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A BRIEF REVIEW ON MUCOADHESIVE DRUG DELIVERY SYSTEM IN PHARMACOLOGICAL TECHNOLOGY

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ABSTRACT

Since 1980 the concept of mucoadhesion has gained considerable interest in pharmaceutical technology. Mucoadhesion describe the attractive forces between a biological material and mucus membrane. Mucoadhesion drug delivery system prolong the resident time and facilitate in contact of the dosage form with the underlined absorption surface which results in improvements of the therapeutic performance of the drug. The mechanism of the mucoadhesive contain context stage and consideration stage which can be explained in diffusion and dehydration theory. Mucoadhesive theory include wetting theory, diffusion theory, fracture theory and electronic theory. Mucoadhesive dosage form an available in tablets patches, gels and solutions in dosage form. The mucoadhesive drug delivery system depends selection of suitable polymer with excellent mucosal adhesive properties. The review aims at compiling to potential benefits of mucoadhesive drug delivery system.

KEYWORDS: Mucoadhesive, Drug delivery, Polymers.

INTRODUCTION

Since the early 1980s, the concept of mucoadhesion has gained considerable interest in pharmaceutical technology.[1] Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface. 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. Mucoadhesive drug delivery systems prolong the residence time of the dosage form at the site of application or absorption. They facilitate an intimate contact of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. In recent years, many such Mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, rectal and vaginal routes for both systemic and local effects.[2] Dosage forms designed for Mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Other desired characteristics of a Mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good Mucoadhesive properties, smooth surface, tastelessness, and convenient application. Erodible formulations can be beneficial because they do not require system retrieval at the end of desired dosing interval. A number of relevant Mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including thyrotropin-releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1– 5%),[3] owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa.

The development of sustain release dosage form can achieve the aim of releasing the drug slowly for a long period but this is not sufficient to get sustained therapeutic effect. They may be cleared from the site of absorption before emptying the drug content. Instead, the Mucoadhesive dosage form will serve both the purposes of sustain release and presence of dosage form at the site of absorption. In this regard, our review is high lighting few aspects of Mucoadhesive drug delivery systems.[4]

Mucoadhesive

Mucoadhesion describes the attractive forces between a biological material and mucus or mucous membrane. Mucous membranes adhere to epithelial surfaces such as

the gastrointestinal tract, the vagina, the lumembranes (mucosae) [Figure 1] are the moist surfaces lining the walls of various body cavities such as the gastrointestinal and respiratory tracts. They consist of a connective tissue layer (the lamina propria) above which is an epithelial layer, the surface of which is made moist usually by the presence of a mucus layer. The epithelia may be either single layered (e.g., the stomach, small and large intestines and bronchi) or multilayered/stratified (e.g., in the esophagus, vagina and cornea). The former contains goblet cells which secrete mucus directly onto the epithelial surfaces; the latter contain, or are adjacent to tissues containing, specialized glands such as salivary glands that secrete mucus onto the epithelial surface. Mucus is present either as a gel layer adherent to the mucosal surface or as a luminal soluble or suspended form. The major components of all mucus gels are mucin glycoproteins, lipids, inorganic salts and water, the latter accounting for more than 95% of their weight, making them a highly hydrated system.[5] The major functions of mucus are that of protection and lubrication.

Mechanisms of Mucoadhesion

The mechanism of Mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage [Figure 2]. The first stage is characterized by the contact between the Mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer.[6] In the consolidation step [Figure 2], 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 van der Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory. According to the diffusion theory, the Mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place, the Mucoadhesive device has features favoring both chemical and mechanical interactions. For example, molecules with hydrogen bond building groups (–OH, –COOH), an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which help in spreading throughout the mucus layer, can present Mucoadhesive properties.

Mucoadhesion Theories

Mucoadhesion is a complex process and numerous theories have been proposed to explain the mechanisms involved. These theories include mechanical interlocking, electrostatic, diffusion interpenetration, adsorption and fracture processes.

Wetting theory

The wetting theory applies to liquid systems which 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 the lower the contact angle, the greater is the affinity [Figure 3]. The contact angle should be equal or close to zero to provide adequate spreadability. The spreadability coefficient, SAB, can be calculated from thedifference betweenthe surface energies γBand γA and theinterfacial energy γAB,as indicated inthe equationgivenbelow. [5] This theory explains the importance of contact angle and reduction of surface and interfacial energies to achieve good amount of mucoadhesion.

Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond [Figure 4]. It is believedthat the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the Mucoadhesive chains, mobility and contact time. According to the literature, the depth of interpenetration required to produce an efficientbioadhesive bond lies in the range 0.2–0.5 μm. This interpenetration depth of polymer and mucin chains can be estimated by the following equation (5)

$L = (tDb)½$

Where t is the contact time and Db is the diffusion coefficient of the Mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similar chemical structures. The greater the structural similarity, the better is the Mucoadhesive bond.[5]

Fracture theory

This is perhaps the most used theory in studies on the mechanical measurement of mucoadhesion. It analyzes the force required to separate two surfaces after adhesion is established. This force, sm, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, Fm, and the total surface area, A0, involved in the adhesive interaction.

Since the fracture theory [Figure 5] is concerned only with the force required to separate the parts, it does not take into account the interpenetration or diffusion of polymer chains. Consequently, it is appropriate for use in the calculations for rigid or semi-rigid bioadhesive materials, in which the polymer chains do not penetrate into the mucus layer.[5,6]

Electronic theory

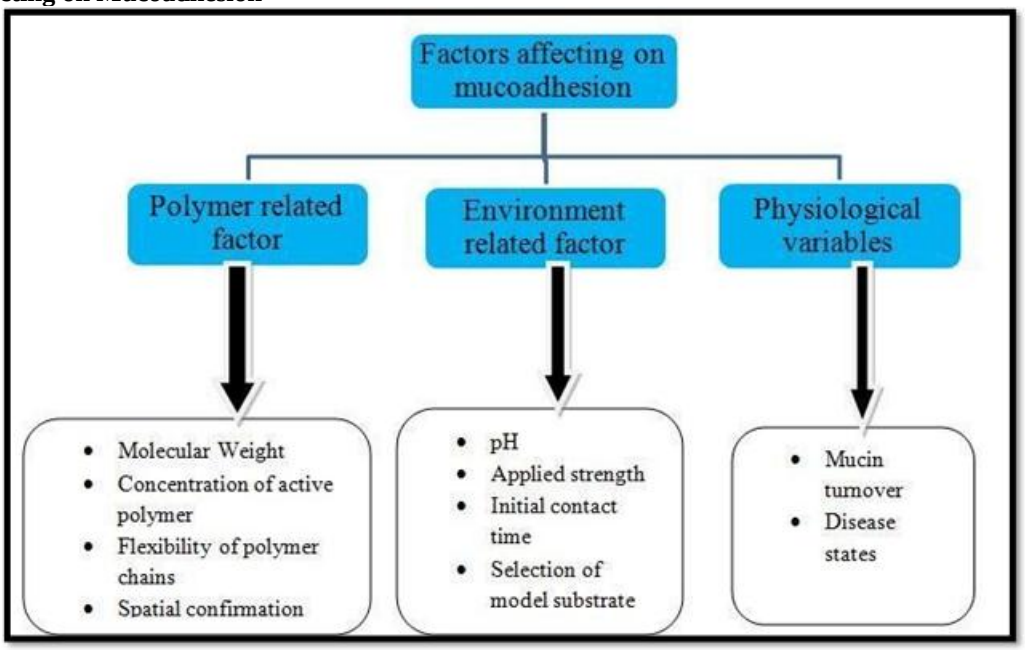
The electronic theory This theory describes adhesion occurring by means of electron transfer between the mucus and the Mucoadhesive system, arising through differences in their electronic structures. The electron transfer between the mucus and the Mucoadhesive results in the formation of double layer of electrical

charges at the mucus and Mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer.[7]

The adsorption theory In this instance, adhesion is the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency.[8] Secondary bonds arise mainly due to van der Waals forces, hydrophobic interactions and hydrogen bonding. Whilst these interactions require less energy to "break", they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi-permanent bonds.[9]

All these numerous theories should be considered as supplementary processes involved in the different stages of the mucus/substrate interaction, rather than individual and alternative theories. Each and every theory is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion. The mechanism by which a Mucoadhesive bond is formed will depend on the nature of the mucus membrane and Mucoadhesive material, the type of formulation, the attachment process and the subsequent environment of the bond. It is apparent that a single mechanism for mucoadhesion proposed in many texts is unlikely for all the different occasions when adhesion occurs.

Factor affecting on Mucoadhesion



1) Polymer-Related Factors

Molecular weight: The optimum molecular weight for maximum bioadhesion depends upon type of Mucoadhesive polymer a tissue. It is generally understood that the threshold required for successful bioadhesion is at least 100000molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20000, has little adhesive character, whereas PEG with 200000 molecular weight has improved, and PEG with 400000 hassuperior adhesive properties. The fact that Mucoadhesiveness improves with increasing molecular weight for linear polymers implies two things: (1) interpenetration is more critical for a low-molecular-weight polymer tobe a good Mucoadhesive, and (2) entanglement is important for high- molecular-weight polymers. Adhesiveness of a nonlinear structure, by comparison, follows a quite different trend. The adhesive strength of dextran, with a high molecular weight of 19500000 is similar to that of PEG, with a molecular weight of 200000. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are primarily responsible for adhesion, unlike theconformation of PEG.

Concentration of active polymer

There is an optimum concentration for a Mucoadhesive polymer to produce maximum bioadhesion. In highly concentrated system, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chain available for interpenetration becomes limited

Flexibility of polymer chains

Chain flexibility is critical for interpenetration and entanglement. As water soluble polymers become cross linked, the mobility of an individual polymer chain decreases and thus the effective length of the chain that

can penetrate into the mucus layer decreases, which reduces Mucoadhesive strength.

Spatial conformation

Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19500000 for dextrans, they have adhesive strength similar to that of PEG, with a molecular weight of 200000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation

Swelling

Swelling characteristics are related to the Mucoadhesive itself and its environment. Swelling depends on the polymer concentration, the ionic strength, and the presence of water. During the dynamic process of bioadhesion, maximum bioadhesion in vitro occurs with optimum water content. Over hydration results in the formation of a wet slippery mucilage without adhesion.

Environment-Related Factors

pH of polymer–substrate interface: pH can influence the formal charge on the surface of the mucus as well as certain ionizable Mucoadhesive polymers. Mucus will have a different charge density depending on pH due to the difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Some studies had shown that the pH of the medium is important for the degree of hydration of cross-linked polycyclic acid, showing consistently increased hydration from pH 4 through pH 7, and then a decrease as alkalinity or ionic strength increases, for example polycarbophil does not show a strong Mucoadhesive property above pH 5because uncharged, rather than ionized, carboxyl group reacts with mucin molecule, presumably through numerous hydrogen bonds. However, at higher pH, the chain is fully extended due to electrostatic repulsion of the carboxyl ate anions.

Strength

To place a solid Mucoadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly (acrylic acid/ di-vinyl benzene) or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum. The pressure initially applied to the Mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become Mucoadhesive even though they do not have attractive interactions with mucin.

Initial contact time

Contact time between the Mucoadhesive and mucus layer determines the extent .of swelling and interpenetration of the Mucoadhesive polymer chains. More Mucoadhesive strength increases as the initial contact time increases

Turnover

The natural turnover of mucin molecules from the mucus layer is important for at least two reasons. Firstly, the mucin turnover is expected to limit the residence time of the Mucoadhesives on the mucus layer. No matter how high the Mucoadhesive strength, they are detached from the surface due to mucin turnover. The turnover rate may be different in the presence of Mucoadhesives, but no information is available on this aspect. Secondly, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with Mucoadhesives before they have chance to interact with the mucus layer. Surface fouling is unfavorable for mucoadhesion to the tissue surface. Mucin turnover may depend on the other factors such as the presence of food. The gastric mucosa accumulates secreted mucin on the luminal surface of the tissue during the early stages of fasting. The accumulated mucin is subsequently released by freshly secreted acid or simply by the passage of ingested food; the exact turnover rate of the mucus layer remains to be determined. Lehr et al. calculated amucin turnover time of 47–270 min. The ciliated cells in the nasal cavity are known to transport the mucus to the throat at the rate of 5 mm/min. The mucociliary clearance in the tracheal region has been found to be at the rate of 4–10 mm/min.

Disease state

The physiochemical properties of the mucus are known to change during disease conditions such as the common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial, and fungal infections of female reproductive tract, and inflammatory conditions of the eye. The exact structural changes taking place in mucus under these conditions are not clearly understood. If Mucoadhesives are to be used in the disease states, the Mucoadhesive property needs to be evaluated under the same conditions.[10,11]

Mucoadhesive Polymers

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking Agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and 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.

- Polymers that become sticky when placed in water and owe their Mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, non-covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site on tile self surface.

Characteristics of an ideal Mucoadhesive polymer

An ideal Mucoadhesive polymer has the following characteristics[12]

- The polymer and its degradation products should be nontoxic and should be non-absorbable from the gastrointestinal tract.
- It should be nonirritant to the mucous membrane.
- It should preferably form a strong non-covalent bond with the mucin-epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site-specificity.
- It should allow daily incorporation to the drug and offer no hindrance toits release.
- The polymer must not decompose on storage or during the shelf life ofthe dosage form.
- The cost of polymer should not be high so that the prepared dosage formremains competitive.[13]

- Molecular characteristics

The properties exhibited by a good Mucoadhesive may be summarized asfollows:

- Strong hydrogen bonding groups (-OH, -COOH).
- Strong anionic charges.
- Sufficient flexibility to penetrate the mucus network or tissue crevices.
- Surface tension characteristics suitable for wetting mucus/mucosaltissue surface.
- High molecular weight.

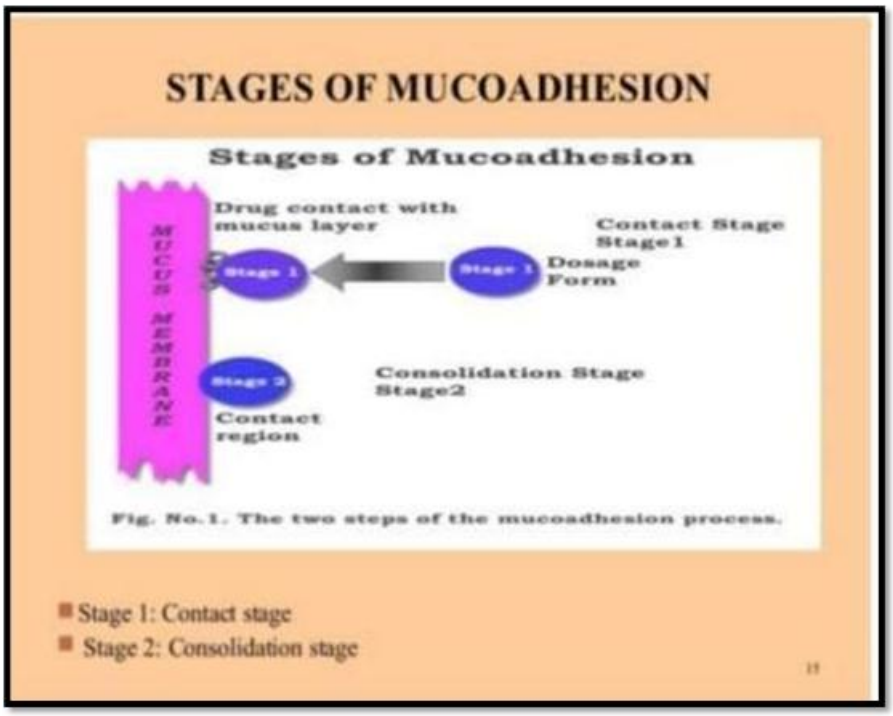
Although an anionic nature is preferable for a good Mucoadhesive, a range of nonionic molecules (e.g., cellulose derivatives) and some cationic (e.g., Chitosan) can be successfully used.[14]

A short list of Mucoadhesive polymers is given below.
Synthetic polymers:Cellulose derivatives (methylcellulose, ethyl cellulose, hydroxy-ethylcellulose, Hydroxyl propyl cellulose,etc., Poly (hydroxyethyl methylacrylate), Poly (ethylene oxide), Poly (vinyl pyrrolidone), Poly (vinyl alcohol).

Natural polymers
Tragacanth, Sodium alginate, Karaya gum, Guar gum, Xanthan gum, Lectin, Soluble starch, Gelatin, Pectin, Chitosan, sodium alginate.[14]

Stage s of Mucoadhesive

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).[15]



Routes of Administration

Oromucosal

With a 0.1-0.7 mm thick mucus layer, the oral cavity serves as an important route of administration for Mucoadhesive dosages. Permeation sites can be separated into twogroups :sublingual and buccal ,in which the former is much more permeable than the latter. However, the sublingual mucosa also produces more saliva, resulting in relatively low retention rates. Thus, sublingual mucosa is preferable for rapid onset and short duration treatments, while the buccal mucosa is more appropriate for longer dosage and onsettimes. Because of this dichotomy, the oral cavity is suitable for both local and systemic administration. Some common dosage forms for the oral cavity include gels, ointments, patches, and tablets. Depending on the dosage form, some drug loss can occur due toswallowing

of saliva. This can be minimized by layering the side of the dosage facing the oral cavity with an impermeable coating(,) commonly seen in patches.[16]

Nasal

With an active surface area of 160 cm^2, the nasal cavity is another noteworthy route of Mucoadhesive administration. Due to the sweeping motion of the cilia that lines the mucosa, nasal mucus has a quick turnover of 10 to 15 minutes. Because of this, the nasal cavity is most suitable for rapid, local medicinal dosages. Additionally, its close proximity to the blood-brain barrier makes it a convenient route for administering specialized drugs to the central nervous system. Gels, solutions, and aerosols are common dosage forms in the nasal cavity. However, recent research into particles and microsphereshave shown increased bioavailability over non-solid forms of medicine largely due to the use of Mucoadhesives.[17]

Ocular

Within the eye, it is difficult to achieve therapeutic concentrations through systemic administration. Often, other parts of the body will reach toxic levels of the medication before the eye reaches the treatment concentration. Consequently, direct administration through the fibrous tunic is common. This is made difficult due to the numerous defense mechanisms in place, such as blinking, tear production, and the tightness of the corneal epithelium. Estimates put tear turnover rates at 5 minutes, meaning most conventional drugs are not retained for long periods of time. Mucoadhesives increase retention rates, either by enhancing the viscosity or bondingdirectly to one of the mucosae surrounding the eye.[15,17]

Intravesical

Intravesical drug administration is the delivery of pharmaceuticals to the urinary bladder through a catheter.[16] This route of administration is used for the therapy of bladder cancer and interstitial cystitis. The retention of dosage forms in the bladder isrelatively poor, which is related to the need for a periodical urine voiding. Some Mucoadhesive materials are able to stick to mucosal lining in the bladder, resist urine wash out effects and provide a sustained drug delivery.[17,18]

Mucoadhesives in drug delivery

Depending on the dosage form and route of administration, Mucoadhesives may be used for either local or systemic drug delivery. An overview on the Mucoadhesive properties of Mucoadhesives is provided by Vjera Grabovac and Andreas Bernkop- Schnürch. The bioavailability of such drugs is affected by many factors unique to each route of application. In general, Mucoadhesives work to increase the contact time at these sites, prolonging the residence time and maintaining an effective release rate. These polymeric coatings may be appliedto a wide variety of liquid and solid dosages, each specially suited for the route of administration.[19]

Dosage Forms

Tablets

Tablets are small, solid dosages suitable for the use of Mucoadhesive coatings. The coating may be formulated to adhere to a specific mucosa, enabling both systemic and targeted local administration. Tablets are generally taken enterally, as the size and stiffness of the form results in poor patient compliance when administered through other routes.[20]

Patches

In general, patches consist of three separate layers that contribute and control the release of medicine. The outer impermeable backing layer controls the direction of release and reduces drug loss away from the site of contact. It also protects the other layers and acts as a mechanical support. The middle reservoir layer holds the drug andis tailored to provide the specified dosage. The final inner layer consists of the Mucoadhesive, allowing the patch to adhere to the specified mucosa.[20]

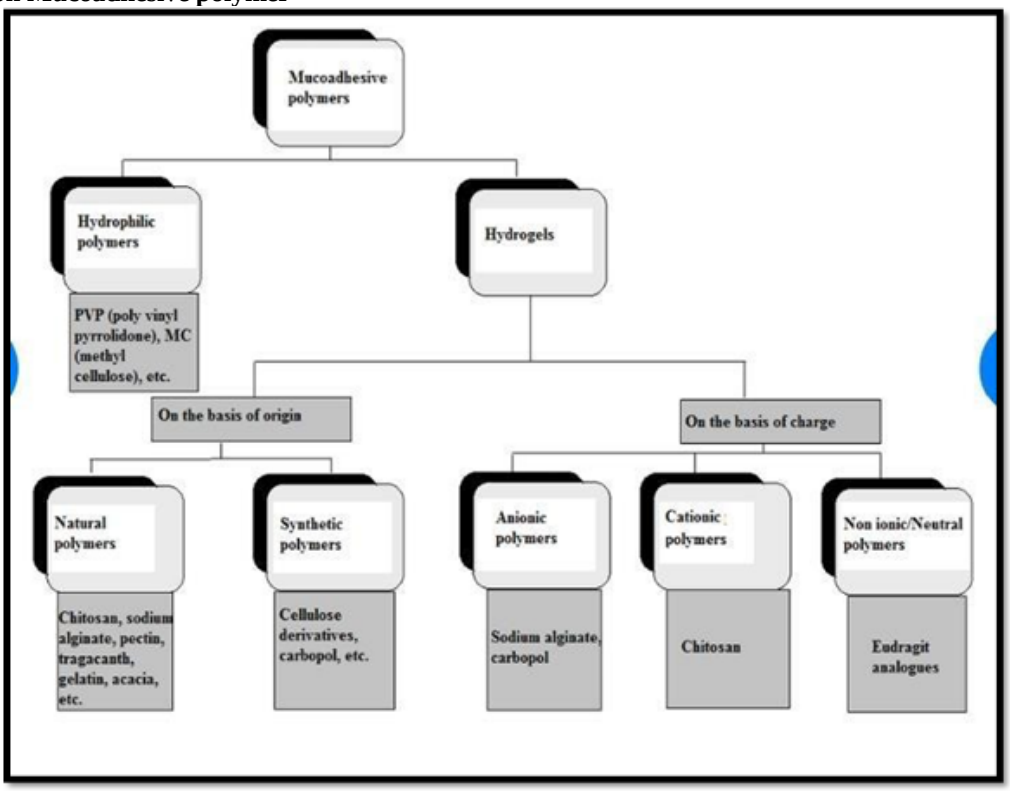
Gels

As a liquid or semisolid dosage, gels are typically used where a solid form would affectthe patient's comfort. As a trade-off, conventional gels have poor retention rates. This results in unpredictable losses of the drug, as the non-solid dosage is unable to maintain its position at the site of administration. Mucoadhesives increase retention by dynamically increasing the viscosity of the gel after application. This allows the gel to effectively administer the drug at the local site while maintaining the comfort of

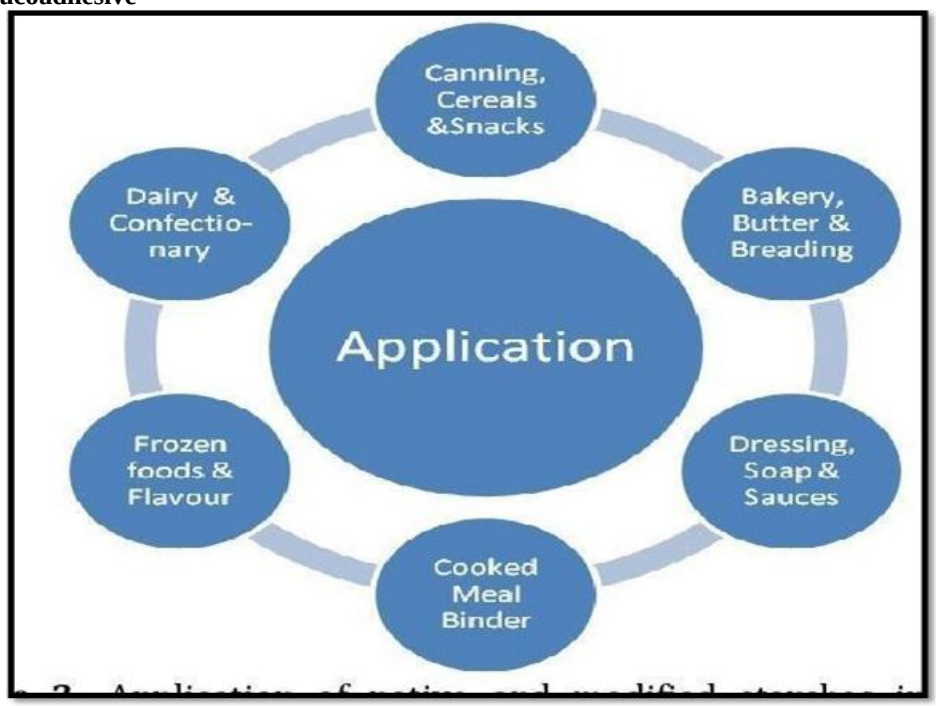
thepatient.[20]

Solutions
These dosage forms are commonly used to deliver drugs to the eye and nasal cavity. They often include Mucoadhesive polymers to improve retention on dynamic mucosalsurfaces. Some advanced eye drop formulations may also turn from a liquid to a gel (so called in situ gelling systems) upon drug administration. For example, gel-forming solutions containing Pluronics could be used to improve the efficiency of eye drops and provide better retention on ocular surfaces.[21]

Classification Mucoadhesive polymer[22]



Application Mucoadhesive[23]



CONCLUSION

The Mucoadhesive dosage forms offer prolonged contact at the site of administration, low enzymatic activity, and patient compliance. The formulation of Mucoadhesive drug delivery system depends on the selection of suitable polymer with excellent mucosal adhesive properties and biocompatibility. Now researchers are looking beyond traditional polymers, in particular next-generation Mucoadhesive polymers (lectins, thiols, etc.); these polymers offer greater attachment and retention of dosage forms. However, these novel Mucoadhesive formulations require much more work, to deliver clinically for the treatment of both topical and systemic diseases.

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