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REVIEW ON MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM

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ABSTRACT

KEYWORDS:

Mucoadhesion ,
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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 gastrointestinal tract (GIT) require increased duration of stay in GIT. Mucoadhesive drug delivery system shows promising future in enhancing the bioavailability and specific needs by utilizing the physiochemical characters of both the dosage form and the mucosal lining. It has to be noted that only a moist surface can bring the muco-adhesive nature of the dosage form.

1. INTRODUCTION:

Mucoadhesive drug delivery system [1]:

Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and surface. The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. It also defined as ability of a material to adhere to a biological tissue for an extended period of time.

Bioadhesion can be classified into 3 types:

- Type 1, adhesion between two biological phases, for example, platelet aggregation and wound healing.
- Type 2, adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio film formation on prosthetic devices and inserts.
- Type 3, adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

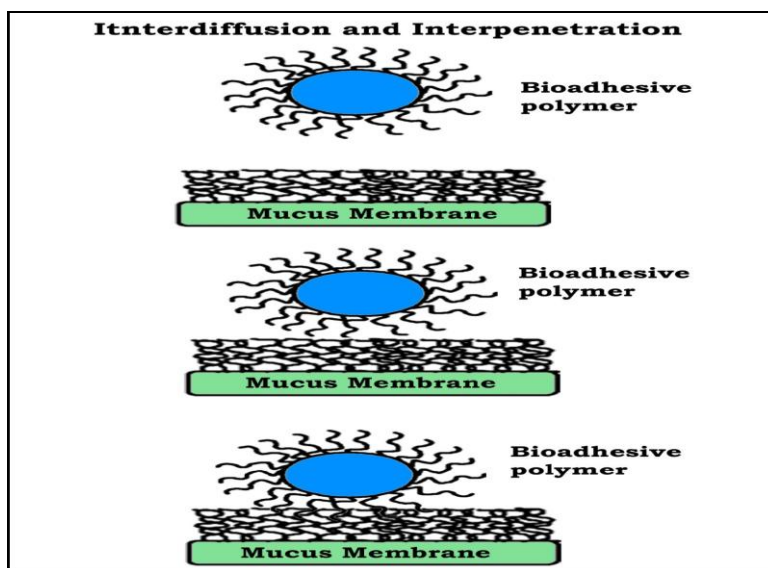
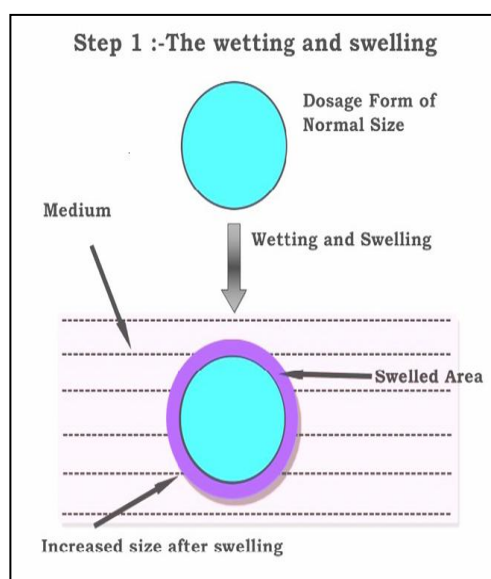
Mucoadhesive drug delivery system utilize the property of bio adhesive of certain water soluble polymer which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time.

The Mucoadhesive drug delivery system may include the following:

Buccal delivery system, Sublingual delivery system, Vaginal delivery system, Rectal delivery system, Nasal delivery system, Ocular delivery system, Gastrointestinal delivery system

2.1.1: Mechanism of Mucoadhesion:

1. Spreading, wetting, swelling and dissolution of Mucoadhesive polymer at the interface, initiates intimate molecular contact at the interface between the polymer and epithelial layer
2. Inter diffusion and interpenetration between the chains of the adhesive polymer and the mucus/epithelial surface .resulting physical cross link or mechanical inter locking
3. Adsorption : the orientation of the polymer at the interface so the adhesive bounding across the interface is possible
4. Formation of secondary chemical bonds between the polymer chains and mucin molecules.



2.1.2. Theories of Mucoadhesion [3]

Various theories exist to explain at least some of the experimental observations made during the bioadhesion process. Unfortunately, each theoretical model can only explain a limited number of the diverse range of interactions that constitute the bioadhesive bond. However, four main theories can be distinguished.

Wetting Theory of Mucoadhesion [4-6]

The wetting theory is perhaps the oldest established theory of adhesion. It is best applied to liquid or low-viscosity bio-adhesives. It explains adhesion as an embedding process, whereby adhesive agents penetrate into surface irregularities of the substrate and ultimately harden, producing many adhesive anchors. Free movement of the adhesive on the surface of the substrate means that it must overcome any surface tension effects present at the interface. The wetting theory calculates the contact angle and the thermodynamic work of adhesion.

The work done is related to the surface tension of both the adhesive and the substrate, as given by Dupre's equation;

$$\omega_A = \gamma_b + \gamma_t - \gamma_{bt} \quad (1)$$

Where, ω_A is the specific thermodynamic work of adhesion and γ_b , γ_t , and γ_{bt} represent, respectively, the surface tensions of the bioadhesive polymer, the substrate, and the interfacial tension. The adhesive work done is a sum of the surface tensions of the two adherent phases, less the interfacial tensions apparent between both phases.

A liquid bioadhesive spreading over a typical soft tissue surface.

Horizontal resolution of the forces gives the Young equation:

$$\gamma_{ta} = \gamma_{bt} + \gamma_{ba} \cos \theta \quad (2)$$

Where, θ is the angle of contact, γ_{bt} is the surface tension between the tissue and polymer, γ_{ba} is the surface tension between polymer and air, and γ_{ta} is the surface tension between tissue and air. Equation (3) states that if the angle of contact, θ , is greater than zero, the wetting will be incomplete. If the vector γ_{ta} greatly exceeds $\gamma_{bt} + \gamma_{ba}$, that is:

$$\gamma_{ta} \geq \gamma_{bt} + \gamma_{ba} \quad (3)$$

Then, θ will approach zero and wetting will be complete. If a bioadhesive material is to successfully adhere to a biological surface, it must first dispel barrier substances and then spontaneously spread across the underlying substrate, either tissue or mucus. The spreading coefficient, S_b , can be defined as shown in Equation 4:

$$S_b = \gamma_{ta} - \gamma_{bt} - \gamma_{ba} > 0 \quad (4).$$

Which, states that bioadhesion is successful if S_b is positive, thereby setting the criteria for the surface tension vectors; in other words, bioadhesion is favored by large values of γ_{ta} or by small values of γ_{bt} and γ_{ba} .

Electrostatic Theory of Mucoadhesion [7]

According to electrostatic theory, transfer of electrons occurs across the adhesive interface and adhering surface. This results in the establishment of the electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers.

Diffusion Theory of Mucoadhesion [8]

Diffusion theory describes that polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow formation of a semi-permanent bond. The process can be visualized from the point of initial contact. The existence of concentration gradients will drive the polymer chains of the bioadhesive into the mucus network and the glycoprotein mucin chains into the bioadhesive matrix until an equilibrium penetration depth is achieved

- (a) Schematic representation of the diffusion theory of bioadhesion. Blue polymer layer and red mucus layer before contact; (b) Upon contact; (c) The interface becomes diffuse after contact for a period of time.

The exact depth needed for good bioadhesive bonds is unclear, but is estimated to be in the range of 0.2–0.5 μm .]. The mean diffusional depth of the bioadhesive polymer segments, s , may be represented by Equation 5:

$$s = \sqrt{2tD} \quad (5)$$

where D is the diffusion coefficient and t is the contact time. Adapted Equation 5 to give Equation 6, which can be used to determine the time, t , to bioadhesion of a particular polymer:

$$t = \frac{l^2}{D_b} \quad (6)$$

in which l represents the interpenetrating depth and D_b the diffusion coefficient of a bioadhesive through the substrate.

Once intimate contact is achieved, the substrate and adhesive chains move along their respective concentration gradients into the opposite phases. Depth of diffusion is dependent on the diffusion coefficient of both phases. Reinhart and Peppas reported that the diffusion coefficient depended on the molecular weight of the polymer strand and that it decreased with increasing cross-linking density.

Adsorption Theory of Mucoadhesion

According to the adsorption theory, after an initial contact between two surfaces, the materials adhere because of surface forces acting between the chemical structures at the two surfaces. When polar molecules or groups are present, they reorientate at the interface. Chemisorption can occur when adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (van der Waal's forces, hydrogen bonding, and hydrophobic bonding).

Fracture Theory of Adhesion [9-10]

This theory describes the force required for the separation of two surfaces after adhesion. The fracture strength is equivalent adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus.

$$\sigma = (E \times \varepsilon/L)^{1/2} \quad (7)$$

Where, σ is the fracture strength, ε fracture energy, E young modulus of elasticity, and L the critical crack length.

Factor Affecting Mucoadhesion:

1. Polymer-related factors:

a. **Molecular Weight of the Polymer [11-12]:** The optimum molecular weight for maximum muco-adhesion depends upon the type of muco-adhesive polymer and tissue. Mucoadhesiveness of a polymer increases with the increase in the molecular weight (MW) of the polymer chain. In general, polymers having $MW \geq 100,000$ have been found to have adequate muco-adhesive property for biomedical applications. For example, polyethylene glycol (PEG), having 20,000 molecular weight has little adhesive character, whereas PEG with 200,000 molecular weight has enhanced, and a PEG with 400,000 has superior adhesive properties. Interpenetration is more critical for lower molecular weight polymers to be an excellent bioadhesive, whereas Entanglement is important for higher molecular weight polymers.

b. **Concentration of Active Polymers [13]:** There is an optimum concentration of polymer corresponding to the best bioadhesion. In extremely concentrated systems, beyond the optimum level, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited. It affects the availability of long polymer chains for penetration into the mucus layer. Thus it is important mainly for liquid and viscous drug delivery system.

c. **Flexibility of Polymer Chains [14-15]:** It is critical for interpenetration and entanglement. Mobility of individual polymer chains decrease as water-soluble polymers become cross-linked and thus the valuable length of the chain that can penetrate into the mucus layer decreases, which reduces muco-adhesive strength.

d. **Spatial Conformation [14-15]:** Despite a high molecular weight of 19,500,000 for dextrans, spatial conformation of a molecule is also important. They have adhesive strength similar to that of polyethylene glycol, which has a molecular weight of 200,000. The helical conformation of electrons may shield many adhesively active groups, primarily responsible for adhesion unlike PEG polymers that have a linear conformation. Also the effect of polymer concentration is dependable on the physical concentration results the higher bioadhesive strength in Solid BDDS while an optimum concentration is required for best bioadhesion in liquids.

e. **Swelling (Hydration)[16]:** Swelling characteristics are related to the Mucoadhesive itself and its environment. Swelling depends upon the concentration of polymer, the ionic strength, and the presence of water. Maximum bioadhesion in vitro occurs with optimum water content during the dynamic process of bioadhesion. Formation of wet slippery mucilage without adhesion occurs due to over-hydration.

2. Environment Related Factors:

a. **Applied Strength[7,11,15]:** It is necessary to apply a defined strength, if you want to place a solid bioadhesive system. The adhesive strength increases with the applied strength or with the density of its application up to an optimum. The depth of interpenetration is affected by the pressure initially applied to the Mucoadhesive tissue contact site. If high pressure is applied for a satisfactory longer period of time, polymers become Mucoadhesive even though they do not have attractive interaction with mucin.

b. **pH at Polymer Substrate Interface [7, 11]:** 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 on the basis of pH due to the difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone.

c. **Initial Contact Time [11]:** 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.

3. Physiological Variables:

a. **Mucin Turnover [7, 11]:** The natural mucin turnover from the mucus layer is important for at least two reasons. **First**, Residence time of the Mucoadhesive on the mucus layer is expected to be limited due to mucin turnover. Due to mucin turnover, mucoadhesives are detached from the surface, no matter how high the Mucoadhesive strength is. The turnover rate differs in the presence of Mucoadhesive.

Second, Substantial amount of soluble mucin molecules results from mucin turnover. Before these mucin molecules have a chance to interact with mucus layer, they first interact with mucoadhesives. Mucin turnover may depend on the other factors such as presence of blood. Lehr et al. (1991) calculated mucin turnover time of 47-270 minutes. In the nasal cavity, the ciliated cells are known to transport the mucus to the throat at a rate of 5mm/min. In the tracheal region, the mucociliary clearance has been found to be in the range of 4-10mm/min.

b. **Disease States [15]:** Physicochemical properties of mucus are known to change during diseased states, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye. Under these conditions, the exact structural changes taking place in mucus are not clearly understood. The Mucoadhesive property must be evaluated when the mucoadhesives are used in the diseased state.

MUCOADHESIVE POLYMERS [16]

Polymer is a generic term used to describe a very long molecule consisting of structural units and repeating units connected by covalent chemical bonds. The term is derived from the Greek words: *polys* meaning ‘many’ and *meros* meaning ‘parts’. A polymer is a substance formed by the linkage of a large number of small molecules known as monomers. Mucoadhesive polymers are watersoluble and water insoluble polymers, which have swellable networks, jointed by crosslinking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucous and optimal fluidity that permits the mutual adsorption and interpenetration of polymer.

CLASSIFICATION OF POLYMERS [17]

Depending upon source

Natural Polymers	Synthetic Polymers
	Agarose Chitosan Gelatin Hyaluronic acid Carrageenan Pectin Sodium alginate.
Cellulose derivatives	Carboxy methyl cellulose. Thiolated Carboxy methyl cellulose Sodium Carboxy methyl cellulose Hydroxyethylcellulose, Hydroxypropylcellulose, Hydroxypropylmethylcellulose
Polymers based on poly(meth)acrylic acid.	Carbopol Polycarbophil Polyacrylic acid Polyacrylates Copolymer of acrylic acid Polyethylene glycol Copolymer of methylvinyl ether and Methacrylic acid Poly-2-hydroxyethylmethacrylate
Others	Poly-N-2-hydroxypropylmethacrylamide Polyhydroxyethylene Poly vinyl alcohol Poly vinyl pyrrolidine Thiolated polymers

Characteristics of ideal Mucoadhesive polymer to be used in drug delivery system [19-20]

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

2.2. Buccal route as a drug delivery [21]

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption.

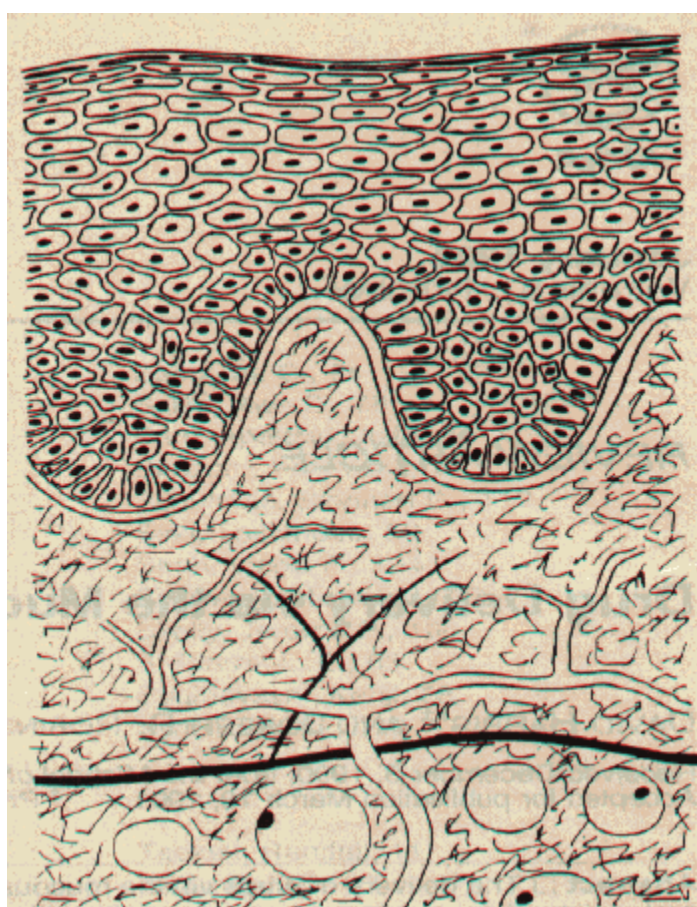
The oral cavity, on the other hand, is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage, and the virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens. Furthermore, oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.

Within the oral mucosal cavity, delivery of drugs is classified into three categories: (i) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, (ii) buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and (iii) local delivery, which is drug delivery into the oral cavity.

Advantages of buccal drug delivery systems [22]

- Excellent accessibility
- Presence of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms
- Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability
- Low enzymatic activity
- Suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa
- Painless administration
- Easy drug withdrawal
- Facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation
- Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc

Buccal mucosal structure and suitability [21]



Epithelium

Lamina Propria

Submucosa

The turnover time for the buccal epithelium has been estimated at 5-6 days [18], and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm , while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm . The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized [18]. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide [19-21]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia [18-20].

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The oral mucosae in general is a somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin [22]. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal [18]. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

2.2.3. Ideal Characteristics of drug to be given as buccal delivery:

- It should have daily dose requirement of 40mg or less.
- It should be low molecular weight for permeability through buccal mucosa. (between 200-500 daltons).

- It should be Stable at buccal pH
- It should have short half life for sustained and controlled delivery.
- Lipid solubility of drug is an important determinant in buccal suitability.
- It must be protected by salivary and tissue enzymes that could cause inactivation.
- Drug and adhesive materials must not damage the teeth, oral cavity or surrounding tissues.
- It should have appropriate pka value for more proportion of unionized species for absorption through buccal mucosa.
- Partition co-efficient should be high for lipophilicity of drug.

Buccal permeation enhancer [17]

Substances that facilitate the permeation through mucosa are referred to as permeation enhancers. Membrane permeation is the limiting factor for many drugs in the development of Mucoadhesive delivery system. The epithelium that lines the mucosa is a very effective barrier to the absorption of drugs especially buccal mucosa (Chattarajee and Walker, 1995). The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties (Shojaei, 1998).

Properties

According to Aungst (1994) permeation enhancers should be:

Safe, Non- toxic, Non –irritant, Non-allergic, Pharmacologically and chemically inert

Surfactants such as anionic, cationic, nonionic and bile salts increase permeability of drugs by perturbation of intercellular lipids. Chelators act by interfering with the calcium ions. Fatty acids act by increasing fluidity of phospholipids. Positively charged polymers act by ionic interaction with negative charge on the mucosal surface.

List of permeation enhancers

Chelators EDTA, Citric acid, Sodium salicylates, Methoxy salicylates

Surfactants Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxyethylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, Cetylpyridinium chloride, Cetyltrimethyl ammonium bromide

Bile Salts Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium taurodeoxycholate

Fatty Acids Oleic acid, Capric acid, Lauric acid, Lauric acid/ propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholine

Non Surfactants Unsaturated cyclic ureas.

Inclusion Complexes Cyclodextrins

Thiolated Polymers Chitosan-4-thiobutylamide, Chitosan-cysteine, Poly (acrylic acid)-homocysteine, Polycarbophil-cysteine, Polycarbophil-cysteine/gsh, Chitosan-4-thioethylamide/gsh, Chitosan- 4-thioglycolic acid

Others Aprotinin, Azone, Cyclodextrin, Dextran sulfate, Menthol, Polysorbate 80 , Sulfoxides and various alkyl glycosides.

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