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GASTRO- RETENTIVE SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

Oral drug delivery is most preferable route of drug administration. This route has high acceptability because of safe and effective delivery of drug. Good bioavailability oral drug delivery depends upon the factors prolong gastric residence time, thereby targeting site specific drug release in the upper GIT for local and systemic effects. The development of a long- term oral controlled- release dosage form has been difficult mainly because of the transit of the dosage form through the gastro intestinal tract. Several approach to prolong gastro intestinal residence time have been tried. The most commonly used system are following:-

1. Intragastric floating system
2. Mucoadhesive system
3. Swellable system
4. Super porous hydrogel system.

The concept of each approach is examined, and improvement that are needed for further development are discussed.

KEYWORDS: Gastro retentive dosage form, drug delivery, sustained release, gastro retentive drug delivery.

INTRODUCTION

Drug delivery system are engineered technologies for the targeted delivery and/or controlled release of drug. Drug have long been used to improve health. The practice of drug delivery has changed noticeable in the past few decades and even greater changes are anticipated in the near future. Biomedical engineers have contributed substantially to our understanding of the physiological barriers to efficient drug delivery, such as delivered in blood and drug movement through cells and tissues; they have also contributed to the development several new modes of drug delivery that have entered clinical practice.

Yet, with all this progress, many drug, even those discovered using the most advanced molecular biology strategies, have unwanted side effects due to the drug interacting with healthy tissues that are not target of the drug. Side effects limits our ability to design optimal medication for many disease such as cancer, infectious diseases. Drug delivery system control the rate at which a drug is released and the location in the body where it is released. This study is known as sustained release drug delivery system.

The following are the rational of developing sustained release

1. To prolong the duration of action of the drug
2. To decrease the frequency of dosing
3. To decrease the fluctuations in plasma level
4. Increase drug utilization
5. Minimum adverse effect

Advantages of sustained release dosage forms

1. The frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient as well.
4. Better absorption of drug can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
5. The amount of drug administered can be reduced, thus:

a) Maximum availability with minimum dose;
b) Reduce local side effects;
c) Remove systemic side effects;
d) Minimum drug accumulation with prolong dosing.

6. Improve efficiency in treatment.

Disadvantages of sustained release dosage forms

1. Probably of dose dumping
2. Reduce potential for dose adjustment.
3. Cost of single unit higher than conventional dosage forms.
4. Enhance potential for first pass metabolism.
5. Decreased systemic availability in comparison to immediate release conventional dosage forms.

Anatomy of the stomach

The gastro intestinal tract can be divided into three main parts.

- Stomach
- Small intestine- duodenum, jejunum, and ileum.
- Large intestine.

The gastro intestinal tract is a muscular tube of about 9m which extends from mouth to anus. Its function is to take nutrients and eliminate out waste product by physiological processes such as digestion, absorption, secretion, motility and excretion. The stomach has three muscle layer called oblique muscle and it is situated in the proximal part of the stomach branching over the fundus and higher regions of the gastric body.

The stomach is divided into fundus, body, and pylorus. The stomach is a J shaped organ located in the upper left hand portion of the abdomen. The main function of the stomach is to store the food temporarily, grind it and release slowly in to the duodenum.

Physiology of the stomach

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into fold called rugae. There are 4 major types of secretory epithelial cells that covers the stomach and extends into gastric pits and glands.

1. Mucosa cells- secrete alkaline mucus
2. Parietal cells- secrete HCL
3. Chief cells- secrete pepsin
4. G cells- secrete hormone gastrin.

Gastric motility and gastric empty rate

Two distinct patterns of gastrointestinal motility and secretion exist to the fasted and fed state. The bioavailability of the orally administered drug depends upon the state of feeding. In the fasted state, it is characterized by a development series of electric event called inter digestive myoelectric cycle.

It is divided into 4 phases.

- Phase I (basal phase) it lasts from 40-60 min with rate contractions.
- Phase II (preburust phase) last from 40- 60 min with intermittent potential and contractions.
- Phase III (burst phase) last for 4-6 min. in this intense and regular contraction occur for short periods. Due to these contractions the indigestive food is swept from stomach to intestine. These are known as house keeper waves.
- Phase IV is lasts for 0-5 min and occurs between phase III and I for two consecutive cycles.

After the ingestion of the mixed meal the pattern of contraction changes from fed to that of fasted state, this is known as digestive motility. Pattern these contraction reduces the size of the food particles to less than 1mm after that it is propelled to the pylorus in the suspension form. During fed state the onset of MMC is delayed which result in slow down of gastric emptying rate.

Unique properties of GI tract

Since the goal of having a proper platform is to overcome some physiological problems (e.g. gastric emptying of solid dosage forms), we will first examine some aspects of the GI tract that are relevant to drug delivery.

A. Gastrointestinal transit times

One of the unique properties of the GI tract is that the food content remains in each segment of the GIT for different time periods. The residence times of both liquid and solid food in each segment of the GIT.

B. Variable absorption abilities in the GI tract

Another factors that makes long-term oral drug delivery more difficult is that drug transport across the intestinal epithelium in each segment is not uniform. The performance of oral controlled dosage forms profoundly depends on transit through the GI tract, because the extent of drug absorption from different regions of the GIT is different.

C. Presystemic clearance

Even with those drugs that can be absorbed equally well throughout the GI tract, bioavailability can still be significantly reduce by site- specific changes in presystemic clearance. Degradation of orally administered drugs can occur by hydrolysis in the stomach, enzymatic digestion in the gastric and small intestinal fluids, metabolism in the brush border of the gut wall, metabolism by microorganism in the colon, and metabolism in the liver prior to entering the systemic circulation(i.e., first pass effect). Such degradation may lead to high variation or poor absorption of drug into the systemic circulation.

Factors affecting gastric retention

Density- The density of the dosage form should be less than that of the gastric contents (1.004g/ml).

Size- Dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form.

Shape of the dosage form- The tetra hadron resided in the stomach for longer period than other devices of similar size.

Single or multiple unit formulation- multiple unit formulation show a more predictable release profile and insignificant impairing of the performance due to failure of the units. Allow co-administration of units with different release profile or containing incompatible substance and permit larger margin of safety against dosage form failure compared with single unit dosage form.

Fed or unfed state- Under fasting conditions, the GI motility is characterized by periods of strong motor activity that occurs every 2 hrs. The MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer.

Nature of meal- Feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state, thus decreasing gastric emptying rate and prolonging drug release.

Caloric content- GRT can be increased by 4-10 with a meal that is high in protein and fat.

Gender- the GRT in male (3.4hrs) is less compared with the age and race matched female (4.6hrs) regardless of height, weight and body surface.

Age- People with age more than 70 have a substantial longer GRT.

Accompaniment drug administration-Anticholinergics like atropine and opiates like codeine can long term GRT.

Frequency of feed- The GRT can be increase over 400 min when successive meals given are compared with the single meal due to low frequency of MMC.

Gastro retentive dosage form

A gastro retentive dosage form (GRDF) that releases medications in a controlled manner is needed to extend the absorption phase of drugs characterized by a limited and narrow absorption window at the upper part of the gastrointestinal tract or drugs intended to treat local ill in the gastro-duodenum.

This mode of administration may prolong the time period in which the blood drug concentrations are within the "therapeutic levels" and improve therapy. Therefore, development of GRDFs has been a major pharmaceutical challenge during the past few decades.

Various GRDFs have been proposed previously, most of them designed according to the following approaches:

- Bio adhesion to the stomach mucosa;
- Buoyancy of low-density dosage form (DF) above gastric fluid
- Expansion by swelling to a large size, which should prevent rapid emptying through the pyloric sphincter.

Classification of GRDF

1. High density system
2. Floating system
3. Muco-adhesive bio adhesive system
4. Swelling system
5. Super porous hydrogel system
6. Magnetic system

1. High density system

This approach involves formulation of dosage forms with density that must high density of normal stomach content (1.004g/ml). These formulations are prepared by coating drug on a heavy core or mixed with heavy inert material such as iron powder, zinc oxide, titanium dioxide, barium sulphate. The resultant pellets can be coated with diffusion controlled membrane.

These systems have some drawbacks like they are technically difficult to manufacture with a large amount of drug because the dry material of which it is made interacts within the gastric fluid to release its drug contents. One other problem is that no such system is available in the market.

2. Floating or low density system

Floating system or dynamically controlled system are low- density system that have sufficiently buoyancy to float over the gastric content and remain buoyant in the stomach without affecting the gastric emptying rate for a prolong period of time.

This results in an increased gastric retention time and a better control of the fluctuation in plasma drug concentration.

Many buoyant system have been developed based on granules, powders, capsules, tablets, laminated film and hollow microspheres.

(a). Volatile liquid containing system

Incorporates an inflatable chamber, which contains a liquid e.g. ether that gas release at body temperature to causes the inflammatory of the chamber in the stomach.

The device may also consist of a bio erodible plug made up of PVA, polyethylene etc. that gradually dissolve causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach.

There systems are very less used as the gas generating system are safer.

(b). Gas-generating Systems
These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over gastric content.

(c). Non-Effervescent system
The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio adhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swell up cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, poly acrylate, poly methacrylate, polystyrene as well as bio adhesive polymers such as Chitosan.[21]

3. Mucoadhesive systems
Muco-adhesive drug delivery systems contain, a muco-adhesive polymers that adheres to the gastric mucosal surface and prolong its gastric retention in the gastro intestinal tract. The capability to adhere to the mucus gel layer makes muco-adhesive polymers very useful excipients in the GRRDS. These polymers can be natural such as sodium alginate, gelatin, guar gum etc. semisynthetic polymers such as HPMC, carbopol, sodium carboxyl methyl cellulose.

The adhesion of polymers with mucous membrane may be mediated by hydration and bonding, receptor mediated. In hydration mediated adhesion, the hydrophilic polymer become sticky and muco-adhesive upon hydration. Bonding mediated involves mechanical or chemical bonding. Chemical bonds may involve ionic or covalent bonds or Vander Waal forces between the polymer molecule and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers can be cationic or anionic or neutral.

4. Swelling system
These are the dosage forms, which after swallowing, swell to an extent that prevent with exist from the pylorus. As a result, the dosage form is retained in the stomach for a longer periods of time. These system may be named as plug type system, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state.

The balance between extend and duration of swelling is maintained by the degree of cross linking between the polymeric chains. A high degree of cross- linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

5. Per porous hydrogel system
These swellable system differ significantly from the conventional type to hold a separate classification. 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 inter connected open pores. They swell to large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by gastric contraction. This is advised by co-formulation of hydrophilic particulate material.

6. Magnetic system
Magnetic nanoparticle-based drug delivery is a means in which magnetic particles such as iron oxide nanoparticles are a component of a delivery vehicle for magnetic drug delivery.

Dosage forms contain a small internal magnet and a magnet and a magnet is placed in abdomen over the position of stomach that retains dosage form in gastric region.

Disadvantages
- External magnet needs to be positioned with degree of precision.
- Patient non-compliance.
- Not very used.

Advantages
- Simple to use.
- Controlled release drug delivery.

Evaluation of gastro retentive dosage forms
In-vitro method of evaluation
1. Fourier transform infrared analysis
Fourier transform infrared spectroscopy is mostly used to identify organic, polymeric, functional group, and some inorganic materials as well. FT-IR measurement of pure drug, polymer and drug filled formulations are obtained by using this technique. The pellets are prepared on kbr press under hydraulic pressure of 150kg/cm and the spectra are scanned over the wave number range of 3600-400cm-1 at ambient temperature.

2. Differential scanning calorimetry
Differential scanning calorimetry are performed to characterize water of hydration of pharmaceuticals. Thermos grams of formulated preparations are obtained using DSC instrument equipped with inter cooler zinc standards are used to calibrate the DSC temperature and enthalpy scale. The sample preparations are sealed in aluminum pan and heated at a constant rate of 10ºC/min over a temp range 25ºC-65ºC.

The particle size and size distribution of beads or microspheres are determined in the dry state using optical microscopy method. The external and cross

sectional morphology is done by scanning electron microscope.

3. Floatation studies

The in-vitro buoyancy is characterized by floating lag time and total floating time. The FLT and TFT are measured by placing the tablets in a 250 ml beaker which containing 200ml of 0.1N HCL.

The time required by the to rise to the surface and float is known as floating lag time and the time period up to which the tablet remained buoyant is called floating time.

4. Swelling studies

Swelling of tablet excipients particles involves the absorption of a liquid resulting in increase in weight and volume. Liquid uptake by the particles may be due to saturation of the capillary spaces within the particles or hydration of macromolecules. The liquid enters into particles through pores and bind then to large molecules, breaking the hydrogen bond and resulting in the swelling of particles. Tablet is weighed and placed in a beaker containing 200 ml of 0.1N HCL. After each interval the tablet is take away from the beaker, soaked by using normal filter paper and again weighed.

Swelling index (SI) = (Wt-WO)/WO × 100

Wt. – weight of the tablet at time t

WO – initial weight of the tablet

Determination of drug content

Percentage drug content provides how much amount of drug is present in the formulation. It should not exceed the limit acquired by the monograph. Drug content is determined by using HPLC, HPTLC methods, Micro titrimetric methods, and by using spectroscopy techniques. To determine drug content 10 tablets are triturated in the mortar. 10 mg of powdered tablet dissolved in 10 ml of 0.1N HCL and then drug sample is analyzed under U.V spectral photometer.

Dissolution studies

The dissolution test are generally performed for calculating the amount of drug release using USP dissolution apparatus. The test is performed using 900 ml of 0.1 N HCL, at 37ºC and 100 rpm. A sample of 10 ml is withdrawn hourly and analyzed under U.V and absorbance is measured. The sample is replaced by the dissolution media. Cumulative percentage is calculated by using equation obtained from standard curve.

X-ray

It helps to locate dosage form in the GIT by which one can predict and connection the gastric emptying time and the passage of dosage form in the GIT. The inclusion of a radio opaque material into solid dosage form enables it to be visualized by the X-ray. The inclusion of a gamma discharge radionuclide in the formulation allows indirect external observation using gamma camera, the gamma rays discharge by radionuclide is focused on the camera which helps to monitor the location of the dosage form.

Gastroscopy

It consist of paroral endoscopy used with a fiber optic. It is used to analyze superficially the effect of long term stay in stomach milieu on the FDDS.

CONCLUSION

Based on the literature survey, it can be concluded that GRDDs offers various advantages for drugs with poor bioavailability. Drug absorption in the gastro intestinal tract is a highly variable process and prolonging gastric retention of the dosage form increase the time for drug absorption.

The control of gastro intestinal transit of orally administered dosage form using GRDDs system can improve the bioavailability of drugs that exhibit site specific absorption. GRDFs also provide an additional advantage for drugs that are absorbed primarily in the upper portion of gastro intestinal tract.

Under certain circumstances, the prolongation of gastric residence time of a delivery system is desirable for achieving a better therapeutic benefit of the drug substance. For instance the drugs that show absorption in the proximal part of the gastrointestinal tract and the drugs which are less soluble in alkaline pH may be benefitted by prolonging the gastric residence time. Prolonged gastric retention of therapeutic moiety offers many advantages like improve bioavailability, reduction of drug wastage and possible reduction of dose size.

Various gastro retentive dosage forms have been designed to increase the gastric retention time. There are opportunity and potential for the development of effective GRDDS with improving bioavailability of the drugs that have absorption window in the proximal and mid GIT.

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