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A SYSTEMIC REVIEW ON FLOATING MUCOADHESIVE DRUG DELIVERY SYSTEM

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Abstract:

Gastro retentive drug delivery system (GRDDS) is one of the novel approaches in the area of oral sustained release dosage forms. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation require frequent dosing to achieve suitable therapeutic activity. The floating drug delivery systems increase the Gastric retention time providing wide therapeutic efficacy. Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastric pH require increased duration of stay in GIT. Thus, floating and mucoadhesive drug delivery systems are advantageous in increasing the bioavailability and enhanced therapeutic activity. In this regard, this review aims to provide information of different floating and mucoadhesive approaches and their importance.

Keywords: *Bioadhesive, floating drug delivery, gastroretentive, mucoadhesive*

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INTRODUCTION:

FLOATING DRUG DELIVERY SYSTEM(FDDS)

Floating drug delivery systems (FDDS) are aimed to retain the drug in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The underlying principle is very simple i.e., to make the dosage form less dense than the gastric fluids so that it can float on them. The density of the system can be reduced by incorporating a number of low density fillers into the systems such as hydroxyl cellulose, lactates or microcrystalline cellulose. However, this system is not ideal because its performance is highly dependent on the presence of food and fluid in the stomach. The basic idea behind the development of such a system was to maintain a constant level of drug in the blood plasma inspire of the fact that the drug dose not undergoes disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood [1,2].

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation.

Advantages of FDDS

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

- ✓ Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- ✓ Controlled delivery of drugs.
- ✓ Delivery of drugs for local action in the stomach.
- ✓ Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
- ✓ Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
- ✓ Simple and conventional equipment for manufacture.
- ✓ Ease of administration and better patient compliance.
- ✓ Site-specific drug delivery [7,8]

Limitations of FDDS

- ✓ Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- ✓ Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
- ✓ High variability in gastric emptying time due to its all or non-emptying process.
- ✓ Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diameter and size. Therefore patients should not be dosed with floating forms just before going to bed [9].

Types of FDDS

(A)Non-effervescent systems: This type of system, after swallowing, swells via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. The formulation methods of such type dosage forms involves the mixing of the drug with a gel, which swells when comes in contact with gastric fluid and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer provides buoyancy these dosage forms. The most commonly used excipients in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, carbopol agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types [3-5].

(i) **Colloidal gel barrier system:** These types of systems contain drug with gel-forming hydrocolloids which allow them to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug at its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid as hydroxypropyl cellulose, hydroxyethyl cellulose. This hydrocolloid hydrates and forms a colloid gel barrier around its surface after coming in contact with gastric fluid and also helps in sustain releasing of drug.

(ii) **Microporous Compartment system:** In this technology, a drug reservoir is encapsulated inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed. This sealing prevents any direct contact of gastric surface with the un-dissolved drug. The flotation chamber containing the delivery system to float over the gastric content entrapped air allows, in the stomach. Gastric fluid enters through an aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

(iii) **Alginate beads:**To develop Multi-unit floating dosage forms, the freeze dried calcium alginate has

been used. Spherical beads of approximately 2.5 mm in diameter can be prepared by the precipitation of calcium alginate via dropping sodium alginate solution into aqueous solution of calcium chloride. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, it leads to the formation of a porous system which can maintain a floating force for over 12 hours. These floating beads prolonged residence time for more than 5.5 hours.

(iv) **Hollow Microspheres/Microballons:** A novel emulsion solvent diffusion method used to prepare hollow microspheres loaded with drug in their outer polymer shelf ethanol/ dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of poly vinyl alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed in the internal cavity of microsphere of the polymer and drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12h.

(B) Effervescent Systems: These buoyant systems utilize matrices prepared with swellable polymers such as methocel polysaccharides (e.g., chitosan) and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that when it arrives in the stomach carbon dioxide is released, causing the formulation to float in the stomach [6].

Practical approaches in designing FDDS

The concept of FDDS was first described in the literature as early as 1968, when Davis (1968) disclosed a method to overcome the difficulty experienced by some persons of gagging or choking after swallowing medicinal pills. The author suggested that such difficulty could be overcome by providing pill having a density of less than 1.0g/cm3, so that pill will float on water surface. Since then several approaches have been used to develop an ideal floating drug delivery system [10].

Formulation approaches of FDDS

The following approaches have been used for the design of floating dosage forms of single and multiple unit systems.

A. Single Unit Dosage Form

In low density approaches, the globular shells apparently having lower density than that of gastric fluid can be used as a carrier like popcorn, poprice, polystrol for the drug for its controlled release. The polymer of choice can be either Ethyl cellulose or HPMC depending on type of release desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid filled floating chamber type of dosage forms includes incorporation of a gas filled floatation chamber in to a micro porous component that houses as a reservoir having apertures present at top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. Hydro Dynamically Balanced Systems are designed to prolong the stay of the dosage forms in the gastric intestinal tract and aid in enhancing the absorption. Drugs having a better solubility in acidic environment and also having specific site of absorption in the upper part of small intestine is achieved by these HBS systems. Among all the advantages single-unit formulations are associated with some limitations/problems such as sticking together or being obstructed in the GIT which may lead to potential danger of producing irritation [11].

B. Multiple Unit Dosage Form

Multiparticulate dosage forms are gaining much favor over single-unit dosage forms. The potential benefits include increased bioavailability; predictable, reproducible and generally short gastric residence time, no risk of dose dumping; reduced risk of local irritation, and the flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability. However, potential drug loading of a Multiparticulate system is lower because of the proportionally higher need for excipients (e.g., sugar cores). Most Multiparticulate Pulsatile delivery systems are reservoir devices coated with a reputable polymeric layer. Upon water ingress, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure build-up within the system. The pressure necessary to rupture the coating can be achieved with swelling agents, gas producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Water soluble drugs are mainly released by diffusion; while for water insoluble drug, the release is dependent on dissolution of drug [12].

Mechanism of floating systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach

without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [13].

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature[14]. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side [15].

FACTORS AFFECTING GASTRIC RESIDENCE TIME OF FDDS

A) Formulation factors

Size of tablets

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves [9]. Floating and non-floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the non-floating forms stayed close to the pylorus and were subjected to propelling waves of the digestive phase.

Density of tablets

Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gas tric fluids floats since it is away from the pyloric spinchter the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e less than that of gastric contents has been reported. However the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most approporiate parameter for describing its buoyancy capabilities.

Shape of tablets

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring, tetrahedron, cloverleaf, string, pellet and disk) were screened in vivo for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24hrs[12].

Viscosity grade of polymer

Drug release and floating properties of FDDS are gre atly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. Inaddition, a decrease in the release rate was observed with an increase in polymer viscosity.

B) Idiosyncratic factors

Gender

Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours),
regardless of the weight, height and body surface.

Age

Low gastric emptying time is observed in elderly tha n do in younger subjects. Intra
subject and intersubject variations also are observed
in gastric and intestinal transit time. Elderly people, e specially those over 70 years have a significantly lon ger GRT.

Posture

i) Upright position

An upright position protects floating forms against postprandial emptying because the floating form remains above the
gastric contents irrespective of its size.

ii) Supine position

This position offers no reliable protection against early and erratic
emptying. In supine subjects large dosage forms

(both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements thatpropel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.

Concomitant intake of drugs

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The co-administration of GI-motility decreasing drugs can increase gastric emptying time.

Feeding regime

Gastric residence time increases in the presence of food, leading to increased drug dissolutionof the dosage form at the m ost favorable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins. [16,17,18,19]

MUCOADHESIVE DRUG DELIVERY SYSTEM (MDDS)

Since from the last 40 years, the concept of mucoadhesion has provided the great application in prolonging the residence time as well as controlled release effect of various bioadhesive dosage forms through different mucosal routes. The formulations based on the mucoadhesive drug delivery system have shown the enhanced bioavailability of many drugs. The use of various mucoadhesive polymers have achieved the significant interest in formulating the sustained release, extended release as well as prolonged release dosage forms. The mucoadhesive drug delivery provides greater absorption and enhanced bioavailability of dosage forms due to the large surface area and higher blood flow in the mucosal cavities. The delivery across the mucus membrane provides various advantages over other drug delivery routes i.e., overcome the hepatic first pass metabolism as well as the degradation of drugs by various gastrointestinal enzymes as well as intestinal flora [20,21.] For the desired mucoadhesive strength of the mucoadhesive dosage forms, there are various mucoadhesive polymers that can be used. These polymers are either natural or synthetic macromolecules which are capable of adhering to the mucosal surfaces. From last three decades, the use of various mucoadhesive polymers has achieved a great interest in the field of pharmaceutical technology. Nowadays, the use of mucoadhesive polymers has been accepted as an important strategy to prolong the residence time and to improve the localized effects of drug delivery systems on various mucus membranes of a biological system [22].

Advantages of mucoadhesive drug delivery system

- ✓ The buccal drug delivery provides a relatively rapid onset of action as compare to the other non-oral routes, hence, has a high patient acceptability.
- ✓ Improved patient compliance due to the easy application of dosage forms in comparison to the injections and they don't provide any painful sensation
- ✓ The mucosal membranes are highly vascularized so that the administration is easy.
- ✓ The sustained drug delivery can be achieved by using the mucoadhesive polymers of 'SR' grades.
- ✓ Due to the high extent of perfusion the rate of drug absorption is faster.
- ✓ The side effect that can arise due to oral administration, such as, nausea and vomiting, they can be avoided completely.
- ✓ The mucoadhesive drug delivery can be easily used in case of unconscious and less Co-operative patients.
- ✓ The drugs, which show poor bioavailability via the oral route, can their bioavailability can be enhanced by formulating their mucoadhesive delivery systems [24,25].

Mechanism of Mucoadhesion

The mucoadhesion can be defined as an interfacial phenomenon in which the two materials, in which one may be artificial such as mucoadhesive polymer and other may be the mucin layer of the mucosal tissue, are held together by means of interfacial forces of attraction. "Mucoadhesive" is defined as an artificial substance that is capable of interacting with mucus membrane and being retained on them or holding them together for extended or prolonged period of time. During the process of adhesion, generally the two stages have been identified. These stages of mucoadhesion are also shown in Figure 1 [26].

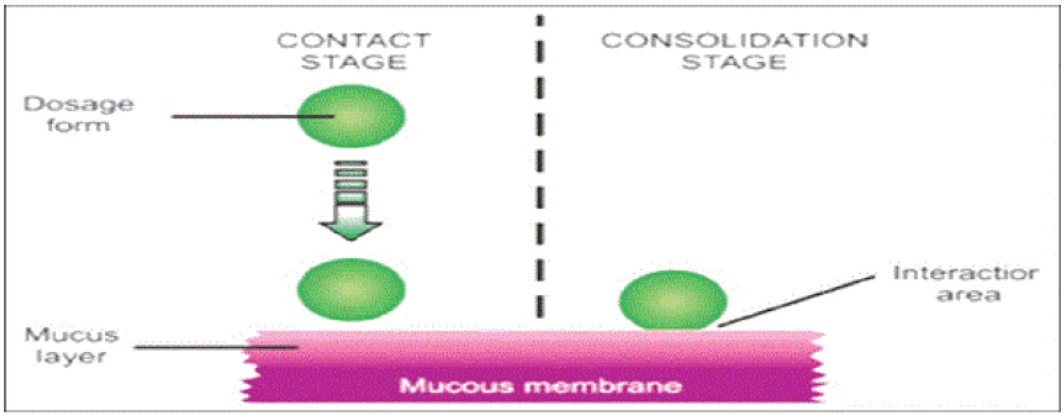

Figure 1: Mechanism of mucoadhesion: The mucoadhesion takes place in two stages. (A) Contact stage: Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon). (B) Interactive stage: Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration).

1. **Contact stage**: During this stage, when the mucoadhesive material comes in contact with mucus membrane, an intimate wetting occurs between the mucoadhesive and mucous membrane. This wetting of the mucoadhesive is done by the mucus present in the mucosal membrane.
2. **Consolidation stage**: By means of different physicochemical forces of attraction the mucoadhesive material gets joined to the mucus membrane and resulting in a long lasting mucoadhesion. This is called as the consolidation stage. After these two stages the process of mucoadhesion completes.

Theories of Mucoadhesion

The process of mucoadhesion is mainly based on formation of two types of bond between bio adhesive system and mucus membrane and they are:

1. **Chemical bond**

It may include covalent bonds, Weak secondary bonds, ionic bond and hydrogen bond etc.

2. **Mechanical bond**

This bond can be arising from the physical connection between two surfaces. It is similar to that of the interlocking system. On the basis of nature and strength of these two kinds of bonds, there are following five theories of mucoadhesion that are been postulated .

3. **Electronic theory**

According to the electronic theory, there is difference in the electronic structure of mucin surfaces and bio adhesive system which results in attaining an electronic gradient. Due to this electronic structure difference, the transfer of electrons occurs in these two systems (mucin surface and bioadhesive system) when they come in contact with each. As a result of this electron transfer there is the formation of an electronic bi-layer at the interface of the two surfaces. This interfacial bi-layer exerts an attractive force in the interface of two surfaces that may produce an effective mucoadhesion [27].

4. **Adsorption theory**

This theory describes the involvement of both type of chemical bond, that is, primary and secondary bond in the bio adhesion mechanism. Both the surface that is mucin and drug delivery system has their own surface energy. When they come in contact, the adhesion occurs due to the surface energy and results in the formation of two types of chemical bond. Primary chemical bond such as covalent bond, which is strong in nature, thus produces a permanent bonding, whereas secondary chemical bond involves Vander-Waals forces, hydrophobic interaction and hydrogen bonding, which are weak in nature, thus produces a semi-permanent bond [27].

5. **Wetting theory**

This theory is based on the mechanism of spreadability of drug dosage form across the biological layer. This theory is mainly applicable to liquids or low viscous mucoadhesive system. According to this theory, the active components penetrate in to the surface irregularities and gets harden it that finally results in mucoadhesion.

6. **Diffusion interlocking theory**

This theory describes the involvement of a mechanical bond between the polymeric chain of drug delivery system and polymeric chain of mucus membrane, that is, glycol proteins. When two surfaces are in intimate contact, the polymeric chain of drug delivery system penetrates in to the glycoprotein network. According to this theory, the bioadhesion basically depends on the diffusion coefficient of both polymeric chains. The other factors that may influence the inter movement of

polymeric chain are molecular weight, cross linking density, chain flexibility, and temperature in order to achieve a good bio adhesion, the bio adhesive medium should have a similar solubility with glycoprotein resulting in effective mucoadhesion [28].

7. Fracture theory

The fracture theory is mainly based on the fact that, the force required detaching the polymeric chain from the mucin layer is the strength of their adhesive forces. This strength may be also called as fracture strength. The fracture strength can be determined by using the formula given below

$$G=(E.\ e/L)^{1/2}$$

Where, G-Fracture strength,
E-Young's modules of electricity,
e-Fracture energy,
L-Critical crack length.

Mucoadhesive polymers properties [29,30]

1. It must be loaded substantially by the active compound.
2. Swell in the aqueous biological environment of the delivery–absorption site.
3. Interact with mucus or its components for adequate adhesion.
4. When swelled they allow, controlled release of the active compound.
5. Be excreted unaltered or biologically degraded to inactive, non-toxic oligomers.
6. Sufficient quantities of hydrogen bonding chemical groups.
7. Possess high molecular weight.
8. Possess high chain flexibility.
9. Surface tension that will induce spreading into mucous layer.

Polymers used for mucoadhesive drug delivery [31]

These polymers are classified as,

1. Hydrophilic polymers

Contains carboxylic group and possess excellent mucoadhesive properties. These are,

• PVP (Poly vinyl pyrrolidine)
• MC (Methyl cellulose)
• SCMC (Sodium carboxyl methyl cellulose)
• HPC (Hydroxyl propyl cellulose)

2. Hydrogels

These swell when in contact with water and adhere to the mucus membrane. These are further classified according to their charge

Anionic polymers - carbopol, polyacrylates
Cationic polymers - chitosan
Neural/ non-ionic polymers - eudragit analogues

Factors affecting mucoadhesion [32]

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

Polymer Based Factors

1. Molecular weight of the polymer, concentration of polymer used of polymer chain.
2. Swelling factor stereochemistry of polymer.

Physical Factors

1. pH at polymer substrate interface
2. Applied strength,
3. Contact time.
4. Mucin turnover rate
5. Diseased state.

Evaluation of mucoadhesion

***In vitro* techniques**

The best approach to evaluate mucoadhesive microspheres is to evaluate the effectiveness of themucoadhesive polymer to prolong the residence time of drug at the site of absorption, there by increasing absorption and bioavailability of the drug. The quantification of the mucoadhesive forces between polymericmicrospheres and the mucosal tissue is a useful indicator for evaluating the mucoadhesive strength of microspheres. In vitro techniques have been used to test the polymeric microspheres against a variety of synthetic and biological tissue samples, such as synthetic and natural mucus, frozen and freshly excised tissue, etc. [33] The different in vitro methods include the following.

i. Tensile stress measurement using Wilhelmy plate technique:

The Wilhelmy plate technique is traditionally used for the measurement of dynamic contact angles and involves the use of a microtensiometer or a microbalance. The CAHN dynamic contact angle analyzer (model DCA 322, CAHN instruments, Cerritos) has been modified to perform adhesive microforce measurements. By using the CAHN software system, three essential mucoadhesive parameters can be analyzed. These include the fracture strength, deformation to failure, and work of adhesion. [34]

ii. Novel electromagnetic force transducer:

The electromagnetic force transducer (EMFT) is a remote sensing instrument that uses a calibrated electromagnet to detach a magnetic loaded polymer mamoparticle/microsphere from a tissue sample. It has the unique ability to record remotely and simultaneously the tensile force information as well as high magnification video images of mucoadhesive interactions at near physiological conditions. The EMFT measures tissue adhesive forces by monitoring the magnetic force required to exactly oppose the mucoadhesive force. The primary advantage of the EMFT is that no physical attachment is required

between the force transducer and the particle. This makes it possible to perform accurate mucoadhesive measurements on the small nanoparticles/microspheres, which have been implanted *in vivo* and then excised (along with the host tissue) for measurement. This technique can also be used to evaluate the bioadhesion of polymers to specific cell types andhence can be used to develop BDDS to target-specific tissues.

iii. Shear stress measurement:

The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact. Adhesion tests based on the shear stress measurement involve two glass slides coated with a polymer and a film of mucus. Mucus forms a thin film between the two polymercoated slides, and the test measures the force required to separate the two surfaces. [35]Mikos and Peppas designed the *in vitro* method of the flow chamber. The flow chamber made ofplexiglass is surrounded by a water jacket to maintain a constant temperature. A polymeric nanoparticles/microsphere placed on the surface of a layer of natural mucus is placed in a chamber. A simulatedphysiologic flow of fluid is introduced in the chamber and movement of nanoparticles/microsphere is monitored using video equipment attached to a goniometer, which also monitors the static and dynamic behavior of the nanoparticles/microparticle.

CONCLUSION:

The Floating drug delivery system and Mucoadhesive drug delivery system have their own advantages and disadvantages also. Thus to create a novel approach limiting their disadvantages, a new dosage form can be designed. A combination of floating and mucoadhesive (FMDDS) has risen as an effective strategy to enhance the bioavailability and control the delivery of numerous drugs that have pH subordinate solubility and instability at intestinal pH.These systems can ease the drug delivery without any side effects. Notwithstanding these points of interest, there are still some uncertain and basic issues identified with the normal improvement of these systems that should be tended to. These issues include: 1) advancement of standard worldwide criteria for assessing the FDDS, 2) the need to comprehend polymer conduct and additionally to create more up to date site coordinated polymers, and 3) more profound examination of GRT and pharmacokinetic attributes of the dosage forms. Complete elucidation of the mechanism of the system, as well as assessing the rate of drug input into the GIT, may be necessary for optimizing the pharmacokinetic and toxicological profiles of drugs of interest. Many drugs whose absorption window is only stomach can be easily formulated in the form of FMDDS to achieve maximum bioavailability and therapeutic efficacy.

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