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Review Article

A REVIEW ON FLOATING DRUG DELIVERY SYSTEM: AN INVENTIVE APPROACH IN GASTRO-RETENTIVE SYSTEM

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Abstract:
The development of an oral controlled release formulation has an incredible impact on the drug delivery area especially for the drugs with a narrow absorption window but the limitation of this approach is insufficient retention of drug in the stomach. Controlled release gastro-retentive dosage forms reside in the gastric region for long duration and thus reduce drug waste and improves bioavailability. Several other advantages are patient compliance, reduced fluctuation in plasma level, decrease intake of dose, reduced drug accumulation with limiting local and systemic side effects. Of several approaches utilized such as swelling and expanding systems, polymeric bio adhesive systems, high-density systems, modified-shape systems; the floating drug delivery system (FDDS) is the most feasible one.

Keywords: *Floating drug delivery system*

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1. INTRODUCTION

Among the various scientific achievements, use of effective medicinal agents plays a vital role for healthy life. The concept of dosage form in which medicine is embedded, regardless of its safety and pharmacological effect is developing successfully. Drug administered via oral route is important and mostly used in view of excellent accessibility, painless dose administration, patient compliance for non-invasive drug delivery.[1,2] Oral dosage forms possess some disadvantages in the stomach and non-uniform drug absorption. Nowadays much attention has been given on modification and transforming oral dosage form to survive in various conditions of GIT to overcome these limitations for drug development, selection and formulation of ideal dosage form is an important step, though the relation between administration of drug and its pharmacologicaleffect is complex parameter. Several intrinsic and extrinsic variables influence drug response within individuals like product bioavailability (drug absorption rate), pharmacokinetics and the particular concentration-effect relationship.[3,4]

1.1 Novel Drug Delivery System (NDDS)

It is evident that the effect of drug substance not only depends on its pharmacological effect but also on the efficacy. Conventional immediate release dosage forms when administered, maintains concentration level of drug in therapeutic range. However, there are significant fluctuations in concentration of drug in plasma. Several attempts have been made for improvement of existing therapy. Formulation

development plays vital role in selecting a method or skill to formulate or pre-formulate drug in form of NDDS.[5,6]

Modified release dosage forms can be broadly classified:

a) Delayed release
b) Site specific release
c) Receptor specific release
d) Sustained release
(i) Controlled release
(ii) Prolonged release[7,8]

1.1.1 Sustained release drug delivery system

These are safe and more effective than other dosage forms. These reduces frequency of dosing, prolonged effect and reduction of side effects. Major advantage of sustained release dosage form is reduced fluctuation in plasma drug concentration and less often administration of medication. Due to which patient compliance is maintained and blood chemistry does not undergo frequent chemical imbalance due to foreign material. Some bioavailability problems may arise owing to variations in gastric emptying process thereby variation during *in-vivo* performance may occur.[9,10]

1.1.2 Oral controlled release drug delivery system

Desired bioavailability of medicament depends upon some factors such as reaching the drug to effective plasma level by consuming less time, maintaining plasma level and avoiding overshoot of drugs which can be rapidly absorbed. The intensity of pharmacological effect of drug is affected. An ideal condition exists when therapeutics index is attained. Invariably, conventional dosage forms lack in maintaining the therapeutics index to its level best.[11,12]

For maintaining the therapeutic index for longer period of time, repeated drug administration at fixed dosing interval is desired, which causes certain problems as patient noncompliance.

Controlled release drug delivery system (CRDDS) planned, predictable sustained manner and maintain drug concentration at effective level by spatial placement or temporal delivery. CRDDS have number of advantages such as better patient compliance, minimum fluctuation in plasma level, reduces total intake of drug, reduces drug accumulation and minimize local and systemic side effects.[13,14]

1.1.3 Advantages of CRDDS:

- To reduce dosing frequency and provide constant therapeutic drug level.
- To maintain uniform pharmacological response.
- To reduce total quantity of drug used.
- Increasing patient compliance by avoiding night-time dosing.
- Decreasing local and systemic side effects.
- Reduce drug accumulation and fluctuation in plasma drug concentration.

Utilize drug having low therapeutic index. Increase in bioavailability of some drugs. Economical to patients. [15,16]

1.1.4 Disadvantages of controlled release drug delivery:

- Possibility of dose dumping.
- Potential for accurate dose adjustment and systemic availability reduced.
- Increase first pass metabolism.
- During serious poisoning or intolerance immediate stoppage of pharmacological action is difficult.
- Drug substances that are particularly absorbed easily from GIT and possess less life span is removed frequently from blood circulation.[17,18]

Such problem can be solved by developing controlled release dosage form that release medicament slowly into GIT and maintains a fixed concentration of drug for prolonged time. The objective of CRDD is to increase bioavailability and achieving more predictable

drug. CRDDS administered orally has some shortcomings like less gastric retention.[19,20]

1.2 Gastroretentive Drug Delivery System (GRDDS)

Various scientific literatures reveal the increased interest of developing gastroprotective dosage form by the industry and academic research groups. The suitable approach for attaining predictable and prolonged drug release in GIT is to maintain residence period in the gastric region by holding the delivery system above the absorption window.[21,22] Thereby developing gastroretentive and sustained release dosage forms which are safe and effective. These formulations retain for various and release drug in sustained manner. Prolonged gastric retention helps in improving bioavailability which having solubility pH conditions and reduces wastage of drug. Applicable for medicaments having less absorption window in GIT. Rate of drug absorption can be increased mutual contact formulation with absorbing membrane.[23,24] Uniform absorption of drug over the GIT may not be achieved, as the dosage forms may be transported rapidly from upper region of intestine (more absorptive) to lower region (less absorptive). Absorption of drugs mostly occurs in stomach and small intestine (upper part) (Davis, 2005). New therapeutic possibilities can provide benefit to the patients by developing gastroretentive dosage forms.[25,26]

1.2.1 Parameters influencing retention

Various parameters which influence the emptying and there by gastric residence of gastroretentive dosage forms are as follows:

***1.2.1.1 Density*:** Certain GRDDS shows prolonged retention in the stomach due to their floating properties. For a formulation to remain buoyant in the stomach its density must be less than that of gastric content. The density of 1.0 g/ml or less buoyancy of dosage form. Bulk density is not the only criteria but buoyancy is also studied by measurement of weight and swelling experiments. However, the magnitude of buoyancy decreases with time where dosage form is placed.[27,28]

1.2.1.2 Size of dosage form: Factor which influences the retention of dosage form is its size. Non-floating dosage form shows high variation in residence time due to small, medium and large unit size. Whereas both type of units having 9.9 mm diameter shows equivalent retention. Floating units remain buoyant during digestive phase whereas non-floating disappeared due to peristalsis in digestive phase.[29,30]

***1.2.1.3 Presence of food*:** In fasting state the gastric emptying time, which increases after meals to about 4 hours. As the gastric emptying depends on the fed condition MMC is delayed which increases the retention. During fed condition by single meals GRT is prolonged by 2 hours for floating dosage form with floating time (FT) of 5 hours. Whereas after successions of meals most of the units have FT of 6hrs with prolongation of GRT up to 9 hours as compared to control. Due to mixing of dosage form with heavy solid food taken the variation in FT and GRT was observed. Basic drugs probably absorb better in fed state rather in fasted condition.[31,32]

***1.2.1.4 Nature of food*:** Caloric contents of meals effects the gastric emptying time. It has been observed that with increase in acidity and caloric values there is decrease in emptying time. After taking meals rich in fats and protein GRT of 4-10 hours can be achieved.

***1.2.1.5 Effect of posture*:** Upright or supine position effects the GRT of floating and non-floating units. Non-floating subject upright position where as floating units lie continuously above the gastric content and thereby showing prolonged GRT. In upright posture, GRT of only non-floating unit is influenced by size and is increased with increase in the size of the units. Whereas in supine posture the size effects the GRT for both types of the units.

***1.2.1.6 Age and sex*:** Gastric emptying duration in females is slower than that of male in spite of weight, height and even when hormonal changes take place during menstrual cycle. Aged peoples about 70 years or more shows prolonged GRT than younger ones.[33,34]

1.2.2 Targets for developing gastroretentive delivery system

GRDDS develop enhancing release of suitable drugs-controlled manner for longer period of time. Several drugs show its highest pharmacological response when they are released in the stomach in controlled manner. This reduces the side effects and frequency of dosing. GRDDS is suitable for certain category of drugs having following characteristics: Drugs whose absorption window is narrow in GIT like riboflavin, furosemide, Ldopa and Para amino benzoic acid. Some important drugs display low bioavailability. Drugs which act locally in the stomach, eg: misoprostol and antacids.[35,36] Highly unstable and rapidly degradable drug molecules in colonic and intestinal environment, eg: ranitidine hydrochloride, captopril and metronidazole. Drugs having less solubility at higher values of pH eg: verapamil hydrochloride, chlordiazepoxide, diazepam. Drugs substances which disturb the microbes in the colonic region, eg: amoxicillin trihydrate and certain antibiotics. Substances with easy absorption from the GIT.[37,38]

1.2.3 Advantages of gastroretentive drug delivery

- ✓ Increased patient compliance.
- ✓ Increases therapeutic efficacy of drugs having short half-life.
- ✓ Increased bioavailability of drugs.
- ✓ Minimizes fluctuation of plasma drug concentration.[39,40]

1.2.4 Limitations of gastro retentive drug delivery system

There are certain conditions when GRDDS is not satisfactory such as:

- ✓ Drugs which cause gastric irritation and lesions should not be released in the stomach in slow manner.
- ✓ Drugs whose absorption is good throughout the gastrointestinal tract are unsuitable for gastric retention eg: isosorbide dinitrate.
- ✓ Drugs with limited acidic solubility will not have good release on gastric retention.
- ✓ Colon specific drug release candidates.
- ✓ Drugs having first-pass metabolism and unstable in gastric fluid.
- ✓ Due to high variation in gastric emptying time unpredictable bioavailability results.
- ✓ Effectiveness of the technique is doubtful due to bioadhesion of drug.
- ✓ Exact buoyancy of the system cannot be predicted. [41,42]

1.2.5 Approaches to gastric retention

Varieties of concepts are involved for developments of successful gastroretentive system. It may increase the residence time of drug in GIT.

1.2.5.1 High density system

Small pellets which is 1.004 g cm-3(density of gastric fluid) will sinks at the bottom of the stomach. These small pellets were prepared by heavy core barium sulphate or titanium dioxide as polymers with density of about 2.5 gcm-3 to produce significant increase in gastric residence time. Good results were reported for ruminants.[43,44]

1.2.5.2 Bioadhesive or mucoadhesive system

Bioadhesive or mucoadhesive system with the help of mucoadhesive polymers by different mechanism. Several mucoadhesive polymers used to develop. The process of mucoadhesion includes the electronic theory which suggested that there is an attractive electrostatic force between the bioadhesive material and glycoprotein mucin network. Adsorption theory on the other hand suggests that there are Van der Waals forces and hydrogen bonding (secondary forces) which helps in mucoadhesion. Development of intimate contact between bioadhesive polymers with mucus layers is the basis of wetting theory. The fast production of mucus secreted in the GIT causes difficulty in maintaining the effective mucoadhesion of polymers. Also the hydrated nature of stomach

reduces the polymer efficacy for bioadhesiveness.[45,46]

1.2.5.3 Expandable or swelling system

Formulations whose sizes are bigger than the pyloric sphincter can survive in gastric transition of the stomach. Thus, three essentials requirements for developing such system are: a small size dosage form for easy oral administration, an expanded gastroretentive form and finally small size which do not easily evacuate and show characteristic drug release. Unfoldable or expandable and swellable systems were investigated. Various biodegradable polymers are used for designing such systems. The system consists of a capsule acting as a carrier which contains a compressed part that expands in the stomach. Different geometric forms of bio erodible polymers that can be compressed in carrier. Expandable systems show some disadvantages like: problem in storage of biodegradable polymers, unfolding system is short-lived and moreover difficult to industrialize.[47,48]

1.3 FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Considering developing GRDDS, floating system is logical and easy to formulate from technological point of view. Such system reduces fluctuations of drug bioavailability as they work independent of variations occurring during gastric emptying process. For supporting the buoyancy of the system different approaches are followed.[49,50]

1.3.1 Effervescent system

This system of FDDS consists of swellable polymers along with carbon dioxide (CO2) or entrapped in swollen hydrocolloids of formulation which acts as effervescent component. Incorporation of gas within the formulation helps in reducing the density and makes the system to buoyant over the gastric fluid. Carbonates apart from providing buoyancy to the system also provides basic micro environment for the polymer to convert to gel. Effervescent system can be further subdivided into two categories:

1.3.2 Gas generating system

In gas generating system drug along with polymer are mixed with gas forming agent and compressed into matrix tablet. Such matrix tablet can be single, doubled or multi layered. In multilayer tablets gas forming substances are compressed in layer having drug and hydrocolloid as outer layer to provide sustained release effect. Water gets diffuse through the swellable membrane generates CO2 neutralization. Multiparticulate formulation containing number of small discrete units shows more reliable gastric emptying patterns in comparison single unit suffering from “all or none concept”.[51,52]

1.3.3 Volatile liquid / vacuum containing system

1.3.3.1 Inflatable GRDDS

In such systems liquids like ether and cyclopentane were incorporated in inflatable chamber

which gasify due to body temperature and helps the chamber to float over the stomach. Drug reservoir is loaded in this chamber as an impregnated polymer matrix, encapsulated in gelatin capsule. The capsule dissolves in the stomach to release the drug substance along with chamber for prolonged period of time.

1.3.3.2 Intragastric osmotically controlled drug delivery system

A hollow polymeric bag of inflatable support will form to float over the stomach. Drug is placed in a pressure responsive collapsible bag not permeable for liquid or gas. A semi permeable membrane containing osmotically active salt acts as osmotically active device. Osmotic salt is dissolved by the absorbed water from the gastrointestinal fluid. The release of drug from the orifice of reservoir will occur as the developed osmotic pressure acts on collapsible bag. It presents in the floating support which gradually dissolves by releasing gas

from inflatable chamber and gets collapsed specific excretion.[53,54]

1.4 Non-effervescent system

Non-effervescent systems does not contain gas forming agents but incorporate one or more cellulose hydrocolloids, poly saccharides as highly swellable and gel forming polymers during formulation. Floating of dosage form occurs due to hydration of polymer in gastric fluid and forming a colloidal gal barrier. Number of approaches in developing non-effervescent FDDS is available.

1.4.1 Hydrodynamically balanced system (HBS) / colloidal gel barrier system

The HBS system is a single-unit dosage form having gel-forming hydrophilic polymer of one or more type. Hydroxypropyl methylcellulose (HPMC) is basically used apart from hydroxy ethylcellulose (HEC), sodium carboxymethylcellulose (NaCMC), hydroxypropylcellulose (HPC), agar, carrageenan polymers. The formulation is composed of a gelatin capsule in which polymer mixed with drug is placed. In the gastric fluid the capsule rapidly dissolved and flotation is achieved owing to hydration and swelling of polymer surface. A barrier of soft gelatin around the dosage form is formed due to hydration. Drug release rate from HBS is controlled by hydrated gel. HBS system has number of approaches as single and bi-layered tablets. Single layer formulation was simply prepared by mixing gel-forming hydrocolloid polymer with drug. The air entrapped within the swollen polymer makes the system buoyant. Intragastric single and bilayer tablets. Multi-layer flexible sheath which is developed by water insoluble polymer containing barrier film and drug has been developed. Both the films were sealed in a manner such as to entrap minute air pockets that help the laminated films to remain buoyant.[55,56]

1.5 Advantages of FDDS

- Substances which get absorbed through the stomach like ferrous salts and antacids when formulated as gastroretentive systems are advantageous as they remain for longer duration at the site of action.
- Certain acidic substances such as aspirin can be delivered as FDDS.
- The dissolution of drug from FDDS will occur in gastric fluid and the system will emptied to small intestine where also some absorption may occur. Thus, even if the drug remains in basic pH of the intestine in the solution form.
- Drugs acting locally in the stomach are advantageous to be formulated as gastroretentive systems.
- The problem encountered with CRDDS taken orally such as short gastric residence time can be overcome with these systems.[57,58]

1.6 Disadvantages of FDDS

- Drugs having insolubility and instability in gastric fluid are not suitable for FDDS.
- FDDS needs large concentration of fluid in the stomach for proper floating of drug and show efficient results.
- Drugs that absorbed significantly throughout GIT, that shows significant first pass metabolism, cannot be delivered as FDDS as the reduced systemic bioavailability will results due to slow gastric emptying time.
- Some drugs formulated as floating system may cause irritation to gastric mucosa.[59,60]

2. CONCLUSION

The process of a medicine being absorbed in the gastrointestinal tract is very variable, and the longer the dosage form is retained in the stomach, the longer it will take for the drug to be absorbed. Gastric retention could potentially be addressed with FDDS. Although there are a number of challenges to overcome in order to achieve prolonged gastric retention, many

businesses are working to commercialise this method.

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