Review Article CODEN: IJPRNK IMPACT FACTOR: 1.862 ISSN: 2277-8713
Akshay Patel, IJPRBS, 2014; Volume 3(2): 449-465 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A REVIEW ON MUCOADHESIVE MICROCAPSULES: NOVEL APPROACH FOR STOMACH SPECIFIC DRUG DELIVERY

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Accepted Date: 19/04/2014; Published Date: 27/04/2014

Abstract: Bioadhesion is a topic of current interest in the design of drug delivery systems. The gastroretentive bioadhesive drug delivery system prolong the residence time of the dosage form at the site of absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and / or better therapeutic performance of the drug. The process of bioadhesion involving a polymeric drug delivery platform is a complex one that includes wetting, adsorption and interpenetration of polymer chains amongst various other processes. There is various factor influences the Gastroretention and bioadhesion. This paper describes some aspects of bioadhesion such as mucus layer, mucoadhesion, and theories of bioadhesion to explain the adhesion mechanism .The factors important to bioadhesion and different type's bioadhesive polymers are described.

Keywords: Gastro Retentive, Bio/Muco-adhesive Drug Delivery System.

PAPER-QR CODE

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How to Cite This Article:

Akshay Patel, IJPRBS, 2014; Volume 3(2): 449-465

INTRODUCTION

Gastro retentive system ensures that whole drug delivery system remains within the gastric region for longer duration of time. This improves gastric retention time for such drug in comparison to conventional dosage form and further minimum effective concentration of drug remains maintained in systemic circulation for longer duration. This also improves the solubility of drugs which are less soluble at alkaline pH of intestine and wastage of drug during the absorption process is reduced remarkably.

Gastro retentive drug delivery systems prolong the dosing intervals and thus improve patient compliance. Presence of drug in solution form is the most essential requisite for a drug to get absorbed. But, if the solubility of drug is poor then the time required for drug to get dissolve within stomach would be high and transit time becomes most stringent factor, which would in turn affect the absorption of drug. So, dose of administration for such drugs should be kept at more frequent intervals in a single day. Gastro retentive drug delivery systems provide a support to reduce the frequent dosing of such drug by producing a controlled delivery within stomach for longer duration. Though, other formulations or novel dosage forms like nanoparticle, microspheres, liposome etc. can also be used for controlled release effect, but gastro retentive system are considered much better alternative for improved absorption through stomach.

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

BASIC ANATOMY OF STOMACH AND ITS PHYSIOLOGY[4-6]

During past 4 decades, the idea of gastro retention is known to researchers and is popularly cultured. Davis, in 1968, 1st described the concept of floating drug delivery systems. To understand the approaches for gastro retention, it is necessary to overview gastric physiology and gastric motility. Human stomach has a resting volume of 25-50ml, which can distend up to 1500ml following a meal. The stomach is a J-shaped organ. It is located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastria and left hypochondria region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Since the drugs are absorbed in the upper small intestine, it will be beneficial to develop the dosage forms that reside in that region.

It is divided into 3 anatomical parts; Fig.1.1

a) Fundus: also called proximal stomach, which acts as food reservoir.

b) Body

c) Pylorus or antrum: also called distal stomach, which acts as a site of mixing motions to propel gastric contents for emptying. Pyloric sphincter has a diameter of 12.8±7mm in humans and serves as a sieve and stricture to passage of large particles.

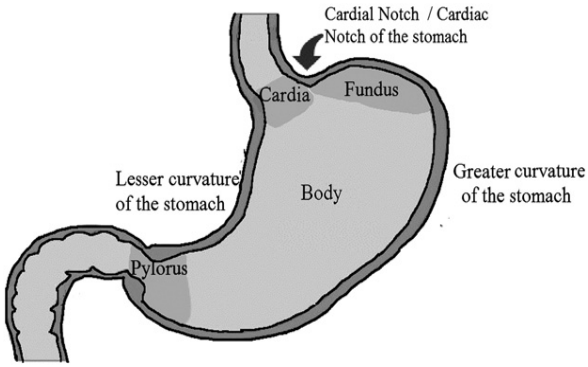

Fig. 1.1 Physiology of the stomach.

Gastric motility is also a key factor in stomach specific drug delivery. Thorough knowledge of motility is prerequisite for developing a retentive form of drug. Gastric motility differs in fasting and fed states. In fasting states, an Inter-digestive myoelectric motor complex (IMMC), a 2 hr. cycle of peristalsis is generated which progresses to ileocecal junction. It consists of 4 phases.[6]

Phase I: also called quiescent period with rare low amplitude contractions, lasting for 30 60 min.

Phase II: it comprises of intermediate amplitude contractions with bile secretion, lasting for 20-40 min.

Phase III: also called Housekeeper waves, it forms of very high amplitude contractions offering maximum pyloric opening and efficient evacuation of stomach contents. It lasts for 10-20 min. with a frequency of 4-5/min.

Phase IV: transitional phase between phase III and I of two consecutive cycles. It lasts for less than 5 min.

In fed states, motility is induced 5-10 min after ingestion and persists as long as food remains in stomach, typically 3-4 hr. Activity is same as phase2 of IMMC.

Gastro retentivity of drug was required to increase the bioavailability of drug and to reduce the undesirable effects caused by exposure of drug to other regions of GIT.

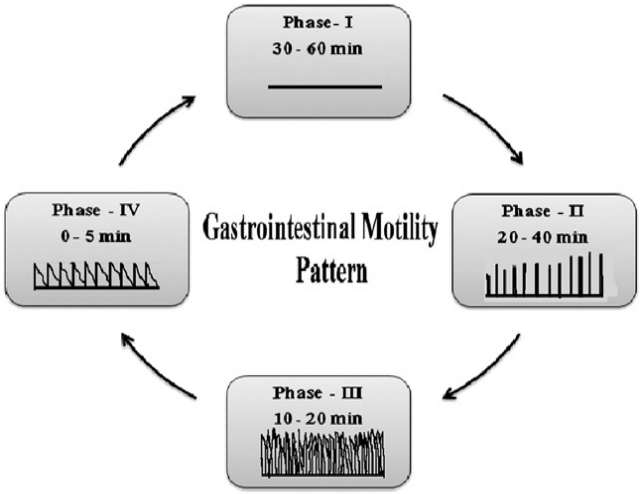

Fig 1.2 Schematic representation of inter digestive gastric motility pattern

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS[8-9]:

- The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastro retentive drug delivery approach in comparison to the administration of non-gastro retentive drug delivery.
- For drugs with relatively short Halflife, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
- They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET).
- Gastro retentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
- The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.
- Minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented.

This feature is of special importance for drug with a narrow therapeutic index, also possible to obtain improved selectivity in receptor activation.

- Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
- The sustained mode of drug release from Gastro retentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

DISADVANTAGES OF GASTRO RETENTIVE DRUG DELIVERY[10]:

- The otherwise-excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in the stomach is sufficient high.
- However, as the stomach empties and the dosage form is at the pylorus, the buoyancy of the dosage form may be impeded.
- Gastric emptying of floating dosage forms in supine subject may occur at random and becomes highly dependent on diameter size.
- The major challenge for a bio adhesive system is the high turnover rate of gastric mucus.
- There is also possibility of oesophageal binding with bio adhesive drug delivery systems.
- Hydrogel based swelling system takes longer time to swell.
- For the unfolding system the mechanical shape memory is relatively short lived, moreover these type of dosage forms are most difficult to prepare commercially
- Size-increasing drug delivery systems potentially present the hazard of permanent retention in the stomach and could lead to life-threatening effects upon multiple administrations. Super porous systems having drawback like problematical storage of much easily hydrolysable, biodegradable polymer.

APPROACHES OF GASTRORETENTIVE FORMULATION [14]

A) Floating drug delivery system (FDDS)

I) Non-effervescent systems:-

1) Colloidal gel barrier system

2) Microporous compartment system

3) Alginate beads

4) Hollow microspheres/micro balloons

II) Gas generating (Effervescent) systems

III) Raft forming systems

IV) In situ oral floating gels

B) Expandable systems

C) Bio/Muco adhesive systems

D) High-density systems

E) Magnetic system

FACTORS AFFECTING THE GASTRORETENTIVE SYSTEM:

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include use of floating dosage forms (gas generating systems and swelling or expanding systems), mucoadhesive systems, high density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Most of these approaches are influenced by a number of factors that affect their bioavailability and efficacy of the gastro retentive system:

- Density – gastric retention time (GRT) is a function of dosage form buoyancy that is dependent on the density.
- Size – dosage form units with a diameter of more than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.
- Shape of dosage form – tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.
- Single or multiple unit formulation – multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

- Fed or unfed state – under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- Nature of meal – feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.
- Frequency of feed – the GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- Gender – mean ambulatory GRT in males (3.4±0.6 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 – elderly people, especially those over 70, have a significantly longer GRT.
- Posture – GRT can vary between supine and upright ambulatory states of the patient
- Concomitant drug administration – anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
- Biological factors – diabetes and Crohn‟s disease, etc.

BIO/MUCOA-ADHESION SYSTEM [16, 17]

Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bio adhesion of certain polymers, which become adhesive on hydration**,** and hence can be used for targeting a drug to a particular region of the body for extended periods of time. Bio adhesion is an interfacial phenomenon in which the two materials, at least one of which is biological, are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to mucin layer of a mucosal tissue, the term "Mucoadhesion" is used. Oral therapy by drugs with a narrow absorption window in the upper part of the gastrointestinal tract or drugs with a poor stability in the colon. Furthermore, the

drug can act locally within the stomach and prolonged intimate contact with the absorbing membrane increases efficacy.

MECHANISM OF MUCOADHESION

The mechanisms responsible in the formation of bioadhesive bonds are not fully known, however most research has described bioadhesive bond formation as a three step process.

***Step 1*:** In this step (fig. 3), when the polymer spreads over the surface of biological substrate or mucosal membrane, the wetting and swelling step occurs in order to develop an intimate contact with the substrate. By the help of the surface tension and forces that exist at the site of adsorption or contact, bioadhesives are able to adhere to or bond with biological tissues. Swellings of polymers occur because the components within the polymers have an affinity for water.

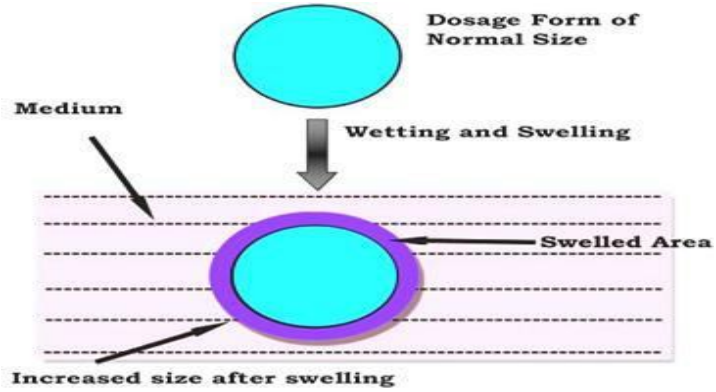

Figure 1.3: Wetting and swelling of polymer[19]

Step 2: The surface of mucosal membranes are composed of high molecular weight polymers known as glycoproteins. In this step (fig. 4) inter-diffusion and inter- penetration take place between the chains of mucoadhesive polymers and the mucous gel network creating a great area of contact. The strength of this bond depends on the degree of penetration between the two polymer groups. In order to form strong adhesive bonds, one polymer group must be soluble in the other and both polymer types must be of similar chemical structure.

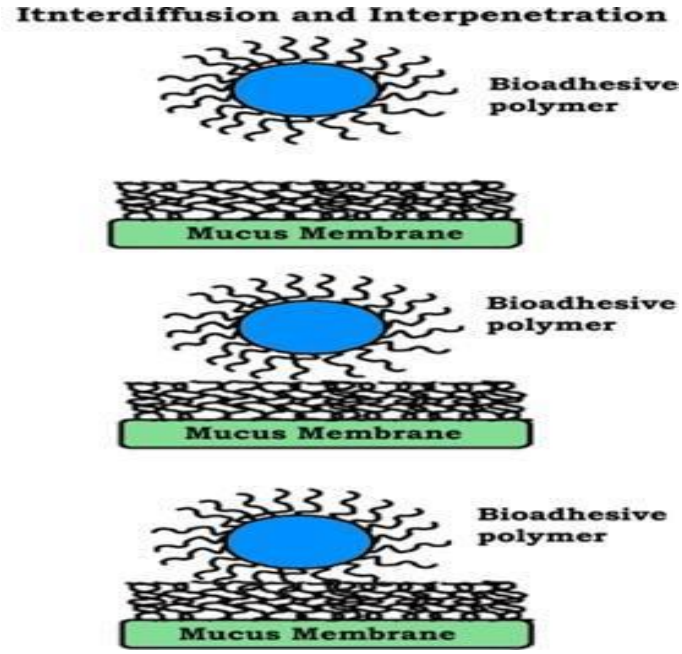

Figure 1.4: Inter diffusion and interpenetration of polymer and mucus

Step 3: In this step (**fig. 5**), entanglement and formation of weak chemical bonds as well as secondary bonds between the polymer chains mucin molecule. The types of bonding formed between the chains include primary bonds such as covalent bond and weaker secondary interactions such as Vander Waals interactions and hydrogen bonds. Both primary and secondary bonds are exploited in the manufacture of bioadhesive formulations in which strong adhesions between polymers are formed.

NEED FOR MUCOADHESIVE DRUG DELIVERY SYSTEM

- Controlled release
- Target & localized drug delivery
- By pass first pass metabolism
- Avoidance of drug degradation
- Prolonged effect
- High drug flux through the absorbing tissue
- Reduction in fluctuation of steady state plasma level.

MICROENCAPSULATION

Microencapsulation is described as a process of enclosing micron sized particles of solids or droplets of liquids or gases in an inert shell, which in turn isolates and protects them from the external environment. The products obtained by this process are called as microparticles, microcapsules and microspheres which differentiate in morphology and internal structure. When the particle size is below 1µm, they are known as nanoparticles or nanocapsules or nanospheres respectively and particles having diameter between 2-1000µm are known as micro particles or microcapsules or microspheres. Particles larger than 1000µm are known as macroparticles. Core material contains active ingredient while coat or shell material covers or protects the core material.

1. Core material

The core material is defined as the specific material to be coated which can be liquid or solid in nature. The composition of the core material can be varied, as the liquid core can include dispersed and/or dissolved material. The solid core can be mixture of active constituents, stabilizers, diluents, excipients and release-rate retardants or accelerators. The ability to vary the core material composition provides definite flexibility and utilization of this characteristic often allows effectual design and development of the desired microcapsules properties.

2. Coat material

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres. While selecting a polymer the product requirements i.e. stabilization, reduced volatility, release characteristics, environmental conditions, etc. should be taken into consideration. The polymer should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability. Generally hydrophilic polymers, hydrophobic polymers (or) a combination of both are used for the microencapsulation process. A number of coating materials have been used successfully; examples of these include gelatin, polyvinyl alcohol, ethyl cellulose and cellulose acetate phthalate. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system. The microcapsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms.

General techniques used for preparation of microcapsules are:

1. Emulsion technique

• Single emulsion technique.

• Double emulsion technique.

2. Polymerization technique

• Normal polymerization technique.

• Interfacial polymerization technique.

3. Phase separation coacervation technique.

4. Spray drying & spray congealing technique.

5. Solvent extraction technique or Solvent evaporation technique.

6. Ionic gelation technique.

IONOTROPIC GELATION

When and aqueous solution of sodium alginate is added drop wise to an aqueous solution of calcium chloride, spherical gel beads of calcium alginate either regular shape and size are obtained. Insoluble calcium alginate is formed by cation exchange between Na+ and Ca+. The ionic gelation and cross linkage are due to the three dimensional network of long chain molecules held together at junction zones, typically considered to be gulucoronic acid blocks, which results in the formation of egg-box junction. Therefore alginic acid or alginate is used as an immobilization matrix for cells and enzymes as well as pharmaceutical. Alginates are established among the most versatile biopolymers, used in a wide range of applications. Alginate is known to be nontoxic, when taken orally and also to have a protective effect on the mucous membrane of upper gastro-intestinal tract. Since dried alginate beads have the property of resewelling they can act as controlled release system and also susceptible to environmental pH, acid sensitive drugs when incorporated into the beads would be protected from gastric juice.

EVALUATION PARAMETER FOR MUCOADHESIVE MICROCAPSULES

Particle size determination

The particle size of prepared microcapsule was determined by optical microscopy method. The mean of 100 microcapsule was noted as particle size. All the studies were carried out in triplicate.

Scanning electron microscopy (SEM)

The microspheres were previously mounted on a brass stub using double-sided adhesive tape and then coated under vacuum with a thin layer of gold (3~5nm) for 75 sec and at 40W to make them electrically conductive. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The surface morphology of blank microspheres, drug loaded microspheres before and after dissolution was studied by photomicrographs at an excited voltage of 20 KV, specific chamber pressure (in mm Hg) under different magnification. Shown in figure 5.13

Micromeritic property of Mucoadhesive microcapsules

Bulk density

It is the ratio of total mass of microcapsules to the bulk volume of microcapsules. It was measured by pouring the weighed microcapsules into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by
Bulk density = Weight of microcapsules / Bulk volume

Tapped density

It is the ratio of total mass of the microcapsules to the tapped volume of the microcapsules. Volume was measured by tapping the powder and the tapped volume was noted. It is expressed in gm/ml and is given by

Tapped Density = Weight of microcapsules / Tapped volume

Carr's Index (I)

Percentage Carr's index was calculated as 100 times the ratio of the difference between the tapped density and bulk density to the tapped density. Effect of Carr's index on flow property showed in Table 1.3.

Carr's index (%) = [(Tapped density - Bulk density) × 100] / Tapped density

Table 1.1: Effect of Carr's index on flow property

Carr's index (%)	Type of flow
5-12	Excellent
12-18	Good
18-23	Fair to possible
23-35	Poor
35-38	Very poor
>40	Extremely poor

Hausner's ratio

One hundred ml capacity graduated cylinder was filled with microcapsules up to at least three fourth of the total height and its volume was measured. The cylinder was tapped for 100 times from a height of approximately 1.5 inches and the tapped volume was measured. The values of bulk and tapped densities were calculated. From the values of bulk density and tapped density, Hausner's ratio was calculated using the following formula.

Hausner's ratio = Tapped density/Bulk density

Table 1.2: Effect of hausner's ratio on flow property

Hausner's ratio	Type of flow
Less than 1.25	Good flow
1.25	Moderate
More than 1.25	Poor

Angle of repose (ϑ)

Angle of repose was determined using funnel method. The microcapsules blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula

$\theta = \tan^{-1} h/r$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Table 1.3: Effect of Angle of repose (θ) on flow property

Angle of repose (θ)	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
Very poor	>35

Swelling study:

The swelling properties of the mucoadhesive microcapsules were determined in SGF (pH 1.2). Samples of microcapsules of known weight (50mg) were placed in petri dish containing 10ml of 0.1 N HCl. At regular intervals of time, the swollen microcapsules were removed from Petri-dish; the excess water was removed with the help of a filter paper and weighed again (W2). The Swelling Index (SI) can be calculated using the formula.

$$\%\text{swelling of microcapsules} = \frac{\text{weight of microcapsules at time t - initial weight of microcapsules}}{\text{Initial weight of microcapsules}}$$

Percentage yield:

The total amount of dried microcapsules was weighed and the percentage yield was calculated by taking into consideration the total weight of the drug and polymer used for preparation of microcapsules.

$$\text{Percentage yield} = \frac{\text{Practical mass (microcapsules)}}{\text{Theoretical mass (microcapsules)}} \times 100$$

Estimation of Drug content:

100 mg of microcapsules was crushed in a glass mortar and suspended in 0.1N HCl for dissolving the coat shell of microcapsules. The suspension was suitably diluted with 0.1N HCl in 100 ml volumetric flask and volume was made up using 0.1N HCl. The solution was filtered to separate the shell fragments and from the filtrate 10 ml was taken. Drug content was analyzed after suitable dilution by UV-Spectrophotometer at a wavelength of 227.20 nm (UV-1601, Shimadzu, Japan) against suitable blank. All the studies were carried out in triplicate.

Entrapment efficiency (EE):

The % EE of each formulation was calculated using the following equation:

$$\%EE = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

***In-vitro* wash off test (Muco-adhesion retention time)**

The chicken stomach mucosa was used for *In-vitro* mucoadhesion evaluation. The mucosa was removed and cut into pieces 2 cm long 2 cm wide and were rinsed with 2ml of 0.1 N HCl (pH 1.2). 100 microcapsules of each were scattered uniformly to the surface of the stomach mucosa. Then, the mucosa with the microcapsules was placed in dissolution chamber and tied with constant stirring speed at 37± 0.5ºC. The number of beads adhering to the tissue was counted at 1-hour interval up to 8 hours.

CONCLUSION-

There is no doubt that the oral route is the most favored and probably most complex route of drug delivery. Critical barriers such as mucus covering the GI epithelia, high turnover rate of mucus, variable range of pH, transit time with broad spectrum, absorption barrier, degradation during absorption, hepatic first pass metabolism, rapid luminal enzymatic degradation ,longer time to achieve therapeutic blood levels, and intrasubject variability, are all possible issues with oral route. The idea of bioadhesive began with the clear need to localize a drug at a certain site in the GI tract. Therefore a primary objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing.

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