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Swelling system of GRDDs: A novel move towards gastroretentive drug delivery system

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ABSTRACT

Swelling Drug Delivery System abbreviated as SDDS is actually a type of gastroretentive drug delivery systems GRDDs. In this system the swallowed tabled swells in the stomach and consequently cannot pass through the pyloric sphincter and is retained in the stomach. Swelling Drug Delivery System is meant to prolong the stay of a drug inside the stomach so as to achieve controlled blood plasma level and increased bioavailability of the drug. In the recent past the advancement of new pharmaceutical technologies has made it possible to greatly improve the modified release oral drug delivery systems by overcoming physiological barriers like short gastric retention time and irregular gastric emptying times. Swelling drug delivery system has many advantages over conventional oral drug delivery system due to increased retention of the drug in the stomach. For example this system is best suited for drugs that act locally for the treatment of peptic ulcer or gastro-esophageal reflux disease GERD e.g. antacids like misoprostol and also for the drugs that are absorbed in the stomach e.g. amoxicillin or the ones that are poorly soluble in alkaline pH or degraded in the colon like captopril. This system improved drug absorption, reduces dosing frequency by providing sustained release and enhances patient compliance. However, this system is not suitable for drugs that are not stable in gastric pH e.g. erythromycin or the ones that are not soluble and absorbed in acidic pH e.g. phenytoin.

Keywords: Gastroretentive drug delivery system, Retention time, Swelling System.

1. INTRODUCTION

The oral drug delivery system, being a more convenient and safer route of administration than other routes like I/V or I/M is the most preferred route of administration that ensures increased patient compliance and safety. [1] Although the traditional oral drug delivery system is effective in obtaining and maintaining therapeutically effective plasma concentrations of a drug but the drug has to be taken several times a day resulting in inconsistent blood levels.

The recent technical advancements, however, have resulted in the development of many new novel drug delivery systems (NDDS) which promise to modernize existing methods of medication providing a number of therapeutic advantages. [2]

Complications in oral sustained drug delivery system arise due to gastric residence times (GRTs) and rapid passage of drug through the stomach and the small intestine not allowing ample time for complete release of the drug in the right area for absorption, there by diminishing the efficacy of the administered dose as most of the drugs are absorbed in the stomach or the first part of small intestine. [3] Although the currently employed controlled release technology can provide drug release at a constant rate over along period, yet it is not suited for

- Drugs which are absorbed in the stomach or in the upper portion of the small intestine.
- Drugs that act locally on the stomach or on the upper part of the small intestine.
- Drugs that are unstable or have poor solubility in the alkaline pH values.
- Exhibit poor solubility's at high pH values.[4]

These were the limitations that actually led to the development of gastroretentive drug delivery systems (GRDDSs) (Figure 1,2). The swelling drug delivery dosage forms swell in the stomach upon oral ingestion and release the drug at a fixed rate at specific absorption sites in the initial part of the intestine. [5]

Retention time of a drug in the stomach or intestine is affected by following factors:

- Density of the drug.
- Size of the dosage form.
- Fasting or fedstate.
- Type of meal taken.
- Sleeping habbits.
- Posture of body, etc.

It also depends on a complex and unpredictable gastric emptying time [6]. The stomach empties itself but in fasting as well as fed state. However, the motility pattern differ smarkedly in two states. In case of fasting, an interdigestive series of electrical events take place in cyclic fashion through the stomach to the part of small intestine every 2-4 hours. This electrical activity is called migratingmy o-electric complex (MMC) which consists of four phases;

1.1. Phase I or basic phase

It is a latent period characterized by occasional contractions not lasting more than 50 minutes.

1.2. Phase II or preburst phase

This phase lasting for 20-40 minutes is characterized by intermittent action potentials and contractions that intensify and increase in numbers with the progression of the phase.

1.3. Phase III or burst phase

In this phase there are large intense contractions consisting of 4-6 minutes. During this phase all undigested materials is propelled from the stomach to the small intestine. Phase III of a fresh cycle starts in the duodenum when the phase III of the previous cycle reaches the end of the small intestine.

1.4. Phase IV

Duration of this phase is 0-5 min. It occurs between phase III and phase I of two cycles. It has been shown in studies the delayed onset of MMC in the fed state slows the Gastric emptying [7, 8].

1.5. Requirements for gastroretentive drug delivery dosage forms

The dosage form should be robust enough to tolerate the force exerted by peristaltic waves, grinding and churning in the stomach. It must resist premature gastric emptying and should be removed from the stomach with ease after the fulfillment of the purpose [9].

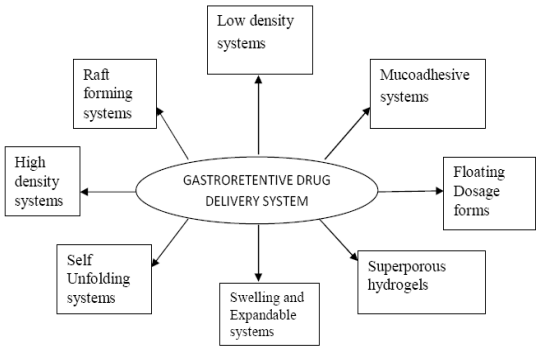

Figure - 1: Different approaches for GDDS.

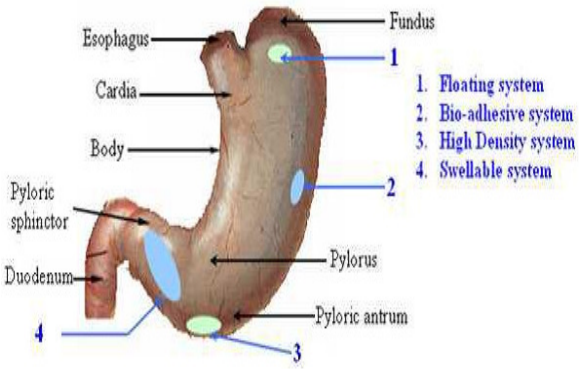

Figure - 2: Physiology of gastrointestinal tract.

1.6. Swelling drug delivery systems SDDS.

Upon ingestion these dosage forms swell in the stomach and increase in size. Due to increase in size, these dosage forms cannot pass through the pyloric sphincter and as a consequence remain in the stomach for a long time even in the fed state. As they stay at the pylorus they are also known as "Plug type systems". A drug can be formulated into modified release by incorporating it with a polymer of suitable molecular weight and swelling properties. In the stomach the polymer swells after absorbing water due to the presence of the physical-chemical cross links in the hydrophilic polymer network. Physical state or integrity of the dosage form is maintained as the dissolution of the polymer is prevented by these polymeric cross-links. The degree of cross-linking between the polymeric chains is responsible for maintaining equilibrium between the degree and duration of swelling (Figure 3-5). Low degree of cross-linking is associated with extensive swelling and rapid dissolution of the polymer where as high degree of

cross linking confers less swelling but retards dissolution [10,11].

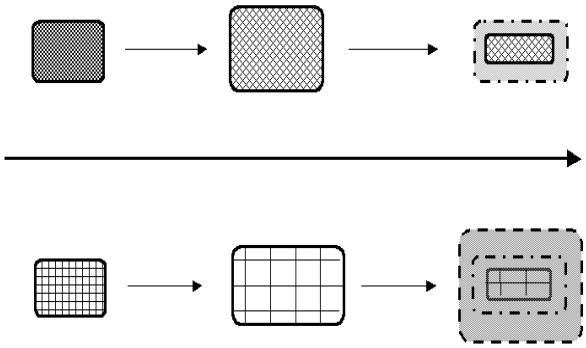

Figure - 3: Relationship between the degree of cross-linking of the polymeric chains and the swelling behavior of swelling systems.

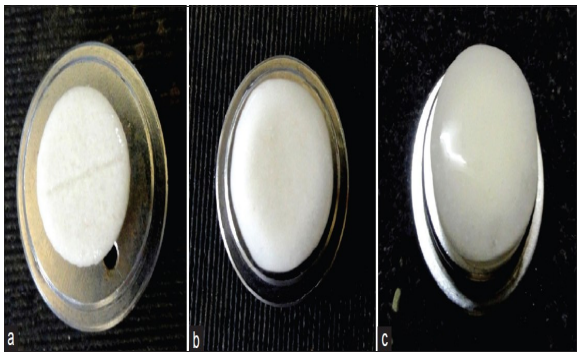

Figure - 4: Tablet condition after swelling.

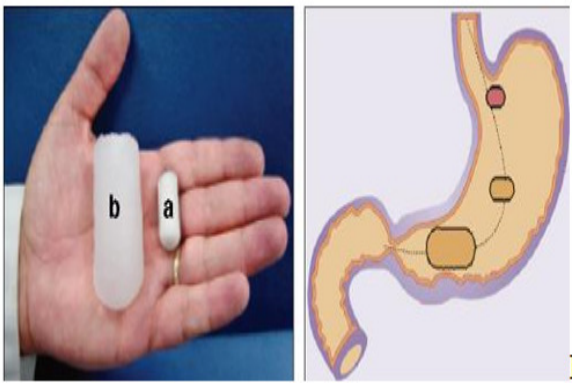

Figure - 5: Tablet in the stomach after swelling.

1.7. Composition

Following types of ingredients can be incorporated into swelling dosage form in addition to the drugs:

1.7.1. Hydrocolloids

- Pectin
- Acacia
- Chitosan
- Casein
- Agar
- Bentonite
- Veegum
- Hydroxy Propyl Methyl Cellulose (K4M,K100M and K15M)
- Gellan gum
- Sodium Carboxy Methyl Cellulose
- Methyl Cellulose
- Hydroxy Propyl Cellulose

1.8. Pharmacokinetic

1.8.1. Absorption window-validation for narrows absorption window drugs

Currently there are different experimental techniques that can be used to verify the absorption properties of the molecule being tested, to evaluate the mechanism of intestinal absorption and to study the permeability at different parts of the GIT. Generally the probable candidates for controlled release gastroretentive dosage forms (CR-GRDF) are molecules that are poorly absorbed in colon but are well absorbed in the upper parts of the GI T. In case of absorption by active transporters the effectiveness of the transport activity may enhance.

1.8.2. Increased bioavailability

The bioavailability is greatly enhanced by the swelling system due to modified release in the stomach. In this delivery system most drugs are better absorbed after oral administration especially the ones defined as narrow absorption window drugs. For example bisphosphonates like alendronates are best absorbed in the stomach. The bioavailability of vitamin B2 and that of levodopa is increased significantly when given by this delivery system as compared to conventional oral dosage form

1.8.3. Increased first pass biotransformation

When the drug is made available to the metabolic enzymes such as cytochrome P450, CYP3A4 in a sustained manner unlike a bolus input, the pre-systemic metabolism of the tested compound may be increased significantly

1.8.4. Decreased dosing frequency

Controlled release gastroretentive dosage forms enable us to reduce dosing frequency of drugs with short biological half-life by providing sustained release and slow input. This results in improved patient compliance.

1.8.5. Targeted therapy for local diseases in the upper GIT

The sustained release of the drug from controlled release gastroretentive dosage forms in the stomach may be quite beneficial for the

treatment of local ailments in the stomach and the upper part of the small intestine. This mode of administration provides therapeutic drug concentrations locally while the systemic concentrations, following drug absorption and distribution, are minimal.

1.9. Pharmacodynamics aspects

1.9.1. Reduced fluctuations of drug concentration

Continuous absorption of the drug from CR-GRDF maintains blood drug concentrations within a narrower range compared to the instant release dosage forms. So there are fewer chances of fluctuations in drug absorption and concentration dependent adverse effects related to peak concentrations can also be minimized. This is particularly important for drugs with a narrow therapeutic index.

1.9.2. Increased selectivity for receptor activation

Decreased fluctuation in drug concentration makes it possible to obtain selectivity in eliciting pharmacological effects of drugs that activates different types of receptors at different concentrations.

1.9.3. Decreased counter-activity of the body

In some instances the pharmacological response of a drug elicits a rebound activity from the body that minimizes the drug effect. Slow absorption of the drug into the body has been shown to minimize the counter activity leading to higher drug efficiency.

1.9.4. Extended time over critical (effective) concentration

Prolonged time over effective concentration fordifferent drugs whose pharmacodynamics is not dependent on concentration for example beta-lactam antibiotics, the clinical response isassociated with the duration of time over a critical therapeutic concentration instead of peak concentration. Extension of time, over a critical (effective) concentration by the sustained mode of administration increases the pharmacological effects and improves the clinical outcomes.

1.9.5. Decrease in the adverse effects on the colon

In case of gastro retentive dosage form (GRDF), the amount of drug reaching the colon is decreased because of drug retention in the stomach. Consequently the unwanted effects of the drug in the colon can be circumvented.

This is an important aspect that justifies the use of GRDF designing for beta-lactam antibiotics absorption of which mainly occurs in the stomach and presence of which in the colon can cause the development of microbial resistance. Due to complex pharmacokinetic and pharmacodynamic parameters, in vivo studies are performed to determine the optimal dosage form for a specific drug. For a drug, interplay of its pharmacokinetic and pharmacodynamic parameters determines the effectiveness and benefits of the CR-GRDF in comparison to other dosage forms.

1.10. Evaluation parameters for swelling drug delivery systems

1.10.1. Ability to uptake water

Swelling of a polymer depends on its ability to absorb water. Every polymer absorbs a specific amount of water. Different techniques can be employed for determination of the swelling property of a developed formulation. For example USP dissolution apparatus type II can be used to perform water uptake study. Double Distilled water can be used as medium. Approximately900 ml of water is rotated at 50 rpm at 37±0.5℃. After predetermined time intervals, the tablets should be taken out from the medium and weighed after removing excess water. Swelling properties can be mentioned in terms of water uptake as (WU) (Figure 6).

WU (%) = weight of the swollen tablet – initial weight of the tablet / Initial weight of the tablet X 100

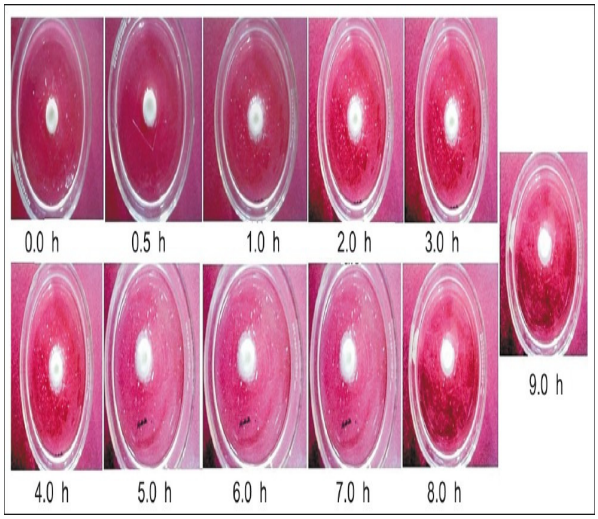

Figure - 6: Tablet during dissolution at different time intervals

1.10.2. XRay/ gamma scintigraphy

These days X-Ray/Gamma scintigraphy is an important technique being used for the evaluation of swelling dosage form. It helps detect dosage form in the gastrointestinal tract (GIT), by which we can estimate and correlate the gastric

emptying time and the movement of the dosage form in the GIT. In this technique addition of a radio-opaque material to the solid dosage form makes it to be visualized by X-rays. In the same way the incorporation of a γ-emitting radionuclide with a formulation permits indirect external observation with the help of a γ-camera or scintiscanner. Duringγ-scintigraphy, the γ-rays given off by the radionuclide are focused on a camera, which helps to follow the dosage form in the gastrointestinal tract.

2. CONCLUSION

It can be concluded from the above discussion that the swelling drug delivery systemhas several advantages over conventional oral dosage form. It can increase bioavailability and patient compliance by decreasing dosing frequency. This dosage form is especially suited for drugs meant to be used for their local action in the stomach or the small intestine and also for the drugs that can be destroyed by alkaline pH of the colon like captopril. For example antacids and antibiotics used for eradication of H. pylori (requiring high concentrations of antibiotics in the stomach) are good candidates to be formulated in this dosage form.

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