

Gastro Retention - An Innovation over Conventional Poorly Soluble Drugs: A Review

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ABSTRACT

Gastro retentive drug delivery system (GRDDS) plays a vital role among novel drug delivery systems. Research is directed towards overcoming physiological adversities such as short gastric residence time (GRT) & unpredictable gastric emptying time (GET). Prolonged GRT may widen the stomach potential as a drug absorbing organ. Many approaches are currently employed in the prolongation of GRT including effervescent drug delivery system (EDDS) followed by swelling system, bio/mucoadhesive system & high density system. These systems will be very much useful to deliver 'narrow absorption window' drugs. The plant derived gums & mucilage comply with many requirements of pharmaceutical excipients as they are non-toxic, stable, easily available, associated with less regulatory issues as compared to their synthetic counterpart & inexpensive. Many plant derived natural materials are studied for use in novel drug delivery systems. This review discusses about approaches of GRDDS & utilization of herbal polymers for the purpose of release retardant action has been focused.

Keywords: Gastric Residence Time (GRT), Effervescent drug delivery system (EDDS), Herbal polymers, Narrow absorption window.

INTRODUCTION

Oral delivery of drug is the most preferred route of drug delivery due to ease of administration, patient compliance & flexibility in formulation. Conventional oral dosage forms achieve as well as maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day. This results in significant fluctuation in drug levels⁵. One requisite for successful performance of oral controlled release drug delivery system is that drug should have good absorption throughout the gastrointestinal tract (GIT). Oral controlled release dosage forms are not suitable for a variety of important drugs characterized by a narrow absorption window in the upper part of the GIT (stomach & small intestine). This is due to the relatively short transit time of the dosage form (DF) in these anatomical segments⁸. Variable & too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leads to diminished efficacy of the administered

dose.^[3] Oral sustained drug delivery system (DDS) is complicated by limited GRT.

To overcome these limitations, various approaches have been proposed to increase gastric residence of DDS in the upper part of the GIT includes gastro retentive drug delivery system (GRDDS)¹. The need for gastro retentive dosage forms (GRDFs) has led to extensive efforts in both academia & industry towards the development of such DDS. These efforts resulted in GRDFs based on the following approaches.

1. Low density form of the dosage DF that causes buoyancy above gastric fluid
2. High density DF that is retained at the bottom of the stomach
3. Bioadhesion to the stomach mucosa
4. Expansion by swelling to a large size which limits emptying of the DF through the pyloric sphincter⁶

Among these systems, FDDS has been the most commonly used. GRDDS can remain in the gastric region for several

hours & hence significantly prolong the GRT of drugs. Prolonged gastric retention improves bioavailability, reduces drug waster & improves solubility of drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with new therapeutic possibilities & substantial benefits for patients.^[4] The use of natural polymers as release retardant for the pharmaceutical applications is attractive because they are economical, readily available, non – toxic & capable of chemical modifications, potentially biodegradable & also biocompatible. Natural gums can also be modified to meet the requirements of drug delivery systems & thus can compete with the synthetic excipients available in the market¹⁰.

Needs for GRDDS⁵

1. Drugs acting locally in stomach.
2. Drugs those are primarily absorbed in stomach.
3. Drugs those are poorly soluble at intestinal pH.
4. Drugs with variable bioavailability.
5. Drugs with short half-life.
6. Drugs with a narrow absorption window i.e. drugs those are absorbed mainly from the proximal small intestine.
7. Drugs those degrade in colon.

Classes of drugs that would benefit from GRDDS

Anti – hypertensive drugs, anti – diabetic drugs for type – II diabetes, anti – histaminic drugs, CNS drugs (for Parkinson disease, epilepsy, Alzheimer & migraine), anti – viral drugs (for HIV, herpes & hepatitis) & certain antibiotics. Drugs for local treatment of GI infections.^[2]

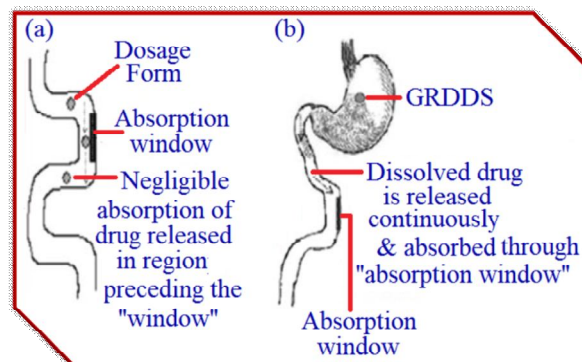


Fig.1: Drug absorption in the case of (a) Conventional DF (b) GRDDS¹

Approaches to GRDFs

Several techniques are reported in the literature to increase the gastric retention of drugs.

1. Effervescent drug delivery system (EDDS):

Gastric contents have a density close to water (1.004 gm/cm^3).^[1] A density of $< 1.0 \text{ gm/cm}^3$ is required to exhibit floating property. EDDS have bulk density less than gastric fluid & so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increased GRT & a better control of the fluctuations in plasma drug concentration⁷.

2. High density system

These systems which have a density of $\sim 3 \text{ gm/cm}^3$ are retained in the rugae of stomach & capable of withstanding its peristaltic movements. The major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug ($>50\%$) & achieve required density of $2.4 - 2.8 \text{ gm/cm}^3$. These polymeric matrices remain in the gastric cavity for several hours even in fed state. Diluents such as barium sulphate, zinc oxide, titanium oxide & iron powder must be used to manufacture such high density formulation⁵.

3. Bio / Mucoadhesive system

Bio/mucoadhesive system binds to the gastric epithelial cell surface or mucin & increase the GRT by increasing the

intimacy & duration of contact between the DF & the biological membrane. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability. A bio/mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane (bioadhesive polymer) or the mucus lining of the GIT (mucoadhesive polymer). Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, carboxy methyl cellulose (CMC) & gliadin, etc^{1,5}. Bioadhesion in the acidic environment & high turnover of mucus may raise questions about the effectiveness of this technique.

4. Swelling / Expandable system

After being swallowed, these DF swell to a size that prevents their passage through the pylorus. As a result, the DF is retained in the stomach for a long period of time. These systems are sometimes referred to as "*plug type systems*" because they tend to remain lodged at the pyloric sphincter. By selection of polymer with the proper molecular weight & swelling properties, controlled & sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water & swells. The extensive swelling of these polymers is a result of the presence of physical chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer & thus maintain the physical integrity of the DF. A high degree of cross linking retards the swelling ability of the system & maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer. An optimum amount of cross linking is required to maintain a balance between swelling & dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion. These

systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration^{1,5}.

Merits of GRDDS^{2,5,7}

1. These systems are particularly advantageous for the drugs absorbed through stomach & for the drugs meant for local action in the stomach & treatment of peptic ulcer diseases.

2. Enhanced bioavailability: The bioavailability of riboflavin control release gastro retentive dosage form (CR-GRDF) is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations.

3. When there is a vigorous intestinal movement & a short transit time as might occur in certain typed of diarrhoea, poor absorption is expected. Under such circumstances, it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

4. Administration of a prolonged release floating DF tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolved drug available for absorption in the small intestine. It is therefore expected that a drug will be fully absorbed from the floating DF if it remains in solution form even at alkaline pH of the intestine.

5. 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 β – lactam antibiotics that are absorbed only from the small intestine & whose presence in the colon leads to the development of micro-organism's resistance.

Utilization of natural polymers in GRDDS¹⁰

Tara gum, Hupu gum, Sesbania gum, psyllium husk, locust bean gum

Review of literature

Basak et al formulated floating tablets of metformin hydrochloride using gel forming hydrophilic polymer. The evaluation parameters performed were *in vitro* buoyancy in *in vitro* dissolution test. 96-99 % of cumulative release was found at the end of 8th hr⁷.

Jaimini et al formulated floating tablets of famotidine using methocel K100 & methocel K15. Gel forming ability was observed of these two grades of methocel. Formulation containing methocel K100 was found to float longer as compared to the formulation containing K15. This may be attributed to decrease in citric acid proportion⁷.

Prajapati et al formulated Domperidone floating matrix tablet to prolong gastric residence time. Release retardant polymers such as HPMC K4M, carbopol 934P & sodium alginate were used alone & in combination. Major evaluation parameters were *in vitro* buoyancy & floating time. The formulation with the combination of all the three polymers & the least proportion of PEG 4000 showed 24 hrs. of floating time¹⁰.

Patel VF et al formulated Dipyridamole floating matrix tablets to evaluate the influence of viscosity of polymer & type of filler. The tablets were evaluated for floating time & *in vitro* dissolution test. % cumulative release was found to be decreased with increase in the viscosity of the polymer. Increasing the viscosity of HPMC from 4000 mPa.s to 15000 mPa.s & 100000 mPa.s, the release rate was decreased. MCC was found to give the highest release rate as filler¹¹.

Ferdous Khan et al formulated theophylline floating tablets based on hydrophilic polymer. Gelling property of polymers, methocel K100M & K15MCR were evaluated. Effervescent agent such as sodium bicarbonate & citric acid were used. Formulation was evaluated for *in vitro* buoyancy & drug release study. Lag time was controlled by citric acid & sodium bicarbonate. 89% cumulative release was found at the end of 8th hr in presence of methocel K15MCR¹².

Bomma R et al developed & evaluated gastro retentive norfloxacin floating tablets. Tablets were prepared using polymers, HPMC K4M, K100M & xanthan gums. The tablets were evaluated for *in vitro* drug release for 9 hrs. The formulation containing HPMC K4M showed lag time of 35 seconds & drug release of 94.3 % at 9th hr¹³.

Martinez IJ et al formulated captopril floating matrix tablets using metolose SH 4000 SR. Increase in polymer content led to decrease in release rate. In addition, the presence of carbon dioxide bubbles decreased the drug release rate. This study was carried out at two different compaction pressures. The result showed that matrices compacted at 55 mPa floated beyond 8 hrs & those compacted at 165 mPa floated only when sodium bicarbonate included in the formulation¹⁴.

Xiaoqiang Xu et al designed phenoprolamine hydrochloride floating matrix tablets based on gas forming agents. Hydrogel drug delivery system was formulated utilizing HPMC K4M & carbopol 971P NF. Tablets floated beyond 6 yr in presence of sodium bicarbonate. The increased bioavailability was attributed to the polymer carbopol¹⁵.

Patel VF et al developed floating drug delivery system of cefuroxime axetil. The formulations were evaluated for *in vitro* buoyancy & drug release study. Floating time & *in vitro* buoyancy was found to be more than 8 hrs & below 120 seconds respectively for all the formulations. The 3² factorial design was used to evaluate contribution of polymers & sodium lauryl sulphate¹⁶.

Dave BS et al designed ranitidine hydrochloride gastro retentive drug delivery systems. Herbal polymers, xanthan gum & guar gum; synthetic polymer HPMC were evaluated for their gelling properties. Effervescent agents such as citric acid, stearic acid & sodium bicarbonate were used. Hydrophobic nature of stearic acid caused the drug dissolution to reduce. However, the combination of citric acid (low concentration) & stearic acid (high

concentration) favoured sustained release action of ranitidine hydrochloride¹⁷.

Baumgartner S et al optimized pentoxyfilline floating matrix tablets & evaluated its gastric residence time. The result reflected that tablet composition & mechanical strength have the greatest influence on the floating properties & drug release. Effervescent agents along with micro crystalline cellulose showed 30 seconds of lag time & floating time beyond 8 hrs.^[18]

Chandrashekhar B et al developed ketoconazole floating tablets. They employed HPMC K15M, HPMC K 100 LV & ethyl cellulose as release retardant polymers. The floating tablets were evaluated for *in vitro* buoyancy & *in vitro* dissolution tests. The final formulation was found to show 89.21% & 35 sec drug release & lag time respectively. The floating time was found to be 20 – 24 hrs¹⁹.

Salve PS developed metformin hydrochloride gas generating floating tablets. As the natural gums impart high matrix strength to the formulation, he utilized natural gums to control drug release. Xanthan gum & locust bean gum were used as natural gums. Locust bean gum was found to be temperature dependent for the solubility & gelling property. He compared the formulations containing drug with synthetic polymer to that of natural polymers²⁰.

Pare A et al reported floating tablets of amlodipine besylate using HPMC K100M, HPMC K15M & carbopol 934P as the polymers. Floating time was found to be 24 hrs. & the drug release was found to be up to 12 hrs²¹.

Mallikarjun V et al formulated glipizide floating tablets using HPMC K4 & K15 polymers for evaluating their gelling properties. The floating tablets were evaluated for *in vitro* dissolution & *in vitro* buoyancy studies. The tablets were found to float for 12 – 20 hrs²².

Chandira R et al fabricated itopride hydrochloride gastro retentive drug delivery system (GRDDS) to prolong gastric residence time followed by increase in drug bioavailability. Carbopol

934 P was also used along with other release retarding polymers. As carbopol is hydrophobic in nature, it helped in reduction of drug dissolution. Itopride hydrochloride GRDDS were prepared by direct compression technique & the tablets were found to show 24 hrs drug release²³.

Chavanpatil M et al fabricated gastro retentive sustained release, swellable & bioadhesive gastro retentive drug delivery system (GRDDS) of ofloxacin using psyllium husk, HPMC K100M as release retarding swelling agents. The formulations were evaluated for *in vitro* bioadhesion, *in vitro* drug release study & swelling characteristics. The bioadhesive property was found to be significant in combination as compared to alone polymers²⁴.

Zate S et al formulated gastro retentive mucoadhesive tablets of venlafaxine hydrochloride using carbopol 971 P in combination with eudragit RS – PO & ethyl cellulose as mucoadhesive & release retardant polymers respectively. Tablets were prepared by direct compression & evaluated for bioadhesion time, swelling index & *in vitro* release. One of the batches was found to show considerable swelling index with 99.85 % of drug release at 12th hr²⁵.

Lin S et al developed & characterized swellable/expandable systems for their potential application as a gastro retentive delivery (GRD) device. Tablets were characterized based in swelling index. Hydroxy ethyl cellulose (HEC) 250 HHX was found to exhibit the greatest swelling index. PEO was found to be superior in swelling index to a greater extent to HEC 250 HHX. The addition of 50% carbopol in HEC was preferred to increase the swelling of tablets²⁶.

Yasir M fabricated theophyllin gastro retentive drug delivery system (GRDDS) using psyllium husk to improve the bioavailability of the drugs that are characterized by narrow absorption window. The aim of this research work was to formulate the theophyllin GRDDS using psyllium husk as release controlling polymer & to compare these formulations with the formulations containing synthetic

polymer. The formulations were prepared by wet granulation technique & evaluated for *in vitro* buoyancy, floating time & dissolution studies. In all aspects of lag time, floating time, stability & release rate of the drug, psyllium husk was found superior to the synthetic polymers²⁷.

Pandit et al formulated floating non effervescent mini tablets of amoxicillin by wet granulation technique. HPMC K4M & HPMC 15 cps were found to play a vital role in achieving maximum buoyancy. The formulated tablets were evaluated for buoyancy & *in vitro* dissolution studies²⁸.

Janardhan et al fabricated gastro retentive tablets of ofloxacin by wet granulation technique. Release retardant polymers used were HPMC K4M & HPMC 5 cps. Quality control tests were carried out for evaluation along with *in vitro* buoyancy & dissolution tests which were then compared with marketed formulations. The *in vitro* buoyancy was found to be below 15 sec & the dissolution profile showed no significant change after storage for 3 months at 25°C/60 % RH & 40°C/75 % RH. Addition of sodium carboxy methyl cellulose along with sodium bicarbonate & citric acid in equal quantities prior to granulation as well as during lubrication was found to significantly increase the drug release. It was also proved that sodium bicarbonate had a considerable effect on the drug release along with hardness as well²⁸.

Controlled release floating matrix tablets of ciprofloxacin hydrochloride were developed by Tadros. Release retarding polymers such as HPMC K15M & sodium alginate were used. The dissolution medium of 0.1 N HCl (pH 1.2) was utilized in the evaluation of swelling ability, floating behaviour, adhesion period & drug release. The mean gastric residence time of the optimum formula loaded with barium sulphate in 6 healthy human volunteer was found to be 5.50 ± 0.77 hr. The optimized formula showed satisfactory result with respect to lag time, floating time, swelling ability, adhesion retention period, sustained drug release & acceptable physical stability at 40°C/75 % RH when stored for 3 months²⁸.

Evaluation parameters for GRDDS

- I. *In vitro* buoyancy (Lag time):³
 - A tablet is placed in a beaker containing 100 – 200 ml dissolution medium & the time for a tablet to emerge on to the surface of the dissolution medium is known as lag time which is measured in minutes or seconds.
- II. Floating time:⁹
 - It is usually carried out in a USP dissolution apparatus containing 900 ml of 0.1 N HCl as dissolution medium maintained at 37°C.
 - After achieving lag time, the time taken for a tablet to remain float on the surface of the dissolution medium is called floating time.
 - It is measured in hrs.
- III. *In vitro* dissolution:
 - It can be performed using USP dissolution apparatus 2 (paddle) wherein 900 ml of dissolution medium is filled in jar.
 - Temperature is maintained at 37°C.
 - Paddles are rotated at 50 rpm.
 - Samples are withdrawn periodically & replaced with fresh medium.
- IV. Swelling Study or Water uptake study:²⁹
 - The swelling of the polymers can be measured by their ability to absorb water and swell.
 - The water uptake study can be done by using USP dissolution apparatus II. Distilled water can be used as medium, 900 ml rotated at 50 rpm.
 - The temperature of medium should be maintained at 37±0.5 °C throughout the study.
 - After a selected time intervals, the tablets should be withdrawn, blotted to remove excess water and weighed.
 - Swelling characteristics can be expressed in terms of water uptake (WU) as

$$\text{WU (\%)} = \frac{\text{weight of the swollen tablet} - \text{initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

Initial weight of the tablet

CONCLUSION

GRDDS has discovered an approach for enhancing bioavailability & drug absorption through GIT by prolonging gastro retention of dosage form & thereby making the pharmacokinetic parameters more uniform as well as reproducible. FDDS promises to be a potential approach for gastric retention. Though there are several difficulties in the retention of drug in stomach, several pharmaceutical industries are focusing toward commercializing GRDDS.

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