H N Santosh et al /J. Pharm. Sci. & Res. Vol. 6(11), 2014, 356-359

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Mucoadhesion: A Neoteric Physician's Approach

[1]Dr H N Santosh
** Post Graduate Student Department of Oral Medicine and Radiology*
DayanandaSagar College of Dental Sciences

[2]Dr Chaya M David
Professor and Head ,Department of Oral Medicine and Radiology
DayanandaSagar College of Dental Sciences, Bangalore .

[3]DrHanoch Kumar Kapuganti
Post Graduate Student Department of Oral Medicine and Radiology
DayanandaSagar College of Dental Sciences, Bangalore

[4]DrAditi Bose,
Senior Lecturer , Department of Periodontics ,
Sri Rajiv Gandhi College of Dental Sciences, Bangalore .

Abstract:
Mucoadhesion is a newstrategy to prolong the residence time of various drugs. The capability to adhere to the mucus gel layer which covers the epithelial tissues makes such mucoadhesive polymers very useful excipients in drug delivery.The oral mucosa is highly perfused with blood vessels, hence therapeutic concentrations of the drug can be achieved rapidly.
Mucoadhesion is known to increase the intimacy and duration of contact between drug- containing polymer and a mucous surface.The bioavailability of the drug is improved becauseof the combined effects of the direct drug absorption and the decrease in excretion rate.Presently there is a plethora of drugs which are being used by mucoadhesion for various oral mucosal lesions ,the most common being aphthous stomatitis.
This article intends to evaluate the newfangled contraption- Adhesive strips in treating aphthous ulcer. At the same time we are trying to evaluate the difficulties faced by the clinician while opting for such a modality.

INTRODUCTION :

Pharmaceutics is a science of possibilities.The journey from conventional system of drug delivery like oral and parenteral to the new targeted drug delivery has been epoch making.Professor Joseph R Robinson of the University of Wiscosin pioneered the concept of mucoadhesion in the late 1980's[1].This was targeted to prolong the residence time of drugs. Leung and Robinson in 1988 described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer.

The oral mucosa has many properties which makes it an attractive site for drug delivery but also provides several challenges for researchers investigating novel delivery techniques to
overcome many different formulations including sprays, tablets, mouthwashes, gels, pastes and patches which are presently used for delivery into and or across the oral mucosa.

Recurrent aphthous stomatitis (RAS), also known as canker sores, is one of the most common oral mucosal diseases. In the largest study on RAS, involving a sample of over 10,000 young adults in 21 countries, 38.7% of men and 49.7% of women had suffered from at least two episodes of RAS in their lifetime. Approximately 25% of the study population reported that an episode had occurred in the year prior to the study.[2]

Presently,there is a plethora of drugs used for treatment of Aphthous stomatitis.The primary goals of therapy for RAU are relief of pain, reduction of ulcer duration, and restoration of normal oral function. Secondary goals include reduction in the frequency and severity of recurrences and maintenance of remission.[3]

Topical medications, such as antimicrobial mouth washes and topical corticosteroids, canachieve the primary goals but have notbeen shown to alter recurrence or remission rates. Systemic medications can be tried if topical therapy is ineffective.

Mucoadhesion[4] :

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(Good, 1983). In biological systems, bioadhesion can be classified into 3 types:

- Type 1, adhesion between two biologicalphases, for example, platelet aggregation and wound healing.
- Type 2, adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio-film formation on prosthetic devices and inserts.
- Type 3, adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydro gels to soft tissues (Henriksen*et al.*, 1996) and adhesion of sealants to dental enamel .

For drug delivery purposes, the term bioadhesion implies attachment of a drug carriersystem to a specified biological location. The biological surface can be epithelial tissue or themucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion.

Advantages of mucoadhesion[5]:

1. Prolongs the residence time of the dosage form at the site of absorption
2. Avoids the first pass metabolism
3. Enhanced absorption increases thetherapeutic efficacy of the drug.
4. Excellent accessibility
5. Rapid absorption because of enormous bloodsupply and good blood flow rates
6. Increases drug bioavailability due to avoidance of first passmetabolism.
7. Protects drug from degradation in the acidic environment of GIT.
8. Improves patient compliance & ease of drug administration.
9. Faster onset of action due to mucosal surface.

Mechanism of mucoadhesion[6]:

The mucoadhesive must spread over the substrate to initiate close contact and increasesurface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must be dominated. Each step can be facilitated by the nature of the dosage form and how it is administered.

Lee, Park, Robinson had described the mechanism of mucoadhesion in four different approaches. These include:

1. Dry or partially hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates administered into the nasal cavity)

2. Fully hydrated dosage forms contacting surfaces with substantial mucus layers (typically particulates of many mucoadhesive that have hydrated in the luminal contents on delivery to the lower gastrointestinal tract)

3. Dry or partially hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically tablets or patches in the oral cavity or vagina)

4. Fully hydrated dosage forms contacting surfaces with thin/discontinuous mucus layers (typically aqueous semisolids or liquids administered into the esophagus or eye)

In the study of adhesion, generally, two stages in the adhesive process supports the mechanism of interaction between mucoadhesive materials and a mucous membrane. Thus, the mechanism of mucoadhesion is generally divided in two stages, the contact stage and the consolidation stage.

Stage 1: Contact stage: An intimate contact (wetting) occurs between the mucoadhesive and mucus membrane.

Stage 2: Consolidation stage: Various physicochemical interactions occur to consolidate and strengthen the adhesive joint, leading to prolonged adhesion.

FACTORS AFFECTING MUCOADHESION:

(Chen J L andCyr G N, 1963; Ch'ng*et al.*, 1985) The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

Polymer Based Factors

1. Molecular weight of the polymer and concentration of the polymer used.
2. Swelling factor stereochemistry of polymer.

Physical Factors

pH at polymer substrate interface appliedstrength, contact time

Physiological Factors

Mucin turnover rate in diseased state

Oral strip technology(OST)[7]:

Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/ capsules to modified release tablets/capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral strip (OS).

Basically the OS can be considered as an ultra-thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other excipients. The advantages of convenience of dosing andportability of OS have led to wider acceptability of this dosage form bypediatric as well as geriatric population equally. OST was already popular amongst thepeople in the early 2000 year with the introduction and widespreaduse of Listerine pocket strips, a new launch in the mouthwash range.

Advantages of oral strip technology:

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
2. As the films are flexible they are not as fragile as most of the oral disintegrating tablets. Hence, there is ease of transportation duringconsumer handling and storage.
3. As compared to drops or syrup formulations, precision in theadministered dose is ensured from each of the strips.
4. Advantage of ease of swallowing and no need of water has ledto better acceptability amongst the dysphagic patients.
5. Larger surface area available in the strip dosage formallows rapid wetting in the moist buccal environment.
6. Dosageformcan be consumed at anyplace and anytime as per convenience ofthe individual.
7. Oral or buccal mucosa being highly vascularised, drugs can beabsorbeddirectly and can enter the systemic circulation without undergoing first-pass hepatic metabolism.
8. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.

However, not all drugs can be incorporated into this dosage form. The disadvantage of OS is that high dose cannot be incorporated into the strip.

Constraints of oral strips:

1. High dose cannot be incorporated
2. Drug should have low dose
3. Should have high oral bioavailability
4. Oral films have expensive packaging

Commercially available strips[8]:

Over-the-counter and nutraceuticals market was the first to move into OST after breath fresheners with a range of fast dissolving strip products which incorporated actives such as vitamins, herbal extracts and non herbal extracts. Pfizer had introduced Listerine in 2001 for bad breath and

Novartis had introduced their famous Triaminic and Theraflu brands in OS.

Biofilm has developed and commercialized OS for various applications in the area of neutraceuticals and improvement in the life style of consumers. Variety of energy booster OS products has been developed and commercialized for specific population such as students, drivers etc. The energy booster OS contain a mixture of caffeine, green tea extract and guarana to maintain energy levels. Similarly, Dyna Tabs has developed OS formulations for delivery of natural products for lifestyle management.

Product	Ingredient	Application
Biofilm Energybooster, Detoxification strip	Caffeine, Green Tea extract	Maintain high energy levels,Green Tea helps in wound healing
Breath Freshner Strip (antibacterial strip)	Mint flavour, antibacterial agents (Cetylpyridinum Chloride)	Stops bad breath
Saliva promoting strips	Fruit acid extracts	Used in dry mouth
Chloraseptic relief strips	Benzocaine 3mg,Corn starch, HydroxypropylMethyl Cellulose	Minor irritation,Pain,Sore throat,sore mouth
Theraflu Thin Strips	DiphenhydramineHcl25mg,Acetone,Hydroxyl propyl cellulose,Sorbitol	Temporarily relieves nasal and sinus congestion due to cold
Listerine pocketpaks	Available in cool mint,cinnamon	Kills 99% of bad breath

The oral strip technology[8]:

The oral strip comprises of the following components :

Component	Purpose	Example
Strip forming polymer	Provide robustness to the strips	Pullalan,Gelatin,Hypromellose
Plasticizer	Improves flexibility and reduces brittleness of the strips	Glycerol,Dibutylphthalate,Triacetin
Active pharmaceutical agent	Active ingredient of the oral strip	Anesthetic or analgesic agent , multivitamins .
Sweetening agents	Taste masking effect	Sucrose,Dextrose,Fructose.Mannitol
Saliva stimulating agents	Stimulates saliva for rapid dissolution of oral strip agents	Citric,Malic,Ascorbic acids.
Flavouring agents	Improves patient acceptability	Peppermint,Raspberry,Strawberry
Colouring agents	Helps better visualization of the strips	Pigments like titanium dioxide
Stabilizing and thickening agents	Improves viscosity and consistency of the strips in dispersion during manufacturing .	Xanthanangum,Carragenan,Cellulose

CLINICAL APPLICATION:

Anabel mouth ulcer film^{T}(Group Pharmaceuticals) is a fast dissolving oral film. Eugenol which is the only active ingredient of the fast dissolving film has analgesic and antiseptic properties.Hydroxypropyl Cellulose is the polymer with Copovidine as a co polymer.Polyvinyl pyrrolidine films are brittle in nature and therefore copovidone is mixed with poly vinyl pyrrolidine in fast dissolving films.

Indications:

1. Solitary ulcers in the oral cavity.
2. Ulcers in accessible areas of the oral cavity like Mucobuccal fold,Labial mucosa.
3. In cases having symptoms like burning sensation and pain.

Limitations:

1. Multiple ulcers in the oral cavity.
2. Ulcers in anatomically inaccessible areas.
3. Patients who are asymptomatic.
4. Patient having allergy to active ingredient - Eugenol.

Application Procedure:

1. Since the films are very thin,they should be handled with bare hands;as they have the tendency to stick to gloved hands.
2. The area should be moist so as to facilitate adherence of the film to mucosal layer.
3. The films should be kept in its place in an undisturbed state for atleast 15 minutes while the film dissolves intra orally.

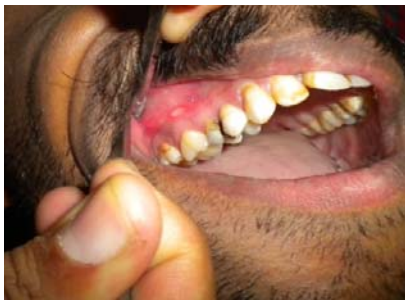
CASE REPORT :

A 28 year old patient visited the department of Oral Medicine Diagnosis and Radiology with a chief complaint of burning sensation in the right cheek region since 2 days.Patient gave history of recurrent ulcerations in different regions of the oral cavity associated with burning sensation.The frequency of the ulceration was 2 times per month and the ulcer used to persist for 4 to 7 days and used to heal.The ulcer was not associated with any history of fever.

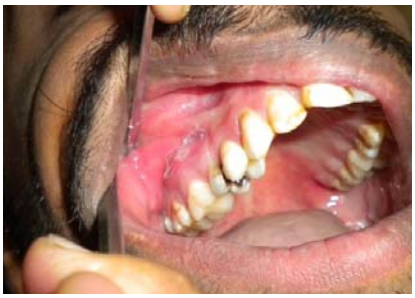
On intraoral examination,solitary ulcer was present in the right mucobuccal fold in the region of 16 .The ulcer was roughly ovoid in shape,measuring about 3 to 4 mm,surrounded by erythematous halo and a whitish base.On palpation the ulcer was tender ,border was blending with the surrounding mucosa and the floor was non scrappable .Based on the patients history and clinical examination a provisional diagnosis of Recurrent Aphthous Minor ulcer was given.

Anabel oral Strip ^{TM} (Group Pharmaceuticals) was applied over the ulcer . There was no increase in erythema indicating absence of hypersensitivity reaction. The oral strip gradually showed signs of dissolution in 20 minutes.There was considerable reduction in burning sensation .There was also considerable reduction in the erythematous halo around the ulcer after 20 minutes of application of the oral strip indicating reduction in the inflammatory process .

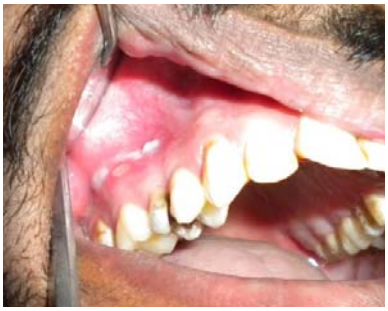
Sequence of events during application of fast dissolving films for RAU minor.



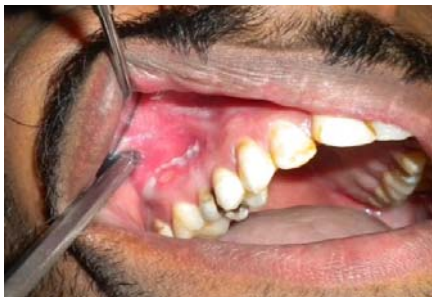
RAU Minor of right mucobuccal fold



Application of Oral Film



10 minutes after application showing dissolving of oral film



20 minutes after application of oral film showing completely dissolved film

DISCUSSION :

Stanley in 1972 classified Recurrent Aphthous Ulcers (RAU) in to Major,Minor and Herpetiform.The episodes of Recurrent Aphthous Ulcer Minor are short lived (4-7 days) and they heal without scarring.They occur as solitary or sometimes multiple and affect the labile mucosa of the oral cavity[9].Presently there is plethora of drugs for RAU which have palliative potential. Oral mucoadhesive strips are advantageous over topical application as the residence time of oral strips is longer. Hence the active pharmaceutical agent in the Oral strip serves dual purpose on analgesia and surface protection.

The oral strip which was in this case (Anabel Oral Strips ™ by Group Pharamceuticals) comprises of Eugenol which is the only active ingredient.It has analgesic, anesthetic and antimicrobial actions. Hydroxypropyl cellulose is the strip forming polymer which adds rigidity to the mucoadhesive strips. Glycerol is the plasticizer which improves the viscosity of the strips in dispersion phase during manufacturing.VinylPyrrilodone , vinyl acetate and copovidone are the co polymers which reduce the brittle nature of the strips imparted by the strip forming polymers.

CONCLUSION:

Although there is a plethora of drugs available for treatment of Aphthous Ulcer,but none have the potential to treat the cause.They are predominantly palliative.Mouth ulcer gels,which are easily available,do not have high residence time.In order to achieve good palliative results,the film should have good adherence to the mucosa so that the active ingredient leaches to the site.

Thus Oral Strip Technology is a good tool for product life cycle management forincreasing the patent life of existing molecules or products. Comparedto some of the complicated and expensive process (like lyophilization) used to manufacture Oral Dispersible Tablets, the Oral Strip Technology is relatively easy to fabricate;thus reducing the overall cost of the therapy.

REFERENCES :

1. PhanindraB . Recent advances in Bioadhesive drug delivery system:A Review int. J. Pharm. Med. & bio. Sc. 2013;2(1):68-84
2. Laura B. Huling . Effect of stressful life events on the onset and duration of Recurrent aphthousstomatitis . Journal Oral Pathol med 2012; 41: 149–152
3. Robert W. BarronsTreatment strategies for RecurrentOral aphthous ulcers Am J Health-Syst Pharm 2001;58(1)
4. Mucoadhesive drug delivery systems .Shaikh r et al journal of pharmacy and bioallied sciences 2011; 3 (1):89-100
5. An overview on buccal drug delivery system. Kaulet al.ijpsr, 2011; vol. 2(6): 1303-1321.
6. Buccal mucoadhesive based drug delivery devices. IzharAhmed World journal of pharmaceutical research 2012;1(3):548-575
7. M.d. NehalsiddiquiA short review on “a novel approach in oral fast dissolving Drug delivery system and their patents”. Journal of advances in biological research 2011;5 (6): 291-303
8. R. P Dixit . Oral strip technology: overview and future potential journal of controlled Release 2009;139: 94–107.
9. Stephen R Porter .Recurrent Aphthous Stomatitis Clinics in Dermatology 2000;18:569-578