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An Updated Review on Trans Labial Mucosa: A Significant Area to Design and Deliver a Drug

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Abstract:
The main aim of this article is to learn the basic anatomy histology, nerve supply, blood supply, muscle supply of the human lips. It also focuses on how the formulations can be design in order to deliver various classes of drugs like antihypertensive, antipsychotic, etc. when lip skin is compared with normal skin it accounts for greater bioavailability with lesser side effects. As devoid of hair follicles, cartilage, bones, sweat glands and presence of numerous blood supply making it red, hence labial mucosa is expected to offer a great advantages to administer a drug for both local and systemic action. These all makes the labial mucosa a significant area for delivering of drugs.

INTRODUCTION: [1, 2]

Translabial drug delivery system defines a system in which the absorption of drug moiety occurs via lips or mucosal membrane. Oral cavity is a better site and ease for the delivery of drugs. Hence, there are many benefits of the system over the other route of drug delivery such as oral route in which there are certain dilemmas i.e., first-pass metabolism and GI degradation, which ultimately reduce the bioavailability of some drugs. Whereas due to the ideal characteristics of labial mucosa, it has become an attractive fact towards the drug delivery system which includes many advantages such as duration of action can be increased and prevent from digestive enzymes and rapid action of suitable drugs. As lips are those parts of the body of human being which are the most delicate and made up of thin layer. These are mainly composed of muscles, skin and mucosa, but there is no any bone and infrastructure in its composition. Mucoadhesive agents play key role in the development of the translabial formulation. Due to the natural origin of mucoadhesive agents, it is biodegradable and biocompatible. Hence, it avoids patient non-compliance in chronic patients. It is also getting more important because multiple modification can be done easily. By this both local and systemic action of drugs can be achieved and also bypasses first pass metabolism reducing dose and side effect.

TRANSLABIAL DRUG DELIVERY SYSTEM: [3, 4, 5, 6, 7, 8]

It is commonly known that lips make the external part of the mouth of living organisms as well as form the entrance of oral route for in-taking the food and other substance along with the production of voice. Due to the rich blood supply, lips appear to be red which consist then tissues below and also have less number of melanocytes than the individuals who have more melanocytes. Lips have dual properties, these provide both local and systematic effect when drug is applied on lips.

After seeing ideal characteristics of lips, it has been found that lips have an important role in the formulation of translabial drug delivery system. Therefore, this system has distinct pros which include natural origin of mucoadhesive agents which are biodegradable and biocompatible. Hence, it avoids patient non-compliance in chronic patients. It is also getting more important because multiple modification can be done easily. By this both local and systemic action of drugs can be achieved and also bypasses first pass metabolism reducing dose and side effect. It is considered that in near days, this system will soon flourish in drug's development.

ANATOMY AND PHYSIOLOGY:

Generally lips contain 3-5 layers. Lips are two full fleshy fold which surrounds orifice of the mouth. Skin, muscles and mucosa accounts for the composition of lips. Mouth is lined by stratified squamous epithelium leads to the arrangement of cells in layers. This also provide the promising chromosomal studies by taking oral smears.

Starting from its unique feature, it is devoid of hair, sebaceous gland and bone which makes lips more flexible in nature. Mucosal tissue is translucent in nature and supplied by a number of blood capillaries it red. Typically, in medical terms upper lips and lowers lip are termed as labia superiors and labia inferiors respectively. The surface of two lips can be differentiated by skin, mucous membrane lining or simply lining. The Junction where the lips meet the surrounding skin of mouth area is known as vermilion border. Typically color of vermilion border is reddish. The comparative figure between regular/normal skin and lip skin are shown below in figure no 1

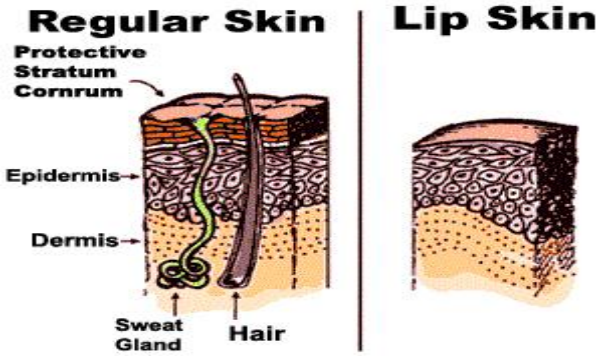

Fig.: 1 Comparison between Regular skin and Lip skin

Histology: [4, 11] Lips skin is comprised of epidermis, sub cutaneous, orbicularis oris muscle and mucosa. Vermilion of lips is composed of non-keratinised squamous

epithelium that covers a number of capillaries. Inner surface of lips is composed of non-keratinised and consist of stratified squamous epithelium whereas outer surface facing towards external environment composed of squamous keratinised epithelial cells.

Blood Supply: [12]

Facial artery of external non-terminal branches provide the blood supply to the stem of lips, labia superios and labia inferios. Later on labia superios and labia inferios bifurcate and anastomase with their companion artery from the other side. The blood supply are shown in figure 2

Nerve Supply: [4]

The maxillary and mandibular branches of fifth cranial nerves provides the sensory stimulation to the lips. The sensory innervation are provided by the branches of mandibular nerve via a mental nerve branch to the lower lip innervation of lip. Whereas the sensory stimulation to the upper lip is received by the branches of maxillary nerve through infra- orbital nerve. The nerve supply are shown in figure 3

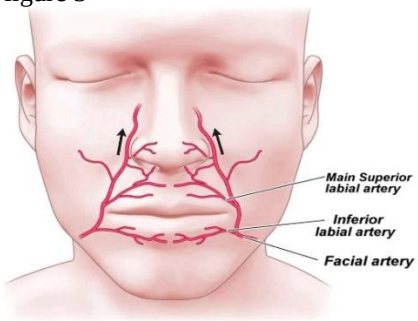

Fig. 2: Blood supply

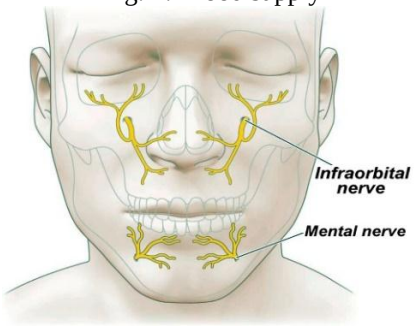

Fig. 3: Nerve supply

Muscle Supply: [12]

Lips with acting muscles are the part of facial muscles and these muscles are emerged from the mesoderm of the second pharyngeal arch. Therefore, it is supplied by the 7th cranial nerve of the second pharyngeal arch. The facial muscles are innervated with specialized members of panniculus carnosus that have attachment with dermis and hence, overlying skin is wrinkle or dimple.

Different muscle acting on lips

- Essential oral sphincter of the oral orifice
    - Buccinator
    - Orbicularis oris
- Muscles act as anchor point for other several other muscle
    - Modiolus
- Muscles that elevate the lips
    - Levator labii superioris
    - Levator labii superioris alaeque nasi
    - Levator anguli oris
    - Zygomaticus minor
    - Zygomaticus major muscle
- Muscles depressing the lips
    - Risorious
    - Depressor anguli oris
    - Depressor labia inferioris
    - Mentalis muscles

Lymphatic drainage: [9, 10]

There is an unilateral lymphatic drainage in the upper lip which attaches and makes 5 primary trunks that pass to the ipsilateral submandibular nodes along with other drainage that also lead to the perparotid lymph nodes. The lymphatics which are attached to lower lip form 5 primary trunks that further lead to bilateral submental nodes via central lip and unilateral submandibular lymph nodes through the lateral lip. Lips have first echelon nodes which are the submental, submandibular and parotid lymph nodes.

PROPERTIES AND FUNCTION OF LIPS: [9, 12, 13]

- Lips play key role in exhibiting the facial expression and emotion of individuals
- Devoid of sebaceous gland
- Devoid of hair follicle
- Absent of skin pigment which leads to visible of blood vessels appearing red in color.
- It is very elastic and pliable in nature due to absent of bones.
- Lips are very sensitive to touch, warm and cold due to number of nerve supply.
- With greater permeability therapeutic concentration can be achieved quickly as it contains non-keratinized squamous epithelium.

ADVANTAGES OF LABIA MUCOSAL DRUG DELIVERY SYSTEM: [9]

- Ease of application and termination of medication
- Allow localized and systemic action of drug formulation
- Avoid patient non- compliance for chronic patients.
- It can also be administered to unconscious patient
- Biocompatibility and biodegradability are key feature of labial delivery.
- Reduction in dose and decrease dose dependent side effect
- It has a great patient compliance due to its non-invasive, painless and simple application in comparison to parenteral route.
- It avoids hepatic degradation of drugs which offers an excellent result for systemic effect. Therefore, it has a high rate of bioavailability.

LIMITATIONS OF LABIA MUCOSAL DRUG DELIVERY SYSTEM: [1, 4, 14, 15, 16]

- Unsuitable for local irritants
- Drug, adhesives, or other excipients providing local arrythmia, erythemia or itching cannot be used.
- Small area featuring in dose limitations
- Peptide delivery is not feasible due to presence of peptidase.
- Drugs with half life having 2-8 hrs only used for translabial purpose.
- Drugs having unpleasant odor, taste cannot be given by this route rather it need to be masked.

PROBABLE DRUG PERMEATION MECHANISM THROUGH LIP SKIN:

There are two pathways for the penetration of drug through lip skin:

a. **Transcellular/intracellular transport**
   It is defined as the passage of drug's molecules across the lip skin epithelium.
b. **Paracellular/intercellular transport**
   It is defined as the transport of drug molecules through junctions between epithelial cell of lip skin.

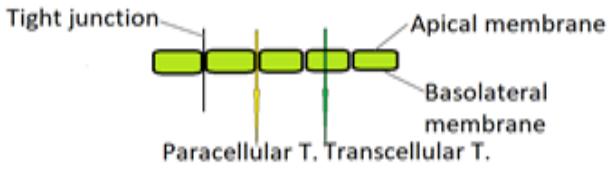

Fig. 4: Mechanism of drug permeation

The permeation of drug through sweat ducts, hair follicles and sebaceous glands which collectively known as shunt route, is not possible due to the absence of hair follicles and sweat ducts in vermillion zone of labial mucosa.

LABIAL SECRETIONS: [1, 17, 18]

The submucosal layer consist of salivary glands which secrete mucous.

Composition of mucous

components	% of composition
water	95%
Glycoprotein and lipids	0.5-5%
Mineral salts	0.5-1%
Free proteins	0.5-1%

LABIAL MUCOADHESION OR BIOADHESION: [1, 17, 18]

The term bioadhesion represents the bond between any two different biological surfaces or else a bond between the biological surface and synthetic surface. But, in the adhesive drug delivery, bioadhesion describes the adhesion between the polymer (either synthetic polymer or natural polymer) with soft tissues or gastrointestinal mucosa. When the bond is generated with mucus, then term mucoadhesion can be used as synonymously adhesion. Mucoadhesion is used as a term to define a phase in which two components, one is if natural origins held together for a longer duration of time with the help of interfacial forces. Commonly, bioadhesion is defined as a term which widely includes adhesive interactions to any naturally derived substance and mucoadhesion can be defined as the development of bond with mucosal surface.

Mechanism of mucoadhesion

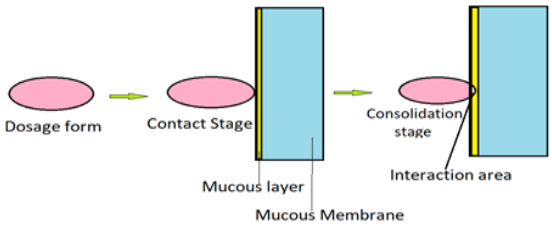

Fig. 5: Mechanism of Mucoadhesion

Mucoadhesion drug delivery system includes various ways of drug delivery systems, they are as follows:

- Buccal drug delivery system
- Vaginal drug delivery system
- Rectal drug delivery system
- Oral drug delivery system
- Nasal drug delivery system
- Ocular drug delivery system

There is not yet a complete mechanism understanding available that how or why certain molecules are attached to the mucus surface, few steps are accepted in the process at least for solid system. There are certain theories which are proposed to comprehend the process for fundamental mechanism of adhesion. Firstly, mucoadhesion should have the capability to spread on the substrate in order to forms the close contact and increasing in surface contact promotes the diffusion of its chain in the mucus. The attraction forces and repulsion forces are a complexity in the mucoadhesion, and for successful adhesion, attractions should be controlled over it. Each step of mucoadhesion can be made easy by the nature of pharmaceutical dosage form and how it takes. For instance, a substrate can adsorb by a partially hydrated polymer due to attraction by water surface. It is more likely mucoadhesion just by one theory, the procedure of mucoadhesion cannot be described. There are four different mechanism of mucoadhesion to describe in different approaches:

- Dehydrated or partially dosage forms make surface contact with substantial mucus layers which is typically particulates administered drugs into the nasal cavity.
- Fully hydrated dosages forms make surfaces with substantial mucus layers which is typically particulates of many mucoadhesive that have hydrated in the luminal contents on administered drugs into the lower gastrointestinal tract.
- Dry or partially hydrated dosages forms make surface with thin/discontinuous mucus layers which is typically tablets or patches into the cavity or vagina.
- Fully hydrated dosage forms make surfaces with thin or discontinuous mucus layers which is

typically aqueous semi-solids or liquids administered rugs into the esophagus or eye.

THEORY OF MUCOADHESION: [5, 6]

- **Electronic theory**:

According to electronic theory, when contact is formed between adhesive polymers and a mucus glycoprotein network, then transfer of electrons takes place due to the alteration in their electronic structures. This leads to the development of double electronic layer at the interface i.e., when a positively charged polymer chitosan and negative mucosal surface interact with each other, it creates adhesion on hydration which generates a contact between pharmaceutical dosage form and the absorbing tissue.

- **Absorption Theory:**

This absorption theory postulates that when a contact is formed between two different surfaces, material and adheres with each other due to surface force which performing between the two atoms in its surfaces. There are two kinds of chemical bonds which formed by these forces that can be differentiated as primary chemical bonds that has co-valent nature and the secondary chemical bonds that have various types of forces of attraction, with electrostatic force, vander-walls force, hydrogen and hydrophobic bonds.

- **Diffusion Theory :**

In diffusion theory, when both the polymeric chain and mucus mix with each other at a sufficient depth, they generate a semipermanent adhesive bond. The penetration at which polymeric chain penetrates, diffusion co-efficient and contact of time of mucus plays a crucial role in this process, in which diffusion co-efficient relies upon the importance of molecular weight between cross-linking that goes down significantly as its density increases. The permeation of mucoadhesive polymer on mucin chains can be calculated by the equation:

$L = (t\, D_b)^{½}$

Where as, t = Contact time

D_b = Diffusion coefficient of the mucoadhesive polymer

- **Wetting Theory:**

This wetting theory proposes that if there is a contact angle of liquids which is lower on the substrate surface, it has great affinity towards the liquid to the substrate surface[31, 32]. In the presence of liquid, when two substrate surface bring together in the contact with each other, liquid acts as an adhesive between the substrate surfaces. The spreadability coefficient (S_{AB}), is found from the alteration between the energies of mucoadhesive dosages form and adhesion surface (γ_B and γ_A) and Interfacial energy (γ_{AB}).

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

- **Cohesive Theory:**

According to cohesive theory, the intermolecular interaction amongst same molecules plays a significant role in the phenomenon of bioadhesion. Depends on the mucoadhesive polymer, bioadhesion can be described into two different categories namely chemical and physical.

- **Fracture Theory:**

This theory is widely employed in the study for the determination of mucoadhesion. It determines the force which is essential to differentiate two different surfaces after adhesion is founded. And this force Sm, is most used to calculate the test of resistance to separation by the ratio of maximal detachment force Fm, and the total surface area, A_O, included in the surface interaction:

$$Sm = Fm/A_O$$

Where, S_m = Actual detachment force

F_m = Maximum detachment force

A_0 = Total Surface area involved in the adhesion

Since this theory is preferred with the force to distinguish the parts. Hence, this is not concerned for the interpretation or diffusion of polymeric chains.

- **Mechanical Theory:**

This theory proposes that adhesion takes place due to the fill up of abnormalities on the surface by a mucoadhesive liquid. Additionally, this roughness enhances the interfacial area which considered as the most important phenomena for the process because of interactions which is available with the help of dissipating energy.

Factors Affecting Mucoadhesion: [9, 17]

Based on Polymer used	Physical factor	Physiological factor
Molecular weight	Ph of substrate interface	mucin turnover
Concenteration	Applied strength	Disease state
Flexibility	Initial contact time	Presence of enzyme
stereochemistry	swelling	

MUCOADHESIVE POLYMER: [5, 6]

Classification

1. On the basis of source

Natural	Synthetic	Others
Agarose	HPMC	PVA
Chitosan	CMC	PVP
Gelatin	Alkylcyanoacrylate	Thiolated polymers
gums	methacrylate	polyoxyethylene

2. On the basis of aqueous solubility

Water soluble	Water insoluble
HPC(water38 8C)	Chitosan
HPMC(cold water)	EC
Sodium alginate	PC

3. On the basis of charge

Cationic	Anionic
Aminodextran	Chitosan-EDTA
Chitosan	Pectin
(DEAE)-dextran	Sodium alginate
TMC	Xanthum gum

4. On the basis of potential mucoadhesive forces

Covalent	hydrogen bond
Polyacrylates	Cyanoacrylate
Hydroxy acrylates	

5. **Electrostatic interaction-** Chitosan

Formulation aspects of TLDDS: [9, 19, 20]

There are various ideal properties which should be taken into account during the formulation of dosage forms:

- It should be non-toxic and convenient to use.
- It should be non-irritant and pleasant.
- It should not dry the skin of lips and should easily remove with the help of water.
- It should be safe, economical and reliable.
- It should be easily applicable and removal along with its bioavailabity property.
- It should deliver the drug effectively and release medicament easily.
- It should have a good homogeneity and having low sensitization index.
- It should be compatible with mucosa and lip skin and should not affect the functioning of lip skin.

Various identified dosage form of translabial drug delivery system

- Lipstick
- Lip rouge
- Lip varnish
- Lip jelly
- Lip salve(lip balm)
- Lip gloss
- Lip pencil
- Lip stain
- Lip liner
- Biostrip
- Bioflexy film
- Mucosal patches

DOSAGES FORM: Bio-flexi films: [23]

Recently, flexy-films are the most advanced pharmaceutical dosage form for translabial mucosal route. Mucoadhesive biofilms may be referred adhesive tablets in their flexibility and comfort. Bio-flexy films as a dosage form in the pharmaceutical department as novel, patients friendly and convenient products and it is also act as a controlled and target specific drug delivery. An ideal bio-flexy films must be flexible, soft and adequately strong to tolerate cracking due to pressure from mouth activities. It must also shows good bioadhesive strength to be stable and retained at the site of action for the required duration of action.

For the formulation of bio-flexy films biopolymers play a vital role. Biopolymers terms are polymers which is formed by living organisms and it contains mono-meric units that are co-valently bonded to the formation of a larger structures. Biopolymers are classified in three different classes based on their differing mono-meric unit and on the bases of the structure of the biopolymer formed:

1. Poly-nucleotides: these polymers containing 13 or more than 13 nucleotide monomers.
2. Poly-peptides: these polymers containing amino acids
3. Poly-saccharides: these polymers are often linear bonded polymeric carbohydrate structures.

There is a main difference between the polymers and the biopolymers is found in their structure. All the polymers are made up of repetitive units called monomers.

Other excipients such as dextrose is widely used in the formulation of bio-flexy films it is used as a plasticizer and provide desired flexibility to the bio-flexy films.

For translabial mucosal, bio-flexy films gives some advantages and more. Due to their small size and thickness of bio-flexy films they have improved patients compliance in comparison to other pharmaceutical dosages form. Moreover, mucoadhesion implies attachment to the mucosa, and bio-flexy films can be formulated to shows good bio-adhesive strength in order to be stable and retained at the site of action for the prolong period of action and act as a local, systemic, controlled and target specific drug delivery.

EVALUATION PARAMETER

- **Physical appearance**- color, clarity, smoothness are visually inspected in order to ensure uniformity in appearance of formulation.
- **Weight uniformity** [22, 23] - formulation is weigh on a digital balance and mean will be calculated.
- **Thickness** [21] - Three specific random formulations are taken and their thickness will be determined using screw gauze. Their mean will be calculated.
- **Folding endurance** [24, 25] biolayers are subjected to repeatedly folding at the same place till it breaks. The number of folding it takes to break is a folding endurance of biolayers.
- **Swelling index** [23, 26] - weigh a biolayers on coverslip and place it in a culture dish containing 10 ml of suitable buffer. After 1 hour, weigh the coverslip with the biolayers. The difference in the weight accounts for the absorption of water and swelling of biolayer. The swelling is given by

$S\% = (Xt\text{-}X_0) *100$

Where, Xt = weight of swollen biostrip after time t

X_0 = initial weight of biostrip.

Percentage moisture absorption [22,27]- Take a biostrip ($1cm^2$) into a watch glass and place in a dessicator containing a saturated solution of aluminium chloride for 72 hr. The percentage moisture absorption is given by:

Moisture absorption % = [(final weight – initial weight)/ initial weight] * 100

Percentage moisture loss[28,29,30] - Take a biostrip ($1cm^2$) into a watch glass and place in a dessicator containing a fused anhydrous calcium chloride for 72 hr. Then weight loss will be determined. The percentage moisture absorption is given by:

Moisture loss % = [(final weight – initial weight)/ initial weight] * 100

- **Surface P^H study**[22,23] - Glass electrode can be used to find the ph. Allow the biolayers in contact with 0.5 ml of distilled water for 1 hr at room temperature. Bring the electrode in contact with the surface of the biolayer and equillibrate it for 1 min. Calculate a ph value.
- **Skin irritancy test** [23, 28] - It is done on anaethesized animal like rabbit by following standard guideline.

Carryout the study for at least 7 days and grade the application sites for redness, erythematic or irritation visually

- **Invivo release study** [23, 26] - Apply the biolayer lips to the lip of anaesthesized rabbit. Collect the blood samples from ear vein at predetermined interval of time to calculate plasma drug concenteration and various pharmacokinetic methods are calculated. AUC can also be calculated.
- **Stability studies** [21, 23] - wrap the biolayer in aluminium foil and pack them in glass vials. Keep these in an incubator (stability study chamber) maintained at 40 ± 2^0C and 75±5% RH for 6 months. And observe change in physical characteristics and study release behaviour of stored biolayers

APPLICATIONS

Although there is no any formulation available in the market, some of the articles shown the application in these type of drugs. This delivery system is generally used for the treatment of lip disorder. Medicated lip roughe containing niosomal acyclovir for the management of recurrent herpes labialis. Anti- diabetic drugs can also be given by this method.

CONCLUSION

The anatomy and histology of skin is different than normal skin. Since it is supplied by vascular and lymphatic drainage making to act drug for longer duration of action. It also reduces the dose and side effect. When translabial route is compared with other route it provide far better various potential advantages. The research evidence signifies the translabial drug delivery system is a novel dosage form.

FUTURE PERSPECTIVE

Translabial drug delivery is potential novelistic approach for the delivery of drugs for both local and systemic effect. Since it is a peculiar delivery system designing a formulation is becoming quite interesting. Systemic delivery of drugs using this labial platform has done yet i.e. no market formulations are available in the market which also lead the researcher to design formulation. In upcoming future labial dosage form like mucoadhesive tablet, patches, films, biolayers, nanosomes, microsomes, emulgels, etc loaded with API can be formulated for significant delivery of drugs.

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