OVERVIEW ON FLOATING GASTRORETENTIVE DRUG DELIVERY SYSTEMS FOR IMPROVING ORAL BIOAVAILABILITY OF DRUGS

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ABSTRECT

In recent decades, extensive research has been conducted to develop a floating gastroretentive drug delivery (FGRDD).Gastroretentive drug delivery systems are a good example; have emerged to increase the bioavailability and efficacy of drugs with a narrow absorption window in the upper gastrointestinal tract and / or to promote local stomach and duodenal activity. drugs that are locally active in the stomach and upper intestine because FGRDD allows the drug to stay in the stomach for a longer period of time. these types of systems have both advantages and disadvantages. Intraindividual and differences in gastric physiology are obstacles to the development of efficient FGRDD. These include gastric pH and gastric motility, which have a significant impact on gastric retention time. Some of these obstacles can be overcome by developing a new floating drug delivery system. In this review, research and development of speed-controlled floating release systems overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET).

Keywords: Floating gastroretentive drug delivery, gastric motility, gastroretentive narrow absorption window, controlled drug release, gastro retentive system, gastric retention time

1.INTRODUCTION

Oral route is the most accepted route for drug delivery due to ease in administration which leads to higher patient compliance and low cost therapy. The major drawback in oral drug delivery is that many drug candidates are ineffectively absorbed and has low bioavailability because of the drugs having narrow absorption window[1]. This results into improper drug release and low bioavailability[2]. Some of the drugs show region-specific absorption in different segments of gastrointestinal tract. This kind of region-specific absorption is directly related to the solubility and stability of the drug in the various sections of intestine which generally occurs due to the change in pH environment, enzymatic degradation or interaction with the bile component. The gastro-retentive dosage forms (Bio-adhesive systems) provides an intimate contact of the drug delivery system with absorbing gastric mucosal membrane which contributes to enhanced and better therapeutic performance of the drug[3].

The basis of controlled release drug delivery system is the bio pharmaceutics, pharmacokinetics, and pharmacodynamics in away that the drug effectiveness is maximized via reduction in adverse effects, heal disease condition in the shortest viable time by the aid of consuming smallest drug amount and administered through most appropriate route. The oral controlled drug delivery system mainly are solids, few of them are liquids, or in suspension form. The oral control drug delivery system are classified on the basis of elements of g.i.t and conceptual approach of design is as follow[4].

Gastro retentive drug delivery systems can localize drug in gastric area for several hours and hence increase the gastric residence time of drug[5]. Increase in residence time of drug in stomach increases bioavailability, decreases wastage of drug, and enhances the solubility of drug that are less soluble in gastric environment[6]. It provides local drug delivery to gastric and colon parts[7].

2.1 Floating drug delivery system They remain buoyant in gastric content due to less bulk density than gastric fluid. Drug releases in a controlled manner from the dosage form which is floating on gastric contents[8]. The remaining part of doses form gets excreted from the stomach as the drug got released from dosage form[9].

2.1.1 Advantages of floating drug delivery system

Increase in bioavailability and curative efficiency of drugs. Minimized factor of risk in resistance in antibiotics owing to stabilized the rapeutic 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. As they sustain drug release and hence, provide local therapy in these organs. This method provides wit a systematic and controlled drug delivery system which minimizes chances of drug over exposure at the diseased site. Providing a narrow curative index, the gastroretentive dosage forms minimizes variance in concentrations of drugs and effects. This system provides higher efficiency due to reduced counter activity by body .As the system provides with controlled rates of fluctuation, a wider array is provided for selectivity in receptor activation[10].

2.1.2 Disadvantages of Floating drug delivery system

Need for increased level of fluids in the stomach. Unsuitable for such drugs as: Problematic with solubility in gastric fluid, Causing gastrointestinal 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., Upon multiple administrations, size increasing drug delivery systems pose the threat to life owing to possible hazard of permanent retention in stomach[11].

Table1. Drug candidates suitable for GRDDS

S No.	Drug candidate	Example
1.	Locally active drugs in stomach	Anti-ulcer drugs, Clarithromycin
2.	Drugs with less absorption in g.i.t	Cyclosporine, Methotrexate, Furosemide
3.	that are unstable in colon and intestine	Captopril, Ranitidine HCl
4.	Drugs causing variance of colonic microbes	Antibiotics against H.Pylori
5.	Drugs that are less soluble at high pH	Diazepam, Chlordiazepam

Table2. Drug candidates unsuitable for GRDDS

S No.	Drug candidate	Example
1.	Drugs that are less soluble in acidic pH	Phenytoin
2.	Drugs that are unstable at gastric pH	Erythromycin
3.	Drugs that are required to be released in colon	5-aminouracil

2.1.3 Gastrointestinal motility

Both the fasting and fed states cause gastric emptying. However, the two states are varied upon pattern of motility. In this phenomenon, series of electric events takes place in cycles via stomach and intestine every 2 to 3 hours[12]. There occurs a phenomenon of interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is divided in 4 phases as given by Wilson and Washington[11].

Features of different phases of gastrointestinal motility

Phase 1	**Phase 2**	**Phase 3**	**Phase 4**
30-60 min 2	0-40 min	10-20 min	0-5 min
Basal phase	Pre Burst phase	Burst phase	Transition period between phase 3 and 1
Rare contraction	Intermittent contraction	Intense and regular contractions	No contraction

Upon food being ingested, the stomach motions vary fasted to fed state. It is termed as digestive motility pattern and constitutes regular peristalsis as in phase II of the state of fast. This incredibly reduces food size (to less than 1mm), propelling food towards pylorus. The gastric emptying rate is delayed during fed state[12-13].

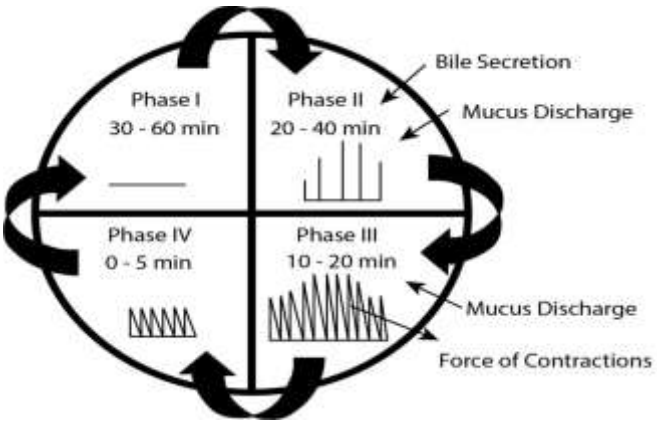
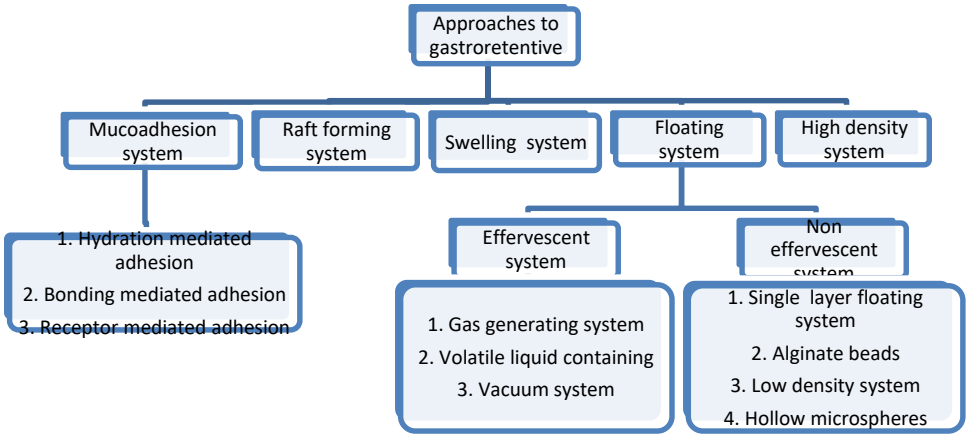


Fig.1 Motility pattern of gastrointestinal tract in the fasted state

2.1.4 Design Approaches for GRDDS

Various methods that are employed for increasing dosage form retention in gastric regionare[3]



3. STOMACH

3.1 Anatomy and physiology of stomach

The stomach is a muscular organ present at uppermost part of abdomen. It extends from the mouth to anus. Digestive system consists of stomach that connects: Esophagus – It is a tube shaped organ that is present between mouth and stomach.

- **Esophagus¬** connects the stomach at the gastro esophageal (GE) junction.
- **Small intestine –** It is a tube shaped organ that connects stomach to colon, an organ of tube¬ shaped that begins from the stomach to the colon. Stomach is connected to small intestine through duodenum.

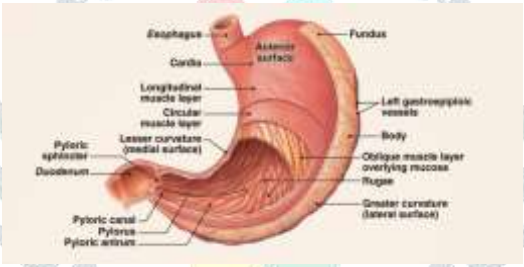


Fig.2 Gastrointestinal tract

3.2 Parts of the stomach

The stomach is classified into 5 parts:

- **Cardia:** The first region of the stomach is cardia. It consists of cardiac sphincter, which prevents back flow of stomach contents from stomach to esophagus
- **Fundus:** It is the round shaped region that is present below the diaphragm in the left of the cardia.
- **Body:** The body is the most important and largest part of the stomach. The mixing and break down of food takes place here.
- **Antrum:** It is the lowermost part of the stomach. Unbroken food is stored here before it is¬ released into small intestine. It is also known as pyloric antrum.
- **Pylorus:** Stomach is connected to small intestine through pylorus. Pyloric sphincter is a¬ valve that controls the unloading of chyme into the small intestine. The pyloric sphincter prevents the backflow of content of duodenum into the stomach[14].

3.3 Layers of the stomach wall

The stomach consists of four layers:

Mucosa: The mucosa is the innermost layer of the stomach that consists of ridges (rugae).¬ When there is no food in the stomach, mucosa appears ridged, mucosal ridges becomes flattened as the stomach is occupied with food.

Submucosa: It is the second layer that covers stomach. It is made up of connective tissue that consists of blood, lymph vessels, nerve cells, and fibres.

Muscularis propria: The muscularis propria coats the submucosa. It is the main muscle of¬ the stomach and is consisted of three layers of muscle.

Serosa: It is the outermost layer made up of fibre that coats stomach. It is also known as¬ visceral peritoneum

3.4 Functions of stomach

The stomach has three main functions:

1. It stores food for about 2 hours or longer before passing it into small intestine

2. By contraction and relaxation of muscles present in the layer of stomach, break down, and mixing of food occurs.

3. Food digestion.

The gastric mucosa contains five different types of cells

1. **Mucoid cells-** Gastric mucus is secreted from mucoid cells. They are mainly found in cardiac¬ and pyloric region of stomach. Mucoid cells are present in the neck of glands in body and fundus region
2. **Zymogenic or chief cells-** They are present majorly in the body and fundic region of stomach. They produce pepsinogen, which is the inactivated form of pepsin (an enzyme which is proteolytic in action). There are two types of pepsinogen, pepsinogen I and pepsinogen II. Mucus and zymogenic glands present in stomach produce pepsinogen I while some specific mucus gland in stomach produces pepsinogen II. Those stimuli that potentiate gastric acid secretion also potentiate pepsin release.
3. **Gastrin cells-** Antrum consists of G cells. As the food reaches the gastric region, the acidity¬ of gastric content reduces. At this moment, G- cells secrets gastrin. Gastrin is transported to the blood from where it reaches to the stomach mucosal layer, where it joins to receptor present on the outermost membrane of the parietal cells. The gastrin-receptor complex consumes an energy molecule using ATPase and potentiates production of hydronium ion in parietal cell.
4. **Parietal or oxyntic cells-** They are located in body and fundic area of the stomach. They secrete H + ions that join chloride ion to form hydrochloric acid (HCl). The acid that is produced drains into the lumen of the gland and then transported to the stomach. This process occurs only when one or more types of receptors on the outer membrane of the parietal cell are bound to histamine, gastrin, or acetylcholine. Prostaglandins, is a hormone that reduces the production of hydrochloric acid. The drug omeprazole also suppresses acid secretion by the parietal cells and is used to treat peptic ulcer. Parietal cells produce most of the water found in gastric juice, they also produce intrinsic factor, which are necessary for the maturation of red blood cells, vitamin B12 absorption, and in the growth of specific cells in the central and peripheral nervous systems.
5. **Endocrine cells-** They are also known as enterochromaffin cells. They are present in the body region of stomach. Several substances including hormone serotonin are secreted by enterochromaffin cells[15].

3.5 Hormonal control of Gastric acid secretion

Several hormones control function of stomach by regulating secretion of stomach acid and release of food in duodenum.

- **Gastrin** is secreted by G cells of stomach. It enhances gastric acid production, contraction of muscles and emptying of gastric content through pyloric sphincter.
- **Cholecystokinin** (CCK) is produced by duodenum mucosa. It slows down the gastric emptying by causing contraction of pyloric sphincter. It is produced when fat and protein rich food is present. By delaying the gastric emptying, it provides longer time to digest food. It also provides time to gall bladder and pancreas to release their bile and enzymes in the duodenum.
- **Secretin** Is a hormone secreted by mucosal layer of duodenum, in response to the activity when chyme enters duodenum from stomach. Secretin reaches stomach through blood and reduces the production of gastric juice from the glands present on the mucosa of stomach. Secretin enhances the secretion of pancreatic enzyme and bile juice that contains bicarbonate ions which neutralizes acid. Secretin protects intestinal layer from harmful effect of acidic chyme.
- **Stomach acid secretion**
  Gastric acid is secreted by parietal cells present within oxyntic glands of stomach. Gastric acid will reduce the pH of gastric chyme to allow conversion of pepsinogen to active pepsin. Stomach consists of mucosal layer which provide sufficient protection from harmful effect of gastric acid[6, 16].

3.6 Mechanism of Gastric Acid Secretion

Gastric acid is derived from carbonic acid that is produced by reaction of carbon dioxide and water. The hydrogen ion of carbonic acid is transported into the stomach by carbonic ion and then it is transported into the blood stream. The bicarbonate ion is later transported to duodenum where it neutralizes gastric acid.

3.7 Molecular mechanism

Carbon dioxide is converted into carbonic acid by carbonic anhydrase within parietal cell which immediately splits into H + and HCO3 - ions. Using an ATPase the H+ ion is transported to oxyntic cells. An exchange of bicarbonate ion and chloride ion occurs, where bicarbonate ion is transported to the blood.

Regulation of gastric acid secretion

Three stimuli that directly affect gastric acid secretion by parietal cell are

- **Acetylcholine-** Vagus nerve consists of parasympathetic fibres which secret acetylcholine.
- **Histamine-** Enterochromaffin cells are present in the oxyntic glands that secret histamine.
- **Gastrin-** Pyloric glands of stomach consist of G cells that produce gastrin.

4. Coordination of gastric acid secretion

The vagus nerve harmonizes these three stimuli. Vagus nerves acts on G cells and stimulate release of gastrin. The Vagus nerve also acts on enterochromaffin cells and induces secretion of histamine.

4.1 Potentiation of gastric acid secretion

These chemical stimuli act on the parietal cells and shows synergistic effects on gastric acid secretion. Therefore, in presence of these stimuli, secretion of gastric acid is potentiated, while inhibition of anyone of them will decrease the secretion of gastric acid.

4.2 Phases of secretion of gastric acid

Secretion of gastric acid occurs in accordance to different levels of food ingestion. Secretion of gastric acid occurs at each phase with different regulatory mechanism.

- **Cephalic phase:** The sensory experience of seeing and eating food commences this phase and causes 20% of total gastric acid secretion. Activation of vagus nerve causes production of gastric acid in this phase.
- **Gastric phase:** This phase begins when food enters into the stomach. Seventy percent of total gastric acid secrets in this phase. During this phase, distension of stomach muscles enhances vagus nerve stimulation. Food metabolite of proteins directly acts on G cells and induces secretion of gastrin.
- **Intestinal phase**: This phase begins when food enters into the duodenum. Ten percent of total gastric acid secretion occurs. Regulation of this phase is not clear but may be secretion of gastric acid in this phase is induced by gastrin.

4.3 Inhibition of secretion of gastric acid

If Over secretion of gastric acid is prevented by several stimuli. Gastric acid can be harmful to stomach as well as duodenum. Inhibitory stimuli are located in duodenum and reduces the secretion of gastric acid. Inhibitory mechanism caused by neural and hormonal factors which are induced by nutrients and acid based irritation of duodenum mucosal wall. Important hormones that inhibit gastric acid secretion are somatostatin and gastric inhibitory peptide.

4.4 Acid reflux or gastroesophageal reflux

Acid reflux or gastroesophageal reflux occurs periodically in a healthy person and has no long lasting effect. Acid reflux occurs when some of the acid content of the stomach flows up into the esophagus. The alimentary tract has various solutions to deal with small amounts of gastric acid that infrequently invades the esophagus. Complex sign and symptoms may occur due to mucosal damage in case of persistence acid reflux. Gastroesophageal reflux is known as chronic form of acid reflux. Acute acid reflux does not require any major treatment. Gastroesophageal reflux and reflux both refers to rising of gastric content into the esophagus. Gastroesophageal reflux is recurrent reflux that causes complex symptoms like esophageal ulcers and reflux-induced adenocarcinoma[17].

4.5 Causes of acid reflux

Acute acid reflux may occur due to

- Rise in volume of gastric contents
- Delayed voiding of stomach
- Decreased tonicity of lower esophageal sphincter

These conditions may appear as a result of

- Consuming alcohol
- Overeating
- Consumption of carbonated drinks
- Doing Exercise after taking meal

Signs and symptoms of acid reflux

Sometimes signs of acid reflux are passed off as indigestion. At other times, acute reflux emerges with following mild or severe symptoms.

- Heartburn
- Regurgitation
- Water brash
- Coughing and throat irritation
- Nausea
- Excessive belching
- Stomach bloating

5. Gastroretentive drug delivery systems:-

Gastroretentive drug delivery systems are able to localize the drug in stomach and proximal small intestines for few hours and hence the gastric residence time of drug is increased. This increase in drug residence time in stomach rises bioavailability, reduces wastage of drug, and enhances the solubility of drug that are less soluble in gastric environment. It provides local drug delivery to gastric and colon parts[18,19]. The duration of time is significant over which the drugs may be released. They not only prolong the dosing intervals, but also increases the patient complian cebeyond the level of existing controlled release dosage forms. Conventional oral controlled dosage forms mainly suffer from two adversities- the short gastric retention time and unpredictable gastric emptying time[20].

5.1 Classification of floating drug delivery system

On the basis of buoyancy mechanism, FDDS are classified as following

- Effervescent system
- Non- effervescent system

5.1.1 Effervescent system-

They are also known as gas generating systems. Gas generation helps to achieve floatability. The swellable polymers like methylcellulose, HPMC, and various effervescent compounds like sodium bicarbonate and citric acid helps in formation of matrix type systems. These systems release carbon dioxide on contact with gastric contents which gets entrapped in swollen hydrocolloids, that makes dosage form buoyant. Effervescent systems are further classified as[4]

- Intragastric floating gastrointestinal drug system
- Inflatble gastrointestinal delivery syatems
- Intragastric osmotically controlled drug delivery system
- Floating capsules, pills

5.1.2 Non-effervescent system

The non-effervescent floating dosage forms have swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers like polycarbonate and polyacrylate. Its creation has simplistic approach, i.e, mixing of drug with gel, followed by swelling on coming in contact with gastric fluid after oral administration and thus maintaining a relatively high integrity of shape and keeping a bulk density less than one. The dosage form gains its buoyancy owing to air trapped in the swelled matrix. This swelled up matrix reserves drug and maintains sustain release via gelatinous mass. The HPMC, polyacrylate and carbopol are the most commonly used excipients[13b].

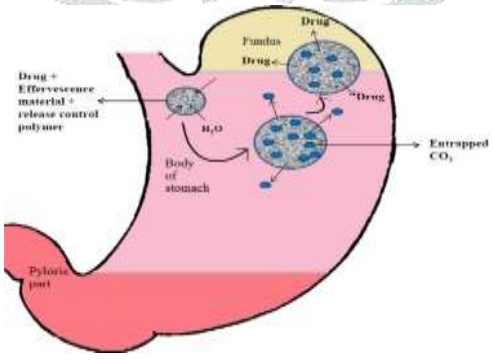


Fig.3 Gastrointestinal Floating drug Delivery

5.2 Matrix tablets

It can be formulated in a single layer matrix tablet by incorporated bicarbonates in the matrix forming hydrocolloid gel agent or in a dual layer matrix along with a gas generating matrix together as an individual layer.

5.3 Gas generating systems-

The dosage form attains floatability due to the gas generation. Carbon dioxide can be generated by incorporating carbonates or bicarbonates which on reaction with gastric acid, releases carbon dioxide. This concept has been used for single and multiple unit systems. In single unit system, effervescent substances are mixed with hydrophilic polymer[8]. In multiple unit systems, gas generating system can be incorporated into any layer. Matrix is coated with a polymer which is permeable to water but impermeable to carbon dioxide[21].

5.4 Non-floating systems

These systems do not float in the gastric fluid but remains in the stomach for a long time period. These are further classified into[22].

a. Expandable systems
Expandable systems acquires three sizes. First is the small size to offer good patient compliance by easy oral intake. Second is expanded form where it gets swelled and forms a large size to get blocked by the pylorus and retains inside the stomach. Third is small size, as the drug gets released and no longer retention of dosage form is required, it acquires small size to get evacuated easily.

b. Super porous hydro gels
Super porous hydro gels consist of a pore that takes up water rapidly through capillary phenomenon and swells to acquire an equilibrium size. They swell to such a large size that they can bear stomach muscle contraction. Hydrophilic particulate materials are used to achieve desirable size. Swollen mass gets blocked by pyloric and remains inside stomach for long time.

c. Muco adhesive or bio adhesive system
The concept behind this system is that dosage form can stick to the mucosal membrane by various mechanisms. Various materials show bioadhesion like poly (acrylic acid), chitosan, cholestyramine, tragacanth, sodium alginate, HPMC, etc. These polymers show the bioadhesion property but it is difficult to maintain the adhesion due to the variance of mucus in GIT.

d. Magnetic systems
These systems consist of small internal magnet inside the dosage form while another magnet is placed over the abdomen at stomach position. In-vivo studies have shown that concentration of acyclovir is remarkably higher in presence of magnet. Although, precision is required in placing magnet over abdomen[23].

e. High density systems

These systems are denser than gastric fluids therefore gets settled to the bottom of stomach and entraps themselves in the folds of antrum. Their density should lie around 2.5g/cm3 to increase the residence time of the system in the stomach region. Barium sulphate and titanium oxide are used as excipients.

f. Raft forming systems

A gel (sodium alginate solution) forming solution in which gas generating system (bicarbonates and carbonates) is incorporated. As the system comes in contact with gastric fluid, a viscous cohesive gel and carbon dioxide bubbles are formed. Aluminium hydroxide and calcium carbonate are also used in this kind of formulation. They forms a layer above gastric content therefore can be used in GERD treatment[24].

6. CONCLUSION

Gastroretentive dosage forms are present in the upper gastrointestinal tract for a prolonged period of time and the continuous and prolonged release of the drug in the stomach and upper small intestine. They are useful for targeting drugs with a narrow window of absorption or when drugs have a local effect in these organs. Systems development requires a deep understanding of the anatomy and physiology of the digestive system, and formulating systems that allow fasting to remain in the stomach for an extended period of time is still a challenge. In this field, floating systems seem to be the ones with the best prospects and more and more studies are combining them with other gastroretentive strategies to overcome their limits and allow an even longer gastric residence time. Gastroretentive forms of administration are promising drug delivery strategies with positive results in human studies for drug administration that exhibit a narrow upper gastrointestinal absorption window and a short half-life. Conflict of Interest The authors confirm that the contents of this review did not generate any conflicts of interest.

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