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# A REVIEW ARTICLE ON GASTRORETENTIVE FLOATING FILMS DRUG DELIVERY SYSTEM.

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**ABSTRACT:**

A lot of scientific and technological advancement have been made in the drug delivery research. Floating film drug delivery system has emerged as an advanced alternative to traditional dosage form like tablets, capsules and liquids. Floating film is drug loaded polymeric film mainly comprised of active pharmaceutical ingredients, polymers, film forming agent and plasticizer with the suitable solvent. Gastroretentive floating films are mainly made by using solvent evaporation and solvent casting methods. Present article gives emphasis on general consideration of gastroretentive floating films drug delivery system, with their advantages, disadvantages, method of preparation, evaluation parameters likes percent moisture absorbtion, folding endurance, tensile strength, drug content, dissolution study, release kinetic study, swelling index, in vitro buoyancy study and its applications. Layer-by-layer film technique will become a alternative for multidrug therapy in which controlled or sustained delivery of drug is possible by using different polymers. Multilayer approach will gain more importance in associated diseases like hypertension and diabetes etc.

**KEYWORDS**: GRDS, FDDS, FFDDS, method of preparations example solvent casting method etc, evaluation parameters.

**INTRODUCTION:** [1.Meenakshi Jassal et al, 2015 - 20. P.Bhardawaj et al, 2014]

The objective of drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve and maintain therapeutic concentration within range that shows pharmacological action with minimum incidence of adverse effects. One should maintain dosing frequency and suitable route of administration to achieve the goal. The oral route is most convenient route of drug administration because of patient acceptability, flexibility and ease of administration in designing the dosage form. Most of oral controlled drug delivery systems release the drug by diffusion, dissolution or combination mechanism in gastrointestinal tract.

**GASTRO RETENTIVE DOSAGE FORM (GRDF):**

A many troubles are looked in structuring continued discharge and controlled discharge configuration for better assimilation and upgraded bioavailability. The troubles like the failure to restrict the measurement frame in the coveted region of the gastrointestinal tract is one of them. Gastro retentive dosage form can stay in the gastric locale for a few hours and consequently fundamentally drag out the gastric living arrangement time of medications.

Delayed gastric maintenance increase bioavailability, lessens medicate wastage, and enhances dissolvability for medications that are less solvent in a high PH condition. GRDF basically widen essentially the term of time over which the medications might be discharged. They delay dosing interims, as well as increase in understanding consistence. Gastro retentive measurement shapes (GRDF), will achieve modern and mandatory helpful alternatives.

This application is particularly compelling in insoluble and sparingly dissolvable medications. It is referred to that, as the solvency of a medication reduces, the time accessible for medication disintegration turns out to be less satisfactory and in this way the travel time turns into a promising factor for influencing drug retention. To defeat this issue, erodible, gastro-retentive measurement frames have been produced that give persistent, controlled organization of sparingly dissolvable medications at the assimilation site.

The stomach through nearby medication discharge, prompting high medication fixation at the gastric mucosa of GRDF incredibly enhances the pharmacotherapy. (e.g. by killing helicobacter pylori from the sub-mucosal tissue of stomach) making it conceivable to treat gastric and duodenal ulcers, gastritis and oesophagitis, decrease the danger of gastric carcinoma and direct non-fundamental controlled discharge acid neutralizer details (calcium carbonate).

GRDF can be used as bearers for medications with related ingestion windows. These are example of antifungal, antiviral and anti-infection operators (sulphonamides, penicillins, quinolones , cephalosporins, aminoglycosides, antibiotic medications and so on.), are ingested just from unmistakable locales of the GI mucosa.

**APPROACHES TO ACHIEVE GASTRIC RETENTION:**

1. **High density system (sinking) or non- floating drug delivery system:**

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm3 ). These formulations are formed by coating drug on a mixed or heavy core with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The substances density should be up to 1.5- 2.4 gm/cm3. A density close to 2.5 gm/cm3 seems necessary for substantial prolongation of gastric residence time. But, forcefulness of this system in mortal commodities wasn't observed and no system has been retailed.

**2. BIOADHESIVE OR MUCOADHESIVE DRUG DELIVERY SYSTEMS:**

Bioadhesive drug delivery systems are used as a delivery device within the human to increase drug absorption in a location-specific manner. In this system, bio-adhesive polymers are used and they can stick to the epithelial surface in the stomach . So there increase in the prolongation of gastric retention. In general the adhesion in that a dosage form can stick to the mucosal surface by different mechanism**.**

**3. SUPER POROUS HYDROGEL SYSTEMS:**

These swellable systems differ sufficiently from the conventional types to warrant different classification. In this system to improve gastric retention time (GRT) super pervious hydrogels of moderate severance size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have required mechanical strength to withstand pressure by gastric contraction.

**4. MAGNETIC SYSTEMS :**

This approach to increase the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the foreign attraction or external magnet must be positioned with a degree of precision that might confront patient compliance**.**

**5. EXPANDABLE, UNFOLDABLE AND SWELLABLE SYSTEM**:
A dosage form should be large enough than pyrolic spinture so that it can withstand gastric transit time. . However, the dosage form must be small enough to be swallowed, and must not cause gastric hindrance either singly or by accumulation. Thus, there is the requirenment to developed an expandable system to prolong gastric retention time (GRT).

**6. FLOATING DRUG DELIVERY SYSTEM**
FDDS belong to the group of gastroretentive dosage forms initially described by Davis in 1968 (Davis, 1968). FDDS dosage forms are able to achieve prolonged gastric residence time (GRT) with increased duration for active pharmaceutical ingredients (API) to be released. Floatation of drug delivery system in the drug can be achieved by incorporating floating chamber filled with vacuum, free air or inert gas from the system. After release of drug, the residual system is voided. This results in an swelled GRT and it will improved the control of fluctuations in plasma drug concentration.

**TYPES OF FLOATING DRUG DELIVERY SYSTEMS:**

**1. NON-EFFERVESCENT FDDS:**
The non-effervescent FDDS is based on mechanism of bioadhesion and swelling of polymer to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are highly swellable cellulose or gel forming type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as carbopol and chitosan.

**2. EFFERVESCENT SYSTEM:**
These are matrix types of systems prepared using swellable polymer such as methylcellulose and effervescent compounds like sodium bicarbonate, tartaric acid. The matrices are fabricated so that upon coming in the stomach, CO2 is liberated by the acidity of the gastric contents and is entrapped in the jellified hydrocolloid. This motion of produces called as upward motion of the dosage form and maintains it's the floating period (buoyancy). A drop in specific graveness causes the dosage form to float on the chime.

**3. BIOADHESIVE SYSTEMS:**
Bioadhesive drug delivery systems (BDDS) are exercised to localise a delivery device within the lumen to enhance the drug absorption in a point-specific manner. This arrival involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. A microbalance-based system is reported for measuring the forces of interaction between the GI mucosa and the individual polymers, and the Cahn Dynamic Contact Angle Analyzer has been used to study the adherence. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The nonstop production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic condensation and the dilution of the stomach content also seems to limit the eventuality of mucoadhesion as a gastroretentive force. Some of the most encouraging excipients that have been used exercised generally in these systems carry polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc. Some investigators have tried out a synergistic approach between bioadhesion and floating systems. Other approaches reported carry use of a new adhesive substances derived from the fimbriae (especially Type 1) of bacteria or synthetic analogues connected with a drug to provide for attachment to the gut, thereby prolonging the transit time, a composition comprising an active ingredient and a material that acts as a viscogenic agent for example curdlan and/or a low-substituted hydroxypropylcellulose, etc.

**4. HIGH – DENSITY SYSTEMS:**
Sedimentation has been assumed as a retention mechanism for pellets that are fragile enough to be reserved in the crowds of the stomach body near the pyloric region, which is the portion of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm3) trapped in folds also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on diameter of the pellets, although many conflicting reports stating otherwise also abound in literature. Excipients like barium sulphate, zinc oxide, titanium dioxide and iron powder, etc are commonly used. These materials boost density by over 1.5–2.4g/cm-3. Still, no successful high-density system has made it to the request.

**5. LARGE SINGLE UNIT DOSAGE FORMS:**

Due to larger form of dosage form than the pyloric opening and so they retained in the stomach. There are some disadvantages associated with this approach. Endless retention of rigorous large-sized single-unit forms can cause bowel inhibition, intestinal adhesion and gastroplasty.

**SUITABLE DRUG CANDIDATES FOR GASTRORETENTION:**

The applicable candidates for CRGRDF are molecules that have poor colonic absorption but are represented by better absorption properties at the upper parts of the GIT:

- The absorption window in GI tract should de narrow, e.g., riboflavin and levodopa.
- Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplements, chlordiazepoxide and cinnarazine.
- The locally acting drugs at the stomach, e.g., Antacids and Misoprostol.
- Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin trihydrate.

**THREE MAJOR REQUIREMENTS OF FDDS FORMULATIONS ARE:**

- Cohesive gel barrier they must form around the drug.
- It must maintain specific gravity lower than gastric contents (1.004-1.01g//c).
- The contents should be released slowly to serve as a reservoir.

**Table 1: different polymer used in FDDS.**

| | |
|---|---|
| Sustained release polymers | HPMC K100M, HPMC K15M, HPMC elv, Polycarbonate, Polyethylene Glycol, SodiumAlginate, Carbopol, Eudragit. |
| Effervescent generating system | Citric Acid, Tartaric Acid, Sodium Bicarbonate, Citroglycine. |
| Polymers which increase buoyancy | Ethyl Cellulose44 |
| Polymers which decrease release | Talc, Magnesium Stearate, Dicalcium, Phosphate. |
| Polymers which increase release | Mannitol, Lactose |
| Inert polymers | Long chain fatty alcohol, fatty acid, beeswax. |
| Plasticizer | Glycerol, Propylene Glycol, Polyrthylene Glycol, Diethyl Phthalate, Actetylated Monoglycerides. |
| Polymers with low density | Foam powder of polypropylene. |

## FLOATING FILMS DRUG DELIVERY SYSTEM:

Floating film drug delivery system has emerged as advanced alternative to traditional dosage forms like tablets, capsules and liquids. A drug loaded thin film strip filled into capsule is typically designed for oral drug delivery. Floating film offers advantages as, preparation of film is very simple, time saving, economically beneficial and chances of cross contamination is very less, also handling of film is very easy as compared with microspheres. Floating film is drug loaded polymeric film which contains an active pharmaceutical ingredient, polymers, film forming agent, plasticizer and suitable solvent. Films can be prepared by solvent evaporation method in which drug and polymer are mixed with sufficient quantity of solvent. Other ingredients are added accordingly, poured in petriplate and allowed to dry to give thin layered smooth film. Drug release profile can be modified by using different polymers can be applied. Layer-by-layer technique in which one layer is of controlled release polymer and another layer is of sustained release polymer. Hence, by this way one can go for multilayer approach so that this drug delivery will play an important role in associated diseases such as diabetes, hypertension etc. In this type of diseases multilayer film can be prepared having different release profile of drug through different layers of film made from different polymers. Solvent plays important role in preparation of gastroretentive films. Water can be used as solvent for drugs which are water insoluble or sparingly soluble so that film gets dried in short period of time after its preparation.

## ADVANTAGES OF FILM DRUG DELIVERY:

- Bioavailability of drug can be significantly increased especially of the drugs which are metabolized in upper GIT.
- For drugs with relatively short half-life, sustained release may result in flip-flop pharmacokinetics and this may also reduce the dosing frequency with improved patient compliance.
- This film is expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of gastric emptying due to low density.
- GRFDDS offers prolonged and sustained drug release in stomach and small intestine hence useful in treatment of disorders related with stomach and intestine.
- Due to site specificity and minimum fluctuations in drug concentration, it reduces undesirable effects or side effects.

## DISADVANTAGE:

- It requires high level of fluid in stomach so that film can float in gastric environment.
- GRFFDDS is not suitable for drugs which cause gastric agony.
- Bioadhesion in acidic environment and high tolerance of mucus may raise question abouteffectiveness of this technique.

**METHOD OF PREPARATION:** [10. P-Shailaja et al, 2022 - 30. Dalia Saff et al, 2022]

### 1. SOLVENT CASTING METHOD:

The film was prepared by using solvent casting method with various polymers. The amount of drug in the film was less than 50mg in 4x2 cm2 film piece. An appropriate amount of api and floating agent was dissolved in a suitable amount of solvent like methanol and added to the polymer solution slowly with continuous stirring with magnetic stirrer, when drug-polymer mixture mixed homogeneously then added proper amount of plasticizer with continuous stirring and the resulting solution poured in a petri dish. Then dried the film and remove film from petri dish and evaluate it.

Advantages:

- Better clarity than extrusion and better uniformity of thickness.
- Film has fine gloss and freedom from defects such as die line.
- Film has better physical properties and more flexibility.

Disadvantages:

- The polymer used should be soluble in volatile solvent or water.
- A stable solution with a reasonable minimum viscosity and solid content should be formed.
- Formulation of a homogenous film and release from the casting support must be possible.


fig 1. solvent casting.

**2. SEMISOLID CASTING:**

The semisolid casting method is mostly preferred when film ingredient involves acid insoluble polymer. In this originally, the water soluble polymers are dissolved in water. The gained solution is added to the acid insoluble polymer solution which is separately formed. Both the solutions are mixed properly. After mixing the two solutions, applicable amount of plasticizer is added to the obtained final solution so that gel mass can be obtained. At last, the gel mass is casted onto the ribbons or films using heat controlled drums. The maximum thickness of the film should be in between 0.015-0.05". The rate of the acid insoluble polymer to film forming polymer should be 1:4. Examples of acid insoluble polymers are cellulose acetate butyrate and cellulose acetate phthalate.

**3. SOLID DISPERSION EXTRUSION:**

Solid dispersion extrusion method involves the solid dispersion of drug induced in melted polymer solution so that drug can be loaded. The drug is dissolved in suitable liquid solvent and obtained solution is added to the suitable polymer, obtainable below 70°C without removing the liquid solvent to obtain the solid dispersion. Finally the obtained solid dispersions are shaped into films by the use of dyes.

**4. LAYER-BY-LAYER TECHNIQUE:**

Layer-by-layer technique in which one layer is of controlled release polymer and another layer is of sustained release polymer. Hence, by this way one can go for multilayer approach so that this drug delivery will play an important role in associated diseases such as diabetes, hypertension etc. In this type of diseases multilayer film can be prepared having different release profile of drug through different layers of film made from different polymers. Solvent plays important role in preparation of gastroretentive films. Water can be used as solvent for drugs which are water insoluble or sparingly soluble so that film gets dried in short period of time after its preparation.

**5. HOT MELT EXTRUSION:**

In the present method, the mass is prepared first under the control of temperature and the steering speed. Afterward, the film is coated and dried in a drying tunnel, one again the temperature, air circulation, and line speed is controlled. The follows a slitting and in the last step the films are punched, pouched and sealed.

Advantages:

- Without the use of any water or solvent.
- A better alternative for poorly soluble drug.
- Compressibility of the API may not be important.
- Fewer processing steps.
- Less energy compared with high shear methods.

Disadvantages:

- A limited number of available polymers.
- Thermal declination due to use of high temperature.
- All excipients must be deprived of water or any other volatile solvent.
- Flow properties of the polymer are fundamental for processing.

**6. ROLLING METHOD:**
In this system, a solution or suspension containing drug is rolled on a carrier. The solvent is basically water and mixture of water and alcohol. The film is dehydrated on the rollers and gives desired shape and size.

**7. MERCURY SUBSTRATE METHOD:**
The film is prepared by using mercury substrate method, in this method drug is dissolved in polymer solution along with other formulation additives like plasticizer, gas generating agents. The solution is to be a leaved mercury surface, covered with inverted funnel to control solvent evaporation.

**EVALUATION PARAMETERS OF FFDDS:** [16. Sharma N et al, 2015 - 36. Shaima Alaithan et al, 2022]

**1. VISUAL APPEARANCE, THICKNESS AND WEIGHT OF FILM:**
Morphological characters like shape, size and surface texture of film can be studied. Thickness of film is directly related to accuracy of dose in the film. Thickness of film should be measured at five different randomly selected spots using micrometer screw gauge. Weight of film is helpful to ensure that the film contains the proper amount of excipient and API, hence film weight should be nearly constant.

**2. FOLDING ENDURANCE OF FILM:**
Folding endurance of the film is essential to study elasticity of the film during storage. It is determined by repeatedly folding the film at same place till it breaks or folding upto 300 times. This is considered to good film properties.

**3. TENSILE STRENGTH OF FILM:**
The maximum stress applied to a point at which the film breaks is known as tensile strength. In this test the film is tied between two clamps and the one end of clamp is directly attached to pan through pulley. The stress is applied to the film by putting load in the pan and finally the reading of load at failure is noted. Tensile strength is calculated by formula,

**Tensile strength of film= Load at failure ×100film / Thickness ×film width …(1)**

**4. PERCENT MOISTURE ABSORPTION STUDY:**
In this, moisture absorption capacity of the film is determined by keeping the pre-weighed film in the dessicator at room temperature for 72 h. After 72 h, film is exposed to 75 % RH (relative humidity). Moisture uptake is measured as percent increase in weight of film. It is calculated by formula,

$$\text{Percent moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Final weight}} \times 100 \quad \ldots(2)$$

The moisture absorption study gives idea about stability of film. An increase in the moisture absorption property of the film indicates that the film will be less stable. It is observed that, when there is increase in polymer concentration, moisture absorption capacity of film also increased. It may be due to hydrophilic nature of polymer.

**5. DRUG CONTENT AND RELEASE KINETIC STUDY:**
Drug content can be determined by dissolving the film containing 50 mg of drug in 100 ml of 0.1 N HCl. An equivalent of 0.2 ml sample is withdrawn, diluted upto 10 ml with 0.1 N HCl and solution is analyzed by UV-Spectrophotometer. Drug content study indicates uniform dispersion of drug throughout the film.
In-vitro drug dissolution study should be carried out at 900 ml 0.1 N HCl using USP dissolution apparatus I (Paddle type) at 37±0.5OC at 500 rpm. The film should be inserted into capsule and submerged in dissolution medium and appropriate samples should withdrawn at particular time interval and should be analyzed spectrophotometrically. The Sink conditions should be maintained throughout the experiment.

**6. SWELLING INDEX:**

Swelling properties of the film can be determined by placing the film in USP dissolution test apparatus I in 900 ml of 0.1 N HCl. The film should be removed periodically from dissolution medium after draining free water by blotting and film weight gain should be measured on electronic balance. Swelling index can be calculated by using this formula,

$$\text{Swelling index} = \frac{\text{Swelling wt. of film} - \text{Initial wt.of film}}{\text{Initial wt.of film}} \times 100 \quad \ldots(3)$$

Swelling study is essential to ensure floating. For floating of the film, there should be appropriate balance between swelling and water uptake. Swelling study has prime importance, as variation in water content causes significant change in mechanical properties of the formulation, especially those comprising of hygroscopic components.

**7. IN-VITRO BUOYANCY STUDY:**

In this floating lag time and total floating time measurement is carried out. The test is performed in 900 ml of 0.1 N HCl using USP paddle type dissolution apparatus at 37±0.5 OC at 500 rpm. The time required for film to rise to the surface of dissolution medium and duration for which the film remains constantly floating on the dissolution medium is noted as total floating time and floating lag time respectively.

**8. STABILITY STUDIES:**

Stability studies are carried out to determine the effect of temperature and humidity on stability of drug in film during storage. The films in capsule are packed in aluminium foil and stored in ICH certified stability chamber maintained at 40±2OC (75% ±5 % RH) for three months. The capsule should be withdrawn periodically for evaluating drug content and release kinetics**.**

**9. SURFACE PH OF THE FILM:**

Surface pH of the films was determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper i,e pH range 1-11 on films. The change in the colour of pH paper should be observed.

**10. DISSOLUTION TEST:**

Dissolution testing can be performed using the standard paddle or basket apparatus described in any of the pharmacopoeias. The dissolution medium will indefeasibly be selected as per the sink conditions and highest
dose of the API. Many times the dissolution test can be rigorous due to a tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.

**CONCLUSION :**

Gastro-retentive floating film drug delivery system have emerged as an efficient means of enhancing the bioavability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increase number of gastroretentive drug delivery to optimize the delivery of molecules that exhibit absorbtion window, low bioavailability and extensive first pass metabolism. Various techniques and approaches have been employed to developed gastro-retentive dosage forms and FFDS has emerged as one of the most promising gastro-retentive drug delivery system. The currently available polymer-mediated noneffervesent and effervescent FFDS system, designed on the basis on delayed gastric emptying time and buoyancy principles, appear to be an effective an rational approach to the modification of controlled oral drug delivery. And it provides several advantages including handling cost, ease of handling, greater flexibility and adaptability of films, which gives new powerful tool to clinicians and those engaged in product development to optimize therapy. It is little wonder therefore such systems are growing rapidly. The market for this drug delivery system has come a long way and will continue to grow at impressive rate.

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