Research progress of buccal mucosal bioadhesive materials

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Abstract. Buccal administration is a convenient way of drug delivery, which can be used for local and systemic administration. Buccal mucous adhesion delivery is a drug delivery system in which a carrier made of biological adhesive materials containing drugs adheres to the mucous membrane for a long time and the drug can be continuously released from the carrier. The most important adhesive form of buccal mucous membrane is biological adhesion material. This paper introduces the structure of buccal mucosa and the basic situation of mucous membrane adhesion, reviews the bioadhesive materials which are commonly used in buccal mucous membrane administration, and summarizes some of the listed buccal mucous membrane adhesion preparations.

1. Introduction
In recent years, mucous membrane administration has become a hot research topic because of its convenient administration and good compliance. At present, the most widely studied ways of mucosal administration include buccal mucosa, nasal mucosa, ophthalmic mucosa and gastrointestinal mucosa. The most critical point of all kinds of mucous adhesion preparations is bioadhesive materials, which should have the characteristics of non-toxic and non-irritable, good biocompatibility and drug release performance, easy to mix with drugs and cheap and easy to obtain.

Many drugs are easily destroyed by gastrointestinal environment after buccal administration, resulting in the loss of drug activity and low bioavailability. However, after buccal mucus administration, it has the following characteristics: the drug enters the internal jugular vein through the hypoglossal vein, facial vein and posterior palatal vein, and enters the internal jugular vein directly into the systemic circulation, avoiding gastrointestinal destruction and the first-pass effect of the liver. The raw material benefit of the drug was improved [1]; Buccal mucosa is basically non-keratinized structure, rich in blood flow, drugs can quickly enter the body, rapid effect; The enzyme activity in buccal cavity was 6.6 ~ 7.2, which was suitable for drugs with unstable enzyme or acid and alkali, and easy to be given to coma patients [2-3]. Buccal mucous membrane adhesion administration has many advantages, so it has been paid more and more attention by pharmaceutical scholars.

This paper mainly introduces the basic situation of buccal mucous adhesion, summarizes the bioadhesive materials commonly used in buccal mucous membrane administration and some of the listed buccal mucous adhesion preparations.

2. Introduction of Buccal mucosal adhesion
Buccal mucosa is epithelial cells, basement membrane, lamina propria and submucous tissue from outside to inside. The area, thickness and keratosis of epithelial cells were different in each part, so the drug permeability of each part was different, as shown in Table 1. The gel secretions of buccal epithelial cells are mucinous layer, which have viscous elasticity and form thin continuous gel on the surface of mucous epithelial cells. The water content of mucus layer is as high as 9.5%, and it also contains 2% ~
5% mucin and a small amount of mineral salt. Mucin is closely related to adhesion. Mucin is composed of flexible crosslinked glycoprotein chain and has strong internal cohesion. Under the condition of physiological pH, due to the existence of sialic acid and other acids at the end of glycoprotein chain, the mucus is negatively charged, which can produce high charge density and is beneficial to the formation of biological adhesion [1]. At present, there are many studies on the mechanism of buccal biological adhesion at home and abroad, including adsorption theory, wetting theory, electronic theory, diffusion theory and disconnection theory [3].

### Table 1. Characteristics of buccal mucosa.

| Tissue          | Structure       | Thickness | Mucus replacement time | Superficial area | Permeability | Residence time | Blood flow velocity per 100g tissue/ml min⁻¹ |
|-----------------|-----------------|-----------|------------------------|------------------|--------------|----------------|------------------------------------------|
| Buccal membrane | Non-keratinization | 500-600 | 5-7 | 50.2±2.9 | medium | medium | 20.3 |
| Hypoglobulins   | Non-keratinization | 100-200 | 20 | 26.5±4.2 | good | poor | 12.2 |
| Gingiva         | Keratinization  | 200      | - | - | poor | medium | 19.5 |
| The upper jaw   | Keratinization  | 250      | 24 | 20.1±1.9 | poor | good | 7.0 |

### 3. Bioadhesive material for buccal mucosa

#### 3.1 Polycrlylate

Polyacrylate includes polyacrylic acid (PAA), polymethacrylates(PMAA) and polycarbophene (PCP) and so on. Polyacrylic acids have excellent mucous adhesion properties because of the existence of a large number of carboxylic acid groups, which can form hydrogen bonds with the oligosaccharide side chains of mucin, and form physical entanglement between polymer chains and mucus layers. It is more beneficial to promote adhesion to mucous membrane.

Carbomer is a polymer of allyl ether bonded with acrylic acid (or pentaerythritol). It is a synthetic crosslinked polymer of acrylic acid. The content of acrylic acid group in carbomer is 56% ~ 68%, which is less affected by temperature, unaffected by microorganism, non-toxic and non-prickly excited, and is the most widely used [4]. Kapil et al. investigated the dosage of carbomer 971P, hydroxypropyl methylcellulose (HPMC K15M), polyethylene glycol 400 (PEG 400) and the type of carbomer, and the influence of stirring time on the corresponding variables, respectively. Results the dosage of carbopol and HPMC had great influence, the higher the content of carbopol, the stronger the adhesion of the mucous membrane of the drug delivery system, and a small amount of HPMC was mainly used to control the release of drugs. Carbomer is an anion adhesive, which can not be combined with divalent alkaline drugs to avoid precipitation. Wong et al compared the adhesion energy of carbopol, sodium Carboxymethyl cellulose (CMC-Na) and HPMC after pressing into tablets. The results showed that the adhesion force of carbomer was the highest, followed by CMC-Na and HPMC.

#### 3.2 Chitosan

Chitosan, also known as deacetylated chitin, is the hydrolysate of chitin after deacetylation under alkali conditions, and its relative molecular weight is 3.0 \times 10^5 ~ 6.0 \times 10^5 [5]. Chitosan is a kind of cationic polymer, which can combine with negatively charged mucin to produce electrostatic binding, so it has better adhesion property of mucous membrane. However, some people think that the mucous adhesion of chitosan is more complex. Sogias et al reported that when the solution containing 0.2 mol/L sodium chloride, the electrostatic force between chitosan and mucin decreased. When the solution contained 8 mol/L or 10% ethanol, the polymerization of mucin and chitosan was affected, which indicated that hydrogen bond binding and hydrophobic effect would affect the mucous adhesion properties of chitosan. In addition, the pH value of the solution and other chemicals also affected the adhesion of the mucous membrane.

Aksungur et al selected mycomycin to prevent buccal mucoiditis. The effects of chitosan, solvent
pH value and chitosan cross-linking on drug release in the membrane were investigated. The results showed that the polymer chitosan, High pH value and cross-linking could lead to the decrease of drug release [6]. Venlafaxine buccal gel was prepared by Kumar et al., using flaxseed adhesive as cementitious agent, chitosan, carbopol 934P, carboxymethyl cellulose and polyvinylpyrrolidone (PVP) as adhesive polymer materials, respectively. The results showed that the gel prepared by 0.5% chitosan and 2% flaxseed adhesive had the best mucous adhesion, gelation strength and drug sustained release performance. The bioavailability of the gel [(63.08 ±1.28)]% was much higher than that of buccal bioavailability [(39.21 ±6.18)%].

3.3 Cellulose
Cellulose derivatives were obtained by esterification, etherification, cross-linking or grafting of hydroxyl groups in cellulose polymers with chemical reagents. The polymers commonly used for mucous adhesion are HPMC, CMC-Na, hydroxypropyl cellulose (HPC) and hydroxyethyl cellulose (HEC). CMC-Na is a kind of anion adhesion material, which has hydrogen bond binding power and good adhesion to mucous membrane [7]. Singh and so on prepared salbutamol sulfate buccal adhesive membrane with CMC-Na as the main adhesion material. It has better expansion coefficient, adhesion force and release behavior in vitro, and the soothing time of bronchi is as long as 4 h, which is longer than that of salbutamol sulfate solution (1.5 h).

Nonionic neutral cellulose derivatives, such as HPMC, have moderate adhesion because they do not contain carboxylic acid groups that contribute protons. The ability to form hydrogen bond was reduced. Shirsand et al. Using HPMC (15 m Pa·s) and carbomer 934P as mucous membrane adhesive material and ethyl cellulose as backing material), atenolol was prepared into buccal adhesion bilayer tablets by direct pressing method. It has good mucous adhesion and can release 89.43% of the drug within 9 hours. Al-Dhubiab et al prepared acyclovir and polylactic acid-glycolic acid copolymer (PLGA) into nanoparticles. The membrane agent with buccal biological adhesion was prepared by using HPMC K15M as adhesive material and Eudragit RL100 as film forming material. The bioavailability of the drug was 8 times higher than that of the buccal dosage form.

3.4 New polymer material
If the polymer materials are modified by chemistry, the materials with better property and wider application can be obtained. A single biological adhesive polymer often does not have the required properties. If a variety of polymers are mixed, a new material may be obtained to meet the needs of various dosage forms. Traditional biological adhesive polymers are not specific and targeted, and their adhesion time is affected by the replacement rate of mucus layer, and its reaction with mucinous layer or tissue surface is essentially non-covalent. The new generation of polymers can covalently bind to the mucus layer or adhere directly to the surface of specific cells, thus improving the adhesion properties. For many new drug molecules, this kind of polymer has a good application prospect, such as sulfhydrylation adhesive polymer material, biologically adhesive polymer material mixed with polymer, targeting, Lectin mediated biologically adhesive polymer materials.

4. Conclusion
With the continuous development of drug delivery technology and new drug delivery system, more and more drug delivery routes have been paid attention to by drug scholars. Nowadays, buccal mucous membrane administration is not only limited to the local treatment of buccal related diseases, such as periodontal disease, buccal ulcer and so on, but also can deliver vaccine and insulin through buccal pathway, so as to achieve systemic administration. In addition to the traditional bioadhesive polymer materials, some new bioadhesive materials not only have excellent adhesion properties, but also can specifically adhere to some cells, which has attracted more and more attention. With the emergence of more new buccal adhesion materials, the development of buccal mucous adhesion drug delivery forms will be promoted to a great extent.
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