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Drug Targeting Using Gastroretentive Drug Delivery Systems for Antihypertensive Drugs

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Abstract
Oral drug delivery system (DDS) is the preferred route of administration of drugs, but poor bioavailability (BA) of orally administered drugs is still a challenging one, though extensive advancements in drug discovery process are made. Drugs with narrow absorption window in the gastrointestinal tract have poor absorption. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Therefore, gastroretentive DDSs (GRDDSs) have been developed, which prolong the gastric emptying time. Most of the antihypertensive drugs have short half-life, short gastric residence time, low BA, and narrow absorption window. GRDDS can be a viable option for management of hypertension for several antihypertensive drugs. Several techniques such as floating DDS, low-density systems, raft systems, mucoadhesive systems, high-density systems, super porous hydrogels, and magnetic systems have been employed. These forms are expected to remain buoyant on gastric content without affecting the intrinsic rate of emptying. This results in prolonged gastric retention time of floating forms which improve BA of drug and also improve clinical situations. Prolonged gastric retention not only improves the BA and reduces drug waste but also improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. Hence, it can be concluded that GRDDS promises to be a potential approach for antihypertensive drugs. This review mainly focuses on the different types of GRDDS used for management of hypertension and also includes the updated compiled study of different antihypertensive drugs explored as GR dosage forms.

Keywords
Bioavailability, gastric emptying, gastroretentive drug delivery systems

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INTRODUCTION

Despite tremendous advancements in drug delivery, the oral route remains the preferred route of administration of therapeutic agents because of low cost of therapy and ease of administration lead to high levels of patient compliance. However, the issue of poor bioavailability (BA) of orally administered drugs is still a challenging one, though extensive advancements in drug discovery process are made.[1]

Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. CRDFs or controlled release drug delivery systems (CRDDS) provide drug release at a pre-determined, predictable, and in a controlled rate. The de novo design of an oral controlled DDS should be primarily aimed at achieving more predictable and increased BA of drugs.

A major constraint in oral CRDD is that not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT). Some drugs are absorbed uniformly throughout the GIT, while some drugs are absorbed in a particular portion of GIT only or are absorbed to a different extent in various segments of GIT. Such drugs are said to have an "absorption window." Thus, only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window, the released drug goes to waste with negligible or no absorption. This phenomenon drastically decreases the time available for drug absorption after it and limits the success of delivery system. These considerations have led to the development of oral CRDFs possessing gastric retention capabilities.[2]

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in GIT is to control the gastric residence time (GRT) using GR dosage forms (GRDFs) that offer a new and better option for drug therapy.

Dosage forms that can be retained in stomach are called gastroretentive DDSs (GRDDS). GRDDS 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 thus ensuring its optimal BA.[3]

Drugs that are easily absorbed from the gastrointestinal tract (GIT) with having a short half-life are quickly eliminated from the blood circulation and require frequent dosing. To avoid this problem, the oral formulations have been developed in an attempt to release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation.

Prolonged gastric retention improves BA, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients.

Physiological Considerations

Stomach-the site for gastro retention

The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm. Its size varies according to the amount of distension up to 1500 ml following a meal; after food has emptied, a collapsed state is obtained with resting volume of 25–50 ml. The stomach is anatomically divided into three parts: fundus, body, and antrum (or pylorus). The proximal stomach made up of fundus and body regions serves as a reservoir for ingested materials, while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying.

Gastrointestinal motility and emptying of food

The process of gastric emptying occurs both during fasting and fed states; however, the pattern of motility differs markedly in the two states. Two distinct patterns of gastrointestinal motility and secretion exist corresponding to the fasted and fed states. As a result, the BA of orally administered drugs will vary depending on the state of feeding.

In the fasted state, it is characterized by an interdigestive series of electrical event and cycle, both through the stomach and small intestine every 2–3 h. This activity is called the interdigestive myoelectric cycle or migrating motor complex (MMC) is often divided into four consecutive phases: basal (Phase I), pre-burst (Phase II), burst (Phase III), and Phase IV intervals.

The motor activity in the fed state is induced 5–10 m after ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2–6 h, and more typically, 3–4 h, with phasic contractions similar to Phase II of MMC.[4]

When CRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total GRT and transit time in GIT.

This assumes even more significance for drugs that have an absorption window because it will affect the

amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of absorption. On the other hand, in the fed stomach the gastric retention time (GRT) of non-disintegrating dosage forms depends mostly on their size and composition and caloric value of food.

Requirements for gastroretention

From the discussion of the physiological factors in stomach, to achieve gastroretention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease.[5]

Factors Affecting Gastric Retention

Density

GRT is a function of dosage form buoyancy that is dependent on the density. Density of the dosage form should be less than the gastric contents (1.004 g/ml).

Size

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

Shape of dosage form

Tetrahedron and ring-shaped unfolding expandable GRDF with a flexural modulus of 48 and 22.5 kilopounds per square inch, respectively, are reported to have better GRT ≈ 90–100% retention at 24 h compared with other shapes such as continuous stick, planar disc, planar multilobe, and string.

Single or multiple unit formulation

Multiple unit formulations show a more predictable release profile and insignificant impairing of the performance due to the failure of units, allow coadministration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed state

Under fasting conditions, the gastrointestinal motility is characterized by the periods of strong motor activity or the MMC that occur every 2–3 h. The MMC sweeps undigested material from the stomach and, if the timing of administration of formulation coincides with that of the MMC, then, GRT of the unit may be expected to be very short. However, in the fed state, MMC is delayed, and GRT is considerably longer.

Nature of meal

Feeding of indigestible polymers or fatty acid salts such as cellulose, starch, polydextrose, and raffinose can change the motility pattern of the stomach by delaying the MMC, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content

GRT can be increased by 4–10 h with a meal that is high in proteins and fats.

Frequency of feed

The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender

It was observed that mean GRT in males is less than the female subjects of same age and race. Females emptied their stomach slowly in comparison to male candidates, regardless of their weight, height, and body surface area.

Age

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

Posture

GRT can vary between supine and upright ambulatory states of the patient. For the floating systems, it was reported that when subjects were kept in the upright ambulatory position, the dosage form stayed continuously on gastric content in comparison to the supine state of the patients. Thus, in the upright position of the patients, floating dosage forms protected against post-prandial emptying.

Concomitant drug administration

Clonidine, lithium, nicotine, progesterone, anticholinergics such as atropine and propantheline and opiates like codeine prolong GRT. On the other hand, erythromycin and octreotide enhance the gastric emptying. [6-10]

Approaches for Gastroretention

Different methods have been devised to improve period of retainment of oral dosage form in the stomach. They may be broadly classified as:

GR drug delivery is an approach to prolong GRT, thereby targeting site-specific drug release in the upper GIT for local or systemic effects. GRDFs can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of drugs. Several GR drug delivery approaches being designed and developed.

Floating DDSs (FDDSs)

FFDDS is an effective technology to prolong the GRT to improve the BA of the drug. FDDS are low-density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a

prolonged period. Floating systems can be classified as effervescent and non-effervescent system.

Effervescent systems

These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, for example, chitosan, and effervescent components, for example, sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. Gas can be introduced into the floating chamber by the volatilization of an organic solvent (e.g., ether or cyclopentane) or by the carbon dioxide produced as a result of an effervescent reaction between organic acids and carbonate–bicarbonate salts. This produces an upward motion of the dosage form and maintains its buoyancy. Recently, a multiple-unit type of floating pill, which generates carbon dioxide gas, has been developed.

Non-effervescent systems

Non-effervescent floating DDSs are normally prepared from gel-forming or highly swellable polysaccharides or matrix forming polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate. In one approach, intimate mixing of drug with a gel-forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxyl, propyl, methyl, cellulose, polyacrylates, polyvinyl acetate, carbopol, sodium alginate, calcium chloride, polyethylene oxide, and polycarbonates.

Raft-forming systems

On contact with gastric fluid, a gel-forming solution (e.g., sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles. This forms raft layer on top of gastric fluid which releases drug slowly in stomach. Such formulation typically contains antacids such as aluminum hydroxide or calcium carbonate to reduce gastric acidity. They are often used for gastroesophageal reflux treatment as with liquid Gaviscon.

Bioadhesive DDSs

Bioadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as the potential means of extending the GRT of DDS in the stomach, by increasing the duration of contact of drug with the biological membrane. The concept is based on self-protecting mechanism of GIT. Mucus secreted continuously by the specialized goblet cells located throughout the GIT plays a cytoprotective role. Bioadhesion is an interfacial phenomenon in which is biological, is held together by means of interfacial forces.

Swelling and expanding systems

These systems since they exhibit the tendency to remain longed at the pyloric sphincter. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymer network. These cross-links prevent the dissolution of the polymer, and hence, maintain the physical integrity of the dosage form. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

High-density systems

These dosage forms have a density (3g/ml) far exceeding that of normal stomach contents (1g/ml) and thus retained in rugae of the stomach and are capable of withstanding its peristaltic movements. The density of these systems should at least be 1.004 g/ml. This is accomplished by coating the drug with heavy inert materials such as barium sulfate, zinc oxide, titanium dioxide, and iron powder.

Self-unfolding systems

The self-unfolding systems are capable of mechanically increasing in size relative to the initial dimension. This increase prevents the system from passing through the pylorus and provides for its prolonged stay in the stomach. A drug can be either contained in a polymeric composition of the gastroretentive systems or included as a separate component. Several methods were suggested to provide for the self-unfolding effect: (1) The use of hydrogels swelling in contact with the gastric juice, (2) osmotic systems, comprising an osmotic medium in a semipermeable membrane, and (3) systems based on low-boiling liquids converting into a gas at the body temperature.[11-14]

Effects of Prolong Gastric Retention of Drugs

Advantages of prolonging gastric retention of drugs Increase in BA and curative efficiency of drugs and economic usage of dosage.

Minimized factor of risk in resistance in antibiotics owing to stabilized therapeutic levels over prolonged periods removing fluctuations.

Optimized release in case of short half-life drugs causes flip-flop pharmacokinetics and also ensures patient compliance with reduced dosage frequency.

- They are advantageous against drawbacks of the gastric retention time (GRT) as well as the gastric

emptying time (GET). The system remains buoyant on gastric fluid because of lower bulk density than gastric fluids.

- These are efficient in repairing stomach and small intestine-related problems. Its attributed to the fact that gastroretentive drug delivery sustains drug release, and hence, avail local therapy in these organs.
- This method provides with a systematic and controlled DDS which minimizes chances of drug overexposure at the diseased site.

Disadvantages of GRDDS

- Need for increased level of fluids in the stomach.
- Unsuitable for such drugs as:
- Problematic with solubility in gastric fluid.
- Causing GI irritation.
- Inefficient in acidic environment.
- Drugs intended for selective release in the colon.
- Unpredictable adherence owing to state of constant renewal of mucus wall of stomach.
- GRDDS is fed into the system after the meal as time of stay in stomach depends on digestive state.

The ability of the drug to remain in the stomach depends on the subject being positioned upright.

GRDDS for Antihypertensive Drugs

Uncontrolled hypertension is a major risk factor for stroke, coronary heart disease, left ventricular hypertrophy, arrhythmia, arteriosclerosis, end-stage renal disease, and other life-threatening disorders. According to the World Health Organization, hypertension is the third leading cause of death worldwide.

Joint National committee VIII (United States) estimates suggest more than 1 billion hypertensive patients worldwide. As per the WHO report on World Health Statistics 2012, one in every three adults has raised blood pressure. [23,24]

This becoming a chronic disease requires long-term treatment. Most of the antihypertensive drugs have short half-life, short GRT, low BA, and narrow absorption window. GRDDS can be a viable option for management of hypertension as several antihypertensive drugs.

It may be beneficial for some of the following drugs having.

- Narrow absorption window, for example, furosemide, atenolol, and diltiazem [23,24]
- Short half-life, for example, losartan and furosemide [25,26]
- Instability, for example, captopril at high pH values [27,28]
- Low solubility, for example, verapamil, furosemide, and propranolol at high pH [29-31]
- Degradation in the colon.

GRDDS is an approach to prolong GRT, thereby targeting site-specific drug release in the upper GIT for local or systemic effects.

Table 2: Marketed GRDFs (products) for treatment of hypertension [34,70]

Drug	Technology	Brand name	Manufacturer
Prazosin HCl	Effervescence and swelling based floating system	Prazopress XL®	Sun Pharma, India
Carvedilol	Osmotic system	Coreg CR®	GlaxoSmithKline, USA
Verapamil HCl	OROS	Covera HS®	DURECT Corporation, USA
Nisoldipine	Geomatrix™	Sular®	Skyepharma, Shionogi Pharma Inc., UK

GRDFs: Gastro retentive dosage forms

This site-specific drug delivery reduces undesirable side effects of administered drug as it can minimize the counter activity of the body leading to higher drug efficiency. GRDDS of antihypertensive drugs may be useful to increase the GRT, BA, henceforth to reduce the dose of the drug, dosing frequency, and increased patient compliance. [32,33]

Hence, to formulate a GRDDS for an antihypertensive drug, to achieve an extended retention in the upper GIT, which may be result in enhanced absorption and thereby improved BA [Tables 1 and 2].

Table 1: Compiled research study on various antihypertensive drugs explored as GRDFs

Drug	GRDF	Referen
Losartan	Tablets	[34,35]
Propranolol	Tablets	[36]
Furosemide	Tablets	[36,37]
Verapamil	Tablets	[38,39]
Captopril	Tablets	[40]
Nimodipine	Tablets	[41]
Nicorandil	Tablets	[42,43]
Quinapril	Tablets	[44,45]
Amlodipine	Tablets	[46]
Atenolol	Tablets	[47]
Metoprolol	Tablets	[48,49]
Ramipril	Tablets	[50]
Lacidipine	Microspheres	[51,52]
Diltiazem	Microspheres	[53]
Propranolol	Microspheres	[54,55]
Furosemide	Microspheres	[56]
Verapamil	Microspheres	[57]
Nifedipine	Microspheres	[58]
Carvedilol	Microspheres	[59]
Diltiazem	Microspheres	[53]
Felodipine	hollow microspheres	[60]
Nicardipine	Capsules	[61]
Lisinopril	Capsules	[62]
Lercanidipine	Capsules	[63]
Furosemide	Films	[64]
Captopril	Films	[40]
Diltiazem	Beads	[65]
Furosemide	Beads	[66]
Verapamil	Beads	[67]
Captopril	Beads	[68]
Lisinopril	Beads	[69]

GRDFs: Gastroretentive dosage forms

CONCLUSION

Increased GRT of a CR system has great practical applications. A CR system with GR ability can significantly improve BA and improve the efficiency of medical treatment. All the GR systems have their positive aspects and drawbacks. For management of hypertension, these systems also meliorate the efficacy of drugs which have altered stability, solubility, and absorption in GIT. These systems have special additional advantages for the drugs that are primarily absorbed from the upper segment of the GIT. It is also evident that the maximum number of commercial products and patents of GR systems belong to the class of floating DDSs. Hence, with an improved knowledge of formulation aspects and physiochemical and pharmacological prospects of drugs, someone can design an optimum system for drug delivery in the gastric cavity.

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