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Current Trends in Gastroretentive Floating-Bioadhesive Drug Delivery System

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ABSTRACT

Gastroretntive drug delivery can be defined as a system which retains drug in the stomach for a sufficient period of time and releasing active moiety in a controlled manner, and finally metabolized in the body. Over the last two decades, numbers of GRDDS have been designed to prolong GRT. Gastroretntive drug delivery gets popularity from a last two decades leading to its potential application to improve oral delivery of some important drugs for which prolonged gastro retention can greatly improve their oral bioavailability. GRDDS not only prolong the dosing intervals but also increase patient compliance beyond the level of existing controlled release dosage from various approaches are available in the GRDDS like Mucoadhesive, floating Hydrodynamically based system, swelling and expanding systems, high-density system etc. These GRDDS approaches have some merits & demerits it can be reduced by the combination of two different Approaches. Floating & bioadhesion are two mostly used approach of GRDDS but demerit of Floating system is, it floats over the surface of the gastric contents when the stomach is full but at the time stomach is emptied and the tablet reaches the pylorus the buoyancy of the dosage may be decreased & disadvantage of bioadhesive system is that it 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. Recently this floating bioadhesive approach is not only used for the single particulate system but also used for multi-particulate system. The objective of this review is to focus on floating bioadhesion drug delivery with its current research work done.

INTRODUCTION

The most principle route of administration for systemic action is oral route. It is probable that at least 90% of all the drugs given by an oral route. There are different drug deliveries to give a drug by an oral route. In conventional oral drug, delivery drug resides for a shorter period time in absorption window, so bioavailability is less. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the various advantages of an oral route of drug administration. This type of drug delivery systems releases the drug with constant or variable release rates.[1,2]

The most popular approach of oral controlled drug delivery is gastroretentive dosage form retain in stomach prolong period of drug profile and control the Gastric residence time in the stomach. GRDDS can be defined as a system which retains in the stomach for a sufficient period of time and releasing active moiety in a controlled manner, and finally metabolized in the body.[3] Over the last two decades, numbers of GRDDS have been designed to prolong GRT. The main aim of preparing GRDDS is to minimize the problem associated with existing oral sustained release dosage form and to develop patient benefited drug delivery[4].

Gastroretentive drug delivery is prepared with the intention to retain drug in the gastric region for a prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the GIT thus leading its optimal bioavailability. Gastroretentive dosage forms greatly improved the pharmacotherapy of the GIT through local drug release, leading to high drug concentrations at the gastric mucosa making it possible to treat various diseases of the GI. Gastroretntive drug delivery gets popularity from last two decades leading to its potential application to improve oral delivery of some important drugs for which prolonged gastro retention can greatly improve their oral bioavailability. GRDDS not only prolong the dosing intervals but also increase patient compliance beyond the level of existing controlled release dosage form.[5]

MODEL DRUG SELECTION CRITERIA FOR GRDDS

1. Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole
2. Drugs those are locally active in the stomach (e.g. misoprostol, antacids)
3. Drugs that have narrow absorption window in GIT (furosemide, riboflavin).

4. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate

5. Drugs absorbed from stomach and upper part of GI-Tract, e.g., calcium supplements, chlordiazepoxide and cinnarizine.[5]

DRUG UNSTABLE FOR GRDDS:

1) Drugs have the suffer instability in Gastric environment

2).Drugs have the Limited acid solubility like Phenytoin.[5]

MERITS OF GRDDS:

1) GRDDS increases Bioavailability drugs
2) This site-specific drug delivery reduces undesirable effects.
3) Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects.
4) In GRDDS increase the residence time in the stomach and reduce the dosing frequency.
5) The drugs have the short half-life and quickly remove from the systemic circulation.
6) GRDDS dosage form has 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) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time as well as the gastric emptying time[6]

DIFFERENT GRDDS DOSAGE FORM

1. Floating microspheres Atorvastatin, Losartan, Rosiglitazone, cefpodoxime, cefuroxime axetil, Nateglinide
2. Floating granule ibuprofen, Lacidipine, Famotidine Ranitidine, simvastatin, metoprolol, atorvastatin
3. Films Cinnarizine
4. Floating capsules theophylline celecoxib, pioglitazone, diazepam, furosemide, misoprostol
5. Floating tablets Cefuroxime axetil, Metformin, Losartan, propranalol, ofloxacin, glipizide, Rosuvastatin

6. Mucoadhesive system Atenalol, Lafutidine venlafaxine, famotidine, Metformin, Metopropalol[7]

APPROACHES OF GASTRO RETENTIVE DRUG DELIVERY:

1) High density system:

Generally, stomach contents have density 1gm/ml. These dosage forms have density more than gastric contents (3gm/cm3). Thus, retains 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 nontoxic, nonabsorbable and chemically inert 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. It has effervescent & noneffervescent approach. The excipients and polymers used for preparation of FDDS have the low density this dosage forms useful 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 noneffervescent in nature. Effervescent gas generating agent is utilized the example sodium bicarbonate, citric acid, tartaric acid, are used that can form a CO_2 in the presence of gastric fluid. In noneffervescent system use high

level swellable and gel forming excipients, is used system based on the super porous hydrogels porous carriers are the new type of noneffervescent floating drug delivery system.[9]

DEMERITS OF FLOATING DRUG DELIVERY

Floating system is, it floats over the surface of the gastric contents when the stomach is full but at the time stomach is emptied and the tablet reaches the pylorus the buoyancy of the dosage may be decreased.

DEMERITS OF BIOADHESIVE DRUG DELIVERY

This bioadhesive drug delivery is one in which use the natural and synthetic bioadhesive polymers used they swell and adhere to the mucous membrane it retains 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 passaged the pylorus & it becomes dislodged from the stomach wall when the system is full.[8,9,10,11]

CURRENT COMBINATIONAL APPROACHES OF GRDDS:

1) Swellable and floating.
2) Bioadhesive and swelling.
3) Bioadhesive and high density.
4) Floating and bioadhesive.
5) Floating pulsatile[12]

SIGNIFICANCE OF FLOATING BIOADHESIVE DOSAGE FORM (FBDF):

Individual disadvantages of Floating dosage form & bioadhesive can be avoided if used a combination of both approaches 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 manner .[13]

MERITS OF FBDF:

1) It avoids disadvantages of the single gastroretentive drug delivery system by using the combinational approach of floating with bioadhesive.

2) Decrease the frequency of drug administration.

3) Increase the desired residence of drug at the site of action mainly in the stomach.

3) Minimize the side effects.

4) Minimize the cost of treatment.

5) Improvement of patient compliance. [13,]

DEMERITS OF FBDF:

Following of category of drug are unsuitable for FBDF

1) Drugs that cause gastric lesions like NSAID & Aspirin.

2) Drugs that have very limited acid solubility like Phenytoin.

3) Bioadhesion in the acidic environment and high turnover of mucus may raise doubts about the usefulness of Floating with bioadhesion[14]

***IN VITRO IN VIVO* CHARACTERIZATION OF FBDF**

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. [15,16,17]

***In vitro* studies:**

a) Buoyancy studies:

The *in-vitro* was buoyancy determined by floating lag time. The time required for the tablet to raise the surface and float was determined as floating lag time. In this, the tablet was placed in 100ml beaker containing 0.1N HCL.

b) Floating time:

Test for buoyancy is usually performed in simulated gastric fluid maintained at 37^0C. The time in 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 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.

Water uptake = wu = (wt-wo)*100/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 900ml in which the paddle is attached 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 gives a maximum absorbance to determined the how much drug release in particularly hour.[18]

***In vivo* studies:**

a) Radiology:

Bioadhesive with floating dosage form API replaced 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 into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99 C23.

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 an iron powder and images taken by very sensitive biomagnetic measurement equipment. This method has less radiation and no hazardous.

e) 13C octonoic acid breath test:

13C Octanoic acid is incorporated in the dosage for detection of tablet which retains in stomach. The important carbon atom which will come in CO_2 is replaced by the 13C isotope and $13CO_2$ observed in the breath can be considered as a gastric retention time of the dosage form at the time tablet move in the intestine is no reaction and no CO_2 release.

***Ex-vivo* studies:**

a) Bioadhesion study:

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

b) Bioadhesive strength test:

Mucoadhesive strength of the tablet determined by the either modified Physical balance or texture analyser.[20]

Table No.1 Current research work done on floating bioadhesive drug delivery

DRUG	DISEASE TARGETED	FBDF	RESEARCH YEAR	REFERENCES
Metformin	Diabetes mellitus	Tablet	2016	21
Amoxycillin	Infection	Microsphere	2016	22
Ofloxacin	Infection	Microsphere	2016	23
Metoprolol	Hypertension	Beads	2016	24
Rantidine	Acidity	Tablets	2015	25
Cefuroxime Axetil	Infection	Tablets	2015	26
Risperidone	Psychosis	Beads	2015	27
Metformin	Diabetes mellitus	Tablet	2014	28
Residronate	Psychosis	Beads	2014	29

Acyclovir	Viral infection	Beads	2013	30
Alfuzosin	BPH	Tablet	2013	31
Ciprofloxacin	Infection	Tablet	2013	32
Ondensetron	Emesis	Tablet	2013	33
Famotidine	Acidity	Tablet	2013	34
Clarithromycin	Infection	Tablet	2012	35
Ranitidine	Acidity	Tablet	2012	36
Tinidazole,	Infection	Tablet	2012	37
Rosiglitazone	Diabetes mellitus	Tablet	2011	38
Clarithromycin	Infection	Microsphere	2010	39
Glipizide	Diabetes mellitus	Tablet	2010	40
Clarithromycin	Infection	Tablet	2010	41
Sotalol HCl	Hypertension	Tablet	1994	42

CONCLUSION

Gastro retentive drug delivery system plays a vital role in novel drug delivery systems. Day by GRDSS getting popular tool to treat various diseases by increasing residence time of the drug. Researchers are extensively doing research on Gastroretentive drug delivery. Floating & Bioadhesive system are main approaches of GRDDS but Floating system means that float over the surface of the gastric contents when the stomach is full but at the time stomach is emptied and the tablet reaches the pylorus the buoyancy of the dosage may be decreased & 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 currently, research in GRDDS is focused on the approach of combining floatation and bioadhesion properties together in order to improve gastroretention of the dosage form by exploiting floatation and bioadhesion. Recently

this floating bioadhesive approach is not only used for single particulate system but also used for multi-particulate system.

So this Floating-bioadhesive dosage forms exhibit a modern combination of floatation and adhesion for a prolonged residence in the stomach.

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