MUCOADHESIVE SYSTEMS: IMPRESSIVE TOOLS FOR IMPROVIZED DELIVERY OF DRUGS

Kaushal Kumar
Assistant professor, Department of Pharmacy, M.J.P. Rohilkhand University, Bareilly

INTRODUCTION

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS) of existing drug molecules to maximize their effectiveness in terms of therapeutic action and patent protection. The development of NDDS has been made possible by the use of various compatible polymers to modify the release pattern of drugs. In the recent years the interest is ever growing to develop a drug delivery system with the use of mucoadhesive polymers that will attach to related tissues or to the surface coating of the tissue for the targeting of various absorption mucosa such as ocular, nasal, pulmonary, buccal, vaginal etc. These systems of drug delivery are called as mucoadhesive drug delivery systems. [1] Adhesion can be defined as the bond produced by contact between a pressure-sensitive adhesive and a surface.[2] The American Society of testing and materials has defined it as the state in which two surfaces are held together by interfacial forces which may consist of valence forces, interlocking action or both. [3] Bioadhesion is defined as an ability of a material to adhere to a biological tissue for an extended period of time. For the case of polymer attached to the mucin layer of a mucosal tissue, the term mucoadhesion is used. [4]

Mucoadhesive dosage forms have three distinct **advantages** when compared to conventional dosage forms-

- These dosage forms are readily localized in the region applied to improve and enhance the bioavailability of drugs. [4]
- These dosage forms facilitate intimate contact of the formulation with the underlying absorption surface. This allows modification of tissue permeability for absorption of macromolecules, such as peptides and proteins. Inclusions of penetration enhancers such as Sodium glycocholate, Sodium taurocholate, L-lysophosphotidyl chlorine and protease inhibitors in the mucoadhesive dosage forms resulted in better absorption of peptides and proteins. [5]
- Mucoadhesive dosage forms also prolong the residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing.

Mechanism of Mucoadhesion [6]

Mucus is composed mainly of water (>95%), glycoproteins of exceptionally high molecular weight, mineral salts (1%) and free proteins (0.5 to 1%). For bioadhesion to occur, a succession of phenomena, whose role depends on the nature of the bioadhesive, is required. The first stage involves an intimate contact between a bioadhesive and a membrane, either from a good wetting of the

bioadhesive surface, or from the swelling of the bioadhesive. In the second stage, after contact is established, penetration of the bioadhesive into the crevices of the tissue surface or inter penetration of the chains of the bioadhesive with those of the mucus takes place. Low chemical bonds can then settle. On a molecular level, mucoadhesion can be explained as based on molecular interactions. The interaction between two molecules is composed of attraction and repulsion. Attractive interactions arise from Vander walls forces, electrostatic attractions, hydrogen bonding and hydrophobic interactions. Repulsive interactions occur because of electrostatic and steric repulsion. For mucoadhesion to occur, the attractive interaction should be larger than nonspecific repulsion.

TYPES OF MUCOADHESIVE DRUG DELIVERY SYSTEMS:

Depending upon the route of administration of the mucoadhesive drug delivery systems, they are of following types-

1. **Buccal** Mucoadhesive Drug Delivery System[7]
2. **Sub Lingual** Mucoadhesive Drug Delivery System [8]
3. **Vaginal** Mucoadhesive Drug Delivery System [7]
4. **Rectal** Mucoadhesive Drug Delivery System [9]
5. **Nasal** Mucoadhesive Drug Delivery System [7]
6. **Ocular** Mucoadhesive Drug Delivery System[10]
7. **Gastro Intestinal** Mucoadhesive Drug delivery System [11]

MATERIALS USED FOR MUCOADHESION:

Generally polymers of natural and synthetic origin are used for mucoadhesion. A mucoadhesive polymer is a synthetic or natural polymer which bonds to biological substance such as mucosal membrane. Such polymers are sometimes referred as to biological glues because they are incorporated into drug so as to make the drug available to the targeted tissues. [12]

Some common naturally occuring bioadhesive polymers are- Accacia gum, Alginic acid, Xanthangum, Guargum, Pectin, Tragacanth, Lectins etc. **Accacia Gum** is dried gum obtained from the stem and branches of tree of *Accacia senegal*. It is used as thickner in pharmaceuticals. **Alginic Acid** is a natural polymer found in cell wall of brown algae. It is widely used in the manufacture of alginate Salt such as sodium alginate used as constituent of Gaviscon liquid. **Xanthan Gum** is an anionic polysaccharide derived from the fermentation of the plant bacteria *Xanthamonas compestris*. It is dissolved in hot glycerine solutions typically in the 1500 to 2500 cps range at 1% in the presence of small amounts of salt. Solution shows good viscosity stability at elevated temperature & over the pH 2 to 12 and good tolerance for water miscible solvents. It is more compatible with most nonionic and anionic gums. **Guar Gum** consists of chiefly a high molecular weight hydrocolloid polysaccharide composed of galactam and mannan units combined through glycoside linkage. Guar Gum is obtained from the ground endosperm of the seeds of *cyamposis tetyragonolobus* family leguminosae and has molecular weight approx 220000. It forms viscous colloidal solution when hydrated in cold water and is stable in solution over a pH range of 1.0 to 10.5. Prolonged heating degrades viscosity.

Common synthetic polymers include- Carbomers, Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Hyaluronate, Hydroxy ethyl Cellulose, Hydroxypropyl Guar etc. **Carbomers** are synthesized by cross-linking of allyl sucrose or allyl pentaerythritol. Carbomers are polyacrylic acid polymer widely used in the pharmaceutical and cosmetic industries as thickening agent. Carbomers have a huge advantage in formulation science because they adhere strongly to mucosal membrane without causing irritation. They exhibit low toxicities profiles and are compatible with many drugs; unaffected by temperature variations but gel looses viscosity on exposure to sunlight. It is excellent thickening, emulsifying suspending and gelling agent. It is common component in bioadhesive dosages forms. **Hydroxy Propyl Methyl Cellulose** is included in preparations used to moisten contact lenses & in oral gels. **Hydroxy Ethyl Cellulose** is a non-ionic polymer made by reacting ethylene oxide with alkali-cellulose under rigidly controlled conditions. It is light tan or cream to white powder, odorless and tasteless; it may contain suitable anticaking agents. It is soluble in hot or cold water. It is susceptible for bacterial and enzymatic degradation. It shows good viscosity stability over the pH 2 to 12 ranges, used as suspending or viscosity builder, binder and film former. **Hydroxy Propyl Guar** is a non ionic derivative of gaur prepared by reacting guar gum with propylene oxide. Hydroxy propyl guar gives high viscosity, pseudoplastic solution that shows reversible decrease in viscosity at elevated temperature. It is compatible with high concentration of most salts and shows better compatibility with minerals than guar gum. It has good viscosity stability in the pH range of 2 to 13. It has more resistance towards bacterial and enzymatic degradation. **Sodium Hyaluronate** is a high molecular weight biological polymer made of repeating disaccharides units of glucuronic acid & N-acetyl D-glucosamine. This polymer is used during intro-ocular surgery to protect the cornea & also acts a tear substitute in the treatment of drug eyes.

Mucoadhesive Polymers are also classified as *Hydrophilic Polymer and Hydrogels.* [13] **Hydrophilic Polymers** such as Poly Vinyl Pyrrolidone (PVP), Methyl Cellulose (MC), Sodium Carboxy Methylcellulose (SCMC), Hydroxy propyl Cellulose (HPC) and other Cellulose derivatives containing carboxylic group exhibit the best mucoadhesive properties. **Hydrogels** are the class of polymeric biomaterial that exhibit the basic characteristics of an hydrogel to swell by absorbing water and by interacting by means of adhesion with the mucus that covers epithelia. Hydrogels include **Anionic group hydrogels-** Carbopol, Polyacrylates and their crosslinked modifications; **Cationic group hydrogels-** Chitosan and its derivatives and **Neutral group hydrogels-** Eudragit-NE30D etc. [14]

Characteristics of Bioadhesive polymers [12]

Polymer must ideally possess certain characteristics in order to adhere to mucosal surface or epithelial cells. **Flexibility** of bioadhesive polymer is important because it controls the extent of the interpenetration between the polymer & mucusol/epithelial surface. Polymers with good **hydrophilicity** are able to form strong adhesive bonds with mucosal membrane because the mucus layers contain large amount of water. **Hydrogen Bonding** between the entangled polymer chain forms strong adhesive bond, therefore, the presence of hydrogen bond forming groups such as –OH, –COOH are vital in large quantities. Polymers with **high molecular weight** are desirable because

they provide more available binding sites. **Surface Tension** plays an important role in spreading the bioadhesive polymer into mucosal layer epithelial surface.

Polymers with **excellent** bioadhesive property are Carboxy methyl cellulose, Hydroxyl propyl methyl cellulose, Carbopol 934, Tragacanth, Sodium Alginate, Polycarbophil, Hydroxyl ethyl cellulose. Polymers with **moderate b**ioadhesive property are Gelatin, Guar Gum, Gum Karaya whereas polymers with **poor** bioadhesive property are - Pectin, Acacia and Polyvinyl Pyrrolidone. [4]

Characteristics of an ideal mucoadhesive polymer: - The polymer and its degradation products should be nontoxic and non absorbable from the GI tract. Polymer should be non-irritant to the mucous membrane. Polymer preferably forms a strong non-covalent bond with the mucin-epithelial cell surfaces. Polymer should adhere quickly to moist tissue and should possess some site specificity. Polymer should allow easy incorporation of the drug and offer on hindrance to its release. Polymer must not decompose on storage or during the shelf-life of the dosage form. The cost of polymer should not be high so that the prepared dosage form remains competitive. (7)

METHODS FOR PREPARATION OF MUCOADHESIVE DRUG DELIVERY SYSTEMS

Various G.I.T. dosages forms which could be made into mucoadhesive drug delivery systems are- Tablets, Capsules and Microcapsules.

For preparation of **Mucoadhesive tablets** an additional adjuvant for bioadhesion, which is a suitable to mucoadhesive polymer, is added for the formulation of tablet. Diluents, fixed quantity of lubricant, drug and other excipients along with selected mucoadhesive polymer are homogeneously blended and compressed into tablets using tablet compression machine.

For the preparation of **mucoadhesive capsule** either complete capsule shell is formed of the mucoadhesive polymer or suitable mucoadhesive polymer in calculated amount is mixed with gelatin, and other materials like plasticizer (Glycerin USP, Sorbital USP) are used. Plasticizer makes capsule shell flexible. For preparing soft mucoadhesive capsule less plasticizer are used. After preparation of mucoadhesive capsule shell, the prepared medicament (drug powder, excipients, fillers) are filled. The soft mucoadhesive capsules are used to dispense a variety of liquids and solids.

For preparation of **mucoadhesive microcapsules** any suitable method of micro encapsulation can be used. Mucoadhesive microcapsules are prepared by orifice ionic gelation method with polymer combinations such as carbopol and HPMC, carbopol and SCMC, carbopol and methyl cellulose, carbopol and guar gum in a suitable drug-polymer ratio. In this method polymer and drug are dispersed in water with a constant stirring for a suitable period of time. The resultant dispersion is added drop wise (through a syringe) into the $CaCl_2$ solution and kept for some time for complete reaction and then microcapsule are recovered by filtration through a filter, under vacuum, and dried in hot air oven.

EVALUATION

In vitro release studies [15]**:** No standard in vitro method has yet been developed for the dissolution studies of buccal formulation. Apparatus of varying designs are used, depending on the shape of application of the dosage form developed. The disintegration tester without the attached disc is used with suitable volume of the dissolution medium for dissolution rate measurement of directly compressed mucoadhesive tablets. For disc like dosage forms dissolution rate is measured by special dissolution apparatus like Toyama-Sangyo TR-553 dissolution tester. For this, 900 ml of purified water is used as dissolution medium, rotating the basket at 100 rpm. This apparatus is also used for the evaluation of oral mucosal dosage forms of insulin.

In vivo release studies [16]**:** A buccal absorption test which involves swirling a buffered drug solution around the mouth has been established. After known time period the solution is expelled and the subjects are rinsed their mouth with buffer. Drug solution and the buffer are then combined, analyzed for drug contents and the amount of drug absorbed estimated from the difference between the entered and recovered. An improvement over this traditional buccal absorption is the test which enables kinetic data to be collected in a single 15 min. This method involves multiple samples being withdrawn from the mouth using a positive displacement pipette.

Percentage Yield [17]**:** The microcapsules are evaluated for percentage yield and percent drug entrapment. The yield is calculated as per the equation.

% Yield = [Weight of microcapsule recovered/ Weight (drug + polymer)] x 100

Flow Properties of Microcapsules [18]**:** Flow ability of microcapsules is investigated by determining angle of repose, bulk density, Carr's index and Hausner ratio. The angle of repose is determined by fixed funnel method. The microcapsules are tapped using bulk density apparatus for 100 taps in a cylinder and the change in volume is measured.

Drug Entrapment Efficiency (DEE) [17]**:** Drug loaded microcapsules are powered and suspended in 100 ml water/solvent system. The resultant dispersion is kept for 30 min for complete mixing with continuous agitation and filtered through a 0.45 µm membrane filter. The drug content is determined by suitable analytical method of drug estimation. The drug entrapment efficiency (DEE) is calculated by the equation,

DEE = (Pc/Tc) X 100

Where, Pc is practical content, Tc is the theoretical content.

All the formulations are generally advised to be analyzed in triplicate.

Percentage moisture loss [19]**:** The microcapsules are evaluated for percentage moisture loss which shares an idea about its hydrophilic nature. Weighed (W_1) microcapsules are initially kept in desiccators containing calcium chloride at 37^0C for 24 hours. The final weight (W_2) is noted when no further change in weight of sample is observed. %Moisture loss is calculated by following equation-

%Moisture loss = [(W_1—W_2) / W_2] X 100

All the experimental are generally advised to be studied in triplicate (n=3).

Determination of swelling properties [20]**:** The dynamic swelling property of microcapsules in the dissolution medium is determined. Microcapsules of known weight are placed in dissolution solution for 6 hr and the swollen microcapsules are collected by a centrifuge and the wet weight of the swollen microcapsules are determined by first blotting the particles with filter paper in order to remove absorbed water on surface and then weighing immediately on an electronic balance. The percentage of swelling of microcapsules in the dissolution media is then calculated by using equation-

$S_w = [(W_t—W_0)/W_0]$ x100

Where, S_W = percentage of swelling of microcapsules, Wt = weight of the microcapsules at time t, W_0 = initial weight of the microcapsules.

All the experimental units are studied in triplicate (n=3)

In vitro druig release [21]**:** In vitro drug release study may be carried out in USP type-II dissolution test apparatus. Microcapsules are placed in basket of dissolution vessel containing 900 ml of dissolution media maintained at desired temperature and stirred at suitable rpm. Aliquots of sample at particular time intervals are withdrawn and filtered through whatman filter paper. The samples are analyzed for drug content by suitable analytical method. Experiment is analyzed in triplicate (n=3)

In vitro drug release kinetic studies: Kinetic model describes drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the microsphere, drug release data is analyzed according to zero order, first order, Higuchi square root, Korsmeyer-Peppas model. The criteria for selecting the most appropriate model are chosen on the basis of goodness of fit test.

CHARACTERIZATION of MDDS:

Scanning Electron Microscopy [20]**:** The SEM analysis for microcapsules is carried out using a scanning election microscope. Prior to examination, samples are mounted on an aluminum stub using double sided adhesive tape and making them electrically conductive by coating with a thin layer of gold in vacuum.

Determining Sphericity of Mucoadhesive microcapsules [21]**:** The particle shape of microspheres is measured by computing circulatory factor (S). The tracing obtained from optical microscopy are used to calculate Area (A) and perimeter (P). This indicates the approximate shape of the prepared microcapsule calculated by the equation: $S = P^2/12.56 \times A$.

Loose Surface Crystals Study [22]**:** Microcapsules prepared by different combination of polymers are evaluated by loose surface crystal study to observe the excess drug present on the surface of microcapsules. Microcapsule are shaken in 20 ml of 0.1N HCl for 5 min and then filtered through whatman filter paper. The amount of drug present in filtrate is determined by suitable analytical method and calculated as a percentage of total drug content.

APPLICATIONS of MDDS:

From a huge list of various and enormous applications of mucoadhesive drug delivery systems few important one can be summarized as follows. Mucoadhesive dosages forms provide a long term

therapeutic response from a single dose and this dosage form eliminates the need of repeated administration several times in a day. Stability problem in the intestinal fluid of the drug can be overcome by the formulation of mucoadhesive dosages forms. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved by the formulation of mucoadhesive dosages forms. Drugs which have short biological half life, poor permeability, sensitive to enzymatic degradation and poor solubility when delivered through mucoadhesive oral drug delivery method solve these problems. Antibacterial drugs in the form of mucoadhesive product maintain effective serum levels during night hours eliminating the necessity of interruption of sleep for administration of the medication. It is applicable in the development of nitroglycerine mucoadhesive tablet for the treatment of angina pectoris. It is applicable to the development of magnetic granules containing ultrafine ferrite; brilliant blue FCP. Bioadhesive polymers have another application in targeting therapy for esophageal cancer. In recent years vaginal mucoadhesive preparations have been applicable to the development as a new type of controlled release form the treatment of both topical and systemic disease. Mucoadhesive dosages form are applicable in controlling of epilepsy and nocturnal seizures. It is applicable to design a mucoadhesive, moderately water soluble polymeric film containing analgesics and antibiotics for the treatment of lesions.

Various mucoadhesive dosage forms for oral use along with their applications have been reported. **Multilayer tablet** allows a variety of geometrical arrangement. Such systems that consist of acrylic polymers or cellulose provide immediate and high adhesive strength at a certain site for prolonged period of time [23]. **Micro and/or Nanoparticles**- despite the limited loading capacity of drug, bioadhesive micro-and/or nanoparticles have been widely investigated for three [24] major features -

- Immobilization of particles on the mucosal surface by adhesive after modification of surface properties via bioadhesive polymers.
- Very large specific surface between the dosage forms and the oral mucosa.
- Sustained release of entrapped drug leading to higher absorption.

Capsules usually gelatin capsules containing a suspension or liquid include bioadhesive polymers such polycarbophil or carbopol. Gelatin interacts with bioadhesive polymer during or following dissolution, and thus bioadhesiveness of the polymer is lost before the bioadhesive polymer has a chance to interact with the mucus layer. [25]

PRESENT STATUS OF STUDIES

Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive delivery systems prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and contribute to improved and/or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal & vaginal routes for both systemic and local effects.

A new sustained release microcapsulated drug delivery system [26] employing sustained release polymers in combination was proposed. The microcapsules were formulated by orifice ionic gelation

technique using famotidine as the model drug and polymers combination forms (Carbopol 934 and Hydroxy propyl methyl cellulose, carbopol 934 and sodium carboxymethayl cellulose) against carbopol 934 only. Microcapsules were evaluated for particle size, percentage yield, flow properties, drug entrapment efficiency, surface morphology by scanning electron microscopy, sphericity measurement, percentage moisture loss, wall thickness, swelling properties, *in vitro* drug release profile, drug release kinetic study and mucoadhesion study by in vitro tests. The effect of drug and different polymer combination on *in vitro* drug release profile was examined. The famotidine micro-capsules with good structure and satisfactory yield were produced. Micro-capsules employing sustained release polymers used in combination exhibited slow release of famotidine over 9 hours with zero ordor release kinetic fashion. It was concluded that the polymer possess substantial release controlling properties used in combination that could be used for sustained delivery. All data were verified statistically by employing one way ANOVA and found to be significant at 5% level of significance.

In another study oral controlled release mucoadhesive hydrophilic matrices was designed to optimize the drug release profile and bioadhesion using response surface methodology [27]. Tablets were prepared by direct compression and evaluated for bioadhesive strength and in vitro dissolution parameters. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile and bioadhesive strength. Carbopol 934 P and sodium carboxy methyl cellulose were taken as the independent variables. Response surface plots and contour plots were drawn, and optimized formulations were selected by feasibility and grid searches. Compressed matrices exhibited non-Fickian drug release kinetics approaching zero-order, as the value of release rate exponent (n) varied between 0.6672 and 0.8646, resulting in regulated and completed release until 24 hours. Both the polymers had significant effect on the bioadhesive strength of the tablets, measured as force of detachment against porcine gastric mucosa. Polynomial mathematical models, generated for various response variables using multiple linear regression analysis, were found to be statistically significant. Validation of optimization study was performed using 8 confirmatory runs indicated very high degree of prognostic ability of response surface methodology. Besides unraveling the effect of the 2 factors on the various response variables, the study also helped in finding the optimized formulation with excellent bioadhesive strength and controlled release.

FUTERISTIC APPROACHES

With the disappointment in the merger of mucoadhesive systems into pharmaceuticals in the site-specific drug delivery area, there has been an increasing interest from researchers in targeting regions of the GIT using selective compounds capable of distinguishing between the types of cells found in different areas of the GIT. Loosely termed “cytoadhesion,” this concept is specifically based on certain materials that can reversibly bind to cell surfaces in the GIT. These next generation of mucoadhesives function with greater specificity because they are based on receptor-ligand like interacting in which the molecules bind strongly and rapidly directly onto the mucosal cell surface rather than the mucus itself [28]. One such class of compounds that has these unique requirements is

called lectins. Lectins are proteins or glycoproteins and share the common ability to bind specifically and reversibly to carbohydrates. They exist in either soluble or cell associated forms and plants, to a lesser extent in some vertebrates (referred to as endogenous lectins), and can also be produced form bacteria or invertebrates. Lectin based drug delivery systems have applicability in targeting epithelial cells, intestinal M cells, and enterocytes. The intestinal epithelial cells possess a cell surface composed of membrance-anchored glycoconjugates. It is these surfaces that could be targeted by lectins, thus enabling an intestinal delivery concept. **Lele** et al [29] investigated novel polymer of Polyacrylic acid (PAA) complexed with Polyethylene Glycolated drug such as indomethacin could be loaded into the devices made from these polymers. An increase in molecular weight of PEG in these copolymers resulted in a decrease in release of free indomethacin, indicating that drug release can be manipulated by choosing different molecular weights of PEG. **Alur H H** et al [30] studied the transmucosal sustained delivery of Chlorpheniramine maleate in rabbits using a novel natural mucoadhesive gum as an excipient in buccal tablets. It was concluded that the gum not only sustained the release of drug but also provided sufficient mucoadhesion to tablets for clinical application.

CONCLUSION

The mucosal adhesive dosages forms now have become traditional for increasing the bioavailability. The advantages are tremendous which have made them suitable drug delivery systems for continuous study in this field. The formulation of these drug delivery systems depends on the development of suitable polymers with excellent mucosal adhesive properties, stability and biocompatibility. Many mucoadhesive drug delivery systems are already in the market and exploration for newer is on. Moreover, active research in this field is coming up with good results with higher degree of cost efficacy, reality for use and effective alternative to controlled release dosage forms for the treatment of both topical as well as systematic disease.

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