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GASTRORETENTIVE DRUG DELIVERY SYSTEM - A REVIEW

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ABSTRACT

English oral delivery of drug was the commonly used modality because of patient compliance and ease of administration. After oral administration of any drug, its bioavailability is affected by its residence time in stomach. Recently, gastroretentive drug delivery systems (GRDDS) have gained wide acceptance for drugs with a narrow absorption window, decreased stability at high alkaline pH, and increased solubility at low pH. This approach develops a drug delivery system, which gets retained within gastric fluid, thereby releasing its active principles in the stomach.[1] A Controlled release dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and times to achieve peak plasma levels.[2] The present study attempts to give an insight into the gastroretentive drug delivery systems, and gastric floating tablets, in particular. These have attracted the interest of many formulators due to their advantages over the conventional drug delivery systems.

KEYWORDS: Novel drug delivery system, Gastroretentive, Bioavailability, gastric retention time, Therapeutics efficiency.

INTRODUCTION

Oral formulations have earned a significant place among the various dosage forms developed so far for human administration. In most of the cases, the conventional oral delivery systems show limited bioavailability because of fast gastric-emptying time among many other reasons involved. However, the recent technological development has resulted to many novel

pharmaceutical products, mainly the controlled release drug delivery systems to overcome this problem. Gastro-retentive drug delivery system (GRDDS) is one such example where the attribute like gastric retention time coupled with the drug release for extended time has significantly improved patient compliance.[3] One novel approach in this area is GRDDS (gastro retentive drug delivery system). Dosage forms that can be retained in the stomach are called GRDDs. GRDDSs can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.[4] Prolonging the gastric retention of the drugs is sometimes desirable for achieving therapeutic benefits of drug that are absorbed from the proximal part of the GIT (gastro intestinal tract) or those are less soluble in or are degraded by alkaline pH or they encounter at the lower part of the GIT.

GRDDS are beneficial for such drugs by improving their.[5]

- Bioavailability
- Therapeutics efficiency and
- Possible reduction of the dose.
- Apart from these advantages, these systems offer various pharmacokinetic advantages like, maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in the therapeutic levels.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

There are many parameters related to stomach's anatomy and physiology that are needed to be considered in the development of gastroretention dosage forms.

1. Particle size Should be in the range of 1-2 mm to pass through the pyloric valves into the small intestine.[6]
2. Density Density of dosage form should be in range of 1g/cm3 to 2.5g/cm3.
3. Size Size should be greater than 7.5 mm in diameter.[7]
4. Shape of dosage forms Ring and tetrahedron devices with flexural modulus of 22.5-48 KSI (keto pound/ inch2 show 90-100 % gastric retention time.
5. Single unit/multiple unit Multiple units are preferable because of predictable release profile, co administration of different units, larger safety margins.
6. Food intake GRT is longer in fed states.
7. Nature, calorie content Indigestible polymers, fatty acid salts, increase calorie content, increase acidity increases GRT, Fat and protein meal increases GRT.

8. Frequency of intake GRT increases 400 times due to low frequency of MMC

9. Posture Varies between spine and upright ambulatory states.

10. Gender Females have shorter GRT than males.[8]

11. Age Age > 70 shows longer GRT.[8]

12. Nature of drug Drugs with impact on gastro intestinal transit time e.g. Codeine and pharmacokinetic agents e.g. metclopramide, cisapride increases GRT.[9]

13. Other factors

- Diseased states of the individual (chronic disease, diabetes etc.)
- Body mass index
- Physical activity
- Molecular weight and lipophilicity of the drug depending on its ionization state.[10]

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1. **Enhanced bioavailability:** The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.[11]
2. **Enhanced first-pass biotransformation:** In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.[12]
3. **Sustained drug delivery/reduced frequency of dosing:** For drugs with relatively short biological halflife, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.
4. **Targeted therapy for local ailments in the upper GIT:** The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.
5. **Reduced fluctuations of drug concentration:** Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range

compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.[13]

6. **Minimization of fluctuations in drug concentration:** It makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
7. **Reduced counter-activity of the body:** In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
8. **Extended time over critical (effective) concentration:** For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
9. **Minimized adverse activity at the colon:** Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.
10. **Site specific drug delivery:** A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine.[14] The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1. Unsuitable for drugs with limited acid solubility. E.g. Phenytoin.
2. Unsuitable for drugs that are unstable in acidic environment. E.g. Erythromycin.
3. Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin & NSAID's.

4. Drugs that absorb selectively in colon. E.g. Corticosteroid.

5. Drugs that absorb equally well through GIT. E.g. Isosorbide dinitrate, Nifidipine.

6. Floating drug delivery systems require high fluid level in stomach to float and work effectively.

CERTAIN TYPES OF DRUGS CAN BENEFIT FROM USING GASTRIC RETENTION DEVICES. These include drugs that.

- Are acting locally in the stomach e.g. Antacids and drugs for H.pylori viz. Misoprostol.
- Primarily absorbed in the stomach. e.g. Amoxicillin.
- Have an absorption window in the stomach or in the upper small intestine.
- Drugs with narrow window of absorption, e.g. Cyclosporine, Methotrexate, Levodopa.
- Are unstable in the intestinal or colonic environment, e.g. Ranitidine, Metformin Hcl.
- Exhibit low solubility at high pH values.

DRUGS THOSE ARE UNSUITABLE FOR GRDDS.

1. Drugs that have very limited acid solubility e.g. Phenytoin etc.

2. Drugs that suffers instability in the gastric environment e.g. Erythromycin, Rabeprazole, Clarithromycin, Esomeprazole etc.

3. Drugs intended for selective release in the colon e.g. 5-amino salicylic acid and corticosteroids etc.

CONCLUSION

From various literature survey it can be concluded that GRDDS having its own advantages and dis advantages but, it offer various advantages for the drugs having poor bio-availability, narrow window of absorption, exhibit low solubility at high Ph value. So, it is expected that in the future, various pharmaceutical companies will come forward to initialize gastroretentive drug delivery technology to create excellent advantages, prolonging patents, and a better outcome for their marketed formulations.

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