International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

ISSN:2347-6567

IJAMSCR |Volume 8 | Issue 2 | Apr - Jun - 2020
www.ijamscr.com

Review article *Medical research*

Gastroretentive drug delivery system: A review

Bhavana. Salunke*, Dr. Rajesh Asija, Mr. Anil Kumar Goyal, Mr. Jitendra Kumar

Dept. of Pharmaceutics, Maharishi Arvind Institute of Pharmacy, Jaipur
***Corresponding Author**: **Bhavana. Salunke**

ABSTRACT

GRDDs are an approach to prolong gastric residence time, there by targeting site-specific drug release in the upper GIT for local or systemic effect. Gastro retentive dosage forms (GRDFs) are being used from a very long time to improve therapy with several important drugs. GRDFs greatly improves the pharmacotherapy of stomach by releasing the drug locally and thus results into high concentration of drug at the gastric mucosa which can be sustained over a longer duration of time. GRDFs enable prolonged and continuous release of the drug to the upper part of Gastro intestinal tract (GIT) and this significantly extend the duration of drug release and improve bioavailability of drugs that have narrow therapeutic window, by this way they prolong dosing interval and increase compliance of the patient. The purpose of this paper is to briefly describe the gastro retentive drug delivery (GRDD), factors related to GRDD, its advantages disadvantages, and emphasis is given over its significance over conventional form of drug deliveries

Keywords: Gastric residence time, Gastro retention, Hydro dynamically balanced system, Effervescent, Non-effervescent

INTRODUCTION

GRDDS is an approach to prolong the gastric residence time, thereby aiming site-specific drug release in the upper GIT for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Prolonged GRT enables the controlled delivery of drugs in stomach which can evade the repeated administration of dosage form of the drugs with short half-life. Literature suggests that GRDDS has gained huge popularity in the field of oral drug delivery recently, as it can release the drug slowly that can combat many shortcomings allied with conventional oral delivery, including poor bioavailability. Studies demonstrate that the drugs which have to be in the upper part of the GIT have been prepared as gastro retentive dosage forms using various approaches. Such formulation improves the therapeutic efficacy of the drug and enhances the patient compliance [1, 2].

GRDFs have been researched for many ant diabetic drugs and studies revealed that the gastro retentive form of drug has led to better management of the disease status. Although, a lot of work has been done, but still there is tremendous scope to develop such dosage form of ant diabetic drugs. Moreover, there are certain ant diabetic drugs which have a strong rationale for developing GRDDS, but no research has been reported to be performed on them [3].

The development of oral controlled release systems has been a challenge to formulation

scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal (GI) tract. Controlled drug delivery systems aim to maintain plasma concentration of drugs within the therapeutic window for a longer period of time, thereby to ensure sustained therapeutic action and for that reason an increasing interest in their development exist. Moreover, many of new therapeutics under development are large molecules such as peptides, proteins, oligonucleotides, and vaccines [4].

Gastro retentive drug delivery systems are designed to prolong the gastric retention time of the drugs which are:

- Locally active in the stomach
- Unstable in the intestinal environment
- Have narrow absorption window in the GIT
- Have low solubility at the high pH regions [5]

Advantages of gastro/intestinal retentive delivery systems

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels.
- Retention of drug delivery systems in the stomach prolongs overall Gastrointestinal transit time there by increasing bioavailability of sustained release delivery systems intended for once-a-day administration.
- For drugs that have low bioavailability in acidic pH, and are well absorbed in intestinal pH, Intestinal retentive delivery system is advantageous.

Limitations of the techniques of gastro/ intestinal retention

- Not suitable for drugs that may cause gastric lesions e.g. Non-steroidal anti-inflammatory drugs.
- More predictable and reproducible floating properties should be achieved in all the extreme gastric conditions
- For Intestinal retention, dosage form has to cross gastric conditions intact, which is not easily achievable.
- Not suitable for drugs that are unstable in the strong acidic or basic environment.
- These systems do not offer significant advantages over the conventional dosage forms for drugs that are absorbed throughout the gastro intestinal tract [6]

Other limitations associated with specific types of GRDDS are given the table below [7].

Technology	Limitations
High density system	Very difficult to incorporate large amount of drugs. No such systems are available in the market till date
Floating system	Floating highly depends on the fed state of the stomach and higher level of fluid is required in gastric region
Expandable system	Chocking problem; storage problem due to hydrolysable and biodegradable polymers; difficult to manufacture and not economical
Mucoadhesive system	Can be detached from gastric mucosa due to rapid turnover of mucus and peristaltic wave of stomach. It may also attach to the mucus of oesophagus
Magnetic system	Problem with patient compliance

FACTORS AFFECTING GASTRIC RETENTION [8-10]

Density

Density of dosage form should be in range of 1g/cm^3 to 2.5g/cm^3.

Size

Dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

Shape of dosage form

Tetrahedron and ring shaped devices are reported to have better GRT and ~ 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation

Multiple unit formulations show a more predictable release profile, co-admiration of different units, larger safety margin.

Fed or unfed state

In the fed state, MMC is delayed and GRT is considerably longer.

Nature of meal

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content and Frequency of feed

GRT can be increased by 4 to 10 hours with a meal that is high in proteins and fats. The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC.

Posture

GRT can vary between supine and upright ambulatory states of the patient.

Gender

Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counter parts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

Age

Elderly people, especially those over 70, have a significantly longer GRT.

Concomitant drug administration

Anticholinergic like atropine and propantheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.

Other factors

Diabetes and Crohn's disease, body mass index, physical activity

DIFFERENT APPROACHES OF THE GRDDS

GRDDS are categorized as

Non-floating system

These systems are retained in stomach by many mechanisms but not by floating. Non-floating system is again divided into:

a) Sinking (High density) drug delivery system
b) Bioadhsive / mucoadhesive system
c) Magnetic system
d) Unfoldable system

Floating drug delivery system (FDDS)

These systems are known as low density system as their density is less than the gastric contents thus they float in stomach. Floating drug delivery systems are classified as:

a) Effervescent system
b) Non effervescent system
- Hydro dynamically balanced system
- Microbaloons or hollow microspheres
- Alginate beads
- Micro porous compartment

Non floating system

High density (sinking) drug delivery system

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the folds of the stomach body near the pyloric region. Dense pellets (approximately 3g /cm^3) trapped in fold also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on diameter of the pellets. Commonly used excipients are Barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–2.4g/cm^3 [11].

Bioadhsive or mucoadhesive system

Bio adhesive or muco adhesive formulations were originally developed for increasing GRT and controlling drug delivery of all kinds of drugs. The technique involves coating of microcapsules with bio adhesive polymer, which enables them to adhere to intestinal mucosa and remain for longer time period in the GI while the active drug is released from the device matrix. The cationic chitosan polymers are pharmaceutically acceptable to be used in the preparation of bio adhesive formulations owing to their known ability to bind well to gastric mucosa [12].

The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are [13]

- The wetting theory, which is based on the ability of bio adhesive polymers to spread and develop intimate contact with the mucous layers.

- The diffusion theory, which proposes physical entanglement of mucin, strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
- The absorption theory, suggests that bio adhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
- The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bio adhesive material.

Magnetic system

This system is based on the simple idea that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Using a extracorporeal magnet, gastric residence time of the dosage form can be enhanced for a prolonged period of time [14].

Unfoldable system

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bio erodible polymer compressed within a capsule which extends in the stomach. Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective [15].

Floating drug delivery system (FDDS)

Effervescent system

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid). The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. This system is further divided as single unit matrix tablets or multiple unit pills. Single unit matrix tablet may be single or multilayer type. Floating system with ion exchange resins has also been reported. Effervescent system and drug release from such system is shown in figure 5 and 6 respectively [16].

NON EFFERVESCENT SYSTEM

Hydro dynamically balanced system

These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxy propyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems [17].

Microbaloons or hollow microspheres

These systems contain outer polymer shell loaded with drug. The outer polymer shell is made up of polymers like polycarbonate, cellulose acetate, calcium alginate, agar, etc. Buoyancy lag time and drug release from the system is dependent on the quantity of polymers used in the formulation. These are prepared by emulsion-solvent diffusion method. The steps involved are summarized in Figure [18].

Alginate beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium-alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate leading to formation of a porous system, when compared with solid beads, which gave a short residence, time of 1 hr., and these floating beads gave a prolonged residence time of more than 5.5 hr. [19].

Microporous compartment

Hollow microspheres

Hollow microspheres (Microbaloons), loaded with ibuprofen in their outer polymer shells were prepared by novel emulsion solvent diffusion method.

The ethanol

Dichloromethane solution of the drug and an enteric acrylic polymer were poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C. The gas phase was generated in dispersed polymer droplet by evaporation of dichloromethane and formed an internal cavity in microsphere of polymer with drug [20].

SUITABLE DRUG CANDIDATES FOR GASTRO RETENTION

- Narrow absorption window in GI tract, e.g., riboflavin and levodopa [21, 22]
- Drugs required to exert local therapeutic action in the stomach e.g., antacids and misoprostol [23, 24]
- Drugs insoluble in intestinal fluids, e.g., quinidine, diazepam [25, 26]
- Drugs that degrade in the colon, e.g., ranitidine HCL [27, 28]
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate [29, 30]

FUTURE PROSPECTS

GRDDS's have a future of not only increasing bioavailability and overcoming other drawbacks related to delivering drug to systemic circulation, instead GRDDS may prove to be an important perspective regarding controlled timed profile of certain drugs which have been found to distribute in certain non-targeted tissues because of fast release. By making GRDDS many drug profiles have been found to be distributed in targeted desired tissue. Along with advantage it is a challenge to design such formulations due to unpredictability of GIT and retaining formulation for long time is not compatible with normal physiology.

REFERENCES

[1]. Ali J, Arora S, Khar RK, Floating drug delivery system: A review. AAPS Pharma SciTech. 06(03), 2001, E372-E390.

[2]. Amit KN, Ruma M, Biswarup D. Gastro retentive drug delivery system; a review. Asian journal of pharmaceutical and clinical research. 3(1), 2010, 2-10.

[3]. Bardonnet PL, Faivre V, Pugh WJ. Piffaretti JC, Falson F. Gastro retentive dosage forms; overview and special case of helicobacter pyroli. J. control. Release. 111, 2006, 1-18.

[4]. Cadwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time. US4735804, 1998.

[5]. Cadwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time. US4758436, 1988.

[6]. Cadwell LJ, Gardner CR, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time. US Patent 4735804, 1988.

[7]. Lee TW, Robinson JR. Remington's the science and Practice of Pharmacy, Lippincott Williams & Wilkings; Philadelphia: 20, 2000.

[8]. Chen YC, Ho H, Lee TY, Sheu MT. Physical characterizations and sustained release profiling of gastroretentive drug delivery system with improved floating and swelling capabilities. International Journal of Pharmaceutics. 44, 2013, 162-169.

[9]. Oth M, Franze M, Timmermans J, Moes A, The bilayer floating capsule: a stomach directed drug delivery system for misoprostol. Pharm Res 9, 1992, 298-302.

[10]. Timmermans J, Gasnsbeka BV, Moes A. Accessing by gamma scintigraphy the in vivo buoyancy of dosage form having known size and floating force profiles as a function of time. Pharm Tech, 1, 1989, 42-51.

[11]. Kagan L, Hoffman A, Systems for regions elective drug delivery in gastro intestinal tract: biopharmaceutical considerations. Expert Opinion. Drug Delivery. 5, 2008, 681–692.

[12]. Pawar VK, Kansal S, Asthana S & Chourasia MK. Industrial Perspective of Gastro retentive Drug Delivery System: Physiochemical, Biopharmaceutical, Technological and regulatory considerations. Expert opinion on drug delivery. 9, 2012, 551.

[13]. Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm, 253, 2003, 13-22.

[14]. Singh B.N, Kim K.H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 63, 2000, 235–259.

[15]. Vyas SP, Khar RK. Controlled drug delivery: concept and advances. Vallabh prakashan: Delhi; 2002.

[16]. Chawla G, Gupta P, Koradia V, Bansal AK. Gastro retention: A Means to address regional variability in intestinal drug absorption. Pharm Tech, 27, 2003, 250-268.

[17]. Muller Lissner SA, Blum AL. The effect of specific gravity and eating on gastric emptying of slow release capsules. New Engl J Med, 304, 1981, 1365-1366.

[18]. 18 Singh BN, Kim KH. Floating drug delivery system: An approach to the controlled drug delivery via gastric retention. J Control Release, 63, 2000, 235-259.
[19]. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. Int J Pharm Res, 1(3), 2009, 623-633.
[20]. Devereux JE, Newton JM, Short MB. The influence of density on the gastrointestinal transit of pellets. J Pharm Pharmacol, 42(7), 1990, 500-501.
[21]. Klausner EA, Eyal S, Lavy E .Novel levodopa gastro retentive dosage form: in-vivo evaluation in dogs. Journal of Control Release. 88(1), 2003, 117-126.
[22]. Soni RP, Patel AV and Patel RB: Gastro retentive drug delivery systems: A review. International Journal of Pharma World Research, 2, 2011, 1-24.
[23]. Oth M, Franz M, Timmermans J, Moes AJ. The bilayer floating capsule: A stomach directed drug delivery system for misoprostol. Pharm Res, 9, 1992, 298.
[24]. Mishra A and Gupta P: Gastro retentive drug delivery system: A review. International Journal of Drug Development and Research, 4, 2012, 28-39.
[25]. Kumar MK, Shah MH, Ketkar A, Madhik KR, Paradkar A. Effect of drug solubility and different excipients on floating behaviour and release from glyceryl monooleate matrices. Int J Pharm. 272, 2004, 151.
[26]. Harrigan RM: Drug delivery device for preventing contact of un dissolved drug with the stomach lining. US Patent 4055178, 1977.
[27]. Dave BS, Amin AF, Patel MM. Gastro retentive drug delivery system of Ranitidine Hydrochloride: Formulation and In Vitro Evaluation. American Association of Pharmaceutical Scientists Pharm Sci Tech. 2004, 5-11.
[28]. Sharma N, Agarwal D, Gupta M and Khinchi M: A comprehensive review on floating drug delivery system. International Journal of Research in Pharmaceutical and Biomedical sciences, 2, 2011, 428-441.
[29]. Yellanki SK, Singh J, Syed JA et al. Design and characterization of Amoxicillin trihydrate muco adhesive microspheres for prolonged gastric retention. International Journal of Pharmaceutical Sciences and Drug Research. 2, 2010, 112.
[30]. Asane GS. Muco adhesive gastrointestinal drug delivery system: An overview. 2007; www.pharmainfo.net.

How to cite this article: Bhavana. Salunke, Dr. Rajesh Asija, Mr. Anil Kumar Goyal, Mr. Jitendra Kumar. Gastroretentive drug delivery system: A review. Int J of Allied Med Sci and Clin Res 2020; 8(2): 299-304.
Source of Support: Nil. **Conflict of Interest:** None declared.