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Labia Oris: A Realistic Platform for Drug Delivery

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ABSTRACT

The labia Oris is an attractive site for the delivery of drugs either locally or systemically for various disorders. Labial mucosa which is a part of the oral cavity is the main point of interest for drug delivery. Lip skin is composed of the epidermis, subcutaneous tissue, orbicularis oris muscle fibre, and mucosa. The vermilion of the lips is composed of keratinized squamous epithelium that covers numerous capillaries. This is the reason why lip has found good absorption potential. The highly perfused blood vessels are responsible for its good permeation ability. The other reason for better drug absorption from the lip is due to its very thin layer of skin. This system possesses various advantages over the other drug delivery systems. It also means that the delivery system can be removed in order to terminate delivery if signs of adverse reactions are observed during treatment. The main aim of this review is to explore more information on the translabial drug delivery system which will be a promising route of drug delivery in the near future.

INTRODUCTION[1-4]

Translabial or the transmucosal route has gained many advantages over the most preferred oral route of drug delivery. As the oral route faces many problems such as hepatic first-pass metabolism and enzymatic degradation within the GI tract, which affect the absorption of certain classes of drugs[1]. Transmucosal drug delivery means absorption of drug formulation through the lips or through the labial mucosa. Lips are the most delicate part of the human body. The lips are (labia oris) two fleshy folds which surround the orifice of the mouth. Lips are composed of skin, muscles, and mucosa. It is devoid of bones and infrastructure. Lips have neither bone nor cartilage and are, instead, composed of only muscle, skin and mucous membrane[2]. Due to the above characteristics of lips, it has found many advantages in developing a translabial drug delivery system. The various advantages of this system include good patient compliance because of less frequent drug administration, less dosing frequency, shorter treatment period, fewer chances of local as well as systemic toxicity, an increased safety margin of high potency drugs and non-invasive route of drug delivery. In the near future, translabial route of drug delivery will be a promising route for local and systemic treatment of various diseases[1].

ANATOMY AND PHYSIOLOGY OF LIPS[1], [3]-[7]

The mouth of humans and animals are surrounded by an external and visible part of the entrance of oral cavity called lips. Lips are fleshy folds lined externally by a skin and internally by a mucous membrane and it bounds the oral fissure. The junction where the lips meet the surrounding skin of the mouth area is the vermilion border and the typically reddish area within the borders are called the vermilion zone[3]. Lips are made up of skin, muscles, and mucosa and are devoid of bones, this is the main reason for their flexible nature[4].

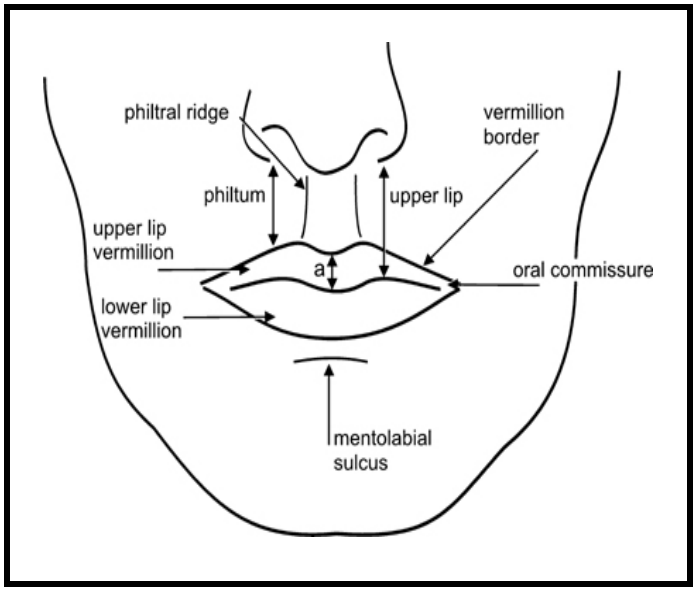

Fig 1: Anatomy and Physiology of lips

The tissue of the mucosal lip is translucent and has many capillaries near the surface, making it red. There are two types of lips; labia superius (upper lips) and another is labia inferius (lower lips). The lips do not contain sebaceous gland, sweat gland and are devoid of hairs are the unique properties of lips[1].

1. Histology [2],[8],[9]

The Upper lip (Labium superioris) extends from the base of the nose superiorly, to the nasolabial folds laterally, and to the free edge of the vermilion border inferiorly. The lower lip (Labium inferioris) extends from the superior free vermilion edge superiorly, to the commissures laterally, and to the mandible inferiorly. Lip skin is composed of the epidermis, subcutaneous tissue, orbicularis oris muscle fibre, and mucosa.

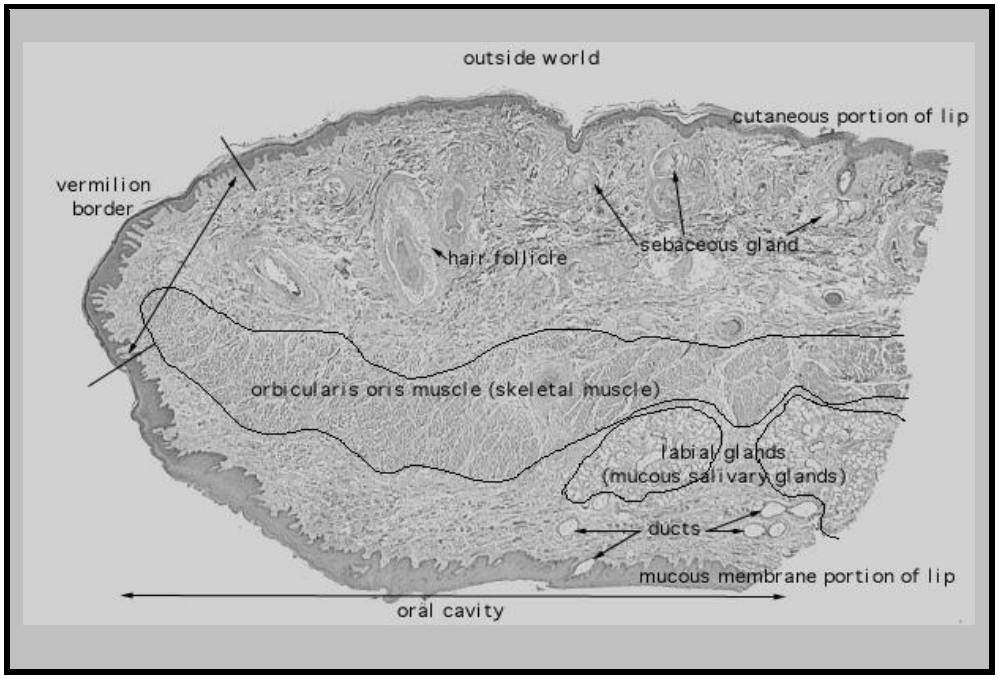

Fig 2: Histology of lips[1]

The vermilion of the lips is composed of keratinized squamous epithelium that covers numerous capillaries. The inner surface of the lip is nonkeratinized and consist of the stratified squamous epithelium. The lips are composed of stratified squamous keratinized epithelium that is facing an outside environment of the lip whereas the internal lip environment is composed of a stratified squamous non-keratinized epithelium. Vermilion border is the border between the stratified keratinized squamous epithelium of external environment and non-keratinized squamous epithelium of the internal environment. It is dominated by non-keratinized epithelium and it possesses many arteries that are closer to the lip surface[2].

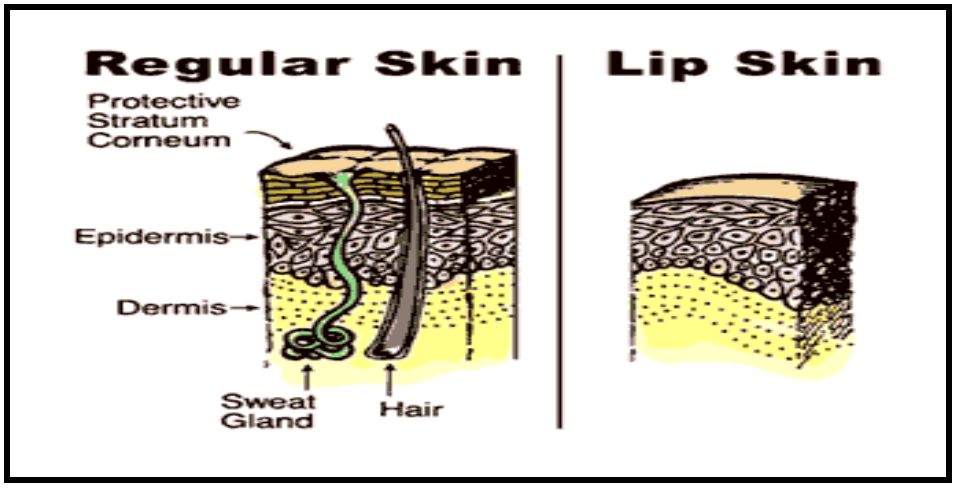

Fig 3: Histological comparison between normal skin and lip skin [3]

1. Blood supply[2],[12]

The blood supply to both the lip stems receives from the external carotid arteries. The facial artery has ascended from the neck over the midbody of the mandible just anterior to the insertion of the masseter muscle. The facial artery branches into the submental artery that passes under the mandibular body in an anteromedial direction. The facial artery ascends in a plane deep to the platysma, risorius, and zygomaticus major and minor muscles and superficial to the buccinator and levatorangulioris. This artery branches into an inferior and a superior labial artery, which course beneath the orbicularis oris and anastomoses with the contralateral vessel.

2. Nerve supply[2],[13]-[16]

The lower lips receive sensory innervations from the branches of the mandibular nerve through amental nerve branch whereas upper lip receives sensory innervations from the branches of the maxillary nerve through the infra-orbital nerve.

3. Muscle supply[3],[17]

The muscles acting on the lips are considered part of the muscles of facial expression. All muscles of facial expression are derived from the mesoderm of the second pharyngeal arch and are therefore supplied (motor supply) by the nerve of the second pharyngeal arch, the facial nerve (7th cranial nerve). The muscles of facial expression are all specialized members of the panniculuscarnosus, which attach to the dermis and so wrinkle or dimple the overlying

skin. Functionally, the muscles of facial expression are arranged in groups around the orbits, nose, and mouth.[3]

The muscles acting on the lips are as follows:

- Sphincters of the oral orifice
- Buccinator
- Orbicularis oris
- Anchor point for several muscles
- Modiolus
- Lip elevation
- Levatorlabiisuperioris
- Levatorlabiisuperiorisalaequenasi
- Levatorangulioris
- Zygomaticus minor
- Zygomaticus major
- Lip depression
- Risorius
- Depressor angulioris
- Depressor labiiinferioris
- Mentalis

4. Lymphatic drainage[1]

Lymphatic drainage from the upper lip is unilateral except for the midline. The lymphatics coalesce to form 5 primary trunks that mainly lead to the ipsilateral submandibular nodes,

with some drainage also going to the periparotid lymph nodes. Occasionally, some drainage may be available to the ipsilateralsubmental lymph nodes. The lower lip lymphatics also coalesce to form 5 primary trunks that lead to bilateral submental nodes from the central lip and unilateral submandibular lymph nodes from the lateral lip. The submental, submandibular, and parotid lymph nodes are the first echelon nodes for the lips. Submental nodes secondarily drain to ipsilateral submandibular nodes, and both submandibular and parotid nodes secondarily drain to ipsilateral jugulodigastric lymph nodes.

5. Sensory innervations[1]

The sensory innervations are from the maxillary and mandibular branches of the fifth cranial nerve. The infraorbital nerve, which is a terminal branch of the maxillary nerve, innervates the upper lip. This nerve exits the infraorbital foramen 4-7 mm below the inferior orbital rim on a vertical line that descends from the medial limbus of the iris. The nerve runs beneath the levator labii superioris and superficial to the levator anguli oris to supply the upper lip. The lower lip and chin receive sensory innervations from branches of the mandibular nerve. The inferior alveolar nerve, a branch of the mandibular nerve, forms the nerve to the mylohyoid just proximal to entering the lingula of the mandible.

6. Labial mucus secretion[1],[18]

The labial mucosa comprised of epithelium, lamina propria, and muscularis mucosa. The epithelium is very and non keratinized. The lamina propria has long slender papillae but wide ridges and dense connective tissues with elastic fibers. The submucosa is attached to underlying muscles and contains minor salivary glands. The mucus is translucent and viscid secretion, secreted by the vesicles within the epithelial cells, which forms a thin, continuous gel blanket adherent to the mucous epithelial surface. The mucus layer contains water 95%, glycoproteins and lipids - 0.5 to 5%, mineral salts - 0.5to 1%, free proteins-0.5% to 1%. The glycoproteins of mucus are known as mucins that are capable of forming slimy, viscoelastic gels. Mucin is a family of high molecular weight, heavily glycosylated proteins produced by many epithet tissues7. Mucin is secreted by the stimulation of MARC-KS (Myristylated Alanine Rich C Kinase Substrate) which coordinates the secretion from the vesicles within the epithelial cells. The fusion of the vesicles to the plasma membrane causes a release of mucin. The molecular weight of mucin varies from 2 x 105 daltons to 14x 106 daltons. Mucins are composed of two regions, the amino acid, and dicarbonyl terminal regions, rich in

cysteine and a large central region composed of 10-80 residue sequences made up of serine or threonine. The drug coated with a mucoadhesive polymer binds to the mucus and hence is retained on the surface epithelium for an extended duration. The drug molecules, in turn, are constantly released from the polymer over an extended duration of time. These surface adhesive properties of mucin are being utilized in the development of mucoadhesive drug delivery systems.

PROPERTIES AND FUNCTIONS OF LIPS[2]

There are various properties and functions of lips which make it unique from the other organs and these are as follows:

- Lips visibly express an individual's emotion and play a key role in facial expressions.
- They help in the eating function by holding food and drink in the mouth.
- They are used to keep unwanted objects out of the mouth.
- Lips are devoid of oil (sebaceous) glands.
- An absence of sweat glands.
- There are no hair follicles on lips.
- The layers of skin present on lips are very thin.
- They are very sensitive to touch, warmth, and cold because of the presence of nerve endings.
- Lips contain no skin pigment and therefore blood vessels are able to show through the thin skin and the lips appear red.
- People with darker skin have some pigment and therefore the red lip color is less prominent.
- They are very elastic and pliable because they do not have any direct bony attachments.

LIP DISORDERS[3],[19]-[24]

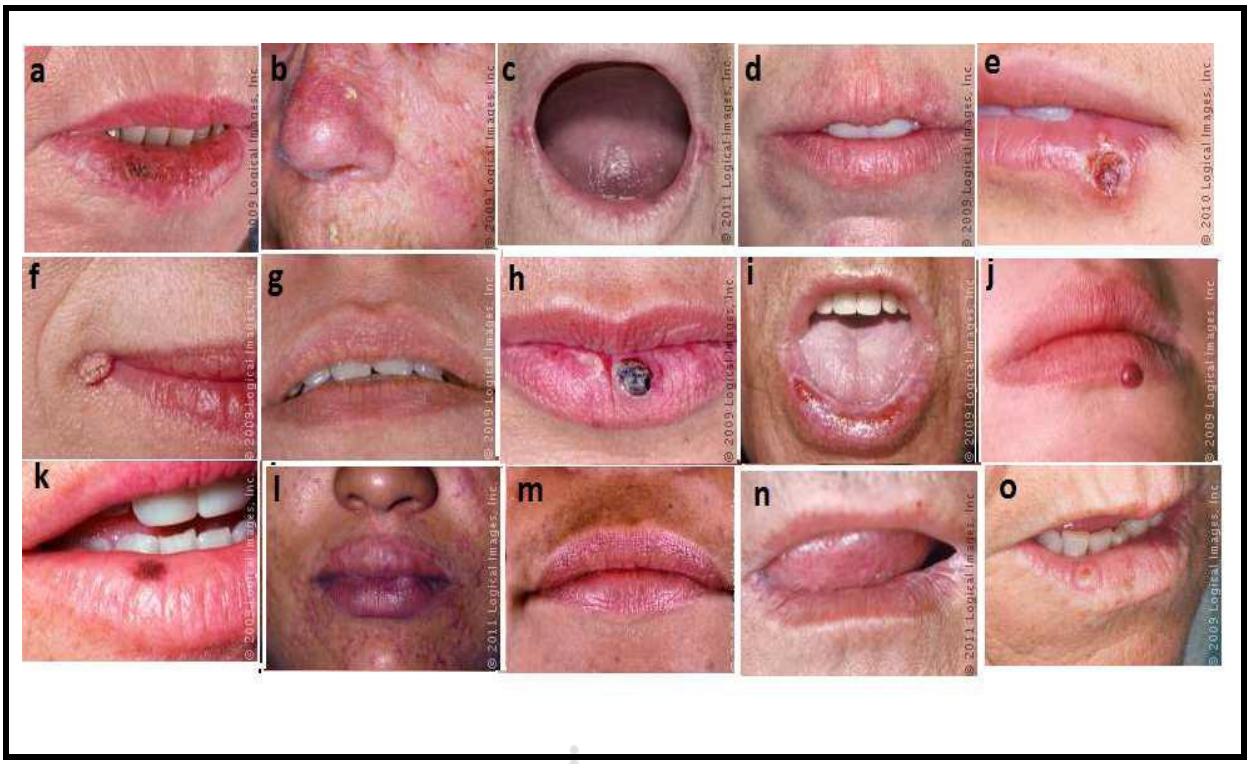

Fig. 4: TYPES OF LIP DISORDERS[3]

The above figure is comprised of the following diseases:

a) Actinic cheilitis

b) Actinic keratoses

c) Angular cheilitis

d) Chapped lips

e) Cold sores

f) Common warts

g) Fordyce spots

h) Keratoacanthoma

i) Lichen planus

j) Melasma

k) Oral Melanotic Macule

l) Perioral dermatitis

m) Pyogenic granuloma

n) Squamous cell carcinoma

o) Thrush (oral candidiasis)

TRANSLABIAL DRUG DELIVERY SYSTEM (TLDDS)[1, 2, 25]

❖ **Desirable features of TLDDS**

- This route provides the most convenient and painless administration.
- This route has found more direct access to target diseases/ various lip diseases or disorders.
- This system permits localized and systemic action of the drug to the oral cavity for a longer period of time.
- A significant reduction in dose can be achieved, thereby reducing dose-dependent side effects.
- This route produces a possibility of producing more uniform plasma level.
- This route offers more convenience for drug administration, which would otherwise require frequent dosing.
- The major advantage of this route is that it bypasses the first pass metabolism by the liver.
- This route will provide higher patient acceptance when comparison with injectibles.
- It can offer increase therapeutic efficacy of the drug.

- Labial mucosa is highly perfused with blood vessels and offers greater permeability than skin. Therapeutic serum concentration of the drug can be achieved more significantly due to the rich blood supply and non keratinized squamous epithelium.

- Drugs which are degraded in the acidic environment of the stomach or destroyed by the enzymatic or alkaline environment of the intestine can be administered by this route.

- This route may be cost-effective as compared with the other oral routes.

- This route for drug administration will be more suitable in very ill and comatose patient who is not able to ingest anything orally.

- It can produce flexibility of terminating the drug administration by simply removing the dosage form from the lip skin.

❖ **Problems associated with TLDDS**

- This route is not practicable for the drug, the adhesive or other excipients which may cause erythema, itching, or local arrhythmia.

- Due to the small area of the lip limited amount of dosing can be achieved.

- The very small quantity of drug may arrive at the site of action.

- For translabial delivery, the maximum daily dose that can permeate the labial skin should be the order of a few μg to mg.

- The chances of losing the drug in saliva are more.

- Restriction arises for eating and drinking during the treatment period

- Drugs which irritate the mucosa or having a bitter and unpleasant taste or odor cannot be administered by this route.

- Drugs which are absorbed by passive diffusion can be administered by this route.

- Drugs should have the short biological half-life (2-8 hours) for delivery through labial route.

- Presystemic metabolism may occur by the enzymes like peptidase and esterase.
- This route is not feasible for peptide delivery due to peptidase.

MECHANISM OF DRUG PERMEATION THROUGH LIP SKIN[2]

The penetration of the drug through lip skin may occur in two pathways:

- **Transcellular/Intracellular transport** is defined as the passage of drug molecules across the lip skin epithelium.
- **Paracellular/Intercellular transport** is defined as the transport of drug molecules through the junctions between the lip skin epithelial cells.

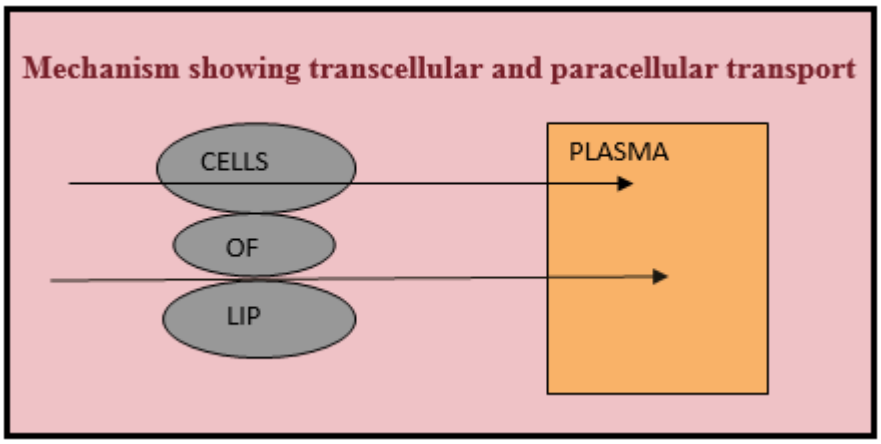

Fig. 5: Diagrammatic representation of Transcellular and Paracellular transport

MUCOADHESION or BIOADHESION[4],[26]-[28]

Bioadhesion i.e. adhesion of any entity over the biological surfaces. 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. In recent years it has been used to describe phenomena related to the ability of synthetic and biological macromolecules and hydrocolloids to adhere to biological tissues. The biological surface can be epithelial tissues or mucous coat on the surface of tissues. If adhesion or attachment is to a mucus coat then it can be called as mucoadhesion.

This is how the bioadhesion can occur:

1. Spreading, wetting and swelling of dosage form at the mucous surface, initiate intimate contact between the polymer and the mucus layer.

2. Interdiffusion and interpenetration take place between the chain of the mucoadhesive polymer and the mucus gel network, creating a greater area of the network.

3. Entanglements and secondary chemical bonds are formed between the polymer chain and the mucin molecules.

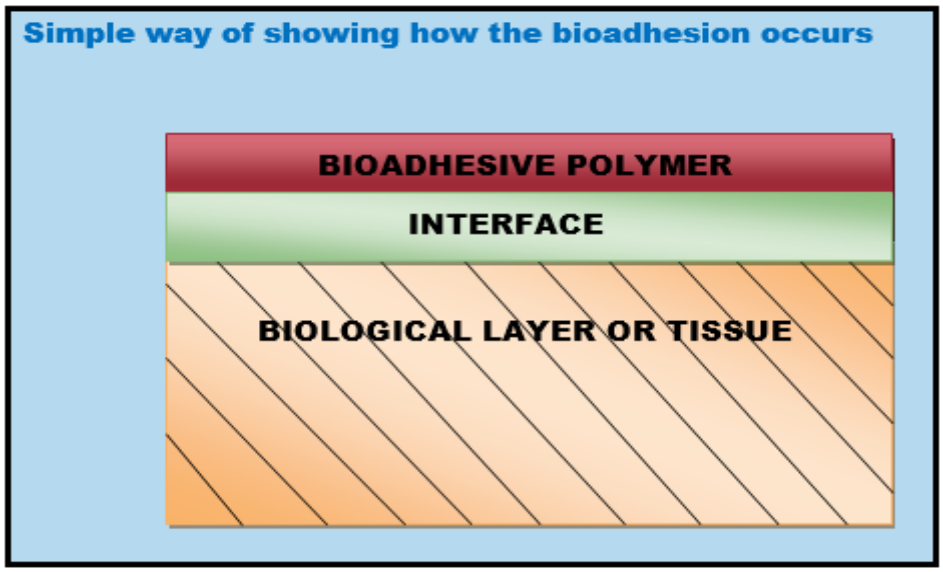

Fig. 6: Diagrammatic representation of the bioadhesive system in contact with lip skin tissue

MECHANISM OF MUCOADHESION [4]

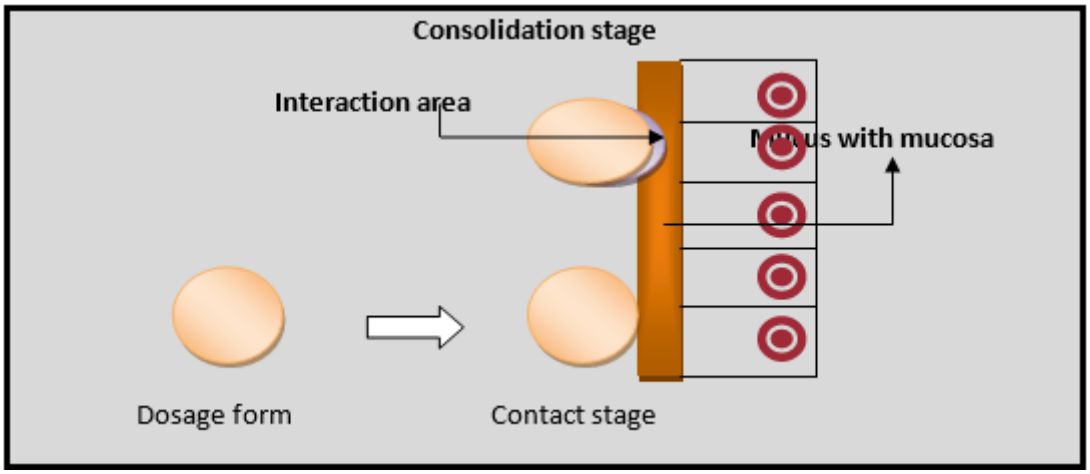

Fig. 7: Diagrammatic representation showing mechanism of mucoadhesion

The mechanism of mucoadhesion has been explained in above fig no. 06

1. Contact stage: In this stage, intimate contact occurs due to the wetting between mucoadhesive and mucous membrane which further leads to spreading and swelling of the formulation to deepen the contact of mucoadhesive with the tissue.

2. Consolidation stage: The mucoadhesive materials are activated by the presence of moisture which plasticizes the system and strengthens the adhesive joint (by various forces), leading to prolonged adhesion.

THEORIES AND MECHANISM OF BIOADHESION[4]

SR NO.	THEORIES	MECHANISM OF BIOADHESION	EXPLANATION
01	Electronic theory	Attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material.	Electron transfer occurs between the two forming a double layer of electric charge at the surface.
02	Wetting theory	Ability of bioadhesive polymer to Spread and develop intimate contact with mucous membrane.	It is applied for the liquid system which spreads. Contact angle must be near to zero.
03	Adsorption theory	Adhesion occurs due to the surface interaction between the adhesive polymer and mucus substrate.	Strong primary forces: covalent bond Weak secondary forces: hydrogen bond and van der Waal's forces.
04	Diffusion theory	Adhesion is due to the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond.	The adhesion force is directly proportional to the degree of penetration of the polymer chains. Usual range is 0.2 – 0.5µm deep.
05	Mechanical theory	Adhesion arises from an interlocking of liquid adhesive into Irregularities on the rough surface.	Rough surfaces provide an increased surface area available for interaction which leads to more interlocking of adhesive.
06	Fracture theory	Analyses the maximum tensile stress developed during attachment of the transmucosal drug delivery system from the mucosal surface.	Does not require the physical entanglement of bioadhesive polymer chain and mucus strands, hence it is appropriate to study the bioadhesion of hard polymer which lacks flexible chain.

FACTORS AFFECTING LABIAL MUCOADHESION [1],[29]-[32]

- **Molecular weight:** The mucoadhesive strength of a polymer increases with molecular weights above 100,000. Direct correlation between the mucoadhesive strength of polyoxyethylene polymers and their molecular weights lies in the range of 200,000-7,000,000.

- **The flexibility of the polymer chain:** Mucoadhesion starts with the diffusion of the polymer chains in the interfacial region. So the polymer chains should have a substantial degree of flexibility in order to achieve the desired entanglement with the mucus.

- **Cross-linking density:** The diffusion of water into the polymer network occurs at a lower rate with the increasing density of cross-linking, which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin.

- **Hydrogen bonding capacity:** Hydrogen bonding is another important factor in mucoadhesion of a polymer. Desired polymers must have functional groups that are able to form hydrogen bonds. Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly (methacrylic acid), as well a small their copolymers, have good hydrogen-bonding capacity.

- **Hydration:** Hydration is required to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucus network.

- **Charge:** In mucoadhesive polymers, nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. The strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. Some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral/slightly alkaline medium. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

- **Spatial conformation:** Besides high molecular weight or chain length, a spatial conformation of a polymer is also important. Polyethylene glycol with a molecular weight of 200,000 has similar adhesive strength like dextran (molecular weight 19,500,000). The

reason is that the helical conformation of dextran masks many adhesively active groups, primarily responsible for adhesion.

- **pH:** The pH at the mucoadhesive to substrate interface can influence the adhesion of mucoadhesives possessing ionizable groups. Many mucoadhesives used in drug delivery are polyanions possessing carboxylic acid functionalities. If the local pH is above the pKa of the polymer, it will be largely ionized; if the pH is below the pKa of the polymer, it will be largely unionized. The approximate pKa for the poly (acrylic acid) family of polymers is between 4 and 5. The maximum adhesive strength of these polymers is observed around pH 4–5 and decreases gradually above a pH6.

- **Initial contact time:** Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Moreover, bioadhesive strength increases as the initial contact time increases.

MUCOADHESIVE POLYMER[1]

Desirable properties of mucoadhesive polymer for TLDDS should be as follows :

- The polymer and its degradation products should be nontoxic and non-absorbable.
- It should be nonirritant.
- It should form a strong non-covalent bond with the mucus or epithelial cell surface.
- It should adhere quickly to moist tissue and possess some site specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not be high.

Classification of the mucoadhesive polymer[33],[34]

1.On the basis of source

- Natural polymers

Examples: Agarose, chitosan, gelatin, hyaluronic acid, gums (guar, xanthan, gellan, carrageenan, pectin, and sodium alginate).

- Synthetic polymers

Examples: Cellulose derivatives [CMC, thiolated CMC, sodium CMC, HEC, HPC,HPMC, MC, methylhydroxyethylcellulose], Poly(acrylic acid)-basedpolymers [CP, polyacrylates, poly (methylvinylether-comethacryliacid), poly(2-hydroxyethylmethaacrylate).

- Others

Examples: Polyoxyethylene, PVA, PVP, thiolated polymers.

2. On the basis of aqueous solubility

- Water soluble

Examples: CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium CMC, sodium alginate.

- Water-insoluble

Examples: Chitosan (soluble in dilute aqueous acids), EC, PC.

3. On the basis of the charge

- Cationic

Examples: Aminodextran, chitosan, (DEAE)-dextran, TMC.

- Anionic

Examples: Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, Sodium CMC, xanthan gum.

- Nonionic

Examples: Hydroxyethyl starch, HPC, poly (ethylene oxide), PVA, PVP, Scleroglucan.

4. On the basis of potential mucoadhesive forces

- Covalent

Example: Cyanoacrylate.

- Hydrogen bond

Example: Acrylates [hydroxylated methacrylate, poly (methacrylic acid)],CP PC, PVA.

- Electrostatic interaction

Example: Chitosan

FORMULATION ASPECTS OF TLDDS

Ideal characteristics for formulation additives of TLDDS [2],[35]-[38]

- It should not cause any kind of irritation to skin or mucosa.
- It should be compatible with APIs.
- It should possess better stability.
- It should not be stainable.
- It should be easily removable with water.
- It should not affect the functioning of lip skin.
- It should have good homogeneity.
- It should have good texture.
- It should be contaminant free.
- It should be easy for application.
- It should be compatible with lip skin and lip mucosa.
- It should have a low sensitization index.
- It should be nonhygroscopic.

- It should be elegant.
- It should be stable in storage.
- It should release medicament easily.
- It should be compatible with medicament and other ingredients.
- It should be safe and reliable.

MARKETED LIP FORMULATIONS

- Lipsticks
- Lip rouge
- Lip varnish
- Lip jelly
- Lip salve
- Lip glosses
- Lip balm
- Lip pencils

RECENT NOVELISTIC TLDDS

Many researchers had carried out various researches on TLDDS and have come out with different kinds of lip formulation for different diseases. The few examples are mentioned here. This review has sited out the various innovation studies carried out by a different researcher on TLDDS.

1. Medicated lip rouge containing niosomal acyclovir for the management of recurrent herpes labialis[39]

One of the novelistic approach taken by researchers in which they had prepared a medicated lip rouge containing acyclovir entrapped in a niosomalvesical to improve its permeability

across the labial membrane. These niosomes were prepared by film hydration method. For determining the better entrapment efficiency, the researchers incorporated the niosomes into three different lip formulations viz, lipstick, lip balm, and lip rouge. Then performed various evaluation studies of the above preparation containing niosomal acyclovir. On the basis of the *in-vitro* profile of above preparations, lip rouge was found to be better in application than the other two. The percentage cumulative release of drug from optimized lip rouge at the end of 8 hr was 84.77%. The percentage cumulative drug release in ex vivo studies for 8 hr was 60.88 %. This study concluded that niosomal acyclovir lip rouge will be a better formulation for treating Herpes labialis than the marketed acyclovir cream.

2. Repaglinidebio strip for TLDDS[40]

The researchers had formulated ***repaglinide***loaded bio strips by utilizing zea mays as a bio-material. Dextrose was used as flexicizer in the formulation. The repaglinide bio strips were then evaluated for thickness, folding endurance and *in-vivo* and *in-vitro* drug release. The *in-vivo* and *in-vitro* studies have shown the potential of Repaginate loaded bio strip for sustained delivery through TLDDS.

3. TLDD utilizing bioexcipients from *Litchi chinesis* for the delivery of rosiglitazone maleate[41]

Another interesting approach is taken by the researcher, in this, they had utilized Litchi chinesis as a strip former and dextrose as a flexicizer. The bio strips were loaded with rosiglitazone maleate and were subjected to various evaluation parameters like thickness, folding endurance and *in-vivo* and *in-vitro* drug release. The *in-vivo* and *in-vitro* studies confirmed that the release of drug from the bio strip was maintained over 24 hr. The bio strips were also screened for its other functional properties such as filmability, bio- or muco-adhesivity. The formulated bio-lip strips were practicable for delivering rosiglitazone maleate by the translabial administration.

APPLICATIONS OF TLDDS[4]

As the TLDDS is not that much well known for drug delivery, but the route can be another option for targeting various lip disorders. They may include conditions like

1. Actinic Chelitis (a precancerous condition related to cumulative lifetime sun exposure)

2. Actinic Keratoses /Solar Keratoses (small rough or scaly areas of skin due to damage from sun exposure)

3. Angular Cheilitis (chronic inflammatory condition of the corners of the mouth)

4. Chapped lips / Cheilitis (lips appear dry, scaly and may have one or more small cracks)

5. Orofacial herpes simplex (a recurrent skin condition associated with infection by herpes simplex virus)

6. Common Wart (growth of skin and mucous membrane)

7. Keratocanthoma (rapidly growing skin cancer usually appears as a volcano – like a bump on the sun-exposed of middle-aged and elderly individuals)

8. Melasma (a disorder of unknown cause that causes dark patches, primarily on the face and lips)

9. Oral Melanotic Macule (non-cancerous dark spot found on the face and lips

10. Oral candidiasis (the infection caused due to yeast *Candida albicans*)

FUTURE SCOPE FOR TLDDS

TLDDS is one of the peculiar drug delivery routes which has eliminated various drawbacks of other conventional drug delivery route. It has been found to be a novelistic platform for both systemic and localized effects. Therefore, this will become a way for a researcher to design novel dosage forms for systemic delivery because as on date there is no formulation available in the market for the systemic delivery of drug using labial skin as a delivery platform. In near future, the formulators can provide us with the following drug delivery systems – mucoadhesive gels, mucoadhesive patches, mucoadhesive powders, mucoadhesive tablet, mucoadhesive ointments, liposomes, neosomes, nanosomes, emulgels, biofilm, bio strips, pharmacosomes, and transferosomes.

CONCLUSION:

Lips are composed of skin, muscles, and mucosa and are devoid of bones and also contain a special region with highly perfused blood supply called a vermillion zone. This uniqueness of lip makes it a most suitable way to deliver the drug without undergoing first-pass metabolism

and gastric troubleas like other delivering routes. At the same time if we concentrate on the labial mucosa, which is supplied with both vascular and lymphatic drainage and hence, makes it suitable for delivering drug for an extended period of time. By considering the formulations such as Repaglinide bio strip, medicated lip rouge containing niosomal Acyclovir and Rosiglitazone-loaded bio-lip strips we can conclude that the TLLDS will be a promising route for drug delivery.

REFERENCES:

1. MadhavSatheesh N.V, Abhay Pratap Y., Lip: An impressive and idealistic platform for drug delivery. J Pharm Res., 2011; 4(4):1060-1062.
2. SatheeshMadhav, AbhijeetOjha, Labial mucosa as a novel transmucosal drug delivery platform, Int J Pharm PharmSci, Vol 4, Issue 3, 8390.
3. Krishnapriya, Karthika Ramesh, Vishnu S., Sreeja C.N., Translabial route: As a platform for systemic drug delivery. J. ChemPharma Res., 2015; 7(5):335-348.
4. Srinivas R.B., Jagadevappa S.P., Alfiha M.M., Priyanka N.C., Esha J.P., Translabial route: A novelistic platform for systemic drug delivery, IJIPSR, 2016; 4(7):840-861.
5. Richard D. Textbook of E-Study guide for gray's anatomy for students. 3rd edition. Elsevier: Churchill Livingstone; 2010.
6. Sigher H. Oral Anatomy. 4th edition. Mosby; St. Louis; 1965.
7. Vishram S. Textbook of anatomy head, neck, and brain. Vol 3, Elsevier Health Sciences; 2014.
8. BabakJahn-Oarwar MD, Keith Blackwell MD, Lips and Perioral Region anatomy, eMedicinemArticle, 2007 October 9.
9. Orban, B. J. And SigherH, 1966. Orban's Oral Histology and Embryology (6th ed.) Mosby, St.Louis, 1966, 216.
10. Shafer, WG, Hone MK, Levy BM, A Textbook of Oral Pathology(2nd ed.), Saunders, Philadelphia,1964, 11.
11. Pinar YA, Bilge O, Govsa F, an Anatomic study of the blood supply of perioral region, clinical anatomy,18 (5), 2005,330-339.
12. Calhoun KH, StiernbergCM., Surgery of the Lip, New York, NY, Thieme Medical Publishers,13,1992, 1-9.
13. Dingman RO, Grabb WC. , the Surgical anatomy of the mandibular ramus of the facial nerve based on the dissection of 100 facial halves, *PlastReconstrSurg*, 29,1962,266-272.
14. Bailey BJ, Head and Neck Surgery-Otolaryngology. *2nd ed*. Philadelphia, Pa: Lippincott- Raven.13,1998, 1510.
15. Freilinger G, Gruber H, Happak W, et al. , 1987. Surgical anatomy of the mimic muscle system and the facial nerve: importance for reconstructive and aesthetic surgery, *PlastReconstSurg*, 80(5),1987, 686-90.
16. Nelson DW, GingrassRP, Anatomy of the mandibular branches of the facial nerve, PlastReconstrSurg, 64(4), 1979, 479-82.
17. Pensler JM, Ward JW, Parry SW, The superficial musculoaponeurotic system in the upper lip: ananatomic study in cadavers, *PlastReconstrSurg*, 75(4), 1985,488-94.
18. Zhang J, Niu S, Ebert C, Stanley TH. An *in-vivo* dog model for studying recovery kinetics of the buccal mucosa permeation barrier after exposure to permeation enhancers: Apparent evidence of effective enhancement without tissue damage. Int J Pharm. 1994; 101: 15-22.
19. Cotaldo E. Solar cheilitis. , J DermatolSurgOncol, 7, 1981,289-95.
20. Manton S, Scully C., Mucous membrane pemphigoid, Oral Surg,66, 1988, 37-40.
21. Nisengard RJ, Nieders M., Desquamative lesions of the gingival, J Periodontol, 52, 1981, 500-510.
22. Picascia DD, Robinson JK. et al. , Actinic cheilitis, a review of the aetiology, differential diagnosis, and treatment, J Am AcadDermatol, 17, 1987, 255-264.
23. Schoenfeld RJ, Schoenfeld FI. , Angular cheilitis, Cutis,19, 1977, 213-216.

24.. Scully C.,Orofacial manifestations in chronic granulomatous disease of childhood, Oral Surg, 51,1981, 148-151.
25. Asane GS. Mucoadhesive gastrointestinal drug delivery system: An overview. 2007; 5(6): http//www.pharmainfo.net
26. Nikkolas AP, Pierre AB. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J. Control Release, 1985; 2: 257-275.
27. Sachan NK, Bhattacharya A. Basics and Therapeutic Potential of Oral MucoadhesiveMicroparticulate Drug Delivery Systems. Int. J Pharm Clin Res, 2009; 1(1): 10-14.
28. John DS. The basics and underlying mechanisms of mucoadhesion. Adv. Drug Deliv. Rev., 2005; 57: 1556-1568.
29. Sachan NK, Bhattacharya A. Basics and therapeutic potential of oral mucoadhesivemicroparticulate drug delivery systems. Int J Pharm Clin Res. 2009; 1(1): 10-14.
30. Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of muco and bioadhesion: Tetheres structures and site-specific surfaces. J Control Rel. 2000; 65 (1): 63-71.
31. Good RJ Surface energy of solids and liquids: Thermodynamics, molecular forces, and structure. J Colloid Interface Sci. 1977; 59: 398-419.
32. Chang HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platform for oral controlled drug delivery, II: Synthesis and evaluation of some swelling water insoluble bioadhesive polymers. J Pharm Sci. 1985; 74: 399-405.
33. Rajput GC, Majmudar FD, Patel JK, Patel KN, Thakor RS, Patel BP. Stomach Specific Mucoadhesive Tablets as Controlled Drug Delivery System – A Review Work. International Journal on Pharmaceutical and Biological Research. 2010; 1(1): 30-41.
34. Yadav VK, Gupta AB, Kumar R, Yadav JS, Kumar B. Mucoadhesive Polymers: Means of Improving the Mucoadhesive Properties of Drug Delivery System. J Chem Pharm Res. 2010; 2(5): 418-432.
35. Jain KK, Transdermal drug delivery: technologies, markets, and companies, Basel, Jain PharmaBiotech Publications, 2008, 230.
36. Mainardes RM, Urban MC, Cinto PO, et a. , Liposomes and micro/nanoparticles as colloidalcarriers for nasal drug delivery, Curr Drug Deliv,3, 2006, 275–285.
37. Sakagami M., *In-vivo*, *in-vitro* and *ex-vivo* models to assess pulmonary absorption and disposition of inhaled therapeutics for systemic delivery, Adv Drug Deliv Rev, 58, 2006, 1030–1060.
38. Ely L, Roa W, Finlay WH, Lobenberg R., 2007. Effervescent dry powder for respiratory drugdelivery, Eur J Pharm Biopharm, 65, 2007, 346–353.
39. Rajalakshmi S. V., Vinaya O. G. Formulation development, evaluation and optimization of medicated lip rouge containing niosomal acyclovir for the management of recurrent herpes labialis. Int J App Pharm, Vol 9, Issue 6, 2017, 21-27.
40. MadhavSatheesh N.V, Abhay Pratap Y. Development and evaluation of novel repaglinide bio strips for translabial delivery. Int. Res. J. Pharm, 2013, 4(5):198.
41. MadhavSatheesh N.V, Abhay Pratap Y., A novel translabial platform utilizing bioexcipients fromLitchi chinesis for the delivery of rosiglitazone maleate. Acta Pharmaceutica Sinica B 2013; 3(6): 408–415.