International Standard Serial Number (ISSN): 2319-8141
International Journal of Universal Pharmacy and Bio Sciences 7(2): March-April- 2018
INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES
*IMPACT FACTOR 4.018****
*ICV 6.16****
Pharmaceutical Sciences **REVIEW ARTICLE ……!!!**

GASTRO-RETENTIVE MUCOADHESIVE PELLETS: A REVIEW

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KEYWORDS:

Gastro-retention, Mucoadhesive, Mucoadhesive polymers, pelletization, *in vitro*, Wash-off test.

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ABSTRACT

The present time is considered as an era of advancements in drug delivery systems. Different novel approaches are under investigation which can provide an effective way to deliver the drug in modified form. Gastro-retentive Mucoadhesive pellets has gained immense popularity in the field of oral drug delivery recently as it retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability and multiple unit formulations has various advantages over single unit. Pelletization is one of the novel drug delivery techniques that provides an effective way to deliver the drug in modified pattern. It is advantageous in providing site specific delivery of the drug. Drugs with unpleasant taste, poor bioavailability and short biological half-life can be delivered efficiently through pellets. Their reduced size makes them more valuable as compared to the conventional drug delivery system. Mucoadhesive pellets maintains intimate contact of the dosage form with absorption surface which improved therapeutic performance of the drug or improved bioavailability of drug, reduced dosing frequency, and improved patience compliance. This current review article discuss briefly about gastro-retentive drug delivery, its approaches, Mucoadhesive drug delivery system and pellets and pelletization techniques.

INTRODUCTION:

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. The problem frequently encountered with sustained release dosage forms is the inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine. Therefore, it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time. One of the feasible approaches for achieving prolonged and predictable drug delivery profile in gastrointestinal tract is to control gastric retention time of the formulation.Dosage forms with prolonged gastric residence time, i.e., gastroretentive dosage forms, will offer new and important therapeutic options. Mucoadhesion can be defined as the state in which two materials adhere to each other for extended periods of time with the help of interfacial forces and when one of these materials is biological in nature, the phenomenon is known as bio adhesion. Multiple unit dosage forms have advantages over single unit dosage form i.e. reduce chances of dose dumping, bioavailability as the surface area increases , less dependency on gastric emptying. An intimate contact of the drug delivery system with absorbing gastric mucosal membranes. It can be achieved by coupling mucoadhesion characteristics to pellets and developing novel delivery systems referred to as gastroretentive mucoadhesive pellets.

GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

Gastro-retentive drug delivery system (GRDDS) has gained immense popularity in the fieldof oral drug delivery recently. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability.

APPROACHES FOR GASTRO-RETENTION

Different innovative approaches like magnetic field assisted gastro-retention, plug type swelling system, muco-adhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS.

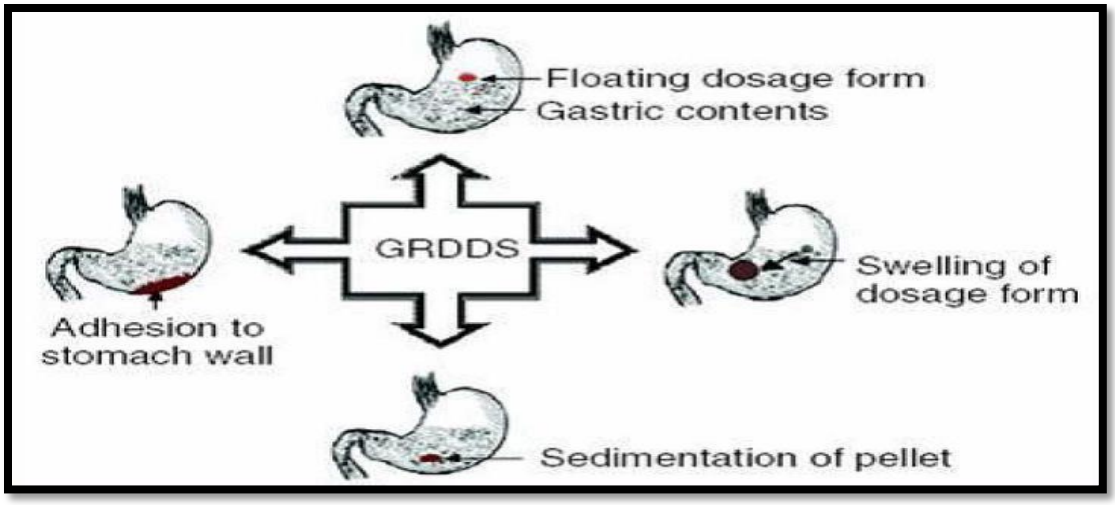

Figure 1: Various Approaches of Gastro-retentive Drug Delivery System

A. HIGH DENSITY SYSTEM

These systems with a density of about 3g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8g/cm3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. A high density formulation includes coated pellets. Coating is done by heavy inert materials such as barium sulphate, zinc oxide, and iron powder.

B. LOW DENSITY SYSTEM To avoid premature evacuation of drug through the pyloric sphincter low density systems with immediate buoyancy have been developed. They are made of low density materials, entrapping oil or air. Most are multiple unit systems and are also called microballoons because of low density core.

C. RAFT FORMING SYSTEMS The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquids swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO2 and acts as a barrier to prevent the reflux of gastric contents like HCL and enzymes into the oesophagus. Usually, the system contains a gel forming agent and alkaline bicarbonate or carbonates responsible for the formation of to make the system less dense and floats on the gastric fluids.

D. MAGNETIC SYSTEMS This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet and a magnet is placed on the abdomen over the position of the stomach. Although a magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. The technological approach in rabbits with bioadhesive granules containing ultra-fine ferrite. They guided them to oesophagus with an external magnet for the initial 2 minutes and almost all the granules were retained in the region after 2 hours.

E. FLOATING DRUG DELIVERY SYSTEM Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability . This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine . This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly.

F.MUCOADHESIVE (BIOADHESIVE) SYSTEM

Bio/Mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system in the stomach, by increasing the intimacy and duration of contact of drug with biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and App. to the development of GRDDS based on bioadhesive/mucoadhesive polymers. The ability to provide adhesion of a drug to the GI wall provides longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect.

Mucoadhesive/biodhesive drug delivery system can be applied to the following systems:

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Composition of mucus layer

Mucus is translucent and viscous secretion which forms a thin, continuous gel layer sticking to the mucosal epithelial surface. Mucus glycoprotiens are high molecular weight proteins possessing attached oligosaccharide units containing, L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine and Sialic acid10-12

Functions of mucous layer

- Mucous layer is protective because of its hydrophobicity.
- It influences the bioavailability of drugs as it acts as a barrier in tissue absorption of drugs and other substrates.
- It strongly bonds with the epithelial cell surface as a continuous gel layer.
- It plays a major role in the lubrication of the mucosal membrane and maintenance of its moisture.

MECHANISMS OF MUCOADHESION

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus.Each step can be facilitated by the nature of the dosage form and how it is administered.The mechanism of mucoadhesion is generally divided into two steps:

(1)contact stage

(2)consolidation stage

The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak Vander Waals and hydrogen bonds

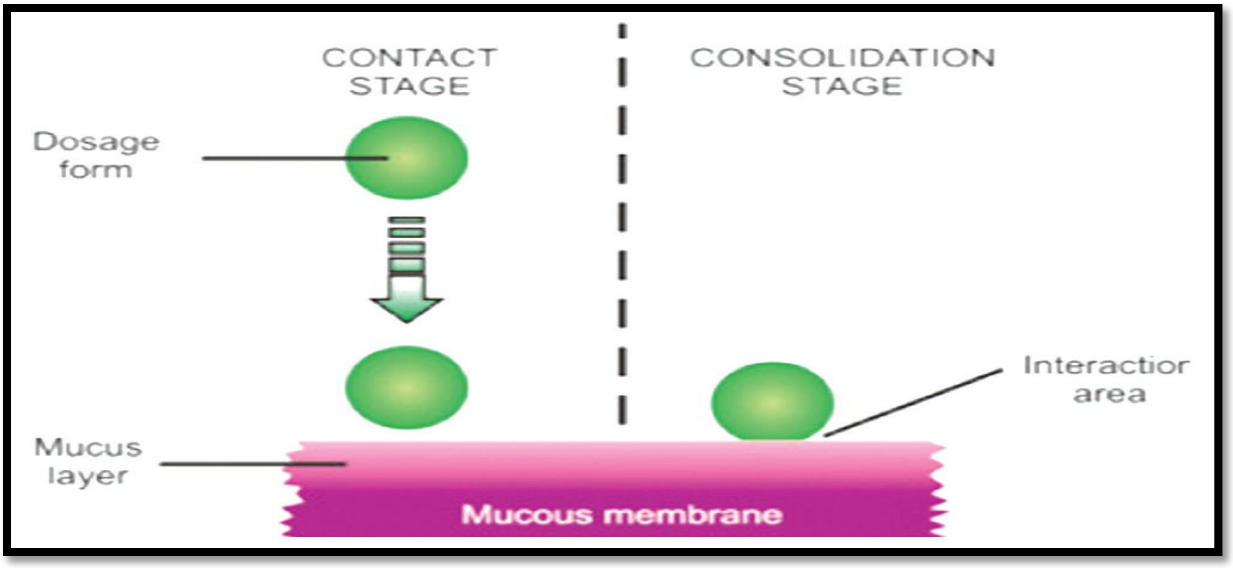

Figure 2: Mechanism of Mucoadhesion

THEORIES OF MUCOADHESION

Several theories have been proposed to explain the fundamental mechanisms of adhesion.

Wetting Theory

The wetting theory applies to liquid systems that present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that lower the contact angle greater will be the affinity. The contact angle should be equal or close to zero to provide adequate spreadability.

Electronic theory

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determine the mucoadhesive strength.

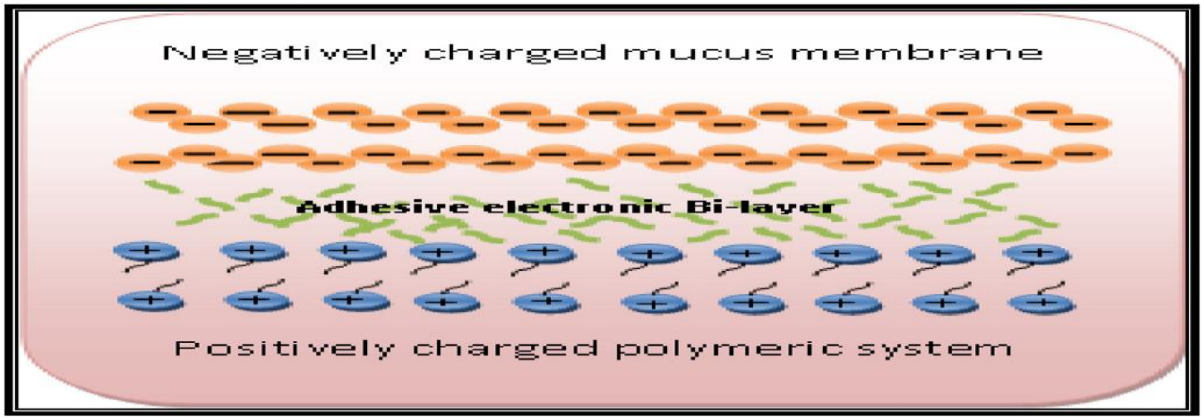

Figure 3:Electronic theory of Mucoadhesion

Adsorption theory

According to the adsorption theory, after an initial contact between two surfaces, the material adheres because of surface forces acting between the atoms in the two surfaces.

Mechanical theory

The mechanical theory assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.

Diffusion theory

According to diffusion theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between crosslinks and decreases significantly as the cross-linking density increases.

Fracture theory

Fracture theory attempts to relate the difficulty of separation of two surfaces after adhesion.Fracture theory equivalent to adhesive strength is given by:

$G = (E/L)\, l\, h$

Where *E* is the Young's modulus of elasticity is the fracture energy and *L* is the critical

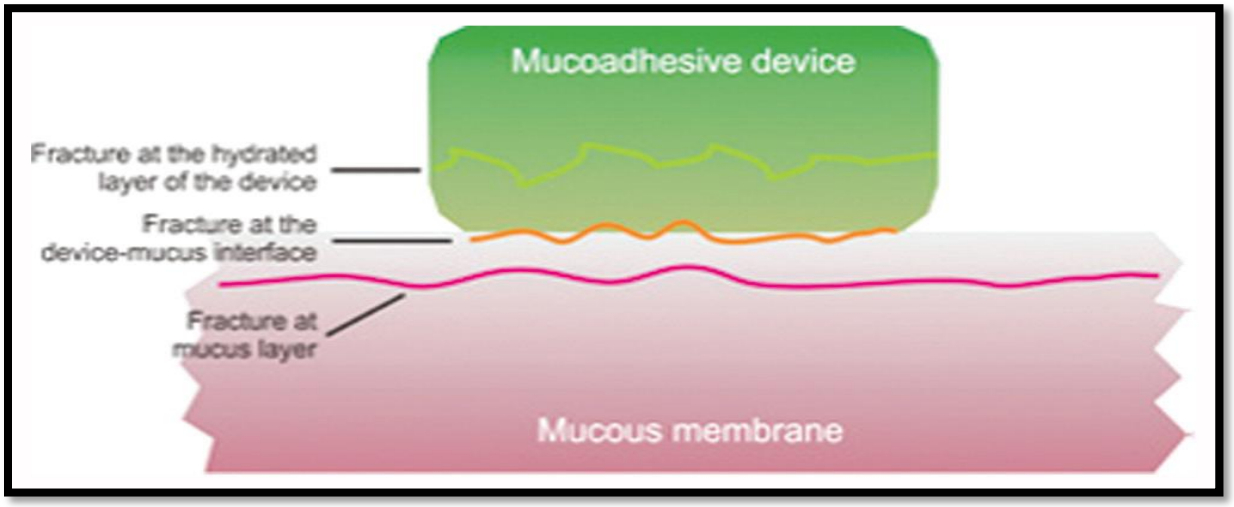

Figure 4: Regions where the mucoadhesive bond rupture can occur

Factors affecting Mucoadhesion

1. Polymer related factors:

i) Molecular weight

ii) Concentration of active polymer

Iii) Flexibility of polymer chains

IV) Special confirmation

v) Swelling

2. Environment related factors:

i) pH of polymer - substrate interface

ii) Applied strength

iii) Initial contact time

3. Physiological factors:

i) Mucin turns over

ii) Disease state

PELLETS

Pellets are small free flowing, spherical dosage forms that are prepared by the agglomeration of fine powder mixture of drug and excipients.

Desired characteristics of pellets

Pellets should be of spherical shape and smooth surface to achieve good flow characteristics, with particle size, preferably in the range of 600- 1000 µm. They should have maximum drug loading capacity to maintain the desired size of the pellets.

Pelletization techniques

Various techniques have been used for pelletization

- Pelletization by:
- Extrusion spheronization
- Drug layering
- Dry powder layering
- Solution and suspension layering
- Direct compression
- Cryopelletization
- Hot melt extrusion
- Balling
- Freeze pelletization

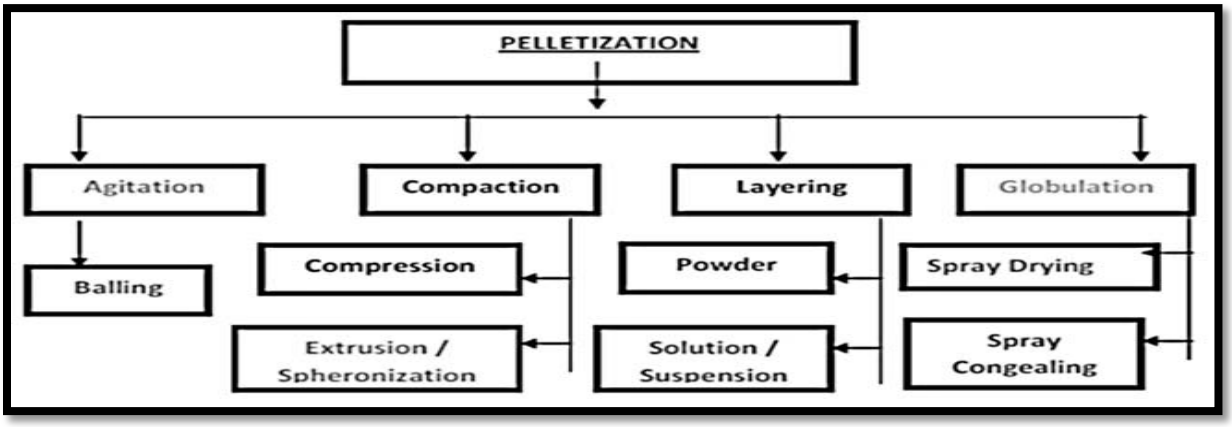

Figure 5:Various techniques of Pelletization

Extrusion spheronization

This technique is used in the pharmaceutical industry for the formulation of spherical particles of even size. It is useful technique for the preparation of pellets/granules with potential of high drug

loading capacity. The formulated pellets can be used for the development of sustained released oral dosage forms. This technique has the benefit of minimum possible use of excipients, simple, easy and fast processing and high efficiency.

Extrusion-Spheronizationis a multi-step process as described below:

1. **Dry mixing**

This step is used to achieve uniform mixing or dispersion of dry powder. A variety of mixers are available that can be used for this purpose like twin shell, high shear, planetary and tumbler mixers.

2. **Wet massing**

This process is comparable to wet granulation technique that is used to produce granules but wet massing in pelletization is used to prepare suitable plastic mass for extrusion. Commonly available mixtures are planetary mixer, sigma blade mixer, high shear mixer and Horbat mixer.

3. **Extrusion**

This is the most important step of pelletization in which pressure is applied to prepared mass to pass it through the opening of extruder of desired dimen- sions. Rod shaped extrudes are prepared with suitable plasticity. Plasticity should be sufficient to resist the deformation of extrudes but not enough to support the adhesion of the agglomerates. The solvent used in pelletization is responsible for binding as well as lubrication to facilitate the extrusion process.

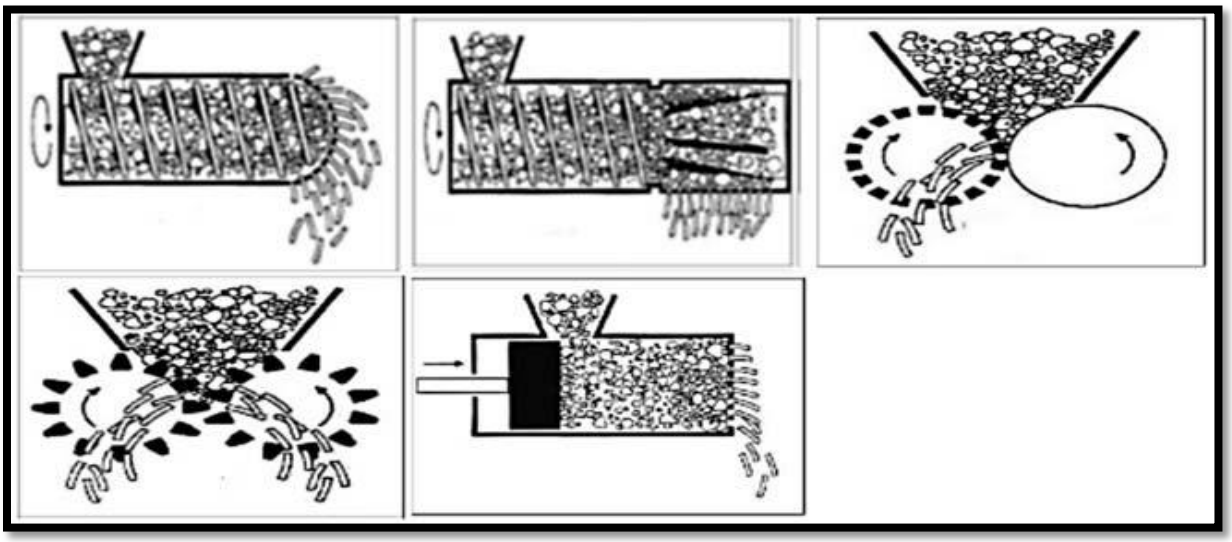

Figure 6: Various types of extruders

4.Spheronization

Rod shaped agglomerates are spheronized in this process. Extrudes are placed in the spheronizer and rotated at high speed by friction plate that convert them to small sized spherical particles.

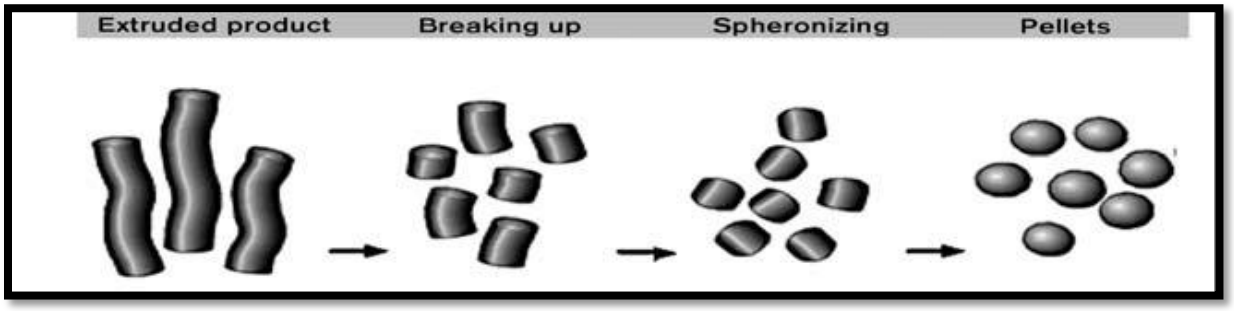

Figure 7:Principle of spheronization process

5.Drying

This process is performed to achieve required level of moisture contents in the formulations. Pellets can be dried at room temperature and even at higher temperature if required. Freeze drying technique,tray drying and fluidized bed drying techniques are available for drying of pellets. Freeze drying technique has the advantage over other techniques that it not only maintains the shape of the pellets but also retains the size.

6.Screening

Desired size of the pellets with uniform distribution is necessary and it is usually achieved by the simple technique of sieving.

Factor Affecting Pelletization Technique

1. Moisture Content

It is one of the critical parameter for pellet growth in pelletization technique .Moisture in the wet mass bring cohesiveness to the powder so that the wet mass can be extracted and spheronize to give spherical shape. High moisture contents lead to agglomeration of pellets during the process of spheronization which is one of the technique of pelletization due to excess of water in the surface of pellets and low moisture content lead to generation of fines with large variation in size distribution.

2. Rheological characteristics

The Rheological condition of the wet mass determines the flow ability in extruder optimum Rheological condition leads to good flow ability in order to extrude the wet mass variation in rheology make improper and non uniform extrusion.

3. Solubility of excipients and Drug in granulating fluid

A soluble drug get dissolve in a granulating liquid .Thus increasing the volume of liquid phase lead to over wetting of system of agglomeration of pellet sand increase in wetting liquid increases plasticity but induces sticky mass.

4. Physical Properties of Starting Material

Formulation variable such as type and content of starting material, type of filler and particle size of constituent have the effect on the pelletization process. Quality of pellets depends not only composition but also on different grades of the same product.30 The swelling property of material used in pelletization technique decides the release rate of the drug in pellets.

5. Speed of the Spheronizer

The speed of the spheronizer affects the size, hardness, sphericity and density of pellets, high speed gives high sphericity, lower friability, smooth surface and higher crushing strength.

6. Drying technique and drying temperature

It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all the batches. Variation in pellet's size, shape and flow will lead to difference in physicochemical properties of final dosage form like weight variation, improper filling etc, which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery. Variation in shape may lead to variation in flow and compressibility.

7. Extrusion Screen

The quality of the extrudate/ pellets is greatly influenced by the characteristics of the orifice of the screen. An increase in orifice dimension resulted in increased mean pellet size. The increase in orifice depth decreased with the presence of water at the extrudate surface, increasing the extrusion force, and then had a negative effect on granulometric distribution and on shape

MUCOADHESIVE GASTRO-RETENTIVE PELLETS

Oral sustained drug delivery system faces challenges due to limited gastroretention time during rapid gastrointestinal transit, can prevent complete drug release in the absorption zone and reduces the efficacy of the administered dose, since majority of drugs are absorbed in stomach or non-specific location in small intestine Formulating mucoadhesive dosage forms is one of the key approaches to overcome issues related to gastric emptying time, as gastric mucoadhesion is the phenomenon where a drug product bears a tendency to associate with mucus membrane of gastric linings and which allows an accurate control of the drug release

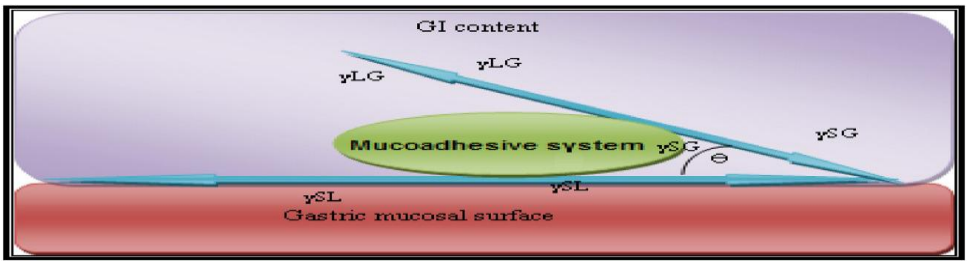

Figure 8: Relation between the contact angle mucoadhesive system gastro mucosal surface and the interface.

Mucoadhesive drug delivery systems involve the use of polymers, which adhere to the epithelial surface in the stomach. Intimate contact between the delivery system and mucosaimproves both the effectiveness and efficiency of the delivery system. Gastrointestinal tract is a potential site which has been explored since long for the development of mucoadhesive based formulations. The manipulation of the transit time of the delivery systems in a particular area of the gastrointestinal system by using mucoadhesive polymers has evinced a great interest among researchers around the world.The problem frequently encountered with sustained release dosage forms is the inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine.

Therefore, it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time. Pellets adheres to mucous layer of GIT and develops novel delivery system referred to as gastroretentive mucoadhesive pellets.

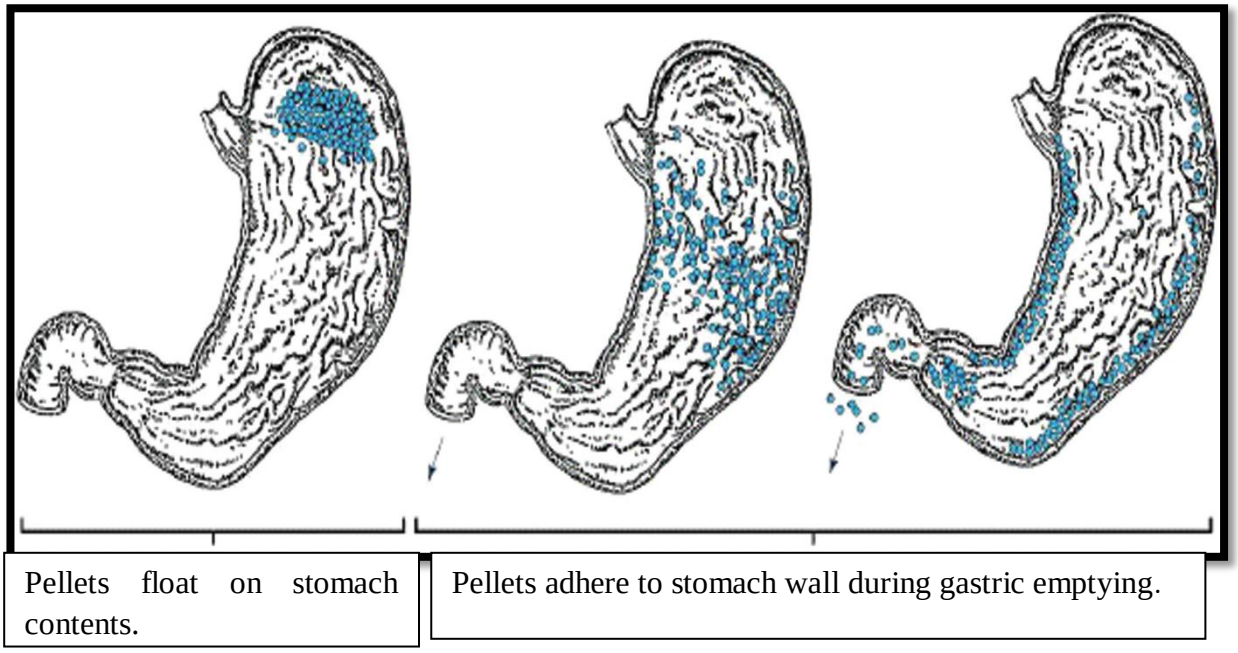

Figure 9: mechanism for retention of pellets in the human stomach

The relatively short gastric emptying time in humans, which normally averages 2–3 hours through the major absorption zone (stomach or upper part of intestine), can result in incomplete drug release from the drug delivery system leading to diminished efficiency of the administered dose. Thus, localization of a drug delivery system in a specific region of the gastrointestinal tract offers numerous advantages, especially for drugs having narrow absorption window. The intimate contact of the dosage form with the absorbing membrane has the potential to maximize drug absorption and may also influence the rate of drug absorption. These considerations have lead to the development of oral sustained release dosage forms possessing gastric retention potential. The primary concern in the development of once daily oral sustained release dosage form is not just to prolong the delivery of drugs for 24 hours but to prolong the presence of dosage forms in the stomach or somewhere in the upper small intestine. Gastroretentive dosage forms through local drug release will greatly enhance the pharmacotherapy of the stomach leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time. Conventional sustained release dosage forms pass the absorption window although they

still contain a large fraction of the drug which is consequently lost and not available for absorption.

Advantages of mucoadhesive pellets

- Readily localized in the region applied to improve and enhance the bioavailability of drugs
- Facilitate intimate contact of the formulation with the underlying absorption surface
- Prolong residence time of the dosage form at the site of application
- Sustained drug delivery
- Reduced frequency of dosing
- Reduced fluctuations of drug concentration.

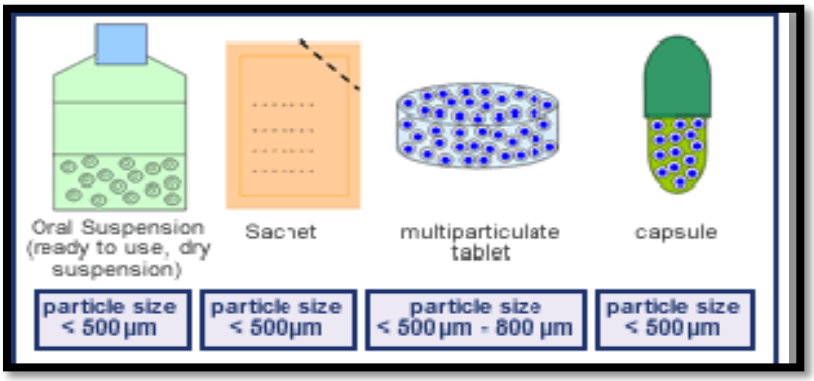

Figure 10: pellets in development of dosage form

Mucoadhesive polymers

The properties of the mucoadhesive microspheres, e.g., their surface characteristics, force of mucoadhesion, release pattern of the drug, and clearance, are influenced by the type of polymers used to prepare them. Suitable polymers that can be used to form mucoadhesive microspheres include soluble, insoluble, nonbiodegradable, and biodegradable polymers. Mucoadhesive polymers are water-soluble or water-insoluble polymers with swellable networks. The polymer should possess optimal polarity to make sure it is sufficiently wetted by the mucus and should have optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:

1. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness
2. Polymers that adhere through nonspecific, noncovalent interactions those are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant)
3. Polymers that bind to specific receptor site on tile selfsurface.

All three polymer types can be used for drug delivery.

Characteristics of an ideal mucoadhesive polymer

1. The polymer and its degradation products should be nontoxic and should be no absorbable from the GI tract.
2. It should be non-irritant to the mucus membrane.
3. It should preferably form a strong no covalent bond with the mucin–epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and should offer no hindrance to its release.
6. The polymers must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.

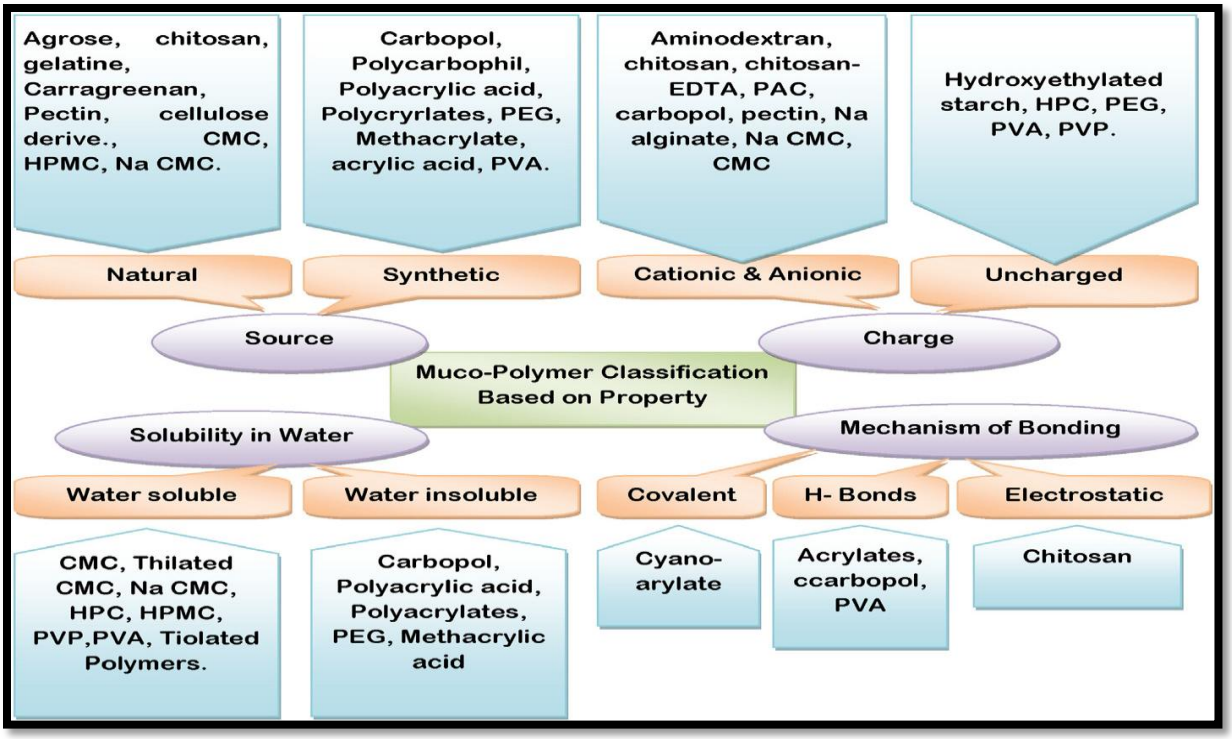

Figure 11: An overview of mucoadhesive polymers classifications

2.5.2 EVALUATIONS

Particle size distribution

Particle size distribution was determined using mechanical sieve shaker. 5 g of the pellets were sifted through a series of sieves (12, 16, 18 and 24 mesh). The machine was operated for 5 minutes and % retained on respective sieve was calculated. The average particle size was determined.

Percentage yield

The percentage yield was calculated by dividing weight of dried pellets (W1) by initial weight of the baclofen and polymers (W2) used for the formulation and converting the weight ratio into percent.

Density and flow property

All formulation batches were evaluated for their physical properties like bulk density, tap density, friability, flow property in terms of angle of repose. All these parameters affect the processing of final formulation.

Loss on drying (LOD*)*

Loss on drying (LOD) was determined by gravimetric technique. A weighed quantity of pellets (10 g) were kept for drying in hot air oven at 60 C and loss in weight was calculated at regular time Interval till constant weight.

Image analysis

The sphericity of the pellets was determined using derived pellet parameters measured by an image analysis system .A random sample of 150–200 pellets from each batch of product was examined.

Swelling property

Swelling property was determined for each formulation batch. A weighed amount of pellets (10 g) were placed in a 100 ml measuring cylinder containing pH 1.2 media. Initial volume (Vo) was noted and change in physical volume was observed (Vt) at regular interval for 6 h.

The degree of swelling was calculated using following formula:

Degree of Swelling = Vt -Vo/Vo

Fourier transform infrared spectroscopy

Drug polymer interaction was studied by FTIR spectroscopy. The spectra were recorded for pure drug and drug loaded pellets using FTIR. Samples were prepared as potassium bromide (KBr) disks by means of a hydrostatic press.

***In Vitro* Dissolution**

Mucoadhesive pellets were introduced into dissolution medium of 0.1N HCl (900ml) for 12 hrs at 37±0.5°C at a rotation speed of 50 rpm by using USP type II dissolution test.Samples of 5ml were withdrawn through a filter at every one hour intervals up to 12th hrs and replaced with equal volume of 0.1N HCl buffer. The samples were analyzed using UV spectrophotometer.

Wash off test for mucoadhesion time

The *ex-vivo* mucoadhesion time studies were performed after application of about 100 pellets on freshly cut goat stomach mucosa. The mucosa was fixed on a glass slide using double sided adhesive and one side of glass slide was fixed to thread whose another end was fixed with the arm of disintegration test apparatus. The beaker was filled with 900 ml of 0.1 N HCL and kept at

37˚C; after 2 minutes the slide was placed in a beaker and the apparatus was started. Every one hour intervals, the equipment was stopped and the number of mucoadhesive microspheres still sticking onto the mucosa was counted and percent mucoadhesion was calculated.

%Adhesive Strength= N_0-N_s *100 /N_s

CONCLUSION

To derive maximum therapeutic benefits from certain drug substances, it is desirable to prolong their gastric residence time. In addition, the delivery system should exhibit a burst followed by a sustained release of the active agent. Various techniques and approaches have been used to develop gastroretentive drug delivery system. Mucoadhesive drug delivery systems are gaining popularity day by day in the global pharma industry and a burning area of further research and development. Mucoadhesive pellets offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue, including those found in eyes, oral cavity, and throughout the respiratory, urinary, and gastrointestinal tract. The mucoadhesive pellets can be used not only for controlled release but also for enhancing bioavailability, for targeted delivery of the drugs to specific sites in the body. Drug delivery through mucoadhesive pellets is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability over longer periods of time and for drug targeting to various sites in the body. Thus, it can be conclude that these dosage forms serve as best in the treatment of GIT diseases as well as for site targeting delivery and for prolonging action of drugs with a short half life for better patience compliance by reducing frequent administration.

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