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Mucoadhesive buccal drug delivery system

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Abstract

Within the oral mucosal cavity, the buccal region offers an adorable route of administration for systemic drug delivery. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily approachable site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces. The mucosa has a rich blood supply and it is relatively permeable. Buccal dosage forms will be reviewed with an emphasis on bioadhesive polymeric based delivery systems. The mucoadhesive interaction is explained in relation to the structural characteristics of mucosal tissues and the theories & properties of the polymers. Degree of mucoadhesion bonding is influenced by various polymer-based properties. Evolution of such mucoadhesive formulations has transgressed from first-generation charged hydrophilic polymer networks to more absolute second-generation systems based on lectin, Thiol and various other adhesive functional groups.

Key-Words: Mucoadhesive; buccal; polymers; retension time; drug delivery system.

Introduction

Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces in the midst of the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time.[1-4] Bioadhesive polymeric systems have been used since extent in the development of products for various biomedical applications which include denture adhesives and surgical glue.[5-8] The adhesion of bacteria to the human gut may be attributed to the interaction of lectin-like structure (present on the cell surface of bacteria) and mucin (present in the biological tissues).[9-12] Various biopolymers show the bioadhesive properties and have been utilized for various therapeutic purposes in medicine.[2] The bioadhesive polymers can be broadly classified into two groups, namely specific and nonspecific.[14]

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Material and Methods

The specific bioadhesive polymers (e.g. fimbrin, lectins) have the ability to adhere to specific chemical structures within the biological molecules while the nonspecific bioadhesive polymers (e.g. polyacrylic acid, cyanoacrylates) have the capability to bind with both the cell surfaces and the mucosal layer. The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the gums (gingival) and the inside of the cheeks (buccal).

In common, the delivery of a drug requires some type of dosage form, present in the oral cavity, to release a drug, which then diffuses through the mucosa into the local blood flow and is then taken added to the systemic blood circulation. Buccal drug delivery has a number of advantages over peroral delivery. Mucoadhesive drug delivery systems are delivery systems which utilized the assets of bioadhesion of certain polymers which become adhesive on hydration and thus can be used for targeting a drug to exacting region of the body for extended period of time.[1]Pharmaceutical aspects of mucoadhesion have been the subject of great significance during recent years because it provides the chance of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug. The mucoadhesive drug delivery system includes the following:[2] The use of mucoadhesive polymers for the development of

pharmaceutical formulations dates back to 1947, when attempts were made to prepare a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth and dental adhesive powders.[15] Improved results were reported when carboxymethylcellulose and petrolatum were used for the development of the formulation. Subsequent research resulted in the development of a mucoadhesive delivery vehicle which consisted of finely ground sodium carboxymethylcellulose, pectin, and gelatin. The formulation was later marketed as Orahesive®. This was subsequently the development of a system where polyethylene sheet was laminated with a blend of sodium carboxymethylcellulose and poly (isobutylene) which provided an added advantage of caring the mucoadhesive layer by the polyethylene backing from the physical interference of the external environment[16-18] Over the years, a choice of other polymers (e.g. sodium alginate, sodium carboxymethylcellulose, guar gum, hydroxyethylcellulose, karya gum, methylcellulose, polyethylene glycol (PEG), retene and tragacanth) have been found to show mucoadhesive properties. During the period of 1980s poly (acrylic acid), hydroxypropylcellulose, and sodium carboxymethylcellulose were extensively explored for the development of formulations having mucoadhesive properties. Since then the use of acrylate polymers for the development of mucoadhesive formulations have improved manyfold, different authors have investigated the mucoadhesive properties of different polymers with varying molecular architecture.[19-21]After a lot of research, the researchers are of the view that a polymer will exhibit enough mucoadhesive property if it can form tough intermolecular hydrogen bonding with the mucosal layer, penetration of the polymer into the mucus network or tissue crevices, easy wetting of mucosal layer and high molecular weight of the polymer chain. The ideal distinctiveness of a mucoadhesive polymer matrix include the rapid adherence to the mucosal layer not including any change in the physical property of the delivery matrix, minimum interference to the release of the active agent, biodegradable without producing any toxic byproducts, inhibit the enzymes present at the delivery site and develop the penetration of the active agent (if the active agent is meant to be absorbed from the delivery site).[21]

Mucoadhesive drug delivery system[22]

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion 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 period of time.

Bioadhesion is an integral phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces. In the case of polymer attached to mucin layer of a mucosal tissue, the term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, urogenital tract, the airways, the ear and eye.

Mechanism of Mucoadhesion[23,24,25]

Several theories have been put forward to explain the mechanism of polymer–mucus interactions that lead to mucoadhesion. To start with, the sequential events that occur during bioadhesion include an intimate contact between the bioadhesive polymer and the biological tissue due to proper wetting of the bioadhesive surface and swelling of the bioadhesive. Following this is the penetration of the bioadhesive into the tissue crevices, interpenetration between the mucoadhesive polymer chains and those of the mucus. Subsequently low chemical bonds can become operative. Hydration of the polymer plays a very important role in bioadhesion. There is a critical degree of hydration required for optimum bioadhesion. If there is incomplete hydration, the active adhesion sites are not completely liberated and available for interaction. On the other hand, an excessive amount of water weakens the adhesive bond as a result of an overextension of the hydrogen bonds. During hydration, there is a dissociation of hydrogen bonds of the polymer chains. The polymer–water interaction becomes greater than the polymer-polymer interaction, thereby making the polymer chains available for mucus penetration. Following polymer hydration intermingling between chain segments of the mucoadhesive polymer with the mucus occurs. The factors critical for this model of mucoadhesion are the diffusion coefficient of the polymer, contact time and contact pressure. The polymer diffusion coefficient is influenced by the molecular mass between cross-links, and is inversely related to the cross-linking density.

Theories of Mucoadhesion[26]

1. Electronic Theory: The adhesive polymer and mucus typically have different
electronic characteristics. When these two surface come in contact, a double layer
of electrical charge forms at the interface, and then adhesion develops due to the
attractive force from electron transfer across the electrical double layer.

2. Adsorption Theory: The adsorption theory of bioadhesion proposes that

adhesion of a polymer to a biological tissue results from: (i) primary chemical
bonds that are somewhat permanent and therefore undesirable in bioadhesion
(ii) van der Waals, hydrogen, hydrophobic and electrostatic forces, which form
secondary chemical bonds.

3. Wetting Theory: Primary application to liquid bioadhesive system, the wetting
theory emphasizes the intimate contact between the adhesive and mucus. Thus, a
wetting surface is controlled by structural similarity, degree of cross linking of the
adhesive polymer, or use of a surfactant.

The work of adhesion [expressed in terms of surface and interfacial tension (Y) being defined as energy per cm2 released when an interface is formed.]

According to Dupres equation work of adhesion is given by

$$Wa = Y_A + Y_B - Y_{AB}$$

Where A & B refer to the biological membranes and the bioadhesive formulation respectively.

The work of cohesion is given by:

$$Wc = 2Y_A \text{ or } Y_B$$

For a bioadhesive material B spreading on a biological substrate, the spreading
coefficient is given by:

$$S_{B/A} = Y_A - (Y_B + Y_{AB})$$

$S_{B/A}$ should be positive for a bioadhesive material to adhere to a biological membrane.

4. Diffusion Theory: The essence of this theory is that chains of the adhesive and
the substrate interpenetrate one another to a sufficient depth to create a semi permanent
adhesive bond. The penetration rate depends on the diffusion coefficient of both interacting polymers, and the diffusion co-efficient is known to depend on molecular weight and cross-linking density. In addition, segment mobility, flexibility of the bioadhesive polymer, mucus glycoprotein, and the expanded nature of both network are important parameters that need to be considered.

5.Fracture:

Fracture theory of adhesion is related to separation of two surfaces after adhesion.

The fracture strength is equivalent to adhesive strength as given by

$$G = (E\varepsilon. /L)\ ½$$

Where: E- Young's modules of elasticity
ε- Fracture energy
L- Critical crack length when two surfaces are separated

Bioadhesive Polymers[27,28]

Bioadhesive polymers have properties to get adhered to the biological
membrane and hence capable of prolonging the contact time of the drug with a body
tissue. The use of bioadhesive polymers can significantly improve the performance of
many drugs. This improvement ranges from better treatment of local pathologies to
improved bioavailability and controlled release to enhance patient compliance.

Characteristics of Ideal Bioadhesive Polymers

- It should show bioadhesive properties in both dry and liquid state.
- It should possess an optimum molecular weight to the bioadhesion.
- It should be able to accommodate both oil and water soluble drugs for the

purpose of controlled drug delivery.

- It should demonstrate local enzyme inhibition and penetration enhancement

properties.

- It should show specificity for attachment to an area or cellular site.
- It should show specificity and stimulate endocytosis.
- It should be inert and compatible with the environment.
- It should be easy and inexpensive to fabricate.
- It should have good mechanical strength.
- It should possess a wide margin of safety both locally and systemically.

- **Mucoadhesive buccal drug delivery systems:[29,30]**

Drug delivery via the membranes of the oral cavity can be subdivided as
Sub lingual delivery, buccal delivery and local delivery.

These oral mucosal sites be at variance greatly from one another, on terms of anatomy,
Permeability, to an applied drug, and their ability to maintain a drug delivery system for desired length of time.

What aspects make the oral mucosa, mainly the buccal site rather attractive?

1. Because of easily accessibility it permits localization of the system.
2. Since the patients are well modified to oral administration of drugs in general, patient recognition and compliance is expected to be good.
3. Its ability to convalesce after local treatment is evident and hence allows a wide range of

formulations to be used e.g. bioadhesive patches and ointments.

Advantages of mucoadhesive buccal drug delivery:

1. Drug administration via the oral mucosa offers a number of advantages
2. Offers an superb route for the systemic delivery of drug which by passes first pass metabolism, thereby offering a greater bioavailability.
3. Permits localization of the drug for a prolonged period of time.
4. Easy of administration and termination of therapy in emergency.
5. Can be administered to comatose and trauma patients.
6. Significant reduction in dose can be achieved, there by reducing dose, dose dependent side effects, and eliminates peakvalley profile.
7. Drugs which are unstable in acidic environment of stomach or are destroyed by the enzymatic or alkaline environment of the intestine can be administered.
8. It offers a passive system for drug absorption.
9. It can be made unidirectional to assure buccal absorption.
10. Flexibility in physical state, shape, size and surface.
11. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, careful uses of therapeutic agents like peptides, proteins and ionized species can be achieved.
12. Maximized absorption rate due to intimate make contact with the absorbing membrane and decreased diffusion barriers.
13. It satisfies a number of futures of the controlled release system.
14. The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus build up beneath the applied dosage form.
15. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
16. Rapid onset of action [30,31].

Limitations of Buccal Drug Administration:

1. Drugs which are unstable at buccal pH cannot be administered.
2. Eating and drinking may become restricted.
3. There is an ever present possibility of the patient swallowing the dosage form.
4. Over hydration may leads to slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers.
5. Drugs which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor cannot be administered by this route.
6. Only drug with small dose requirement can be administered.
7. Only those drugs which are absorbed by passive diffusion can be administered by this route.
8. Drugs contained in the swallowed saliva follows the pre-oral and advantages of buccal route are lost [12,29].

III. BUCCAL ROUTES OF DRUG ABSORPTION[29]

The are two permeation pathways for passive drug transport across the oral mucosa:

- Paracellular routes
- Transcellular routes.

Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubilities in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a squat partition coefficient. Therefore, the intercellular spaces pose as the main barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds. Since the oral epithelium is stratified, solute permeation may involve a combination of these two routes. The route that predominates, however, is generally the one that provides the least amount of hindrance to passage.

An ideal mucoadhesive polymer has the following characteristics [30,31].

1. The polymer and its degradation products should be non-hazardous and should be non absorbable from the gastrointestinal tract.
2. It should be nonirritant to the mucous membrane.
3. If possible form a strong non-covalent bond with the mucin-epithelial cell surfaces.

4. It should adhere quickly to most tissue and should possess some site-specificity.
5. It should allow daily incorporation to the drug and offer no hindrance to its release.
6. The polymer must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be elevated so that the prepared dosage form remains competitive.

Molecular Characteristics[12,32,33,]

Investigations into polymers with various molecular characteristics conducted by many authors have led to a nurnber of conclusions regarding the molecular characteristics required for mucoadhesion.

The properties exhibited by a good mucoadhesive may be summarized as follows :

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

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.

Method used to study bioadhesion:

Several test methods have been reported for studying bioadhesion. These tests are
important during the design and development of bioadhesion controlled released system
as they guarantee compatibility, physical and mechanical stability, surface analysis and
bioadhesion bond strength.

The tests can be broadly classified into 2 major categories

1. In-vitro / Ex-vivo methods
2. In-vivo methods

1. In-vitro / Ex-vivo methods:

Most in-vitro methods were based on either tensile or shear stress. a. Modified balance or tensile testers.

b. Wilhelm plate method (shear stress).

c. Other in-vitro methods

A number of other methods including thumb test method, adhesion weight
method, flow channel method ,fluorescent probe method, falling liquid film method,
colloidal gold staining method, have been used for the determination of bioadhesion.

2. In-vivo methods:

Rathbone et al. has discussed several methods to study rate and extent of drug loss
from human oral cavity. These include buccal absorption test, disks methods and
perfusion cells. These methods have provided information on mechanism by which drugs
are transported across the oral cavity membranes , [37]

Factors Important To Mucoadhesion[37]

The bioadhesive power of a polymer or of a progression of polymers is affected by the nature of the polymer and also by the nature of the surrounding media.

1. Polymer-Related Factors

(a) Molecular Weight:

The optimum molecular weight for most bioadhesion depends on the type of bioadhesive polymer at issue. It is usually implicit that the threshold required for successful bioadhesion is at least 100,000 molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has enhanced, and a PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness improves with increasing molecular weight for linear polymers imply two things:

- Interpretation is more critical for lower molecular weight polymers to be a excellent bioadhesive,
- Entanglement is important for higher molecular weight polymers.

Adhesiveness ofa nonlinear structure follows a quite different tendency. The adhesive strength of dextran, with a very high molecular weight of 19,500,000 is similar to that of PEG, with a molecular weight of 200,000. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are mainly responsible for adhesion, unlike the conformation of PEG.

(b) Concentration of active polymers:

There is an optimum concentration of a bioadhesive polymer to produce maximum bioadhesion. In extremely concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

(c) Flexibility of polymer chains:

It is critical for interpenetration and entanglement. As water-soluble polymers become crosslinked, mobility of character polymer chains decrease and thus the valuable length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

(d) Spatial conformation:
Besides molecular weight or chain length, spatial conformation of a molecule is also main. In spite of a high molecular weight of 19,500,000 for dextrans, they have related adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily dependable for adhesion, unlike PEG polymers which have a linear conformation.

2. Environment Related Factors

(a) Applied strength:
To place a solid bioadhesive system, it is required to concern a defined strength. Whatever the polymer, poly(acrylic acid / vinyl benzene poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the period of its application, upto an optimum. the pressure initially applied to the mucoadhesive tissue contact site can influence 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 interaction with mucin.

(b) pH:
It can manipulate the formal charge on the surface of mucus as well as certain ionis capable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of efficient groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration of crosslinked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then a reduce as alkalinity and ionic strength increases.

(c) Initial Contact Time:
Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Bioadhesive strength increases as the initial contact time increases.

(d) Swelling:
It depends on the polymer concentration, ionic concentration, as well as the presence of water.Over hydration results in the formation of a slippery mucilage without adhesion.

3. Physiological Variables

a) Mucin Turnover:
The natural turnover of mucin molecules is important for as a minimum two reasons. First, the mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layer. No matter, how high the adhesive strength, mucoadhesive are detached from the surface due to mucin turn over. Second, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with the mucoadhesive before they have a chance to act together with the mucus layer. Mucin turnover may depend on other factors such as presence of food.

b) Disease States:
The physiochemical properties of mucus are known to adjust during disease conditions such as common cold, gastric ulcers, and ulcerative colitis, bacterial and fungal infections of the female reproductive tract.

Mechanism of Buccal Absorption Enhancer: [35,36,]
The mechanism by which enhancers act are been unsuccessfully understood. Surfactants such as sodium lauryl sulphate interact at either the polar head groups or the hydrophilic tail regions of the molecules comprising the lipid bilayer disrupting the packing of the lipid molecules, increasing the fluidity of the bilayer and facilitating drug diffusion. Interaction of enhancers with the polar head groups may also cause or allow the hydrophilic regions of adjacent bilayers to take up more water and more apart, thus opening the Paracellular pathway. Non ionic surfactants and long chain acids and alcohols also increase membrane components, thereby increasing the permeability. Agents such as DMSO, polyethylene glycol, and ethanol can, if present insufficient high concentrations in the delivery vehicle enter the aqueous phase of the stratum corneum and alter its solublizing properties, thereby attractive the partitioning of drugs from the vehicle into the skin.

Mechanisms by which permeation enhancers are thought to improve mucosal
absorption include the following:

- Overcoming the enzymatic barrier
- Increasing the thermodynamic activity of drugs
- Changing mucus rheology
- Affecting the components involved in the formation of intracellular junctions
- Increasing the thermodynamic activity of drugs

Permeation enhancers: [12]
Permeation enhancers are substances added to pharmaceutical formulation in
order to increases the membrane permeation rate or absorption rate of a co-administered
drug. They are used to improve bioavailability of drugs with normally poor membrane
permeation properties without damaging the membrane and causing toxicity.
Enhancer efficacy depends on the physiochemical properties of the drug,

administration site, nature of the vehicle and whether enhancer is used alone or in combination.

Categories and examples of membrane permeation enhancers

- Bile salts : Sodium glycocholate, Sodium deoxycholate, Sodium taurocholate, Sodium glycodeoxycholate, Sodium glycodeoxycholate,
- Surfactants : Sodium lauryl sulphate, Polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride,
- Fatty acids : Oleic acid, Capric acid, Lauric acid, Lauric acid/ propylene glycol, Methyloleate, Lysophosphatidylcholine, Phosphatidylcholi
- Chelators: EDTA, Citricacid, Sodium salicylate, Methoxy salicylates
- Non-surfactants: Unsaturated cyclic ureas.:
- Inclusion complexes: Cyclodextrins
- Others :Aprotinin, Azone, Cyclodextrin, Dextran sulfate, Menthol, Polysorbate 80, Sulfoxides and various alkyl glycosides.
- Thiolated polymers:Chitosan-4-thiobutylamide, Chitosan- 4-thiobutylamide/gsh, Chitosan-cysteine, Chitosan- 4-thiobutylamide/gsh,

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Table 1: Classification of polymer [40]

Property used for classification	Synthetic	Natural polymers
Source	Agarose, Chitosan, Gelatin, Hyaluronic acid, Carrageenan, Pectin, Sodium alginate. Cellulose derivatives CMC, thiolated CMC, Na CMC, hydroxyethylcellulose, HPC, HPMC, methylcellulose, Methylhydroxyethylcellulose.	Polymers based on poly(meth)acrylic acid. Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates, Copolymer of acrylic acid andPEG, Copolymer of methylvinyl ether and Methacrylic acid, Poly-2-hydroxyethylmethacrylate, Copolymer of acrylic acid and Ethylhexylacrylate, Polymethacrylate, Polyalkylcyanoacrylates:- Polyisobutylcyanoacrylate, Polyisohexylcyanoacrylate
Solubility in water	Water-insoluble Polymers based on poly(meth)acrylic acid Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates, Copolymer of acrylic acid and PEG, Copolymer of methylvinyl ether and Methacrylic acid, Poly-2-hydroxyethylmethacrylate, Copolymer of acrylic acid and Ethylhexylacrylate, Polymethacrylate, Polyalkylcyanoacrylates:- Polyisobutylcyanoacrylate.	Water-soluble Cellulose derivatives CMC, Thiolated CMC, Na CMC, Hydroxyethylcellulose, HPC, HPMC, Methylcellulose, Methylhydroxyethylcellulose. Others Poly-N-2-hydroxypropylmethacrylamide, Polyhydroxyethylene, PVA, PVP, Thiolated polymers. Ethylcellulose, polycarbophil
Charge	Cationic and Anionic Aminodextran, dimethylaminoethyldextran, chitosan, quaternized chitosan Chitosan-EDTA, PAC, carbopol, polycarbophil, pectin, sodium alginate, Na CMC, CMC	Uncharged Hydroxyethylated starch, HPC, PEG, PVA, PVP
Possible mechanism of formation of Bioadhesive bonds	Covalent Hydrogen bonds Electrostatic interactions	Cyanoacrylate Acrylates, carbopol, polycarbophil, PVA Chitosan
Notes	CMC = carboxymethylcellulose; HPMC = hydroxypropylmethylcellulose; PEG = polyethylene glycol; PVA =polyvinyl alcohol; PVP = polyvinylpyrrolidone; HEC = hydroxyethylcellulose; HPC = hydroxypropylcellulose; PAA = polya crylic acid; EDTA = ethylene diamine tetra acetate.	