



## Gastro Retentive Drug Delivery Systems - A Comprehensive Review

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### ABSTRACT

Floating drug delivery systems are promising systems that float immediately upon contact with gastric fluids which may increase the bioavailability of encapsulated drugs along with absorption in the intestine. The physiological and formulation variables affect the gastric retention towards the successful development of floating drug delivery formulations. Floating drug delivery formulation designs include single-unit and multiple-unit floating systems. Gastric emptying rate prolong and control the emptying time residing the stomach which supports the prolonged drug release. The mechanism by which gastro retentive systems work include upon contact with gastric fluids this system prolongs the residence time thereby improves bioavailability/solubility at the elevated pH condition and maximizes the drug at the target site. Here in the proposed review will provide insights towards the different gastroretentive drug delivery systems, polymers both natural and synthetic and applications of gastroretentive drug delivery systems. Special emphasis will be made towards the factors affecting gastro retentive drug delivery systems. Additionally, the process challenges and future perspectives towards the commercialization of gastroretentive drug delivery systems will be also discussed.

**Keywords:** Gastro retentive, floating, gastric, bioavailability.

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### INTRODUCTION

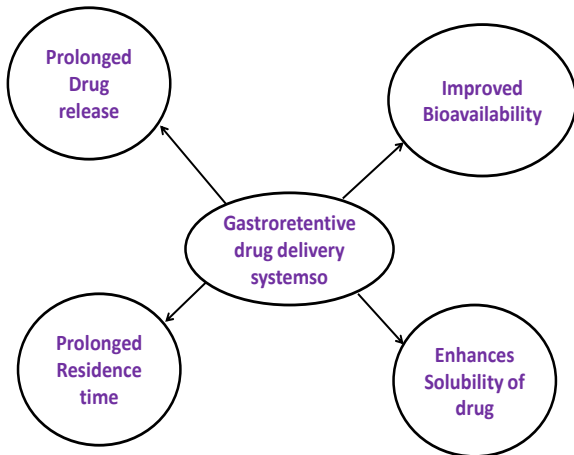
Gastro retentive drug delivery systems is a type of system which prolongs the residence of administered drug in the gastric region for several hours thereby the bioavailability and solubility of challenging drugs may get enhanced, and improves the patient compliance. Gastric emptying delaying conceptual mechanisms of mucoadhesion, flotation and sedimentation supports the gastro retentive drug delivery systems<sup>1</sup>. Thereby gastro retentive drug delivery systems enhance the absorption of drugs in the gastrointestinal tract drug by improving the contact time with the small intestinal mucosa. Gastric retention based drug delivery systems in turn provide a newer therapeutic possibilities and substantial benefits for researchers. Gastro retentive drug delivery systems may reduce the drug wastage. Gastro retentive drug delivery systems offer a controlled drug delivery profile with effective plasma drug concentration, reduces dosing frequency and minimizing plasma fluctuations<sup>2</sup>. Drugs suitable for gastro retentive drug delivery formulations include drugs that have low absorption in the lower part of the GIT, unstable, poorly soluble at alkaline pH, short half-life, and show local activity at the upper part of the intestine<sup>3</sup>. Due to the sustained/controlled release effect gastro retentive drug delivery formulations minimize the mucosal irritation

which may provide a desired plasma drug concentration and prevent drug fluctuations without causing dose dumping. Unstable drugs can also be delivered by this approach. The various approaches utilized in gastro retentive drug delivery system include extended gastric residence time, low-density (floating), high-density (sinking), expandable (swelling), and mucoadhesive systems.

The better understanding on the anatomy and physiology of the stomach (specifically proximal stomach- fundus and body; and the distal stomach- antrum and pylorus) plays a crucial role for the successful development of the gastro retentive dosage form. The critical factors which affect the gastro retentive drug delivery systems are size/ shape/density of gastro retentive formulations, caloric density, factors associated with patients etc. The passage through the pyloric antrum can be prevented by an increase in the size of the dosage form. The lower density of gastro retentive drug delivery formulations than that of gastric fluids favors the floating capacity of the gastro retentive formulations. Caloric density of the ingested food increases the gastro retentive property, herein the gastric emptying rate also gets affected by the gastro retentive formulations. The other factors related to patient such as gender, age, illness, and emotional state also influence the delivery of gastro retentive formulations. Diseases conditions of Parkinson's disease, diabetes also influence the gastric emptying rate. Elderly patients and males have superior gastric emptying rate compared to females and younger's. In addition factors influencing the delivery of gastro retentive formulations work by accelerating or delaying gastric emptying in other related conditions of fear and apprehension, acute /chronic



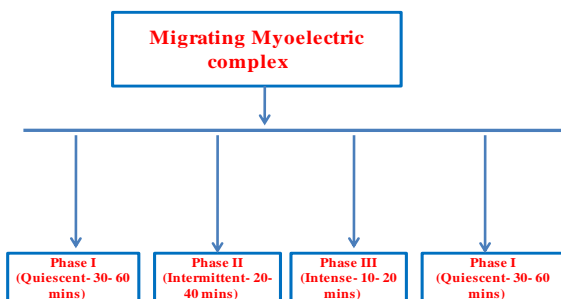
diseases, trauma, drugs, and surgery. The gastroretentive dosage formulation has been regulated by various factors such as polymer types (nonionic, cationic, and anionic polymers), polymer composition, viscosity grade, polymer molecular weight, and drug solubility. The advantages of Gastroretentive drug delivery systems is shown in Figure. 1.



**Figure 1:** Advantages of Gastro retentive drug delivery systems

**Physiology of Stomach**

The successful development of the gastroretentive dosage form depends upon the anatomy and physiology of the stomach. The migrating myoelectric complex (MMC) supports the mobility pattern of the stomach. Improved gastric retention time (GRT) of the dosage form may be achieved due to the presence of food in the gastrointestinal tract (GIT) which may improves the drugs absorption for a longer period. The different phases of Migrating myoelectric complex is shown in Figure. 2. The stomach separated from the duodenum ie the Pylorus acts in the improved gastric residence time of the ingested materials.

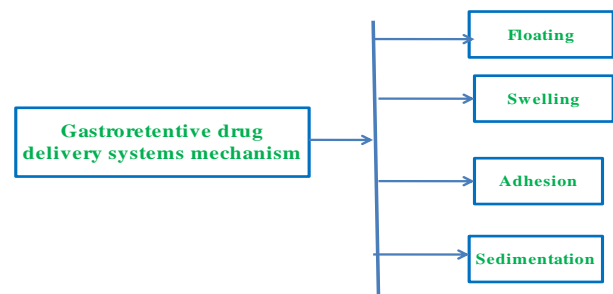


**Figure 2:** Phases of Migrating myoelectric complex

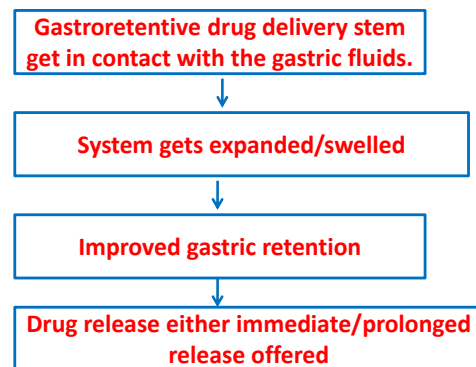
**Polymers used in gastro retentive drug delivery systems**

The development of gastro retentive drug delivery systems involves the role of polymers towards the successful formulation development. In order to afford the floating capacity numerous approaches has been attempted by researchers such as maintaining the hydrodynamically balanced systems, gas-generating systems, raft-forming

systems, low-density systems etc <sup>5</sup>. The different mechanisms of gastroretentive drug delivery systems are shown in Figure. 3. Approaches of effervescent and non effervescent systems with the concepts to generate effervescence and concepts of swelling property have been also attempted by researchers. Here in natural, synthetic and semi synthetic polymers are utilized for the development of gastro retentive drug delivery systems. When compared to synthetic/semi synthetic polymers the natural polymers which are naturally available are widely used for gastro retentive drug delivery systems due to the versatile properties of non-toxic, non-irritant, and biocompatible<sup>6</sup>. The release mechanism of gastroretentive drug delivery system was shown in Figure. 4.



**Figure 4:** Gastro retentive drug delivery system mechanisms



**Figure 5:** Release mechanism of Gastroretentive drug delivery system

Raffi Malik et al; 2015 developed diacerein loaded nanofibers based gastroretentive dosage form in order to improve the solubility of diacerein using Poly L-(lactic acid) by the electrospinning technique. Their developed nanofibers were smooth, discrete, & non-woven. as determined by X-ray crystallography analysis which largely contributes to higher drug solubility in the nanofibers developed. The results of their buoyancy studies demonstrated that the diacerein loaded nanofibers exhibited zero lag time with 61.3% of diacerein release in 30 h facilitating the slow release from the nanofiber. They concluded that the electrospun nanofibers may offer gastroretentive property to deliver diacerein in the gastro intestinal tract <sup>6</sup>.

The cationic polysaccharide chitosan is obtained by deacetylation of chitin. Chitosan offer paracellular

permeation enhancement by opening the tight junctions of the intestinal epithelium along with mucoadhesion properties. Chitosan is used as a tablet filler and as a polymer. The mucoadhesion property of chitosan is afforded by linkage of primary amino group with sialic acid and sulphonic acid of mucus<sup>8</sup>.

Su, C et al; 2018 developed complex hydrogels formed with chitosan and ring-opened polyvinyl pyrrolidone as a swellable mucoadhesive gastroretentive drug dosage formulation. Their developed complex hydrogels possessed optimal swelling and mucoadhesive abilities and rheological properties. Results of in vitro dissolution revealed a sustained release with a plasma profile of sustained manner with 3-fold enhancement of the oral bioavailability<sup>9</sup>.

Lais Nohemann et al; 2017 developed gastro retentive metronidazole microparticles using two approaches based on the solubility of the polymer via an aqueous dispersion based formulations using a hydrophilic polymer hydroxyl propyl methyl cellulose and emulsion based formulations in case of ethyl cellulose by incorporating chitosan in both the formulations. They observed that all microparticles floated immediately in contact of simulated gastric fluid. Finally they observed that chitosan and hydroxypropyl methylcellulose based microparticles revealed the best relationship between floating duration and drug release, towards the ideal condition for the floating gastroretentive systems<sup>10</sup>.

The mucoadhesive sodium alginate is biocompatible, non-toxic, and biodegradable. Alginates offer better mucoadhesive property. The gelation property of alginate with divalent metal ions such as Ca<sup>2+</sup>; concept has been applied in many formulation development approaches.

Shadab Md et al; 2019 developed spherical acyclovir loaded mucoadhesive alginate microspheres using a simple emulsification phase separation technique with the maximum particles of an average size ( $70.60 \pm 2.44 \mu\text{m}$ ) in order to prolong the gastric residence they observed a better release profile of in simulated gastric fluid (SGF pH 1.2). They observed that the mean particle size of the microspheres gets increased upon polymeric concentration gradient and decreased with increase in stirring speed with an entrapment of 51.42–80.46%. Calcium chloride (10 % w/v) present in the formulation supports the extended release of acyclovir. They observed that the optimized acyclovir loaded mucoadhesive alginate microspheres showed good mucoadhesion ( $66.42 \pm 1.01\%$ ). Their results of Gamma scintigraphy analysis revealed the gastroretention effect of optimized formulation for more than 4 h, suitable for gastroretentive systems<sup>11</sup>.

Hydroxypropyl  $\beta$ -cyclodextrin is used as a polymer for various pharmaceutical formulations. Hydroxypropyl  $\beta$ -cyclodextrin has shown to improve the solubility of lipophilic drugs by forming a complex between Hydroxypropyl  $\beta$ -cyclodextrin and the drug of choice

utilized for the pharmaceutical formulations. The formation of guest-host type complex may enhances the solubility of lipophilic drugs in case of Hydroxypropyl  $\beta$ -cyclodextrin.

Sharad S.Darandale et al 2012 developed Furosemide loaded gastroretentive formulation by polymeric film made up of a bilayer of immediate/controlled release layers folded into a hard gelatin capsule here in furosemide shown narrow absorption window using hydroxypropyl  $\beta$ -cyclodextrin. Here in the gastroretention mechanism works based on the unfolding and swelling of the film and its bioadhesion to the gastric mucosa. Carbopol® 971P NF used in the bilayer film formulation supports optimum drug release, bioadhesion and mechanical properties. Their developed film with zig-zag folding in the capsule swell under acidic conditions with immediate release profile for 1 h followed by controlled release characteristics for up to 12 h in acidic medium. They concluded that gastroretentive dosage form may provide controlled release with narrow therapeutic windows<sup>12</sup>.

The film coated Eudragit based polymers which are being whitish and faint characteristic odor are resistant to gastric media but soluble in intestinal fluids above pH 6 and shows miscibility in acetone-alcohols, dichloromethane, ethyl acetate and sodium hydroxide. Eudragit polymers shown effective and stable enteric coatings with a fast dissolution in the upper bowel. Eudragit polymers of different grades shown variable release profiles and site specific drug delivery<sup>13</sup>.

Sivakumar M et al 2002 developed spherical shaped and porous nature gentamycin loaded poly(methyl methacrylate) microspheres for hard tissue repair and regeneration by solvent evaporation technique. They confirmed the presence of characteristic groups and compatible nature of the formulations using <sup>1</sup>H-FT-NMR spectroscopy. Their observations of equilibrium swelling studies of microspheres carried out in pH 7.4 phosphate buffer and pH 1.2 gastric medium shown that the developed microspheres were able to float in the pH 1.2 and 7.4 media and gets settled also further they observed a longer period of release. They emphasized that the carboxylic groups of PMMA-F microspheres were coupled with amino groups of gentamicin using 1-ethyl-3-(3-dimethylpropyl) carbodiimide as coupling agent<sup>14</sup>.

The biocompatible and biodegradable aliphatic polyester synthetic polymer Poly (e-caprolactone) is approved by Food and Drug Administration. The hydrophobic crystalline polymer Poly (e-caprolactone) is widely used in drug delivery systems, sutures, devices, wound dressings and act as an adhesion barrier. The melting point of Poly (e-caprolactone) melting point is 59–64 °C<sup>15-21</sup>.

Umar Farooq et al; 2017 developed Eudragit E 100 and polycaprolactone based floating, metronidazole benzoate microspheres using Polyvinyl alcohol as an emulsifier prepared by oil in water solvent evaporation method in order to improve the enhanced gastric



retention. *Their results of in vitro* drug release studies revealed that metronidazole benzoate microspheres were able to release the drug up to 12 h in the simulated gastric fluid. *The developed* microspheres were hollow and has the capacity to float above the surface of simulated gastric fluid. The developed metronidazole benzoate microspheres are free flowing as revealed by rheometer analysis. Further they observed that formulations containing higher amount of Eudragit E 100 released metronidazole benzoate in a rather abrupt release manner in the beginning. Whereas the formulation which contains both the PCL/Eudragit E 100 (50:50) was found to be best releasing in both mediums of pH 7.4 and pH 1.2<sup>22</sup>.

Shin S et al; 2019 developed acyclovir loaded gastroretentive (GR) drug delivery systems to prolong gastric residence time and to improve the oral bioavailability with a narrow absorption window in the upper part of the gastrointestinal tract using 3D printing technology. They developed the 3D printer based system using gastro-floating device, which can float in the gastric fluid upon placing the acyclovir sustained release tablet in to the floating device. The *in vitro* dissolution test, *in vivo* pharmacokinetic study, and abdominal X-ray imaging are used to check the buoyancy and sustained-release property of the developed GR system. They observed a sustained-release characteristic of the GR system with 80% dissolution ( $T_{80}$ ) of 2.52 h. They observed that the developed GR system stayed in the stomach for more than 12 h. They monitored the gastric residence of GR system by X-ray images, and proved the prolonged plasma drug concentration profiles with the increased bioavailability by the *in vivo* pharmacokinetic studies. They predicted that the developed gastroretentive system could be applied to various drugs and had great prospects in the design and development of novel controlled-release formulations<sup>23</sup>.

Lee WL et al; 2014 developed fenofibrate and piroxicam loaded spray-coated floating microcapsule system with prolonged gastric residence by enhancing and tuning drug release rates. Incorporating fenofibrate into rubbery poly(caprolactone) (PCL) coating layer resulted in a complete and sustained release for up to 8 h. They developed the system by specific tailoring of coating polymers offering a double-profile (i.e. an immediate burst release as the loading dose, followed by a sustained release as the maintenance dose) based release manner with excellent buoyancy in simulated gastric fluid offering potential as a rate-controlled oral drug delivery system<sup>24</sup>.

Kadivar A et al; 2015 developed floating sustained-release Imatinib mesylate tablets by wet granulation method using Hydroxypropyl Methylcellulose (HPMC K4M), with Sodium alginate (SA) and Carbomer 934P (CP) as release-retarding polymers, sodium bicarbonate ( $\text{NaHCO}_3$ ) as the effervescent agent and lactose as a filler. Further they checked the floating behavior, *in vitro* drug release, and swelling index by comparing with that of commercial tablet (Gleevec) in 0.1 N HCl (pH 1.2) at  $37 \pm 0.5^\circ\text{C}$  for 24 h. They

observed that tablets (composition of 14.67% w/w HPMC K4M, 10.67%, w/w Na alginate, 1.33%, w/w Carbomer 934P and 9.33%, w/w  $\text{NaHCO}_3$ ) elicits 24 h sustained-release behaviour with optimum floating behavior and satisfactory physicochemical characteristics with lower  $C_{\text{max}}$  and higher  $T_{\text{max}}$  compared to the conventional tablet (Gleevec). Thus, formulated SR tablets preserved persistent concentration of plasma up to 24 hours. They conclude that imatinib mesylate floating sustained-release tablets can be a promising candidate for cancer chemotherapy due to its constant favorable release, resulting in optimized absorption and less side effects<sup>25</sup>.

Chen Y C et al; 2015 developed different drugs (metformin, ciprofloxacin, and esomeprazole) loaded gastroretentive drug delivery system (GRDDS) composed of hydroxyethyl cellulose (HEC) and sodium carboxymethyl cellulose (NaCMC) and checked the solubility and floating characteristics. Their findings showed that in deionised water the combination of HEC 250HHX and NaCMC of 450 cps in a ratio of 60:40 exhibited an enhanced swelling index (13.45) with no deterioration of the floating period due to repulsive forces of the negative charge carried by NaCMC, which was substantially better than the combinations of NaCMC of 2500 cps with PEO 8000K. Whereas they observed decreased degree of swelling with enhanced floating duration in case of formulation (HEC 250HHX and NaCMC 450 cps). They concluded that formulation composed of HEC 250HHX and NaCMC of 450 cps exhibits better swelling and desired floating characteristics with sustained-release property<sup>26</sup>.

Satishbabu BK et al; 2010 developed famotidine loaded oral floating drug delivery system based sodium alginate beads to prolong gastric residence time, target stomach mucosa and increase drug bioavailability using cod liver oil by emulsion gelation method using different ratios of sodium alginate, hydrophilic copolymers such as carbopol 934P and hydroxypropylmethylcellulose K15M grade. They checked the *in vitro* famotidine release from beads and observed a sustained release pattern for 8 h in simulated gastric media. They observed that beads formulated using sodium alginate alone could not sustain the drug release up to 8 h. Overall they found that cod liver oil entrapped calcium alginate beads were promising as a carrier for intragastric famotidine based floating drug delivery<sup>27</sup>.

Sathiyaraj S et al; 2011 developed Lornoxicam loaded floating sustained release matrix tablets using hydroxyl propyl methyl cellulose K15M in order to overcome the short half life of 2 to 3 h. Further they evaluated the directly compressed tablets for physical parameters such as weight uniformity, hardness, friability, drug content, *in-vitro* buoyancy with axial and radial enlargement measurement, swelling index. They observed that buoyancy lasted for up to 24 h<sup>28</sup>. The different formulation approaches of gastro retentive drug delivery systems are shown in Table. 1.





**Table 1:** Formulation approaches of gastro retentive drug delivery systems

S No	Drug	Formulation approach	Excipients/Polymer	Methodology	Therapeutic approach	References
1	Diacerein	nanofibers	Poly lactide co glycolide	Electrospinning technique	Exhibits zero lag time with 61.3% release in 30 h	7
2	Metronidazole	Microparticles	Hydroxyl propyl methyl cellulose	Aqueous dispersion	Exhibits floating property	10
3	Acyclovir	Microspheres	Alginate	Simple emulsification phase separation technique	Good mucoadhesion with extended release	11
4	Furosemide	Polymeric film	hydroxypropyl cyclodextrin $\beta$ -	zig-zag folding	Gastroretentive dosage form may provide controlled release with narrow therapeutic windows	12
5	gentamycin	microspheres	poly(methyl methacrylate)	solvent evaporation technique	Exhibits floating prespectives	14
6	Metronidazole benzoate	Microspheres	Polyvinyl alcohol	Oil in water solvent evaporation method	Higher amount of Eudragit E 100 released metronidazole benzoate in a rather a burst release	22
7	Acyclovir	gastro-floating device	-	3D printing technology	Retention in the stomach for more than 12 h	23
8	fenofibrate and piroxicam		poly(caprolactone)	spray-coated	double-profile (immediate burst followed by a sustained pattern)	24
9	Imatinib mesylate	tablets	Hydroxypropyl Methylcellulose, Sodium alginate and Carbomer 934P	wet granulation method	preserved persistent concentration of plasma up to 24 h	25
10	Metformin, Ciprofloxacin, and Esomeprazole		hydroxyethyl cellulose and sodium carboxymethyl cellulose		decreased degree of swelling with enhanced floating duration in case of formulation	26
11	famotidine loaded based	oral floating drug delivery system beads	sodium alginate	Bead technology	sustained release pattern for 8 h in simulated gastric media	27
12	Lornoxicam	sustained release matrix tablets	hydroxyl propyl methyl cellulose K15M	Compression	buoyancy lasted for up to 24 h	28

### Gastroretentive drug delivery systems novel technologies

The novel gastroretentive drug delivery systems reported were non-effervescent systems (single/double layer floating tablets, and microballoons/hollow microspheres) in which highly swellable cellulose derivatives or gel-forming polymers are used for its formulation development. The gas generating agent and volatile liquids are used in case of effervescent floating systems. This combination of effervescent agents (sodium bicarbonate, calcium carbonate, tartaric acid, and citric acid) and hydrophilic polymers are used in case of effervescent floating systems. The buoyancy will be exhibited due to the liberated CO<sub>2</sub> gas which may elicit the drug release properties. In case of high density systems the formulations will be developed by enhancing the density of the gastroretentive drug delivery formulation to be greater than that of gastric fluid using excipients such as barium sulfate, zinc oxide, iron powder,

and titanium dioxide. Expandable based gastroretentive drug delivery systems drug delivery systems works in such a way by increasing the volume or shape of the formulations. This system works on the principle of plug type system. In case of mucoadhesive based gastroretentive drug delivery systems the adherence towards the gastro epithelial cells will be achieved using natural/synthetic based mucoadhesive polymers (carbopol, chitosan, polyethylene glycol, polyethylene glycol, polyacrylic acid, hydroxypropyl ethyl cellulose etc). The Raft-forming systems based gastroretentive drug delivery systems involves sustained release behavior using effervescent excipients and gel forming polymers. The magnetic based gastroretentive drug delivery systems involves internal magnet to control the delivery. The ion-exchange resin based gastroretentive drug delivery systems involves cationic/anionic based water insoluble

cross-linked polymer (resin) that can be designed to release the drug in a controlled manner<sup>28-37</sup>.

### Patents in Gastroretentive drug delivery systems

The patents in Gastroretentive drug delivery systems includes various approaches in which Vishwanath Sudhir Nande patented a technology of novel gastro-retentive drug delivery system comprising inert core, polymers and plasticizer that floats for an extended period of time over the simulated physiological fluids owing to its low density<sup>38</sup>. Hassan Mohammad; 2013 patented a technology based pharmaceutical product for retention in the stomach comprising of a sheet of hydratable polymer which will not pass out of the stomach<sup>39</sup>. It has been reported that gastroretentive floating drug formulation comprising at least one functionalized natural and/or synthetic calcium carbonate-comprising mineral and at least one pharmaceutically active ingredient and at least one formulating aid wherein said functionalized natural or synthetic calcium carbonate is a reaction product of natural or synthetic calcium carbonate with carbon dioxide and one or more acids, wherein the carbon dioxide is formed in situ by the acid treatment and/or is supplied from an external source<sup>40</sup>.

### Future perspectives of gastroretentive drug delivery systems

The future with industrial focused perspectives of gastroretentive drug delivery systems includes development of novel gastroretentive drug delivery formulations by overcoming the drawbacks associated with oral drug delivery. The Pharmacotherapy of disease states, assessment of fed and fasted condition should be considered during development strategies. The scope of scaling up the technology should be also considered to improve marketability of gastroretentive drug delivery formulations.

### CONCLUSION

Gastro retentive drug delivery systems offer benefits to improve the bioavailability of drugs. The added advantage of improved absorption of drugs in the duodenum, stomach upper part and jejunum will be achieved. Hence Scientists were attempting to develop different approaches for gastro retentive drug delivery formulations for various categories of drugs using different polymers/excipients. Hence gastro retentive drug delivery systems may be found to be more efficacious for the delivery of drugs to the systemic circulation.

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