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Buccal drug delivery system: A review

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Abstract---The buccal area of the oral mucosa provides an adorable channel of systemic medication distribution within the mouth mucosa. Drugs are delivered via oral mucosal layer, that has a higher first-pass metabolism and degrades gastrointestinal. The medication is immediately transmitted via the systemic circulation via the buccal drug delivery mechanism, which allows for painless administration, quick enzymatic action, high bioavailability, and reduced liver metabolism. The disadvantages of the oral drug delivery route include substantial presystemic metabolism, which causes medicines to a break down in an acidic environment due to poor absorption. Buccal delivery is an attractive administrative route due to its ease of delivery through the buccal mucosal membrane lining of the oral cavity. This review paper provides a comprehensive overview of the oral mucosa, mucoadhesion, variables influencing the whole process, assessment methodologies, and how to eliminate obstacles when formulating buccal drug delivery formulations.

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1. Introduction

Concept of Bio adhesion/Mucoadhesion

Bio adhesion is a process characterised by interfacial molecular attracting interactions between the biological substrate surfaces and naturally or synthetically occurring polymers, allowing polymer to stick to the surface biological layers over a delayed period (Mukhopadhyay et al., n.d.) . Buccal dose forms are placed into the cheek and upper gums in the mouth to treat systemically and locally occurring diseases. For big, hydrophilic oligonucleotides, unstable proteins and tiny drug molecules, as well as polysaccharides the buccal route is one of the possible routes (Smart, 2005). The mouth cavities are used to administer both systemic and localised drugs. However, due to drawbacks such as enzyme breakdown and hepatic first pass metabolism inside the GI tract, orally administered groups of medications, particularly proteins and peptides, is not recommended. Therefore, absorption mucosal layer is thought to be potentially for administrating sites for drugs. For local and systemic site of action for delivery of drug the oral cavities are seen to be useful. Localized therapies are used for treating disorders like oral candidiasis, dental caries, gingivitis, oral lesions, and xerostomia whereas systemically the delivery is seen for treating angina and asthma (Kurian Mathew, n.d.).

Delivery of drug via oral cavity membranes is sub-divided as following (Hearnden et al., 2012):

- **Buccal drug delivery systems** delivering drugs via mucosal membranes in blood stream by placing drug in between gums and the cheeks.
- **Sublingual drug delivery systems** delivering drugs via mucosal membranes that lined the flooring of mouth inside the blood stream.
- The local drug delivery systems delivering drugs inside the oral cavities.

Table 1 describes the various bio adhesive formulations reported in the literature.

1.1 Advantages of bio adhesive drug delivery systems:

- a) Bioavailability enhancement: For bio adhesive formulation the residence time is more in comparison to conventional dosage forms so the drug is more available at the site of absorption leading to the enhancement of the bioavailability.
- b) Rapid onset of action: Bio adhesive formulations show the rapid onset of the pharmacological action in comparison to the conventional dosage forms.
- c) Protection from the acidic environment: The drug is matrixed into the polymeric system that protects from the acidic environment of the stomach.
- d) Reduction in dosing frequency:

Controlled release bio adhesive dosage forms give prolonged-release characteristics with reduced dosing frequency.

1.2 Disadvantages/Drawbacks of the bio adhesive drug delivery system:

a) Ulcer development:

Due to the prolonged adhesiveness of the formulation, there may be chances of ulcer development at the site of application.

- b) Lack of *in vitro* model: So far there is no accurate in vitro model available to simulate the drug action in vivo.
- c) Drug dilution:Due to the continuous secretion of the saliva, there are great chances of drug dilution leading to the submissive therapeutic response.
- d) Patient non-compliance: Patient compliance is observed very less due to prolonged adhesion of the formulation at the site of action

2. Mechanisms For Bioadhesion (Palacio & Bhushan, 2012):

Bio adhesion is an interfacial occurrence that occurs when two materials, in which any one should be biological, is kept intact together because of interfacial force. Adherence may occur between artificial materials & biologicals, like the adhesion of a polymer-copolymer to a biological membrane. Bio adhesion is greatly influenced by the polymer's hydration. Some critically known degree of hydration is required for optimal bio adhesion. The active adhesion site may not fully be freed and ready for interacting if there is partial hydration. Polymer is bound to mucosal tissue consisting of mucin layers in the process of mucoadhesion has been the subject of several theories. Hydrogen bonds between polymer chains dissociate during hydration. The interaction between the polymer and the other polymer. Mucoadhesion is mainly classified into two stages as shown in **Figure 1**:

Contact stage:

Both a fair wetting of the bio adhesive and the swelling of the bio adhesive cause close contact (wetting) between the mucus (membrane) and the mucoadhesive membrane.

Consolidation stage:

Physicochemical interactions include hydrogen bonding dispersion forces and hydrophobic interactions help to consolidate and increase the adhesive junction, resulting in longer adhesion.

2.1 Bio adhesive Drug delivery System into Oral Cavities (Reddy, Ksc, & Rao, n.d.):

- a) Sublingual delivery: This involves systemic medication distribution via mucus layer membrane that line the mouth's flooring.
- b) Buccal delivery: The administration of drug is via the mucus layer membrane that line the cheeks (buccal mucosa), and

- c) Local delivery: The delivery of drug into the oral cavities.
- **3. Outline of the Oral Mucosa** (Markiewicz, Margarone, Barbagli, & Scannapieco, 2007):

A. Structure:

The outermost layer of the stratified epithelium makes up the oral mucosa. Underneath the skin, there is a foundation membrane, a lamina propria, and the submucosa, which is the inmost layering. The epithelia are identical to the stratified squamous epithelium seen throughout. It starts with a mitotically active basal cellular layers and goes via several growing intermediate layer to superficial layer, here cell shed off the epithelial surfaces. The buccal mucosa epithelia have about 40-50 cellular layering's, while the sublingual epithelium has only a few. Epithelium related cells develop in sizing and flatten out as it progresses starting the basal up to the superficial layering's. The buccal epithelia turnover time seen to be expected to be 5- 6 days, which is likely indicative of the oral mucosa layer as entire structure. The buccal mucosa is 500-800m thick, while the mucosa thickening of soft and hard palate, the roof of the mouth, the ventral tongue, and also gingiva is 100-200m thick. Figure 2 depicts the architecture of the oral mucosa.

- A. Saliva's Function
- 1. A protecting fluids for the entire mouth cavity tissue.
- 2. A tooth enamel continues to mineralize.
- 3. To keep oral mucosal dosage forms hydrated.
- B. Mucus's Function
- 1. Proteins and carbs are present.
- 2. Adhesion between cells.
- 3. Lubrication is third.

C. Permeability

- 1. The oral mucosa is a leaky epithelium that lies somewhere between the epidermis and the intestinal mucosa.
- 2. The buccal mucosa permeability is believed as 4-4000 times larger than skin. Overall, oral mucosa permeabilities decline in way of sublingual bigger than buccal, buccal bigger than palatal.
- 3. The sublingual mucosal layer is comparatively fine and non-keratinized, whereas the buccal mucosa layer is thick and non-keratinized, and the palate mucosa is average in thickness but keratinized.

Buccal Dosage Structure and Design (R. J. Reddy, Anjum, & Hussain, n.d.)

1. Matrix type: It has a mixture of medications, adhesives, and additives.

2. Reservoir type: It has a cavity for the medicine and additives that is distinct from the adhesive. For controlling the way of drug distribution, decrease patch deformed and the disintegration as in mouth, and avoid loss of drug, an impenetrable backing is used. Permeability of Drugs through Buccal Mucosa Absorption of drugs via the squamous stratified epithelium of the oral mucosal layer might be transcellular or intracellular (intracellular, passed inside the cell). Paracellular microorganisms (ii) (intercellular, passed around the cell). The major route of penetration over the buccal mucosa is the paracellular pathway via intercellular lipid formed by membrane-coating granules.

Buccal medication delivery system disadvantages 10 :

- Limited absorption area: The oral cavity membranes, overall surface area is available for absorption of drug of 170cm² with non-keratinized tissue, like buccal membrane, accounts about ~50cm²
- Absorption of drug via the mucosal layer is slowed by barriers such as mucus, saliva, basement membrane, membrane coating granules, and others.
- Drug dilution occurs as a result of continuous saliva secretion (0.5-2 L/day).
- The higher risk to getting chocked if the swallowing of drug is involuntary, is a worry.
- If the saliva is swallowed it may result into the loss of suspended or dissolved medications, also the unintentional the dosage form removal.

4. Formulation Components Of The Mucoadhesive Drug Delivery System:

It consists of the following components.

- a) Drug or Active pharmaceutical ingredient (API):
 - The selection of the API is very critical in this drug delivery system. The API is decided based on physicochemical properties, dose, and type of the formulation to be developed. The drugs which have higher first-pass metabolism are considered an ideal candidate for the oral mucoadhesive drug delivery system.
- b) Mucoadhesive polymers:

Different polymers are seen to be used for mucoadhesion in formulations. These polymers are classified as follows. Table 2 represents the classification of the polymers

Characteristics of the ideal mucoadhesive polymers:

- It should be inert and should not cause any chemical or physical interaction with the biological system
- It should be biocompatible
- The by-products of the polymer should also be nontoxic and absorbable through the mucosal lining
- It should be economical and easily available
- It should not get decomposed upon storage or over the shelf-life period
- It should have sufficient capacity to adhere to the biological tissues
- It should have mucoadhesion property in dry as well as wet condition
- It should have a wetting, swelling, solubilising property in a biological system
- c) Permeation enhancers:

Permeation enhancers are added to the pharmaceuticals to boost the penetration rates of the membrane of the co-administered drug. Increment in drug bioavailability with low membranal penetration either of producing toxicity or harming the membrane. The potential to improve penetration is dependent on whether used in combination or separately, the physiochemical properties of the medication, the type of the vehicle, and administering

location. Table 3 summarises the various permeation enhancers used in the oral mucoadhesive drug delivery system.

Factors affecting mucoadhesion (Boddupalli, Mohammed, Nath A., & Banji, 2010):

- Polymer-related factors: Numerous qualities or properties of the active polymers are important in mucoadhesion. Concentration, polymer, swelling, specific confirmation, molecular weight, and polymer chain flexibility are all factors that may influence mucoadhesion.
- Environmental factors: mucoadhesion may influenced by the pH of the polymer-substrate interface, first contact time and functional strength.
- Physiological variables: Mucin turnover and status of diseases are vital physiological factors influencing mucoadhesion.
- 5. Some factors that affect mucoadhesion in the oral cavity

A. Polymeric Factors (Sharma, Singh, Kumar, & Singh, 2012)

a. Molecular weight:

In linear polymers, the bio-adhesiveness improves as the molecular weight increases. The optimal molecular weight for maximal mucoadhesion varies depending on the tissue and the kind of mucoadhesive polymer. High molecular weight polymers enhance physical entanglement, while lowering molecular weight polymer permeate the mucosal layer easier.

Higher molecular weight polymers will not wet as fast as lower molecular weight polymers, exposing free groups for substrate contact. Low molecular weight polymers, on the other hand, disintegrate fast.

b. Active polymer concentration:

The type of dosage form has an impact on this element. The higher the polymer content in a solid dosage form, the stronger the mucoadhesion. However, when using a liquid dose form, maximal mucoadhesion is achieved when an appropriate polymer concentration is used to induce the highest degree of bio adhesion.

c. Polymer chain flexibility:

This is required for growth and interpenetration. If water-soluble polymers are cross-linked, the individual polymer chains reduce in mobility, reducing the effective length of the chain that show penetration of the mucosal layers and therefore lowering bio adhesive strength.

- d. Spatial Conformation:
 A molecule's spatial confirmation is also a significant aspect. Despite its enormous molecular weight of 19,500,000, dextran's has the same adhesive strength as polyethylene glycol (molecular weight 200,000). The PEG polymers, having linear conformation, dextran's helical shape can hide many active groups that are adhesive and reason for adhesion.
- e. Cross-Linking Density: Water migration into the polymer networking reduces as cross-linking density is seen to increase, resulting in insufficient polymers to swell and a reduced rate of interpenetration is seen in mucin and polymer. As per Flory, the degree of swelling at equilibrium has inverse proportion to degree of cross-linking, which is a common property of a polymer.
- f. Hydrogen Bonding Capacity:

It's another important aspect of polymeric mucoadhesion. It has been stated that for occurrence of mucoadhesion, desirable polymers should create hydrogen bonds and have functional groups. It was discovered that the polymer's flexibility is critical for improving hydrogen bonding potential. Polymers with high hydrogen bonding capability include hydroxylated methacrylate, polymethacrylic acid, polyvinyl alcohol, as well as all of their copolymers.

g. Charge sign of polymer:

This is a crucial component of bio adhesion. Non-ionic polymer has a low degree of adhesion comparing the anionic polymer. One of the essential features for mucoadhesion, according to Peppas and Buri, is a significant anionic charge on the polymer. Several cationic high-molecular-weight polymers, in a neutral or slightly alkaline media, like chitosan, is found to have good adhesion capabilities.

h. Hydration (Swelling):

Swelling of Polymer allows mechanical entanglement and expose the bio adhesive sites for hydrogen bonding and/or electrostatic interaction in both the polymer and the mucosal system. Though, optimal swelling and bio attachment need a certain level of hydration of the mucoadhesive polymer.

B. Environment Related Factors (Roy, Pal, Anis, Pramanik, & Prabhakar, 2009) **a. Applied Strength:**

The adhesion strength of any polymer rises with application of strength or the length of its applicability. The depth of interpenetration can be affected by the initial pressure application to the mucoadhesive tissue contact point. Polymers become mucoadhesive when exposed to high pressure for a long time, even though they have no favourable interacting with mucin.

b. pH:

pH has a big impact on the charge of the surface of mucus and polymers. As there is a difference functional groups dissociation of amino acids and the moiety of carbohydrate of the polypeptide backbone, mucus is seen to have varying density charge that depends on the pH. It's also worth noting that the degree of hydration of cross-linked polyacrylic acid is influenced by the medium pH, with hydration increasing from pH 4 to 7 and later decreasing when alkalinity rises.

c. Initial Contact Time:

The level of swelling and interpenetration of the bio adhesive polymer chain is determined during the first contact period between the bio adhesive and mucus layers. Furthermore, as the initial contact time rises, so does the bio adhesive strength.

C. Physiological Variables (Bagan et al., 2012)

a. Mucin Turnover:

The mucoadhesive residence period on the mucus layer is limited by mucin turnover. Mucoadhesive are removed from the surface because of mucin turnover, regardless of mucoadhesive strength. Mucin turnover produces a large number of soluble mucin molecules. Before they may engage with the mucus layer, these molecules interact with the mucoadhesive.

b. States of disease:

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If they are utilised in a sick state, the mucoadhesive property must be assessed. Mucus' physicochemical qualities alter with illness, such as bacterial and fungal infections, the common cold, and so forth.

6. Mechanism Of Mucoadhesion [(Smart, 2005b), (Chatterjee, Amalina, Sengupta, & Mandal, 2017)

The mechanism by which some macromolecules adhere to the surface of mucous tissue is still unknown. The main factors for mucoadhesion are attraction and repulsion between the polymer and the mucus membrane. For effective mucoadhesion, the attraction force must be dominant. The processes of mucoadhesion may be broken down in two stages: contact & consolidation. The nature of the dose form and its administration technique might help with each phase. The first step of the contact stage, as shown in the diagram, is characterised by contact in between the mucosal membrane and the mucoadhesive by spread and swell of formulations, therefore establishing deep contacting the mucosal layer. In the presence of moisture, mucoadhesive molecules break away and connect via hydrogen bonds and weak van der Waals. Different hydrolysing enzymes, such as pepsin, trypsin, and chymotrypsin, contribute to the enzymatic activity of buccal mucosa, Different theories about the much addition are as follows:

a. Electronic Theory:

The electronic transfer, according to this theory, happens when a sticky polymer and mucosal glycoprotein network come into contact. Since variances in the electrical structures, this is the case. The forming electrical double layer at the contact is predicted as a result of this.

b. Adsorption Theory:

Adhesive attachment is based on hydrogen bonding and Vander Waal's forces, according to the adsorption hypothesis. According to this idea (figure 4), following first contacts in between the two surfaces, surficial forces act in the atoms into two surfaces induce the materials to adhere.

c. Wetting Theory:

The hypothesis is applicable to liquid system or low viscosity bio adhesives that develop an affinity for the surface and spread across it. Contact angle, which should be as equal to or near zero, can be used to determine this affinity. The work of adhesion, according to Dupre's equation, is:

Wa = YA + YB - YAB

The biological membranes and bio adhesive formulation are referred to as A and B, respectively. Cohesion work is performed by: Wc = 2YA or YB

d. Diffusion Theory: In this theory, mucus and polymer chains mix deeply enough to establish a semi-permanent adhesion bond whose penetrating action is determined by diffusion coefficient.

e. Fracture Theory: The relevant force necessary to remove or separate two surfaces following adhesion is known as the adhesion fracture theory. According to, the fracture strength is equal to the adhesive strength given by G = (E ϵ . /L) ¹/₂, Where: E- Young's modulus of elasticity, ϵ - Fracture energy, L- Critical crack length when two surfaces are separated.

All of these ideas do not provide a full picture of the mucoadhesion process. Mucoadhesion can be caused by a variety of hypotheses. When it comes to

mucoadhesion, the wetting theory applies first (polymer gets wet with mucous layer and swells), then the electronic and adsorption theory applies (formation of bonds and electron transfer between the polymer and mucous), then the diffusion theory applies (interpenetration of proteins and polymers), and finally, the electronic and adsorption theory applies again (formation of bonds and electron transfer between the polymer and mucous) (formation of non-covalent and covalent bonds).

7. Evaluation Of Mucoadhesive Formulations [(Mishra, Kumar, & Kothiyal, 2012), (Semalty, Semalty, & Nautiyal, n.d.), (Fonseca-Santos & Chorilli, 2018)] a. pH of surface:

The pH surface of the mucoadhesive formulation is measured to see whether there are any potential negative effects in vivo. The buccal patches are to be expanded for 2 hours at room temperature on an agar plate surface which is in contact with 1 ml of distilled water. To measure the pH, the swollen patch's surface is placed with the pH paper.

b. Measurements of thickness:

This test is applied for the mucoadhesive patch formulations. Each film's thickness is measured at five separate spots using an electronic digital micrometre (centre and four corners).

c. Folding Endurance:

It's determined manually. The patch is folded at the same location over and over until it ruptures or breaks. The patch's folding endurance is tested by folding one patch at similar location till its breaking or manually folding it up to 200 times, which is regarded as sufficient to disclose decent patch qualities. The folding endurance was determined by the number of folds necessary to fracture or break a patch.

d. Swelling Study:

Swelling causes weight gain. Buccal patches are independently weighed (W1) and put in 2 percent and for 37°C 1°C agar gel plates are incubated, and evaluated for physically occurring changes. To quantify the growth in the area, graph paper is placed beneath the Petri dish. Patches are taken from the gel plates at 3-hour intervals, & excess surface water using filter paper is removed carefully. The swollen patches are then again weighed (W2) and using the following formula

swelling index (SI) was calculated.

 $SI = \{(W2-W1)/W1\} \times 100$

Due to water absorption and patch swelling, the weight differential causes the weight to grow.

e. Study of thermal Analysis:

Using a differential scanning calorimeter (DSC) thermal analysis study is performed.

f. Morphological Characteristics: (Wang, Zuo, & Guo, 2021)

Using scanning electron microscope (SEM) morphological characters are studied

g. Test for water absorption capacity (Abruzzo, Cerchiara, Bigucci, Gallucci, & Luppi, 2015):

Circular Patches with 2.3 cm² surface area and is allowable to swell on the agar plate surface with preparation of simulated saliva and incubated at $37^{\circ}C$ 0.5°C in an incubator. Samples are weighed at different intervals (0.25, 0.5, 1, 2, 3, and 4 hours) and then dried in desiccators over anhydrous calcium chloride at RT for 7 days before the final constant weights are recorded.

Water Uptake (%) = $\{(Ww - Wf) / Wf\} \times 100$

Where, Ww is the wet weight and Wf is the final weight. Measurement of swelling of each film is done.

h. Measurement of mechanical properties 20:

A microprocessor-based advanced force gauze with a motorised test may be used to examine the mechanical characteristics of the patches. A tensile tester is used to evaluate the mechanical properties of the films (patches), which include elongation at break and tensile strength. The dimensions of a film strip of 60×10 mm and no evident flaws were cut and positioning was done between two clamps spaced by 3 cm. The bottom clamp stays fixed while the top clamp pulls the strips apart at a rate of 2 mm/sec till the strip breaks, keeping the patch in place during the test without crushing it. The force and elongated film are measured at the point where the strip breaks are recorded. The formula is used for calculating tensile strength and elongation at break values.

[T= (M X g) / (B X T)]

Where M is the mass in grams, g is the acceleration due to gravity (980 cm/sec²), B is the specimen's width in centimetres, and T is specimen's thickness in centimetres. The force at break (kg) per initial cross-sectional area of the specimen is defined as tensile strength (kg/mm²) (mm²).

i. Stability study in human saliva:

The stability of optimal bi-layered and multi-layered patches can be tested using human saliva. Human saliva is taken from people aged 18 to 50 years old. Buccal patches containing 5ml of human saliva are put in separate Petri plates and baked for 6 hours at 37°C 0.2°C in a temperature-controlled oven. According to ICH requirements, all batches of films are subjected to a stability test.

8. Conclusion

Buccal drug delivery has various benefits, that includes comfort of administration, accessibility and withdrawal, retentivity, high patient compliance, cost, and low enzymatic activity. This method can be utilised to avoid 1st-pass metabolism in liver as well as pre-systemically occurring clearance in the GIT. This site is also seen to be appropriate for a retentive device and is agreeable to any patient. Another advantage is that the permeability in the locally appearing environment of the mucosal layer and may be managed and altered to provide accommodation to drug absorption with correct dosage form designs and formulations. Buccal drug administration has the potential to be a practical and interesting method for non-invasive delivery of strong peptides and protein therapeutical agents, as well as a means of systemic dispersion of orally ineffective drugs. Absorption enhancers, on the other hand, are a critical component for the future of buccal buccal medication administration for safer and effective permeation. Mucoadhesive systems may become more essential in the development of new pharmaceuticals as a result of the massive influx of novel substances emerging from pharmacological research. The buccal and sublingual routes provide advantageous potential and various formulation techniques due to the success, benefits, and simplicity of access to drug administration through oral mucosal tissue, while the present commercially available formulation is primarily restricted to tablets and films. As a result, the buccal mucosa has various benefits for long-term regulated drug administration as well as a suitable environment for systemic distribution.

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Figure 1: Mechanism of bio adhesion showing contact stage and consolidation stage



Figure 2: Anatomy of the oral mucosa

List of Tables

Sr. No	Dosage form	Polymer used	Drug
1	Tablets	HPMCK100M, Carbopol 943P, Sodium CMC, chitosan	Acyclovir, Repaglinide, Propranolol, Lisinopril
2	Gel	Carbopol, Carbopol 974P, HPMC and Poloxamer 407, Chitosan	Metronidazole, Cidofovir, lidocaine, Itraconazole
3	Patch	Eudragit, Chitosan, NaCMC, HPMC	Tizanidine, Ketoprofen, Gentamicin
4	Microspheres	Carbopol, HPMC, Chitosan, Gelatine	Raloxifene, Berberine HCl, Acyclovir
5	Nanoparticles (23)	Chitosan, Gelatine, Carbopol, HPMC	Clofazimine, Tenofovir, Neostigmine.

Table 1: Details of bio adhesive formulations

Table 2: Types of mucoadhesive polymers that are employed in oral cavity

Sr. No.	Type of polymer	Example
1	Natural	Xanthan gum, pectin, sodium alginate, agarose
2	Synthetic/Semisy	Hydroxypropyl methylcellulose, thiolate chitosan,
	nthetic	sodium carboxymethylcellulose (CMC), polyacrylic
		acid, polycarbophil
3	Cationic	Chitosan, amino dextran,
4	Anionic	Pectin, Carboxymethyl cellulose, polyacrylic acid
5	Nonionic	Polyethylene oxide, polyvinyl alcohol, PVP
6	Water-soluble	Hydroxyethylcellulose, sodium alginate,
		hydroxypropyl cellulose (HPC)

Table 3: Classification of permeation enhancers

Sr. No	Туре	Example	Mechanism of action
1	Chelators	Sodium citrate, EDTA	Interact with Calcium
2	Fatty acids	Oleic acid, ceprylic	Enhances the fluidity of the
		acid	phospholipids
3	Cyclodextrins	μ, β cyclodextrins	Inclusion complex
4	Cationic	Chitosan, Trimethyl	Interaction with a negative charge
	polymers	chitosan	on the cell membrane
5	Surfactants	Cationic	cetylpyridinium chloride
		Anionic	Sodium lauryl sulfate
		Nonionic	Tween, Span, Myrj, Poloxamer