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Review Article

A REVIEW ON RECENT ADVANCES IN FLOATING DRUG DELIVERY SYSTEM

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Abstract

Oral route is the most convenient and excessively used for administration of drug because of patient acceptability and ease of administration. Controlled Release Drug Delivery System basically release drug at predetermined rate and helps to predict peak plasma concentration (C_{max}) of drug. Gastric emptying of dosage form is a variable process hence prolonging and controlling the gastric emptying is a valuable step for dosage form to reside in stomach for longer time than conventional dosage form. In recent years various scientific and technological advancements have been made for oral drug delivery system. Various approaches have been proposed to increase gastric residence time. It include Floating drug delivery system, Swelling or expanding system, Mucoadhesive system, Magnetic System, Modified shape system, hydrodynamically balanced system etc. Floating drug delivery system is commonly used among these techniques. Floating drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. Treatment of gastrointestinal disorders such as gastro-esophageal reflux improved drug absorption, because of increased gastric retention time (GRT) and more time spent by the dosage form at its absorption site. Ease of administration and better patient compliance and minimizing the mucosal irritation due to drugs.

Keywords: Mucoadhesive system, hydro-dynamically balanced system, gastro-esophageal reflux, gastric retention time (GRT) etc.

Introduction

Oral route is most preferable route for drug administration. It is very popular due to its ease of administration or patient compliance⁽¹⁾. Floating drug delivery system (FDDES) is belonging to oral controlled drug delivery

system. It is also known as gastric floating drug delivery system (GFDDDS) which float the drug in stomach and release it in a controlled manner for longer duration and increase the gastric residence time (GRT) of

drug⁽²⁾. Basically floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time⁽³⁾.

Anatomy and Physiology of GIT

Physiology and anatomy of GIT is found to be very complex, variation in acidity, bile salts, enzyme content etc. from mouth to rectum which influences the absorption, release and dissolution of drug from oral dosage form. Stomach is divided in three regions-

- Fundus: Proximal part of stomach.
- Body: It acts as a reservoir for undigested materials.
- Antrum: It is the main site for mixing motion and act as a pump for gastric emptying propelling action.

GI motility and secretory pattern depends upon two modes in fasted and fed state. Due to this bioavailability of drug administered orally is different depend upon the state of feeding. During fasting state inter-digestive series of electrical event take place between stomach and intestine which is called as inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC). It is divided into four phases:-

1. Phase-I:- It is a basic phase, remain 30-60 minutes, it lacks any secretory activity and contractile motion.
2. Phase-II:- It is also known as pre-burst phase, intermittent contractions occur and it last for 20-40 minute.

3. Phase-III:- It is known as burst phase; remain for 10-20 minute. It includes intense and regular contractions for short time.
4. Phase-IV:- It remains for 0-5 minute, occur between Phase III and Phase I.

After ingestion of the meals, the pattern of contraction changes from fasted to feed state. These contractions result in reducing the size of food particles to less than 1 mm⁽⁴⁾.

Factors affecting gastric retention:

The most common factors affecting gastric emptying, and hence, the gastric retention time of Oral dosage forms are as follows:-

1. Density, Shape and Size of the device.
2. Concomitant intake of food and its caloric content and frequency of intake.
3. Biological factors like Gender, Age, Posture, BMI (body mass index) and disease state.
4. Simultaneous administration of drug with impact on gastrointestinal transit time; for example drugs like Anti-cholinergics (e.g.: Atropine), opiates (e.g.: Codeine).
5. Nature of meal^(5,6)

Advantages of Floating Drug Delivery System^(7, 8, 9)

1. Enhance bioavailability.
2. Reduce dosing frequency.
3. Site specific delivery.
4. Reduced fluctuations of drugs concentration.
5. Minimize adverse activity at the colon.

6. Ease of administration and patient compliance.

Disadvantages of Floating Drug Delivery System ^(10, 11)

1. Require high amount of fluid in stomach to float.
2. Not feasible for those drugs having solubility or stability problems in gastric fluids.
3. Drugs such as nifedipine, which undergoes first pass metabolism may not be desirable for the preparation of these types of systems.
4. Drugs which are irritants to gastric mucosa are also not suitable.

Floating Drug delivery System (FDDS):-

Low density system that floats on gastric contents due to buoyancy and remain in stomach for a prolonged period. Hence drug released slowly at the desired rate. Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability ⁽¹²⁾. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine

Floating drug delivery systems are classified as:-

- Effervescent system
- Non Effervescent system

Effervescent system ^(13, 14)

Matrices prepared with swell able polymer and effervescent components. When administer dosage form comes in contact with gastric fluid it produces effervescent and

evolved CO₂ gas. It helps the fluid to penetrate in tablet ad float. The matrices are fabricated in such a way that upon arrival I stomach carbon dioxide is liberated by the acidity of gastric contents and entrapped in the gellified hydrocolloids.

Recently a multiple unit type of floating pill developed which is surrounded by double layers like seed. The inner layer of pill was an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swell able membrane layer containing poly vinyl acetate and purified shellac. Effervescent layer is subdivided in two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bi carbonate was present in inner sub layer and tartaric acid was in outer layer.

Non Effervescent system ⁽¹⁴⁾

This system works on the mechanism of polymer swelling, bio-adhesion of the polymer to mucosal layer of GI tract. Gel forming or swell able type hydrocolloids, polysaccharides and matrix forming polymers like polymethacrylate, polycarbonates and polyacrylates are used for non-effervescent system. In the development of these floating dosage forms involve thorough mixing of drug and gel forming hydrocolloids. After administration when dosage forms come in contact with gastric fluid they get swollen and form a gelatinous barrier at the surface. The swollen dosage forms maintain a relative integrity of shapes and bulk density less than 1.

Microporous compartment system, Alginate bead system and Hollow microspheres or micro-balloons are some of the other types of non-effervescent system.

Drugs used for various floating dosage forms ⁽¹⁵⁾

S. No.	Dosage form	Name of drugs
1	Microspheres, Tablets and Pills	Aspirin, Isosorbide mononitrate, Sotalol, Captopril, Theophylline, Atenolol, Griesoflulin, Ibuprofen, Terfenadine, Ampicillin, Chlorpheniramine maleate.
2	Films	p- Aminobenzoic acid, Cinnarizine, Prednisolone, Piretinide.
3	Granules	Cinnarizine, Diclofenac sodium, Diltiazem, Indomethacin, Fluorouracil, Prednisolone.
4	Capsules	Verapamil hydrochloride, Chlordiazepoxide hydrochloride, Diazepam, Furosemide, Propranolol hydrochloride, Nicardipine

Polymers and other ingredients used to prepare floating dosage forms ⁽¹⁶⁾

S. No.	Polymers and other ingredients	Examples
1	Polymers	HPMC K4M, Eudragit S100, Eudragit RL, Ethyl cellulose, HPMC4000, HPMC K 15 M, Sodium alginate, Calcium Alginate, Polycarbonate, Carbopol, Poly methyl meth acrylate, Carbopol 934P
2	Inert fatty materials	Bees wax, Fatty acids, Gelucires 39/01 or 43/01.
3	Effervescent agent	Sodium bicarbonate, Citric acid, Tartaric acid, Citroglycine (CG)
4	Release rate accelerants (5-60%)	Lactose, Mannitol
5	Release rate retardant (5-60%)	Dicalcium phosphate, Talc, Magnesium stearate.
6	Buoyancy increasing agents (up to 80%)	Ethyl cellulose
7	Low density material	Polypropylene foam powder (Accurel MP 1000)

Evaluation of floating drug delivery system

Evaluation of any drug product is basically done to ensure Performance and Batch to Batch quality control. Routine tests are appearance, hardness, friability, weight variation, disintegration and drug release etc. Specific tests carried out for FDDS evaluation are as follows:

1. **Floating time**:- Floating time is determined by USP Dissolution apparatus containing 900 ml of 0.1N HCl as medium. The time taken by the dosage form to float is termed as floating or floatation time or floating lag time and the time for which the dosage form floats is termed as floating or floatation time⁽¹⁷⁾.

2. **Swelling index**:- Swelling behavior of a dosage form was measured by its weight gain. Swelling index is determined by placing the tablets in 0.1N HCL. After every one hour up to 24 hours the tablets were withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance. It is calculated by the following formula-

$$S.I. = \frac{W_t - W_o}{W_o}$$

W_t = weight of tablet at time t.

W_o = Weight of tablet before immersion

3. **Drug Content Estimation**:- Drug content was determined by triturating the 20 tablets and powder equivalent to average weight was added in 100ml of

.1N HCL followed by stirring for 30 minutes. The solution was filtered, diluted suitably and absorbance of resultant solution was measured spectrophotometrically using 1N HCL as blank⁽¹⁸⁾.

4. **Resultant weight determination**:-

Resultant weight is basically used to determine the buoyancy of the system. Method is based on the concept of force i.e. floating force produced by the object. Positive resultant weight signifies that object is able to float and vice-versa.

5. **Specific gravity**:- It can be determined by displacement method using benzene as displacement medium⁽¹⁹⁾.

6. **In-Vitro drug release**:- This test is usually carried out in simulated gastric fluid. Dissolution test was performed by using the USP dissolution apparatus. Samples are withdraw periodically from the dissolution medium, replaced with the same volume of fresh medium each time and then they analyzed for their drug content on UV spectrophotometer after an appropriate dilution⁽¹⁷⁾.

Application of floating drug delivery system

This system offers various applications for the drugs having poor bioavailability due to the narrow window of absorption in the upper part of the gastrointestinal tract. It increase the gastric residence time of drug, retain the dosage form at the site of absorption and thus

enhance the bioavailability. These are summarized as follows:

- It enhances the bioavailability of drug.
- It provides the site specific drug delivery.
- Minimized the adverse activity of drug at the colon.
- Reduced the fluctuation of drug concentration in plasma.
- It enhances the absorption of drug.
- It provide the sustained release of drug from the dosage form.(2)

Conclusion

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

Recent advances in FDDS

Among the drugs currently in clinical use are several narrow absorption window drugs that may benefit from compounding into a FDDS. Replacing parenteral administration of drugs to oral pharmacotherapy would substantially improve treatment.

1. Identification of a minimal cut off size above that dosage forms retained in the human stomach for prolonged period of time. This would permit a

more specific control to be achieved in gastroretentivity.

2. Design of an array of FDDS each having a narrow Gastric Retention Time (GRT) for use according to clinical need e.g. dosage and state of disease. This may be achieved by compounding polymeric matrices with various biodegradation properties.
3. Study of the effect of various geometric shapes, in a more excessive manner than previous studies extended dimensions with high rigidity, on gastroretentivity.
4. Design of novel polymers according to clinical and pharmaceutical need.(20,21)

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