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Floating with Bioadhesion: A Unique Expansion in Gastroretentive Drug Delivery System

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ABSTRACT

Gastro retentive drug delivery system is benefited system in which dosage form retained in stomach prolong period of time and drug release long period of time. Floating system means that float over the surface of the gastric contents when the stomach is full but at the time stomach is empties and the tablet reaches the pylorus the buoyancy of the dosage may be decrease & bioadhesive system becomes dislodged from the stomach wall when the system is full but a floating -bioadhesive system would overcome these drawback of floating and bioadhesive system and improving the therapeutic effect of the drug involved. So this Floating-bioadhesive dosage forms exhibit a unique combination of floatation and adhesion for prolonged residence in the Stomach. Currently this floating bioadhesive approach is not only used for tablets but also for microsphere, beads & other dosage forms. This review article focus on recently used combination approaches to deliver drug by gastrointestinal drug delivery like Bioadhesive and floating.

Keywords: Oral drug delivery, floating with bioadhesive, Gastric residence time, Polymers etc.

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INTRODUCTION

Oral delivery of the drug is most preferred which have the ease of administration, flexibility in formulation, and patient fulfillment. Conventional oral dosage form delivery achieves as well as maintained the therapeutic concentration range needed for effective treatment when dosage form taken several time in a day. In recent trend scientific and patient literature interest in novel dosage forms which retain in stomach prolong and predictable period of time exist today in academic and Industrial group. Most reliable approaches for dosage form retain in stomach prolong period of drug profile and control the Gastric residence time in the stomach.¹

Gastroretentive drug delivery system approaches which increase the bioavailability of drug and increase the Gastric retention time in stomach the model drug release in control and sustain manners the various approaches are available in the GRDDS like Mucoadhesive , Hydrodynamically based system, swelling and Expanding system, High density system etc. GRDDS approaches have a few drawbacks it reduces by the combination of two different approaches. GRDDS approach produce drawback like Floating drug delivery system it dosage form have a tendency in which consist of a gas generating agent to contact with water and produce a gas then float on the surface of the gastric media have sufficient buoyancy to retained in stomach prolong period of time and release the drug in sustain manners to prevent the fluctuation of drug in plasma on the basis which float requirement of retains in stomach based upon the dosage form float it require a sufficient volume of gastric contain in stomach may be possible a peristalsis movement and may be a empty stomach that condition not suitable for the floating system at the time the dosage form buoyancy is reduce and which passage the gastric pylorus. in case of the bioadhesive in which use the natural and synthetic bioadhesive polymers they swell and adhere to the mucus membrane it retain in stomach prolong period of time and drug release in sustain manners prevent the dosage form passage through the pylorus. If the stomach is full after the meal bioadhesive dosage form not properly adheres may be passage the pylorus. If used a combination of both approaches to avoid above drawback name as a Floating with bioadhesion at the time available the full gastric media in stomach will be dosage form float over the surface when stomach is empty at the time dosage form is adhere to the stomach mucosa prevent the passage of the stomach and dosage form is retained in stomach prolong period of time get the drug release in sustained manners.²

Selection of drug candidates for GRDDS:

- 1) Drugs should be a narrow therapeutic window in stomach.

- 2) Drugs should be a greater solubility in Gastric environment.
- 3) Drugs should be act locally in stomach.
- 4) Drugs should be poor soluble in alkaline pH.
- 5) Drugs should be degraded in intestine and colon.
- 6) Drugs should be a used in a Peptic Ulcer and Acidity.^{3,4}

Drug unstable for GRDDS:

- 1) Drugs have the Limited acid solubility like Phenytoin.
- 2) Drugs have the suffer instability in Gastric environment.⁵

Advantages of GRDDS:

- 1) GRDDS maintain the therapeutic concentration in blood plasma dosage form retained prolong period of time.
- 2) Improvement of Bioavailability and therapeutic efficacy of drug by using this delivery system.
- 3) In GRDDS increase the residence time in stomach and reduce the dosing frequency.
- 4) The development of oral sustained and controlled release system.
- 5) The drugs have the short half life and quickly remove from the Systemic circulation.
- 6) GRDDS dosage form have the primarily site specific drug delivery stay in the stomach prolong period of time release the drug.
- 7) Increase the solubility of drugs which have the less soluble at high pH environment like Domperidone.
- 8) GRDDS provide the SR and CR site specific devices.
- 9) Targeted therapy is possible with this drug delivery system.⁵

Disadvantages of GRDDS:

- 1) GRDDS not suitable for the drugs cause gastric lesion like NSAID.
- 2) Not suitable for those which unstable in strong acidic environment.
- 3) Those drugs have a limited acid solubility like Erythromycin.
- 4) That drugs absorbed in Colon like Corticosteroids.
- 5) In floating system it required full stomach contents.
- 6) In bioadhesive system not suitable for the available in full gastric contents.
- 7) Some drugs use in the floating system it produce a gastric mucosa irritation.
- 8) The drugs under go First pass metabolism it not suitable for GRDDS.⁶

Physiology of stomach:

Anatomically stomach divided in a three parts regions best to food handling and gastric emptying time.

- 1) Fundus: it is upper and superior parts of stomach.
- 2) Body : it is larger portion of the stomach.
- 3) Pylorus: the proximal part of stomach is made up the fundus and carpus act as a reservoir for undigested food material, Antrum is the main part for mixing motions and act as a pump.

Gastric emptying time occurs during the fasting as well as fed states but the pattern of motility is distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This called as the interdigestive myoelectric cycle or MMC (migrating myoelectric cycle), which divided in to a 4 phases.⁷

Phase I : it is a basal phase this period lasts about 30 to 60 minutes with no contractions.⁶

Phase II: it called as a preburst phase it lasts about the 20 to 40 minutes. The period consist of intermittent contractions that increase gradually in intensity as the phase progresses, gastric discharge of fluid and very small particles begins later in the phase.

Phase III: known as the Burst phase it is a short period of intense distal and proximal gastric contraction lasting about 10 to 20 minutes these contraction also known as the “House-keeper wave” sweep gastric contents down the small intestine.

Phase VI: this is a short transitory period of about 0 to 5 minutes and the contractions dissipate between the last part of phase III and quiescence of phase I.

Factors affecting the Gastro retentive Drug Delivery System

- 1) Density: Gastric retention time is the is a function of floating dosage form to float on the surface of the gastric media.
- 2) Size: in most cases larger the size of dosage forms gain a greater residence time because large size not passage through the Pylorus to intestine.
- 3) Shape : Tetrahedron shape exhibit the nearly 100% retain in stomach up to 24 hrs and Ring shape also better GRT as compared others size.
- 4) Food volume: The presences of food in stomach increase the GRT of the dosage form and it stay in stomach a longer time also increase the drug absorption.

- 5) Nature of food : indigestible polymers and fatty acids salts can change the motility pattern of the stomach to the fed state, thus decreasing the gastric emptying time and prolong period of drug release.
- 6) Caloric contents: the presence of high protein and fats GRT can be increase the four nto ten hours.
- 7) Drugs administrate: some time the presence of drugs which affect on the floating time like propantheline, atropine, opiates, prokinetics agents like metoclopramide and cisapride.
- 8) Biological factors: Cohn's and Diabetes disease.
- 9) Age: GRT longer in patient age over 70 elderly.
- 10) Posture: Varies between spine and upright ambulatory states.
- 11) Sex: Female has slower gastric emptying rate. It found that gastric emptying in womenis slower than men regardless body weight, height, surface area.⁹

Approaches of Gastro retentive Drug Delivery System:

1) High density system:

Generally stomach contents have density 1 gm/ml. These dosage forms have density more than gastric contents (3gm/cm^3), thus retain in stomach. Various materials used for manufacturing of such high density formulation are barium sulphate, zinc oxide, titanium dioxide, iron powder etc.

2) Swelling and expanding system:

In this system dosage form is retained by increasing its size. It should have the longer size than gastric pylorus and preventing transit from the stomach.

3) Bioadhesive system:

In this system utilize the various bioadhesive polymers with molecular flexibility, hydrophilic functional groups, and specific molecular weight they should have the non toxic, non absorbable and chemically inserts substance. In which the dosage form bind to the gastric epithelial cell surface means adhere to the gastric mucosa and increase the GRT and drug release in sustained manners Polymers like polybrene, polylysine, dextran sodium.

4) Floating drug delivery system:

Floating dosage forms have the sufficient buoyancy to float over the gastric contents for a longer time. The excipients and polymers used for preparation of FDDS have the low density this dosage forms use ful for drug acting locally in proximal GI tract and this system is used for drug which is poorly soluble or unstable in intestinal fluids. Floating system can be

effervescent or non effervescent in nature. In effervescent gas generating agent is utilize the example sodium bicarbonate, citric acid, tartaric acid, are used that can form a CO₂ in the presence of gastric fluid. In non effervescent system use high level swellable and gel forming excipients are used system based on the super porous hydro gels porous carriers are the new type of non effervescent floating drug delivery system.⁹

a) **Effervescent system:**

In this system use a gas generating agent such as bicarbonate tartaric acid, citric acid and its matrix system prepared by the use a swellable polymer like methylcellulose, chitosan. Formulated dosage forms contact with a acidic gastric contents CO₂ is liberated and gets entrapped in the swollen hydrocolloids, which provide buoyancy to the dosage forms.

b) **Non effervescent system:**

In this system usually high level about 75% highly swellable and gel forming excipient are used.¹⁰

Recent Combinational Approaches of GRDDS:

- 1) Swellable and floating.
- 2) Bioadhesive and swelling.
- 3) Bioadhesive and high density.
- 4) Floating and bioadhesive.¹¹

Rational of Floating Bioadhesive dosage form design:

Floating dosage form are low density that have a sufficient buoyancy to float over the gastric contents and stay in stomach for a prolong period of time the drug is release the slowly at the desired rate which result increased GRT and reduce the fluctuation in plasma drug concentration. Bioadhesive system is capable to adhere mucous membrane that prevents their passage through the pylorus and the dosage forms are retained in the stomach for a longer period of time. Floating system means that float over the surface of the gastric contents when the stomach is full after a meal but at the time stomach is empties and the tablet reaches the pylorus the buoyancy of the dosage may be decrease the dosage forms is passage through the pylorus. Bioadhesive system it is quite likely that the becomes dislodged from the stomach wall when the system is full and the semi liquid contents are churning around due to the effect of peristalsis. A floating -bioadhesive system would overcome these drawback of floating and bioadhesive system and improving the therapeutic effect of the drug involved.¹²

Advantages of Floating with bioadhesion:

- 1) Increase the desired residence of drug at the site of action mainly in stomach.
- 2) Minimize the side effects.
- 3) Decrease the frequency of drug administration.
- 4) Minimize the cost of treatment.
- 5) To overcome the drawbacks of the single gastro retentive drug delivery system by using the combinational approach of floating with bioadhesive.
- 6) Improvement of patient compliance.¹³

Formulation of floating mucoadhesive drug delivery:

1) Drugs which are suitable for gastroretentive drug delivery can be used for floating with bioadhesion.

2) Polymers:

Carbopol : synonym Acrylic acid polymer, carbomer, carboxy polymethylene, polyacrylic acid, carboxyvinyl polymer, these have the functional category like bioadhesive, emulsifying agent, release modifying agent, tablet binder, viscosity increasing agent. Carbopol polymers used in the controlled release solid dosage form formulations since last four decade. Tablet formulations using carbopol are demonstrated zero order and near zero order release kinetics.¹⁴

Others polymers:

Sodium carboxyl methyl cellulose, Methyl cellulose, Chitosan, Xanthan gum, Pectin, Guar gum, HPMC, thiolated polymers & other various gums etc.

3) Gas generating agents:

Sodium bicarbonate. Citric acid, tartaric acid etc.

Evaluation of Floating with Bioadhesive dosage form

- 1) Pre-compression Parameter:
 - a) Angle of Repose
 - b) Compressibility Index
- 2) Post-Compression Parameters
 - a) Shape of Tablet
 - b) Tablet Dimensions
 - c) Hardness
 - d) Weight Variation Test
 - e) Tablet Density
 - f) Friability Test

- g) Buoyancy Test
- h) Swelling Study
- i) In Vitro drug release studies
- j) If floating beads or microsphere prepared all evaluation parameters of multiparticulate system will be used.^{15,16}

In vitro studies:

a) Buoyancy studies:

The in-vitro was buoyancy determined by floating lag time. The time required for the tablet to rise the surface and float was determined as floating lag time. In this the tablet were placed in 100 ml beaker containing 0.N HCL.

b) Floating time:

Test for buoyancy is usually performed in simulated gastric fluid maintained at 37 0C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.¹⁷

c) Specific gravity/Density:

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

d) Swelling index study:

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particles may be due to saturation of capillary spaces within the particles or hydration of macromolecules. It is an indirect measurement of swelling property of swellable matrix. Here tablet is removed out at 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 = weight of tablet before placing in the beaker.

e) Dissolution test:

Dissolution test of floating with bioadhesive dosage form carried in the paddle or basket using the 0.1N HCL as a dissolution media up to 900 ml in which the paddle is attach to the shaft it rotates in media and dosage form float on the surface of the media after intervals (1hrs) take a liquid sample and study in UV spectrophotometer at particularly wavelength

give a maximum absorbance to determine how much drug release in particularly hour.^{18,19}

In vivo studies:

a) Radiology:

Bioadhesive with floating dosage form API replace by the Barium sulphate it is a radio opaque media and X-ray is widely used for examination of internal body system.

b) Scintigraphy:

Same to X-ray emitting materials are incorporated in to dosage form and then images are taken by scintigraphy. Widely used emitting material is $^{99}\text{C}^{23}$.

c) Gastroscopy:

Gastroscopy is used to inspect usually the effect of prolongation in stomach.

d) Magnetic Marker Monitoring:

Dosage form means a tablet which incorporated by the magnetically marked like a iron powder and images taken by very sensitive bio-magnetic measurement equipment. It method have the less radiation and no hazardous.

e) ^{13}C octanoic acid breath test:

^{13}C Octanoic acid is incorporated in the dosage for detection of tablet which retain in stomach. The important carbon atom which will come in CO_2 is replace by the ^{13}C isotope and $^{13}\text{CO}_2$ observed in the breath can be consider as a gastric retention time of dosage form at the time tablet move in the intestine is no reaction and no CO_2 release.²⁰

Ex-vivo studies:

a) Bioadhesion study:

Wash off method is used for to determine the mucoadhesive properties of bioadhesive dosage form. Pieces of stomach mucosa were mounted on the glass slide connect with suitable support dosage is attach to the stomach mucosa on glass slide support was used as the disintegration apparatus was given as the up and down movement in the 0.1 N HCL at 37C temperature. The time is noted tablet detachment on the surface of the stomach mucosa was noted down.^{21,22}

b) Bioadhesive strength test:

Mucoadhesive strength of the tablet determined by the Physical Balance it consist of the double beam balance in which the detachment of tablet from the stomach mucosa is determined.^{23,24}

CONCLUSION

Now days researchers giving more focus on Gastro retentive drug delivery system because in this system drug retained in stomach prolong period of time and drug release long period of time in site of action those drug use in drug delivery system have a absorption from upper proximal part. Recently floating bioadhesive combination approaches of GRDDS is most preferred because Floating system means that float over the surface of the gastric contents when the stomach is full but at the time stomach is empties and the tablet reaches the pylorus the buoyancy of the dosage may be decrease & bioadhesive system becomes dislodged from the stomach wall when the system is full but a floating -bioadhesive system would overcome these drawback of floating and bioadhesive system and improving the therapeutic effect of the drug involved. Thus floating bioadhesive is unique advantageous expansion in GRDDS.

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