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An overview on recent advancements and developments in gastroretentive buoyant drug delivery system

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ABSTRACT

Oral drug delivery route is the most preferable route of drug delivery. It is due to various advantages of this route like ease of administration, patient compliance and flexibility in the formulations. Oral dosage form has really progressed from immediate release to site-specific delivery. The recent scientific and patented literature concluded that an increased interest in novel dosage forms which retained in the stomach for prolong and predictable period of time has been shown by various industrial research groups. Various technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological diversities such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET) using gastro retentive dosage forms (GRDFs). It is a well known fact that differences in gastric physiology, such as, gastric pH and motility exhibit both intra as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behavior. Various attempts have been made to develop Gastro retentive delivery systems. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review the current & recent developments in the field of stomach specific gastro retentive drug delivery systems are discussed along with description of gastro retentive drug delivery system (GRDDS).

Keywords: gastric residence time, gastroretentive dosage form, gastroretentive drug delivery system

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INTRODUCTION

The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. Although a lot of advancements have been

seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GI transit time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of pharmaceuticals is highly variable and dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence time usually ranges between 5 minutes to 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and the transit of dosage forms. It is characterized by four Phases [1]:

Phase I– Period of no contraction (40-60 minutes)
Phase II– Period of intermittent contractions (20-40 minutes)
Phase III– Period of regular contractions at the maximal frequency also known as housekeeper wave (10-20 minutes)
Phase IV– Period of transition between Phase III and Phase I (0-5 minutes)

Drugs having a short half-life are eliminated quickly from the blood circulation and therefore bioavailability of the drug suffers. Gastro retentive dosage form improves bioavailability, therapeutic efficacy and may allow a reduction in the dose because of steady therapeutic levels of drug, for example furosemide and ofloxacin. The reduction of fluctuations in the therapeutic levels minimizes the risk of resistance especially in case of β-lactam antibiotics (penicillins and cephalosporins) [2]. Gastric emptying of dosage forms is an extremely variable process. The ability of a dosage form to prolong and control the gastric emptying time is a valuable asset for drugs acting on GIT. Drug absorption from the GIT is a complex procedure and is subjected to many parameters to become bioavailable. It is widely acknowledged that the contact time with the small intestinal mucosa is related with the degree of GIT drug absorption [3]. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Gastro retention provides better availability of new products with new therapeutic possibilities and substantial benefits for patients. Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations. Such retention systems (i.e. GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that act locally in the stomach. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they get emptied from the stomach. These systems are also advantageous in improving GIT absorption of drug having narrow absorption windows and site-specific absorption limitations. These systems are useful in case of those drugs which are best absorbed in stomach for eg. albuterol [4]. Hence, this review article focuses on the current technological developments and advancements in gastro retentive drug delivery system with special emphasis on the approaches and the advantages along with some marketed preparations of GRDDS.

APPROACHES TO GRDDS

To formulate a successful stomach specific or gastro retentive drug delivery system (GRDDS) several techniques currently used are:

1.1 Hydrodynamically balanced systems (HBS)- The incorporated buoyant materials enable the device to float [5, 6].

1.2 Raft systems incorporating alginate gels- These have a carbonate component and upon reaction with gastric acid, bubbles form in the gel, enabling floating [5, 7, 8].

1.3 Bioadhesive or Mucoadhesive systems- In these approaches bioadhesive polymers are used that can be adhere to the epithelial surface of the GIT. The proposed mechanism of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer interface boundary [6].

1.4 Modified shape systems- These are non-disintegrating geometric shapes molded from silastic elastomer or exuded from polyethylene blends and extended the gastric transit time (GTT) depending on the size, shape and flexural modulus of the drug delivery device.

1.5 High density systems- They include coated pellets and have density greater than that of the stomach content (1.004 gm/cm^3). This formulation of high-density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are position in the lower part of the antrum [2, 9, 10].

1.6 Swelling type system- These types of products swell to extents that prevent their exit from the stomach through the pylorus. These systems may be referred as a "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters [11-13].

1.7 Magnetic systems- These are the systems which includes external stimuli as magnetic field for site specific delivery. Some magnetically active compounds are incorporated in the dosage form to achieve site specificity [11-13].

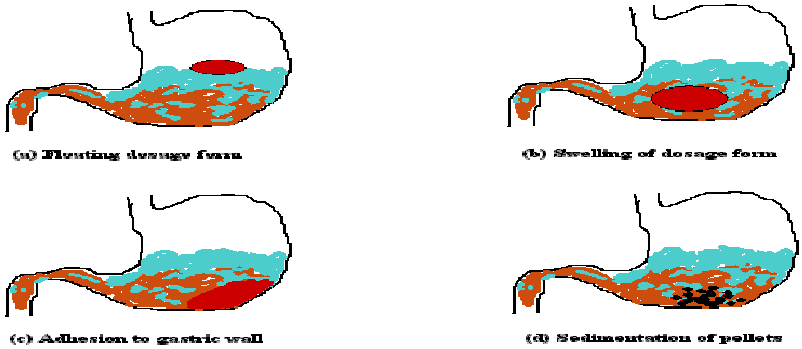

Fig. 1 Different approaches for GRDFs

DRUGS USED IN THE GASTRO RETENTIVE FORMULATIONS [14-22]

2.1 Floating microspheres- Aspirin, Griseofulvin, P-nitroaniline, Indomethasone, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol , Tranilast and Terfinadine

2.2 Floating granules- Diclofenac sodium, Indomethacin and Prednisolone

2.3 Films – Cinnarizine, Albendazole

2.4 Floating tablets and pills- Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Cephalexin, Cefuroxime, Fluorouracil, Isosorbide mononitrate, Isoniazide, Para-amino benzoic acid, Piretanide, Theophylline, Verapamil hydrochloride, Chlorpheniramine

maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, Pentoxyfilline and Diltiazem hydrochloride.

2.5 Floating capsules- Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid, Pepstatin and Propranolol.

POLYMERS AND OTHER INGREDIENTS [23]

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

3.1 Hydrocolloids- Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, Hydroxy Propyl Methyl Cellulose (HPMC) (K4M, K100M and K15M), Gellan gum(Gelrite®), Sodium Carboxy Methyl Cellulose (CMC), Methyl Cellulose (MC), Hydroxy Propyl Cellulose (HPC).

3.2 Inert fatty materials- Bees wax, Fatty acids, Long chain fatty alcohols, Gelucires® 39/01 and 43/01.

3.3 Effervescent agents- Sodium bicarbonate, Citric acid, Tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate), CG (Citroglycine).

3.4 Release rate accelerants- Lactose, Mannitol.

3.5 Release rate retardants- Di-calcium phosphate, Talc, Magnesium stearate.

3.6 Buoyancy increasing agents- Ethyl cellulose.

3.7 Low density material- Polypropylene foam powder (Accurel MP 1000®).

MARKETED PREPARATIONS [5, 24]

Table 1: List of various floating gastroretentive marketed formulations

Sr. No.	*Drug*	*Brand name*	*Manufacturer*
1.	Diazepam floating capsule	Valrelease®	Roche, USA
2.	Antacid preparation	Almagate Flot-Coat®	----------
3.	Aluminium – Magnesium antacid	Topalkan®	Pierre Fabre Drug, France
4.	Benserazide and L-Dopa	Madopar®	Roche Products, USA
5.	Ciprofloxacin floating tablets	Cifran OD	Ranbaxy, India
7.	Effervescent floating liquid alginate preparation	Liquid Gaviscon®	Glaxo Smithkline, India
8.	Ferrous Sulphate colloidal gel forming FDDS	Conviron®	Ranbaxy, India
9.	Misoprostol bilayer floating capsule	Cytotec®	Pharmacia, USA

ADVANTAGES OF FLOATING DRUG DELIVERY [24-27]

- Enhanced bioavailability
- Enhanced first-pass biotransformation
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT

- Reduced fluctuations of drug concentration
- Improved receptor activation selectivity
- Reduced counter-activity of the body
- Extended time over critical (effective) concentration
- Minimized adverse activity at the colon
- Site specific drug delivery

LIMITATIONS [13, 28]

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritant to gastric mucosa are also not suitable.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- The dosage form should be administered with a full glass of water (200-250 ml).
- These systems are not advantageous over the conventional dosage forms for those drugs, which are absorbed throughout the gastrointestinal tract.

RECENT ADVANCEMENTS AND FORMULATIONS IN THE FIELD OF STOMACH SPECIFIC GASTRORTENTIVE DOSAGE FORMS

Table 2: List of various drugs along with their dosage forms and constituents which are used in recent years as a stomach specific gastroretentive dosage forms

Drug	*Floating Dosage form*	*Constituents*	References
Ranitidine [29]	Tablet	HPMC K4M, Sod. bicarbonate	Jain et al., 2010
Mosapride[30]	Beads	Sodium alginate, HPMC	Kumuran et al., 2010
Domperidone[31]	Tablets	HPMC K4M, Eudragit L100	Shah et al., 2010
Famotidine [32]	Tablet	HPMC K4M, Sod. bicarbonate	Patel et al., 2009
Silymarin [33]	Tablet	HPMC K4M, HPMC K15M, Psyllium husk, Crosspovidone	Garg et al.,2009
Dipyridamole [34]	Capsule	HPMC K4M, Sod. chloride	Zang et al.,2009
Ciprofloxacin [35]	Tablet	HPMC K100M,Crospovidone, Starch, Sod. bicarbonate	Arza et al., 2009
Ofloxacin [36]	Tablet	HPMC K4M, HPMC 5cps, Sod. CMC, Sod. bicarbonate	Janardhan et al., 2009
Zidovudine [37]	Tablet	HPMC K4M, MCC, Citric acid, Sod. Bicarbonate	Dalavi et al., 2009
Propranolol HCL [38]	Tablet	HPMC K4M, HPMC E15 LV, HPC, Xanthan gum, Sodium alginate, Sod. bicarbonate	Jagdale et al 2009
Norfloxacin [39]	Tablet	HPMC K4M, HPMC K100M, Xanthan gum, Sod. bicarbonate	Bomma et al., 2009
Ranitidine HCL [40]	Tablet	HPMC K4M, Plaxomer, Sod. bicarbonate	Dhamecha et al., 2009
Salbutamol [41]	Tablet	HPMC K4MCR, HPMC K100MCR	Rao et al., 2009
Verapamil [42]	Tablet	HPMC K4M, Carbopol, Xanthan gum	Patel et al.,2009
Famotidine [43]	Tablet	Poly styrene-divinyl benzene, Xanthan 150, HPMC (K15M,	Raval et al., 2009

		K100M), Sodium alginate	
Famotidine [44]	Tablet	HPMC (K4M, K15M), Carboplol 934P	Kumar et al.,2009
Furosemide [45]	Minitablet	HPMC K100, Ethyl cellulose	Meka et al., 2009
Famotidine [46]	Beads	Sodium alginate, Pectin, Calcium chloride	Elmowafy et al., 2009
Domperione [47]	Tablet	HPMC K4M, Carbopol 934P, Sod. Alginate, Sod. bicarbonate	Prajapati et al., 2008
Atrovastatin [48]	Tablet	HPMC K4M, Ethyl cellulose, Sod. bicarbonate, Bees wax	Kumar et al., 2008
Clarithromycin[49]	Tablet	HPMC K4M, Carbopol 934P, Xanthan gum	Nama et al., 2008
Amlodipine [50]	Tablet	HPMC(K100M, K15M), Carbopol 934	Pare et al., 2008
Captopril [51]	Tablet	HPMC (K15MCR, K100MCR), Ethyl cellulose.	Patel et al ., 2008
Propranolol [52]	Tablet	PVA, Kollicoat® SR30 D/Kollicoat®	Strübing et al.,2008
Celiprolol [53]	Capsule	HPMC (K4M, K15M, K100M), Ethyl cellulose	Qurashi et al.,2007
Glipizide [54]	Tablet	HPMC 4000CPS, Eudragit RS 100	Prabhu et al., 2007
Acyclovir [55]	Tablet	HPMC (K4M, K15M), Crosspovidone, MCC	Grag et al., 2007
Rifampicin [56]	Tablet	Poly ethylene oxide, MCC	Gohel et al., 2007
Rosiglitazone [57]	Tablet	Methocel K100M	Sonar et al., 2007
Glipizide [58]	Microsphere	HPMC, Ethyl cellulose	Gupta et al., 2007
Ranitidine [59]	Microsphere	Ethyl cellulose, Eudragit RLPO, Eudragit L100-55	Mahor et al.,2007
Tizanidine [60]	Tablet	Xantan gum, HPMC(K 15M, K100M)	Chaudhari et al., 2007
Diltiazem HCL [61]	Tablet	Methocel K100M, Compretol 888, Sod. bicarbonate	Gambhre et al., 2007
Celecoxib [62]	Capsule	HPMC K4M, Eudragit RL100, PEO (WSR 1105, WSR 301, WSR 303, WSR 60K, and WSR N80; Amerchol, Edison, NJ)	Ali et al., 2007
Metformin [63]	Capsule	Poly ethylene oxide, HPMC K4M, tc99m-per technate	Ali et al., 2007
Famotidine [64]	Tablet	Methocel K100M, Methocel K15M	Jaimini et al., 2007
Cefuroxime auxetil [65]	Tablet	Methocel K4M, Methocel K100LV, Tablettose 80, Sod. bicarbonate	Patel et al., 2006
Theophylline [66]	Pellet	MCC, HPMC E15LV, PEG 6000, Eudragit® (RL30D, RS 30D, NE 30D)	Sungthongjeen et al., 2006
Carbamazepine [67]	Tablet	HPMC K4M, Ethyl cellulose, Sod. bicarbonate	Patel et al., 2005
Diltiazem HCL [68]	Granules	Gelucire 43/01, Glyceryl monostearate, Methocel K4M, Ethyl celluose	Shimpi et al., 2004

FUTURE POTENTIAL

Floating dosage form offers a great future potential as evident from several recent updated research and publications. Among the recently used clinical drugs several narrow absorption window drugs may benefit from compounding into a FDDS. Replacing parentral administration of drugs to oral pharmacotherapy would substantially improve treatment and patient compliances

too. Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently by FDDS. Thereby maximizing their absorption and improving their absolute bioavailability. The floating concept can also be utilized in the development of various anti-reflux formulations. Developing a controlled release system for the drugs, which have potential to treat the Parkinson's disease, is also an important area of consideration. Combination therapy for FDDS needs to be developed to treat H. Pylori infection. The study of the effect of various geometric shapes must be carried out for future aspect of GRDDS. A design of novel polymers can be investigated according to clinical and pharmaceutical need of a GRFDDS.

CONCLUSION

Drug absorption in GIT is a variable process and gastric retention extend the time for drug absorption. Floating dosage form is a potential approach for gastroretentive dosage forms. A huge work has been done in the field of gastro retentive dosage form with the rationale to increase the patient compliances. The review summarizes the progress of FDDS in the literature and market with their advantages, disadvantages.

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