDS for its evaluation parameters and future perspectives.

Keywords: Gastro-retentive dosage form, gastric retention time, bioavailability.

Introduction

The traditional medication types remain half to two hours in the stomach and are absorbed within three to six hours into the small intestine, making difficult over prolonged periods of time to modify release duration and stomach retention [1] The idea of the gastro-retention mechanism was built on the assumption that the drug is located in a certain region in the body. When the drug absorption site is the stomach or upper intestine, at the absorption site, a dose form must be sustained, for this sort of posing, gastrointestinal transit is a constraint. [2] Gastroretentive dosage forms are therefore formulated in order to increase the period of gastric residence. [3]

Gastroretentive dosage forms are therefore prepared in order to increase the duration of the gastric stay. By the introduction of a different guided delivery mechanisms, modern tablet or capsule has drawbacks that resulting in a temporary high dose, a the underdose has taken a long time, has been surpassed. [4] Yet, this advantage did not satisfy a number of vital drugs that was currently engaged locally in the stomach

(ii) had absorption gap or the upper intestine part, (iii) in the gut's or gastric system they were unstable, or (iv) had low solubility at higher pH levels. These limits encouraged growth of gastro-retentive system for drug supply. In addition to be willing to deliver drugs continuously and to the small bowel uptake area sustainable manner, advancements have been made by GRDDS include: attaining a better and longer influence and thereby lowering the frequency of dosing, creating more efficiencies: gaining a more sustained impact and reducing administration duration, and offering successful local stomach care treatment or local abnormalities of the stomach and the reduction of drug inactivation and medicines impact both on the small opening of the bowel uptake. [5]

Bioavailability of a drug is basically a critical phenomenon, which refers to the degree and pace at which the active drug or metabolite enters the systemic circulation and reaches the site of action. Drugs delivered by mouth must travel along the wall of the intestine and then follow the portal circulation to the liver. These are the places where absorption occurs before the drug enters systemic circulation. This ensures that many of the medications may be metabolized before adequate plasma concentrations are reached. The bioavailability of drugs is calculated by the characteristics of the dosage type, which depend on the design as well as on the manufacture. Clearly, there is a demand from formulation scientists in the pharmaceutical industry for GRDDS formulations to be processed.

Various marketed formulations are formulated for gastro retentive dosage forms in different modes as follows: [6]

i) Sinking Systems or high density
ii) Floating Systems or low density
iii) Superfluous or hydrogel systems
iv) Expandable systems
v) Muco- adhesive systems
vi) Magnetic systems

Various technologies of Gastroretentive drug delivery system:

a. Floating Drug Delivery System

Floating forms of medication have less bulk density than gastrointestinal juice and thus hold on fluids in the abdomen outwardly impacting on gastric emptying rate at greater length. During the test on the gastric tract the drug is slowly released from system at appropriate rate once the drug has been released; the remaining product is drained of the abdomen. This leads to improved GRT and greater leverage of variances in the concentration of plasma drugs. FDDS indeed be classified as follows. [7]

i. Non-effervescent floating system:

This sort of system, after ingesting, inflates closely by restraining of gastrointestinal fluid to the degree prevents that the gastric fluid from exiting the stomach. It is one of the formulations. Dosage approaches of these kinds involve combining of a drug with such polymer that swells in conjunction with digestive liquid and preserves relative strength of shape as well as a less mass density after ingestion. The air contained in the polymer imparts floating to such dosage forms. Inactive ingredients widely used in GRDDS contains hydrophilic polymers and gums.[8]

ii. Effervescent floating system:

These GRDDS uses matrices manufactured with swelling polymers like HPMC (Hydroxypropyl methyl cellulose), polysaccharides, effervescent couple. The

system is sufficiently designed that carbon dioxide is produced when entered in the stomach and the product can float in stomach.

Effervescent floating systems can be classified as floating tablets with one and two layer of effervescent, multi-unit floating systems. Single-layer effervescent system (tablet) are closely developed by incorporating effervescent, polymer, drug and excipients. In bi-layer system, one layer is composed of a medication, release polymer, and CO2-generating agent, while the other layer is a medication and excipient that is immediately released. [9]

b. High density system

High-density systems which have's greater density than gastric fluid because of that the system sinks to the bottom and stays in the stomach for prolong period. Generally used excipients of these type systems contains barium sulfate, zinc oxide, and TiO2. These formulations are including coated pellets with a density more than the stomach content (approx. 1,004 g / cm3).

c. Mucoadhesive System [10]

Such devices are used to locate the delivery system in the body pit and lumen to facilitate the drug absorption phase in a particular location. The method requires bio adhesive polymers which binds to epithelial layer of the Gastrointestinal tract. The suggested bio adhesion system is hydrogen formation and electrostatic contact at the surface of the mucosa polymer. Expeditious hydration in connection with muco-epithelial layer adherence seems to be in favor, especially if water expelled from reactive surfaces. A mucoadhesive material is a naturally derived from plant or synthetic resin effective of attaching to a biological membrane (bio adhesive polymer) or to a GIT mucus lining. The features of these polymers/resins are including molecular resilience, hydrophilic operational groups, and molecular mass, chain limit, and arrangement. In addition, they should be non-toxic and un-absorbable, shape mucin bonds that are non-covalent – epithelial surfaces, prompt attachment to wet surfaces, simple introduction of a drug, and give no obstacle to drug release, have a peculiar attachment site, and cost effective.

d. Magnetic System [11]

In magnetic systems, the dosage form comprises of active pharmaceutical ingredients, excipients and also a small quantity of internal magnets. An extracorporeal magnet is positioned over stomach to regulate the position of the dosage form comprising the inner magnet. This approach to improving stomach retention.

Swelling Drug Delivery Systems

Such kinds of formulations after ingesting, expand in certain degree that inhibits them from abandoning the stomach via the pylorus. Therefore, formulation remains in the abdomen for a prolonged duration. Such systems can be accrediting to as ' plug type systems' as they tend to stay stuck at the pyloric sphincter. Enlargement might be accomplished by expanding in stomach. Swelling typically happens owing to osmosis. The disclosing occurs in view of mechanical size of dosage forms are produced in a bulkier scale and are folded into a drug carrier, e.g. a gelatin capsule, for conducive consumption. The carrier in the stomach is absorbed, and gastro-retentive delivery forms unfold or expand to achieve prolonged configuration.

Advantages of GRDDS

➢Sustained drug delivery/reduced frequency of dosing

Drugs having shorter biological half-life, prolonged and low ingestion through CR-GRDF can minimize dosing intervals. This is associated to better patient adherence and therefore upgrades the treatment. [12]

➢Minimize drug concentration fluctuations

Constant drug consumption following administration of GRDDS induces narrower amounts of blood drugs relative to immediate dosage forms. As a result, variations in drug effects are reduced and harmful symptoms linked with maximum amounts can be concentration- dependent can be avoided. This function emphasis for drugs having a small therapeutic index.

Reduce variation to achieve a sure acumen in pharmacological effect of drugs which trigger various receptor forms at various stages.

➢Improves Bioavailability of drug: [13]

Drugs with low bioavailability because of upper site-definitive absorption of the GI tract are pre-qualified for formulation as floating dosage form, thus enhances absorption.

Bioavailability increases after the first pass effect as a result of variations in the concentration of plasma drugs; the necessary concentration of plasma drugs is preserved by continuous drug release

➢ Site specific drug delivery: [13]

Long-term and continuous administration of GRDDS could be useful for site action/site peculiar in stomach. This administration form results in local concentrations of therapeutic drugs, however systemic levels, following absorption and distribution of drugs, are limited.

A buoyant dosage form is a workable solution, particularly for drugs with restricted places of absorption in the upper bowel. Sustained release of drugs to stomach provides enough inhabitant therapeutic scale and reduces systemic access to the medication. It eliminates adverse effects of the drug in the circulation of the blood.

➢ Minimize adverse reaction:

Constant maintenance the drug concentration at therapeutic level and below toxic level over longer period resulting in adverse effect reduction.

Disadvantages or Limitation of Gastro retentive drug delivery system

➢ Drugs with stability problems in the highly acidic condition cannot be formulated as GRDDS.

➢ Drugs with low pH solubility can experience problems of dissolution and may not fully release the drug.

➢ This only works if the fluid level is high enough in the stomach.

➢ Some drugs cause irritation to the gastric mucosa.

➢ Drugs which undergo equal absorption throughout all the regions and sites of gastrointestinal tract are not desired candidates. [14]

Evaluation Parameters of GRDDS

In Vitro Evaluation Parameters

In vitro assessments of GRDDS can be used to predict the in vivo performance. The routine evaluation methods of gastroretentive tablets include measurement of tablet tensile strength, weight variation, friability, drug content, content uniformity, and in vitro drug release. Floating behaviors such as floating lag time and total floating duration have been used for the assessment of floating behavior of low-density systems. Furthermore, floating force is also used to measure the floating capacity of the floating tablet. In addition, swelling rate, water uptake capacity, and gel strength of the polymeric dosage form

can be evaluated using dissolution medium and tested for at least 8 h to ensure the floating mechanism, drug release, and gel strength. [15]

In Vivo Evaluation Parameters

In order to provide the evidence of in vivo efficacy of GRDDS, a well-designated in vivo study in an animal model or humans is required. In vivo studies provide information about the GRT and bioavailability of the drug. Selection of a suitable animal model is the first requirement for a successful in vivo study. For example, in small animals such as mouse, rat, guinea pig, and rabbit, there might be an issue of animal handling especially for large dosage forms. As a result, measurements of the GRT and bioavailability are still difficult. [16]

Various diagnostic imaging techniques including gamma scintigraphy, radiology, gastroscopy, ultrasonography, and magnetic resonance imaging (MRI) can be applied for in vivo evaluations of GRDDS. Gamma scintigraphy studies have been conducted to determine the location and extent of GRDDS and their transit through the GIT. In this technique, small amounts of stable isotope are added to the dosage form during its preparation. Then, this isotope is converted into γ-emitting material by irradiating the dosage form in a neutron source. Gamma rays are released and captured as an image after processing by a computer. This method can also be used for the identification of dissolution and disintegration properties of the dosage form. A good safety profile and relatively low doses of radiation are the major advantages of the technique.

Likewise, the radiology/X-ray technique is used for the preclinical evaluation of GRT, disintegration rate, dimensions of the dosage form, and esophageal transit of GRDDS. In this technique, a radio-opaque material such as barium sulphate is incorporated with the dosage form, and radiographs taken after ingestion of the dosage form help in locating the dosage forms at various periodic time intervals. Its major advantages compared to γ-scintigraphy are simplicity and cost. Even though this technique has been successfully used in human volunteers, dogs, and rabbits, safety issues still need to be considered because repetitive exposure to x-rays may lead to various health hazards.[17]

Gastroscopy is a type of per-oral endoscopy used for the diagnosis and monitoring of GRDDS. This technique composed of optical fibers and a video camera to determine the location of the dosage form. This method is applicable for all types of GRDDS; however, it is less convenient and might require minor or complete anesthesia to assess gastric retention of GRDDS. Similarly, ultrasonography is an alternative technique used in GRDDS. Ultrasonic waves are generated that enable the imaging of some abdominal organs and determine the intragastric location of the hydrogels, solvent penetration into the gel, and interactions between the dosage form and gastric mucosa during peristalsis [6]. MRI is another technique for determining the in vivo gastric retention of GRDDS. This technique uses magnetic fields and radiowaves to view the complete anatomical structure as well as location of the ingested dosage form [6,36]. The compounds with super paramagnetic properties (e.g., ferrous oxide) are incorporated for visualization purposes. Steingoetter et al. used this technique to report the in vivo gastric retention of

gadolinium chelates floating tablets containing Fe3O4 as a super paramagnetic agent and succeeded in analyzing intra-gastric tablet position and residence time in human volunteers. [18]

Future Perspectives of GRDDS

The GRT of the conventional dosage form is one of the main challenges in the pharmaceutical industry, especially for drugs that are absorbed from the upper part of the intestine. Developing GRDDS will help to overcome the drawbacks associated with conventional dosage form, although further work is needed on its shortcomings. To date, many studies have been performed on GRDDS utilizing the single system approach such as floating, expandable, and mucoadhesive systems.

Even though various GRDDS technologies have been extensively explored to achieve successful gastroretentive systems, most have their own limitations. The variation in GRT, especially in the fed and fasted states, is still one of the main challenges faced by many formulation scientists. No single approach might be the best for resolving the problems. Therefore, it is desirable to explore suitable GRDDS that can overcome the limitations of a single approach. Using combination approaches such as expandable and effervescent floating systems, mucoadhesive and floating systems, swellable and floating systems, and mucoadhesive and high-density system may be useful strategies for minimizing the variability of GRT. Moreover, dual-working systems are less affected by the physiological condition of the stomach such as the fasting and fed states and these systems can ensure delayed gastric emptying. Therefore, future works on GRDDS should be focused on combinations of different mechanisms in order to prolong gastric retention of dosage forms even in the fasted state. [19]

It is essential to assess gastroretentive dosage forms on a case-by-case basis because the physiochemical nature of drug and excipients, types and composition of polymers, drug dose, and manufacturability may depend on product specification. Another important aspect for improving GRDDS is to understand the effects of formulation and process variables on the critical quality attributes of GRDDS. The critical quality attributes of GRDDS include floating behavior, floating force, gel strength, mucoadhesive strength, mucoadhesive time, in vitro drug release, swelling capacity, porosity of hydrogel, tablet tensile strength, and friability. From formulation viewpoints, understanding polymer behavior and its role in formulation is crucial for the rational development of the gastroretentive dosage form. Furthermore, selection of an appropriate concentration of polymer is equally important for designing such dosage forms. In this regard, the quality by design (QbD) approach can be a useful tool for investigating the influence of formulation and process variables on the critical quality attributes of GRDDS. [20] With implementation of the QbD approach in pharmaceutical fields, there has been a significant transformation in the understanding and control of the manufacturing process, which notably minimizes the risk of product failure. [21]

Some gastroretentive approaches such as magnetic systems have not been extensively studied. The clinical studies of these systems have not yet been reported in detail. Therefore, future works on magnetic systems need to be focused on clinical candidates to specify their practical

applications in humans. Moreover, incorporating magnetic systems into the superporous hydrogel system can help extracorporeal magnets precisely locate the ingested dosage form since it swells and occupies larger volume. The advancement of technologies offers efficient measurement tools that can help to predict and correlate the gastric emptying time and passage of drug into the GIT. For example radiology and scintigraphy can be used for the in vivo evaluation of gastric emptying of dosage forms from the stomach. Moreover, magnetic marker monitoring techniques can also be utilized to capture images of dosage forms in the stomach.22.

Conclusions

Drugs with small therapeutic windows, high solubility at acidic pHs, and instability at alkaline pHs have a lot of room for improvement with GRDDS. The successful design of GRDDS depends on investigations into the effects of formulation and process variables on dosage form quality as well as a thorough understanding of the anatomy and physiological state of the stomach. Even though a number of GRDDS, including bio/mucoadhesive, magnetic, low-, and high-density systems, have been described in the literature, further research is still needed to determine their clinical significance. Future GRDDS directions may need to concentrate on a combination approach in order to improve product quality from a pharmaceutical perspective.

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