REVIEW ARTICLE

ISSN:2394-2371
CODEN (USA):IJPTIL

RECENT TRENDS IN ETIOLOGY AND MANAGEMENT OF XEROSTOMIA: A REVIEW

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ABSTRACT

The delivery of drug substance through the mucosa (oral) presents a great opportunity but also poses continuing challenges. Xerostomia, the excessive dryness of mouth, and reduction in the saliva secretion poses a debilitating condition for majority of patients. Evaluation of xerostomia starts with a careful and complete examination of mouth. Numerous treatments are available for the management of xerostomia including salivary stimulants, saliva substitutes, topical agents and sialogogues for systemic effect. The purpose of this article is to investigate the existing knowledge on management and cureing patients affected by dryness of mouth or with altered salivation.

Keywords: - Xerostomia, Dryness of mouth, Sialogogues, Systemic sialogogues.

INTRODUCTION

Delivery of the drugs through the mouth (oral cavity) provides an potential site for both local and systemic effects. The benefits of oro-mucosal route to administration drug substance provides fast onset of action and bioavailability of drug may be enhanced as it bypasses the liver and GI degradation are avoided. To another note, the oral mucosal cavity is easily accessible for application and withdrawl of API, if needed. However, there are limitations associated with this route for drug administration including restricted permeability and surface area for absorption relative to gut. And as such primary function of saliva is to cleanse the oral cavity, swallowing and motility of the tongue will facilitate the concentration of drug substance from the absorption site unless the dwell time can be increased. One approach to overcome this limitation is, bioadhesive formulation where a formulation is adhered to the oral mucosa and thus provide longer residence time which inturn will give better absorption. By adding the drug substance into a mucoadhesive dosage form it will increase the contact time at the mucosal

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Article Published: July-Sept 2016

surface. Simple diffusion is responsible to deliver the drug directly into the blood circulation. So by keeping the concentration gradient for entire duration, the bioavailability can be enhanced.

Do's and Dont's through mucosal drug delivery [2,4]

The mucosal cavity poses certain issues for systemic drug delivery. The drug substance should to be released from the dosage form to the site of delivery and pass through the mucosal barrier to reach blood circulation. Certain aspects of the mucosal cavity is vital in this journey, including pH, saliva volume, enzymatic action and the penetration through mucosa of the mouth. But for the systems meant for modified release in the oral mucosa (e.g. mucoadhesive systems), the structure of the mucosa also plays a crucial role. Table 1 provides a tentative values of the structural characteristics of the mucosa and the GI tract. The environment of the mucosal cavity, in terms of pH, its composition and volume, is driven by the secretion of saliva. In humans, Saliva is primarily secreted by parotid, submandibular glands which constitutes around 20-25% & 70-75% respectively. Minor salivary glands (sublingual) present in the mucosa. The parotid and submaxillary glands produce watery secretion, whereas the sublingual glands produce relatively viscous saliva with less enzymatic activity. The saliva is meant to cleanse, lubricate the cavity, helps in swallowing and prevents demineralization of the teeth. In addition, it also allows digestion of certain foods and regulates oral microbial flora by maintaining the homeostasis of oral cavity. The normal individual on an average secretes around 0.5 and 2.0 liters of saliva every day. But the residual volume of saliva is only 1.1 ml, hence, providing a less fluid volume for drug release compared to the GI tract. As compared to the GI fluid, saliva is less viscous and contains mainly 1% organic and inorganic materials. In addition, saliva has a slight buffering capacity with a pH ranging from 5.5–7.0. The salivary compositions and pH of the saliva depends on the secretary rate which in-turn depends upon factors like: the time of day, the stimulus type and the intensity of stimulation. For example, at high flow rates, the concentration of Na and HCO3 s is found to increase which in-turn causes the salivary pH to increase.

Inspite of the the advantages through this route, this route has certain inherited limitations in terms of restricted absorptive surface area and retention of the dosage form for extended period of time. This can be overcome to good extent by adding a mucoadhesive parameter by using some suitable polymers like Chitosan, PLA, PVP and Carbomer. Usually the blood supply to the mucosa is adequate, and is not the rate limiting factor for the penetration and absorption of

drugs. The buccal and sublingual routes are mainly focused to deliver the drug through the oral mucosa because of the better permeability.

Oral transmucosal drug delivery techniques

Various dosage forms are available in the market ranging from solutions, tablets/lozenges, chewing gums, sprays, patches and films and hydrogels [8]. Drugs can be delivered for local and systemic effect through transmucosal route. The success of buccal drug delivery is influenced primarily by the dwell time in the oral cavity and limited absorptive surface area. The use of mucoadhesive systems helps to good extent in maintaining the intimate contact of the formulation with the oral mucosa for a prolonged time. The adhesive systems can be customized to deliver the drug from the mucosa only (unidirectional) with an impermeable surface facing the oral cavity which inhibits the drug release into oral cavity or can be tailored to deliver the drug on either side (bidirectional). Anionic polymers like polyacrylic acid (PAA) and sodium CMC are the most widely used mucoadhesive polymers within pharmaceutical formulations as they possess low toxicity and better mucoadhesive nature primarily due to the formation of strong hydrogen bonding with mucin., undoubtedly chitosan is the most preferred among the cationic polymer systems owing to its biocompatibility and biodegradability properties.

Etiology of xerostomia [4]

Disorder of the salivary gland causes salivary gland to enlarge, discomfort, and dryness for stretched time in oral cavity. Dryness of mouth is the most prevalent problem for the majority of affected patients. The prevalence rate is around 40% but it can hit 70% in certain hospice patients. Dry mouth can be caused due to various reasons, including due to Sjogren's syndrome and for people who has undergone chemotherapy or radiation of the head and neck region. Rarely, xerostomia may be subjective, with no clear evidence of reduced salivary flow but could be due to change in the composition of saliva. Saliva substitutes and local sialogogues are usually given as a first preference, but now various therapies are avialable for chronic xerostomia. The unstimulated salivary flow rate is 0.3 mL/ min, whereas the flow rate during sleep is minimal to 0.1 mL/min, but it goes to 4.0 to 5.0 mL/min during stimulation for example while eating or chewing. In humans, saliva is always hypotonic, (sodium and chloride ion concentrations is less than that of plasma). The tonicity of the saliva is directly proportional to the flow rate of saliva. Long-standing xerostomia can be caused by numerous factors but it is predominantly caused by some of the commonly prescribed drugs including tricyclic antidepressants, α, β blockers, diuretics and antihistamines etc. Xerostomia as such is caused

by more than 400 commonly prescribed medications. Also, some of the medications are known to give synergistic effects and are alarmingly prevalent among geriatric population taking multiple medications. The mechanism of drug-induced xerostomia is due to their anticholinergic or sympathomimetic action. Salivary tissues are highly susceptible to damage when exposed to the radiation, especially the parotid gland being most vulnerable[12], Even a radiation exposure as low as 20 Gy can cause cessation of salivary flow. But at doses above 52 Gy, it causes severe dysfunction.

Consequences of long standing Xerostomia: Xerostomia usually leads to-

- Burning tongue/depapillation of tongue
  Oral mucosal soreness
- Dysarthria (speech disorder)
  Salivary gland enlargement
- Dysphagia (difficulty in swallowing)
- Dysgeusia (distortion of sense of taste)
- Dry and bruised lips

MANAGEMENT OF PROLONGED XEROSTOMIA

Until now, there is no as such permanent treatment and most of the treatments available mainly gives symptomatic relief and a localized effect predominantly. Xerostomia is controlled mainly by the avoidance of factors which trigger or aggravate the xerostomic condition, it can be controlled by using some of the following techniques- Tell dentist all the medications you are taking, Sugarless gum, humidifier at night, Increase fluid intake, avoid excessive alcohol, high acidic juices and No alcoholic mouth rinses. As such, local treatments only provides transient relief. However there are products like Salagen tablets(Pilocarpine) and Evosac capsules (Evosac) which are used for systemic effects and are approved by the USFDA.

Saliva substitutes improves overall hydration of oral mucosa and maintaining the overall mucosal homeostatis, but they are usually inconvenient and affect end user compliance especially those who wear dentures cannot chew gum. A saliva substitute which restores mineralization on enamel and gives a long lasting effect is preferred. Tooth pastes are available with fluoride but they have SLS too which is abrasive and toxic to respiratory tract.

Systemic agents

Muscarinic M3 receptor (pilocarpine and cevimeline) have been approved by the USFDA for systemic use in Xerostomia. Initially, systemic pilocarpine was approved for xerostomic condition mainly caused by radiation of the head and neck; but recently, more studies has been done and have shown the potential benefit in Sjogren's disease. Pilocarpine is a parasympathetic agonist of acetylcholine muscarinic receptors and thus stimulates

secretion by exocrine glands such as the salivary, sweat, lacrimal glands. Pilocarpine is readily absorbed from the GI tract, and max plasma concentrations reached within one hour. Pilocarpine is metabolized by the hepatic route and excreted mainly through kidneys, with a biological half-life is approximately one hour. Although no serious side effects has been reported with the use of pilocarpine but common side effects associated with pilocarpine are sweating, headache, nausea, mild abdominal pain and GI upset, urinary urge and, rhinitis, flushing, increased lacrimation, and palpitations. However, despite these symptoms, the end user compliance is not compromised as none of the symptoms are life threatening. Clinical data, to date shows that pilocarpine is safe and well tolerated, and does not possess any serious ADRs or drug-to-drug interactions. Systemic pilocarpine as such should be used with caution for patients suffering from respiratory disease (eg. Asthma and copd) and those taking antihypertensive drugs because interactions with β-blockers would rarely be possible.

The results of open-ended studies of orally administered pilocarpine in pilot study after radiation suggested that it reduces the intensity of xerostomia associated with radiation. More recently, Four controlled trials were carried out, three of which used pilocarpine topically, and all results were promising in improvements in general feelings of xerostomic condition, speech, and chewing. However, more studies needs to be done on larger population to get meaningful information. [20,25,30]]. The pilocarpine is normally given as 5 mg t.i.d/q.i.d and if this does not show significant results then in certain cases the dose can be increased to 10 mg t.i.d. It is generally recommended that pilocarpine should be prescribed for few weeks ranging from 8 to 12 weeks. Pilocarpine can't stimulate the function of salivary glands that are completely dysfunctional by exposure to radiation, but it mainly enhances the function of minor salivary glands that may be more resilient to the damaging effects of radiation compared with the major glands. Another placebo-controlled pilot study with limited number of subjecs with Sjogren's Sndrome showed that pilocarpine administered systemically increases salivary flow in around two to three hours of administration and alleviates symptoms of dryness of mouth. This clinical efficacy of pilocarpine given orally has been confirmed in a larger study, placebo controlled, fixed-dose multicenter trial.[40,44]. And suggesting that many patients with dryness of mouth especially caused by Sjogren's Syndrome gets benefited with this.

Bethanechol, is another drug which acts on both muscarinic as well as nicotinic receptors, and is found to have some promisin positive effect in

the management of drug-induced xerostomic conditions [50] Bethanechol which is prescribed as 25 mg t.i.d orally was found to increase the unstimulated and stimulated saliva in certain patients with dryness of mouth who have undergone radiation of head and neck region[55]. *Cevimeline.* (Evoxac) which is a analog of acetylcholine and has a affinity for mainly M3 receptors both of lacrimal and salivary glands. Cevimeline is usually given as 30 mg t.i.d and is well tolerated and not associated with any serious side effects, but in rare cases this dose can be increased to 60 mg t.i.d. In rare cases GI upset is observed especially with a high doses[57].

Other methods of stimulating salivation

Minor methods of increasing saliva include Electrostimulation, Acupuncture, Primrose oil and chewing of cappuccino coffee for alleviating the symptoms of xerostomia.

CONCLUSION

The oral route is still the most preferred route of administration in most cases as it is most versatile and convenient route. Lot of efforts and experiments are going on for the delivery of drugs through oral mucosal route. This route provides the additional advantages of ease of application and better absorption and also bypassing the hepatic metabolism and inturn get faster onset of action. Through this route the drugs can be delivered for both local and systemic effects. In addition Oral mucoadhesive dosage forms will continue to be an exciting research focus for improving drug because it withholds the dosage form for a longer period of time and thus increasing the dwell time for better absorption. Certainly more elaborative studies needs to be done in order to increase the quality of life of a patient. One approach could be to develop a combination product which will give local and systemic effects in a single delivery system.

REFERENCES

1. *Michael B. Chancellor, Rodney A. Appell, Gayatn'Sathyan,* A Comparison of the Effects on Saliva Output of Oxybutynin Chloride and Tolterodine Tartrate, Clinical therapeutics vol. 23, NO. 5,2001
2. Viralkumar F. Patel a, Fang Liu a, Marc B. Brown, Advances in oral transmucosal drug delivery, Journal of Controlled Release 153 (2011) 106–116
3. A. Manosroi a,b, P. Jantrawuta, J. Manosroi, Anti-inflammatory activity of gel containing novel elastic niosomes entrapped with diclofenac diethylammonium, International Journal of Pharmaceutics 360 (2008) 156–163.
4. S. R. Porter, C. Scully, An update of the etiology and management of xerostomia, Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:28-46.

5. Christine Delporte, Aquaporins in salivary glands and pancreas, Biochimica et Biophysica Acta 1840 (2014) 1524–1532
6. Richard A. Cone, Barrier properties of mucus, Advanced Drug Delivery Reviews 61 (2009) 75–85
7. Omar Samia, Refai Hanan, and El Tahir Kamal, Carbamazepine Mucoadhesive Nanoemulgel (MNEG) *as* brain targeting delivery system via the olfactory mucosa, *Drug Delivery*, 2012, 1–10, Early Online© 2012 Informa Healthcare USA, Inc.ISSN 1071-7544
8. Loustaud-Ratti VE, Riche AG, Liozon ER, Labrousse FR, Soria PA, Rogez SY, Babany GE, Delaire LA, Denis FR, Vidal EL. Prevalence and characteristics of Sjögren's syndrome or Sicca syndrome in chronic hepatitis C virus infection: a prospective study. The Journal of rheumatology. 2001 Oct 1;28(10):2245-51.
9. Amornrat Klaewklod , Vimon Tantishaiyakul, Namon Hirun, Characterization of supramolecular gels based on β-cyclodextrin and polyethyleneglycol and their potential use for topical drug delivery, Materials Science and Engineering C 50 (2015) 242–250
10. Manish Kumar Jeengar, Sri Vishnu Kiran Rompicharla, Shweta Shrivastava, Emu oil based nano-emulgel for topical delivery of curcumin, International Journal of Pharmaceutics 506 (2016) 222–236
11. Katrine D. Madsen, Camilla Sander, Stefania Baldursdottir, Development of an ex vivo retention model simulating bioadhesion in the oral cavity using human saliva and physiologically relevant irrigation media, International Journal of Pharmaceutics 448 (2013) 373– 381
12. Scully C, Epstein JB. Oral health care for the cancer patient. European Journal of Cancer Part B: Oral Oncology. 1996 Sep 30;32(5):281-92
13. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4278738/#!po=1.82927.
14. Vinay K.Singh, Preeti M.Pandey, TarunAgarwal, Development of soy lecithin based novel self-assembled emulsion hydrogels, j o u r n a l o f t h e m e c h a n i c a l b e h a v i o r o f b i o m e d i c a l m a t e r i a l s 5 5 (2 0 1 6) 2 5 0 – 2 6
15. Villa, Alessandro, Christopher L Connell, Diagnosis and management of xerostomia and hyposalivation, Therapeutics and clinical risk management, Dec 2014
16. Anne S. McMillan a,*, C.S. Peter Tsang a, May C.M. Wong, Efficacy of a novel lubricating system in the management of radiotherapy-related xerostomia, Oral Oncology (2006) 42, 842– 848

17. Bhavna Dhawan, Geeta Aggarwal, and SL Harikumar, Enhanced transdermal permeability of piroxicam through novel nanoemulgel Formulation, Int J Pharm Investig. 2014 AprJun;4(2): 65–76
18. Choon Fu Goh a,b, Majella E. Lane, Formulation of diclofenac for dermal delivery, International Journal of Pharmaceutics 473 (2014) 607–616
19. Vinay K. Singha, Indranil Banerjeea,□, Tarun Agarwala Guar gum and sesame oil based novel bigels for controlled drug delivery, Colloids and Surfaces B: Biointerfaces 123 (2014) 582–592
20. *Anurag Gupta, Joel B. Epstein*, Hyposalivation in Elderly Patients, J Can Dent Assoc 2006; 72(9):841–6
21. Johnson JT, Ferretti GA, Nethery WJ, Valdez IH, Fox PC, Ng D, Muscoplat CC, Gallagher SC. Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. New England Journal of Medicine. 1993 Aug 5;329(6):390-5.
22. Supranee Dalodom, Aroonwan Lam-ubol, Sutha Jeanmaneechotechai, Influence of oral moisturizing jelly as a saliva substitute for the relief of xerostomia in elderly patients with hypertension and diabetes mellitus, Geriatric Nursing 37 (2016) 101e109.
23. Ritika Arora, Geeta Aggarwal, S. L. Harikumar, and Kirandeep Kaur, Nanoemulsion Based Hydrogel for Enhanced Transdermal Delivery of Ketoprofen, Advances in Pharmaceutics Volume 2014, Article ID 468456.
24. Swati Pund , Satish Pawar, Shashikant Gangurde, Transcutaneous delivery of leflunomide nanoemulgel: Mechanistic investigation into physicomechanical characteristics, in vitro anti-psoriatic and anti-melanoma activity, International Journal of Pharmaceutics 487 (2015) 148–156
25. Mark Donaldson, Joel Epstein, Dana Villines, Managing the care of patients with Sjögren syndrome and dry mouth, JADA 2014;145(12):1240-1247.
26. Joensuu H, Boström P, Makkonen T. Pilocarpine and carbacholine in treatment of radiation-induced xerostomia. Radiotherapy and Oncology. 1993 Jan 31;26(1):33-7.
27. Kalpesh Chhotalal Ashara, Jalpa S. Paun, Moinuddin M. Soniwala, Micro-emulsion based emulgel: a novel topical drug delivery system, Asian Pac J Trop Dis 2014; 4(Suppl 1): S27-S32
28. Monzer Fanun, Microemulsions as delivery systems, Current Opinion in Colloid & Interface Science 17 (2012) 306–313
29. Heuschkel S, Goebel A,. Neubert reinhard , Microemulsions—Modern Colloidal Carrier for Dermal and Transdermal Drug Delivery, Published online in Wiley InterScience

(www.interscience.wiley.com). DOI 10.1002/jps.20995

30. B. Beheraa, D. Biswala, K. Uvanesh, Modulating the properties of sunflower oil based novel emulgelsusing castor oil fatty acid ester: Prospects for topical antimicrobialdrug delivery, Colloids and Surfaces B: Biointerfaces 128 (2015) 155–164.
31. Hamlar DD, Schuller DE, Gahbauer RA, Buerki RA, Staubus AE, Hall J, Altman JS, Elzinga DJ, Martin MR. Determination of the efficacy of topical oral pilocarpine for postirradiation xerostomia in patients with head and neck carcinoma. The Laryngoscope. 1996 Aug 1;106(8):972-6.
32. Carla M. Caramella , Silvia Rossi, Franca Ferrari, Mucoadhesive and thermogelling systems for vaginal drug delivery, Advanced Drug Delivery Reviews 92 (2015) 39–52.
33. Alexandra Partenhauser and Andreas Bernkop-Schnurch, Mucoadhesive polymers in the treatment of dry X syndrome, Drug Discovery Today _ Volume 21, Number 7 _ July 2016.
34. Padmadevi Chellapa, Aref T. Mohamed, Eseldin I. Keleb, Nanoemulsion and Nanoemulgel as a Topical Formulation**,** *IOSR Journal Of Pharmacy, Volume 5, Issue 10 (October 2015), PP. 43-47.*
35. Gregor Cevc , Ulrich Vierl, Nanotechnology and the transdermal route- A state of the art review and critical appraisal, Journal of Controlled Release 141 (2010) 277–299.
36. Vissink A, Burlage FR, Spijkervet FK, Jansma J, Coppes RP. Prevention and treatment of the consequences of head and neck radiotherapy. Critical Reviews in Oral Biology & Medicine. 2003 May 1;14(3):213-25.
37. *Fayez Hamama, Mayyas Al-Remawi,* Novel delivery system of curcumin through transdermal route using sub-micronized particles composed of mesoporous silica and oleic acid, journal of functional foods 8C (2 0 1 4) 87–99.
38. A. Wolff *, F. Strietzel, R. Mart´ın-Granizo, Saliwell: intra-oral electrostimulator for the treatment of xerostomia, Oral and Symposium abstracts.
39. Cornel Burger, Minja Gerber*, Jan L. du Preez, Optimised transdermal delivery of pravastatin, International Journal of Pharmaceutics 496 (2015) 518–525
40. Chaudhary h, Kohli k, Amin s**,** Optimization and Formulation Design of Gels of Diclofenac and Curcumin for Transdermal Drug Delivery by Box-Behnken Statistical Design**,** *Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22292*
41. Papas AS, Fernandez MM, Castano RA, Gallagher SC, Trivedi M, Shrotriya RC. Oral pilocarpine for symptomatic relief of dry mouth and dry eyes in patients with Sjögrens

syndrome. InLacrimal Gland, Tear Film, and Dry Eye Syndromes 2 1998 (pp. 973-978). Springer US.

42. Hendrickson R. G,. Morocco A. P, and. Greenberg M. I, pilocarpine toxicity and the treatment of xerostomia, The Journal of Emergency Medicine, Vol. 26, No. 4, pp. 429–432, 2004
43. Eid A. M, El-Enshasy H. A, Aziz R, Preparation, Characterization and Anti-Inflammatory Activity of Swieteniamacrophylla Nanoemulgel, Eid et al., J Nanomed Nanotechnol 2014, 5:2
44. Thanou-Stavraki A and A Judith. James,Primary Sjogren's Syndrome,Current and Prospective Therapies.
45. Nusair S, Rubinow A. The use of oral pilocarpine in xerostomiaand sjögren's syndrome. InSeminars in arthritis and rheumatism 1999 Jun 30 (Vol. 28, No. 6, pp. 360-367). WB Saunders.
46. Bhide S. A. Miah A. B,. Harrington K. J, Radiation-induced Xerostomia: Pathophysiology, Prevention and Treatment, Clinical Oncology (2009) 21: 737e744
47. Liu F, Tang C, Reprint of "Soy glycinin as food-grade Pickering stabilizers: Part. III. Fabrication of gel-like emulsions and their potential as sustained release delivery systems for b-carotene, Food Hydrocolloids 60 (2016) 631e640
48. Perioli L, Pagano C, Mazzitelli S, Rheological and functional characterization of new anti-inflammatory delivery systems designed for buccal administration, International Journal of Pharmaceutics 356 (2008) 19–28.
49. Sateeshsagiri , Singh V, Kulanthaivel S, Stearate organogel–gelatin hydrogelbasedbigels: Physicochemical,thermal,mechanical characterizations and in vitro drug delivery applications, j o u r n a l o f t h e m e c h a n i c a l b e h a v i o r o f b i o m e d i c a l m a t e r i a l s 4 3 (2 0 1 5) 1 – 1 7
50. Zoppi A, Linck Y,. Monti G.A, Studies of pilocarpine:carbomer intermolecular interactions, International Journal of Pharmaceutics 427 (2012) 252– 259
51. Everett HC. The use of bethanechol chloride with tricyclic antidepressants. The American journal of psychiatry. 1975 Nov.
52. Man D. F, Joseph. Schwarz, and Elsspaplr M. W, Submicron Emulsion Vehicle for Enhanced Transdermal Delivery of Steroidal and Nonsteroidal Antiinflammatory Drugs, Received June *27,* 1994, from the *Pharmos* Ltd., *Kiryaf Weizmann, Rehovof* 76326, *Israel.*
53. Ijaz M, Matuszczak B, Rahmat D, Synthesis and characterization of thiolated _-cyclodextrin asanovel mucoadhesive

excipientforintra-oraldrugdelivery, Carbohydrate Polymers 132 (2015) 187–195

54. Dojicic T. Varjacic M, testing the efficacy of metronidazol containing lipogel in treatment of periodontal disease**.**
55. Dong L, Liu C, Cun D, The effect of rheological behavior and microstructure of the emulgels on the release and permeation profiles of Terpinen-4-ol, European Journal of Pharmaceutical Sciences 78 (2015) 140–150
56. Epstein JB, Burchell JL, Emerton S, Le ND, Silverman S. A clinical trial of bethanechol in patients with xerostomia after radiation therapy: a pilot study. Oral surgery, oral medicine, oral pathology. 1994 Jun 30;77(6):610-4.
57. Ibrahim M.M,. Shehata T.M, The enhancement of transdermal permeability of water soluble drug by niosome-emulgel combination**,** J. DRUG DEL. SCI. TECH., 22 (4) 353-359 2012
58. Fife RS, Chase WF, Dore RK, Wiesenhutter CW, Lockhart PB, Tindall E, Suen JY. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomized trial. Archives of internal medicine. 2002 Jun 10;162(11):1293-300.
59. . Diaz-Arnold A M, and A. C, The impact of saliva on patient care: A literature review, The Editorial Council of *The Journal of Prosthetic Dentistry*.0022-3913/2002
60. Sintov A C, Botner S: Influence of skin storage conditions on the in vitro permeability of diclofenac from aqueous vehicle systems, International Journal of Pharmaceutics 311 (2006) 55–62.
61. Itthagarun A, Wei SH. Chewing gum and saliva in oral health. The Journal of clinical dentistry. 1996 Dec;8(6):159-62.
62. Adamczaka M,. Martinsen G, Smistad G, Water sorption properties of HM-pectin and liposomes intended to alleviate dry mouth, International Journal of Pharmaceutics 506 (2016) 201–206
63. Davies AN. A comparison of artificial saliva and chewing gum in the management of xerostomia in patients with advanced cancer. Palliative Medicine. 2000 Apr 1;14(3):197-203.
64. Challecombe scale of Clinical oral dryness developed by the Kings College of London.

Table 1 Physiological characteristics of buccal mucosa

Absorptive site	Approx Total S.A	Local pH	Enzymatic Activity	Relative Drug Absorption
Mucosal cavity	0.01	5.8-7.6	Medium	Medium
Stomach	0.20	1.0-3.0	High	Medium
Small intestine	98.76	5.0-7.0	High	High
Large intestine	0.99	6.0 -7.4	Medium	Less
Rectum	0.04	7.0-7.4	Less	Less

Table 2 Marketed Products

Product	Manufacturer/Supplier	Reference
Salagen Tablets [Pilocarpine)	MGI Pharma	[19]
Evosac Capsules[Cevimeline]	Daiichi Pharma	[19]
Optimist Spray	Colgate-Palmolive	[19]
Saliva Substitute	Roxane Labs	[19]
Oral Balance Gel	Laclede Pharma	[19]