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### REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYSTEM

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#### ABSTRACT

Gastric retention along with oral controlled drug delivery is advantageous to many drugs having low absorption window and hence poor bioavailability. Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy and minimize the adverse effects and increase the bioavailability of drugs. It is most widely utilized route of administration among all the routes that have been explored for systemic delivery of dosage forms. In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of emptying. Unfortunately floating devices administered in a single unit form (Hydro dynamically- balanced system) HBS are unreliable in prolonging the GRT owing to their emptying process and, thus they may cause high variability in bio-availability and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract. It is a new drug delivery system to maximize effectiveness and compliance. For minimizing the limitations and achieving better gastric retention various combinational approaches floating and swelling, floating and bio-adhesion, etc., multi-particulate systems, super porous hydrogel, etc have been discussed. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Gastro retentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastro intestinal tract improving the oral sustained delivery of drug. In this paper current and recent gastro-retentive approaches have been presented.

#### KEYWORDS

Gastro-retentive drug delivery system, Physiology of stomach, Current approaches in GRDDs and Evaluation parameters.

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#### INTRODUCTION

Gastro retentive drug delivery system belongs to oral controlled drug delivery system group that are capable to retain in the stomach by passing the gastric transit. These dosage forms are also defined as floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time. The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug.

The real challenge in the development of a gastro retentive drug delivery system is not just sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper part of the GIT until all the drug is completely released. This can be accomplished by floating drug delivery system which helps to retain dosage form in the stomach and releases the drug in controlled manner for longer period of time. GRDDS is retained for longer periods of time in the stomach e.g. hydrophilic matrix tablets, floating capsules and bio-adhesive tablet. Thus the longer period of gastric retention as compared to other oral controlled drug delivery system can be attributed. The floating results in release of the drug in to the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic. This is achieved by adjusting the time period of release for the drugs by changing the concentrations of polymers. Prolonged gastric retention improves bioavailability, reduces drug waste, and 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 intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients<sup>1</sup>.

Drugs that are required to be formulated into gastro retentive dosage forms include.

1. Drugs acting locally in the stomach.  
E.g. Antacids and drugs for H. Pylori viz., Misoprostol
2. Drugs that are primarily absorbed in the stomach.  
E.g. Amoxicillin
3. Drugs that is poorly soluble at alkaline pH.  
E.g. Furosemide, Diazepam, Verapamil, etc.
4. Drugs with a narrow window of absorption.  
E.g. Cyclosporine, Methotrexate, Levodopa, etc.
5. Drugs rapidly absorbed from the GI tract and  
E.g. Metronidazole, tetracycline
6. Drugs that degrade in the colon.  
E.g. Ranitidine, Metformin HCl.
7. Drugs that disturb normal colonic microbes  
E.g. antibiotics against Helicobacter pylori.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time. Dosage forms that can be retained in the stomach are called gastro-retentive drug delivery systems (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 bioavailability<sup>3</sup>. Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bio-adhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease<sup>2</sup>.

#### **Advantages of GRDDS<sup>3</sup>**

1. Enhanced bioavailability.
2. Enhanced first-pass biotransformation.
3. Sustained drug delivery/reduced frequency of dosing.
4. Targeted therapy for local ailments in the upper GIT.
5. Reduced fluctuations of drug concentration.
6. Minimization of fluctuations in drug concentration.
7. Reduced counter-activity of the body.
8. Extended time over critical (effective) concentration and Minimized adverse activity at the colon.
9. Site specific drug delivery and Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide.
10. Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the

risk of resistance E.g. beta-lactam antibiotics (penicillin's and Cephalosporin's).

11. The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs.
12. Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. This feature is of special importance for drug with a narrow therapeutic index.
13. Minimize the counter activity of the body leading to higher drug efficiency<sup>4</sup>.

#### **Disadvantages of GRDDs**

1. Unsuitable for drugs with limited acid solubility.  
E.g. Phenytoin
2. Unsuitable for drugs that is unstable in acidic environment.  
E.g. Erythromycin
3. Drugs that irritates or causes gastric lesions on slow release.  
E.g. Aspirin and NSAID's
4. Drugs that absorb selectively in colon.  
E.g. Corticosteroid
5. Drugs that absorb equally well through GIT.  
E.g. Isosorbide dinitrate, Nifedipine
6. Floating drug delivery systems require high fluid level in stomach to float.
7. Some drugs present in the floating system causes irritation to gastric mucosa<sup>5</sup>.

#### **Physiology of stomach**

The stomach is a muscular, hollow, dilated part of the alimentary canal. The main function of the stomach is to store food temporarily, grind it, and then release it slowly in to the duodenum<sup>6</sup>. The stomach is an important site of enzyme production. The excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in the stomach is sufficiently high. However, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded. Area, very little absorption takes place from the stomach. It provides a barrier to the delivery of drugs to the small intestine. The stomach is located below the diaphragm. Various factors such as volume ingested, posture and

skeletal build affect the exact position of the stomach (Figure No.1).

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions<sup>7</sup>. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the inter-digestive myoelectric cycle or migrating mylo-electric cycle (MMC), which is further divided into 4 phases<sup>8</sup>.

#### **Gastrointestinal motility and gastric emptying**

Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1-3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes, inter-digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The inter-digestive motility pattern is commonly called as Migrating Motor Complex (MMC) and is organized in cycles of activity and quiescence<sup>9</sup>. Each cycle lasts 90-120 minutes and consists of four phases. The concentration of the hormone motility in the blood controls the duration of the phases. In the inter-digestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90-120 minutes. A full cycle consists of four phases, beginning in the lower esophageal sphincter/ gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum.

**Phase I** (basal phase) - lasts from 40 to 60 minutes with rare contractions.

**Phase II** (pre-burst phase) -lasts for 40 to 60 minutes with intermittent action potential and

contractions. As the phase progresses the intensity and frequency also increases gradually.

**Phase III** (burst phase) - lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the "house keeper wave"<sup>10</sup>.

**Phase IV** lasts for 0 to 5 minutes and occur between phases III and I of 2 consecutive cycles<sup>11</sup>. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

**Scintigraphic studies** determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate<sup>12</sup>.

### **Various Approaches for Gastric Retention**

#### **Floating system**

1. Swelling and expanding system
2. Bio-adhesive systems
3. Modified-shape systems
4. High density systems

#### **Floating Drug Delivery Systems**

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time<sup>13</sup>. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

**FDDS can be divided into non-effervescent and gas generating (effervescent) system**

#### **a. Non-Effervescent Systems**

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Ex: hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

**This system can be further divided into four sub-types**

#### **(i) Hydro dynamically balanced system**

Contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption<sup>14</sup>. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydroxy ethylcellulose, hydroxypropyl methyl cellulose (HPMC), polysaccharides and matrix forming polymer such as polycarboxophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.

#### **(ii) Microporous Compartment System**

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption<sup>15</sup>.

### (iii) 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<sup>16</sup>.

### (iv) Hollow Microspheres / Microballons

Hollow microspheres loaded with drug in their outer polymer shell were prepared by a novel emulsion solvent diffusion method<sup>17</sup>. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40°C<sup>18</sup>. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 24 hr.

### (b) Gas-Generating (Effervescent) Systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid)<sup>19</sup>. The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach.

Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating capsules with a core of sodium bicarbonate, lactose and poly-vinyl pyrrolidone coated with hydroxyl propyl methyl cellulose (HPMC), and floating system based on ion exchange resin system.

### B. Expandable systems

These are easily swallowed and reach a significantly larger size in the stomach due to

swelling or unfolding processes that prolong their GRT<sup>20</sup>. After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastro retentive is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties.

### C. Bio/Muco-Adhesive Systems

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastro retentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

### D. High-Density Systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm<sup>3</sup>) trapped in rugae 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 the 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.

### **E. Super porous hydrogel system**

In this approach to improve the GRT super porous hydrogels of average pore size > 100 micrometer, swell to equilibrium size within a minute due to the rapid water uptake by capillary wetting through numerous interconnected open pores<sup>21</sup>. They swell to large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction, advised by co-formulation of hydrophilic particulate material.

### **2. Gas generating (effervescent) system**

A drug delivery system can be made to float in the stomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas by volatilization of an organic solvent or by effervescent reaction between organic acids and bicarbonate salts. These are matrix type of systems prepared with the help of sellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO<sub>2</sub> is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

### **3. Volatile liquid containing systems**

These devices are osmotically controlled floating systems containing a hollow deformable unit that can be converted from a collapsed to an expanded position and returned to collapse position after an extended period. A deformable system consists of two chambers separated by an impermeable, pressure responsive, movable bladder. The first chamber contains the drug and the second chamber contains volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of bio-erodible plug made up of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse to permit the spontaneous ejection of the inflatable system from the stomach.

### **Evaluation of gastro-retentive dosage form**

#### **A) In vitro Evaluation**

##### **i) Floating systems**

###### **a) Buoyancy Lag Time**

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

###### **b) Floating Time**

Test for buoyancy is usually performed in SGF-Simulated Gastric Fluid maintained at 37°C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

###### **c) Specific Gravity / Density**

Density can be determined by the displacement method using Benzene as displacement medium.

###### **d) Resultant Weight**

The bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixing polymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form.

##### **ii) Swelling systems**

###### **a) Swelling Index**

After immersion of swelling dosage form into SGF at 37°C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time.

###### **b) Water Uptake**

It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time.

$$\text{Water uptake} = \text{WU} = (\text{Wt} - \text{Wo}) * 100 / \text{Wo}$$

Where, Wt = weight of dosage form at time t.

Wo = initial weight of dosage form.

## B) *In vitro* Evaluation Test

*In vitro* dissolution test is generally done by using USP apparatus with paddle and GRDDs is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results.

In order to prevent such problems, various types of modification in dissolution assembly made are as follows (Figure No.2). 1. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium<sup>22</sup>. 2. Floating unit can be made fully submerged, by attaching some small, loose, non-reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release. 3. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit. 4. Other method suggests placing dosage form between 2 ring/meshes. 5. Change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions, this gives more area for dosage form. 6. In spite of the various modifications done to get the reproducible results. Dissolution test apparatus with modification of Rosette-Rice test Apparatus was proposed.

## C) *In vivo* Evaluation Test

### a) Radiology

X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker.

### b) Scintigraphy

Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is <sup>99</sup>Tc<sup>23</sup>.

### c) Gastroscopy

Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach<sup>24</sup>.

### d) Magnetic Marker Monitoring

In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

### e) Ultrasonography

Used sometimes, not used generally because it is not traceable at intestine.

### f) <sup>13</sup>C Octanoic Acid Breath Test

<sup>13</sup>C Octanoic acid is incorporated into GRDDs. In stomach due to chemical reaction, octanoic acid liberates CO<sub>2</sub> gas which comes out in breath. The important Carbon atom which will come in CO<sub>2</sub> is replaced with <sup>13</sup>C isotope. So time up to which <sup>13</sup>CO<sub>2</sub> gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO<sub>2</sub> release. So this method is cheaper than other.

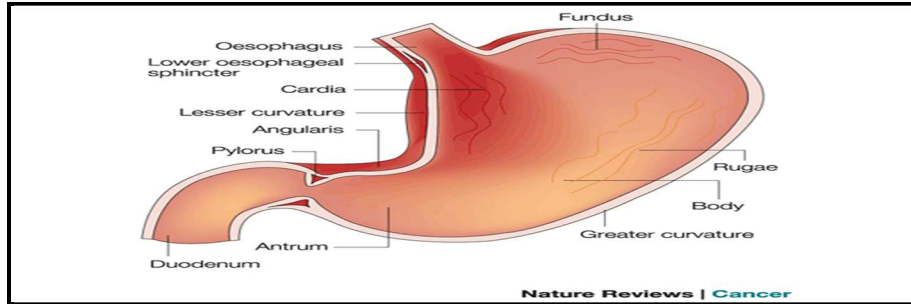


Figure No.1: Anatomy of the gastrointestinal tract

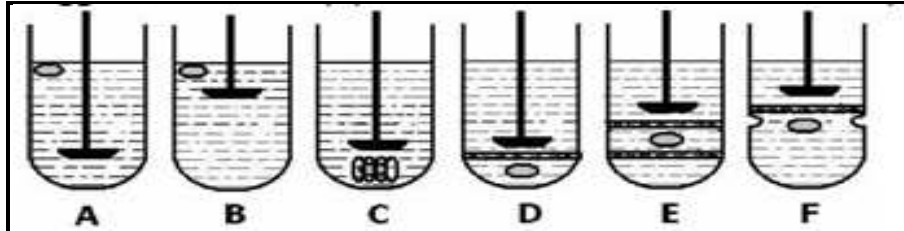


Figure No.2: Various types of modification in dissolution assembly made

## CONCLUSION

To derive maximum therapeutic benefits from certain drug substances, it is desirable to prolong their gastric residence time. Different approaches have their own advantages and disadvantages. Floating, and bio-adhesive and swelling systems appear to be the promising GRDDs. And recently, to avoid the disadvantages of the gastro-retentive approaches combinational gastro-retentive approaches are seems to be beneficial in better gastric retention and increase the efficiency of the medical treatment. Nevertheless, there are opportunity and potential for development of effective gastro-retentive delivery systems with the aim of improving bioavailability of the drugs that exhibit absorption window in the proximal and/or mid gastrointestinal tract. In the field of gastric retention, drug absorption in the gastro intestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. The control of gastro intestinal transit of orally administered dosage forms using GRDDs systems can improve the bioavailability of drugs that exhibit site specific absorption.

## FUTURE PROSPECTS

In the future, it is can be easily assumed that GRDD systems will become more popular in delivering drug to the systemic circulation with improving efficiency of various type of pharmacotherapy's.

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## CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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