

Nanoparticles for Oral Transmucosal Drug Delivery –A Review

Deepti Anna John

*Graduate Student, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences,
Chennai, Tamil Nadu.*

Anitha Roy

Professor, Department of Pharmacology

*Saveetha Dental College and Hospitals, Saveetha, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil
Nadu'*

Jaiganesh Ramamurthy

*Reader, Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and
Technical Sciences, Chennai, Tamil Nadu.*

Abstract:

The oral mucosal drug delivery is now being opted for the treatment of systemic diseases as it has many advantages compared to the other routes of administration such as increased bioavailability providing the drug rapidly into the circulation and also avoiding first pass metabolism. Drugs such as Oral Nystatin, Chlorohexidine, Curcumin etc are administered using this delivery mechanism. Toothpastes and mouth rinses have been sought as treatment to systemic ailments by infusing nanoparticles with chemotherapeutic agents attached to them that target specific cells. The objective is to understand whether this method of drug delivery of nanoparticles could benefit patients that are using drugs with poor solubility and poor absorption in the gut. The oral vestibule and gingiva are considered as the promising sites of immunotherapy as it has minimal mast cells and increased inhibitory cytokines therefore using nanoparticles in toothpastes and mouth rinses can be a beneficial method of modern drug delivery preventing even drug induced side effects.

Key words: drug delivery, nanoparticles, oral mucosa, pharmaceuticals.

INTRODUCTION:

Oral drug delivery systems are mostly used due to the many advantages it possesses over the other routes of administration such as being convenient and pocket friendly. These delivery systems are usually limited due to the degradation effect of the gastrointestinal tract because of their varying molecular weights of the drugs administered leads to low bioavailability but show most patient acceptance. Different strategies for better therapy are being studied such as delivery through the transmucosal routes such as the oral, nasal, ocular, rectal and vaginal mucosa which could provide as an alternative route for biopharmaceuticals [1]. The drug delivery via oral mucosa is accepted because the mucosa is highly vascularized and permeable so the drugs enter the systemic circulation immediately; skipping first pass metabolism, thus ensures rapid onset of the drug [2]. The oral mucosa also recovers in a short period after acted upon by stress or damage and is free of Langerhan cells that makes it tolerant to potential allergens. The different sites for drug delivery in the oral mucosa include buccal, sublingual, gingival, palatal and labial mucosa. So this system is more convenient drug delivery route compared to intravenous systems [3]. Not all the particles used for medical purposes are of the specific size accepted i.e. $\leq 100\text{nm}$ (The Royal Society and Royal Academy of Engineering 2004) such as drugs with complex structures, unstable hydrophilic proteins, polysaccharides etc, but that does not have to make an impact on their function in medical applications. This is where Nanotechnology

comes into play which is 'the engineering of functional systems at the molecular scale'; the application of this science to oral drug delivery could lead to precise delivery for bioactivity. Nanoparticles (NP) have unique features such as the ability to absorb and carry other compounds "carrier" and their surface to mass ratio that is larger than most particles. These NP's are engineered using components of biological origin such as phospholipids, dextran, lipids, lactic acid, and chitosan or made up of chemical like polymers such as carbon, silica and metals [4]. Biodegradable nanoparticles are used to improve the therapeutic values of both soluble and insoluble medicinal drugs by improving the bioavailability, solubility and retention time [5]. Nanoencapsulation of medicinal drugs increases efficacy, tolerability, specificity and therapeutic index and protect the drugs from premature degradation and interaction with the biological environment and enhanced absorption into the targeted tissue with reduced chances of side effects [6]. In the recent few decades, a number of nanoparticles-based therapeutic and diagnostic agents have been developed for the treatment of cancer, diabetes, candidiasis, asthma, allergy and more, as a result nanoparticles based therapeutic products have been introduced into the market with numerous ensuing products currently under in vivo and in vitro testing [7]. With the addition to this development, studies are being done to use these nanoparticles as additives to toothpastes and other oral products, which could be a promising means of drug delivery.

Structure of the Oral mucosa:

The mucous membrane of the oral cavity is different from the gastro intestinal system with which it is continuous. The mucous membrane consists of two layers: the epithelium and connective tissue known as the lamina propria. The soft tissues of the human oral cavity are covered by stratifying squamous epithelium. The oral mucosa is classified into three types that are masticatory, lining and specialized. The gingiva and the hard palate are covered by the masticatory mucosa which is bound down tightly by the lamina propria to the bone; the mucosa is keratinized due to formation of bolus during mastication. The lining mucosa is flexible and not keratinized to ensure mobility seen in the floor of the mouth, buccal region and esophagus; the specialized mucosa covers the dorsal surface of the tongue consisting of a mixture of keratinized and non keratinized mucosa with taste buds and papillae [8]. The masticatory mucosa is approximately 25%, the lining mucosa is 60% and the specialized mucosa is 15% of the total mucosal surface area [9].

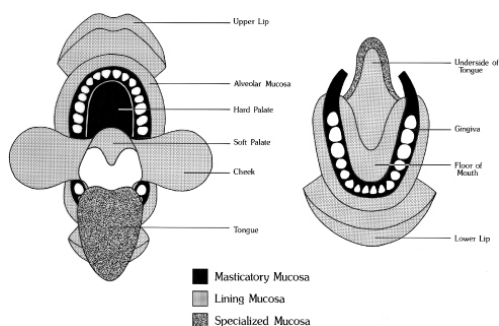


Figure1 showing the different sites of the various types of oral mucosa.

The epithelium of the oral mucosa is composed of several layers. The keratinized epithelium is made up of the keratinized layer, granular layer, prickle-cell layer and the basal layer. The non keratinized epithelium is composed of the superficial layer, intermediate layer, prickle-cell layer and the basal layer.

The mucosal lamina propria consists of cells, blood vessels, neural elements and fibers embedded in an amorphous ground substance [10].

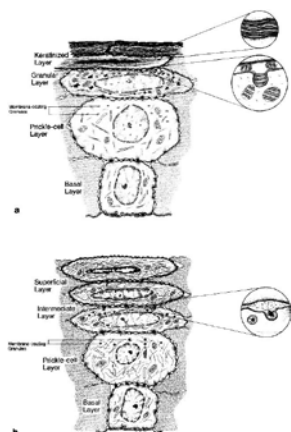


Figure 2- showing the Different layers of the epithelium (a)Keratinized epithelium (b)Non keratinized Epithelium

Factors that cause challenges in Oral transmucosal drug delivery:

The oral cavity has an environment that poses some challenges for drug delivery, the drug has to travel from the site of delivery to the target site and has to pass through the layers of mucosa. Certain aspects of the oral cavity play an important role in the process such as pH, fluid volume,enzyme activity and permeability of the mucosa. All of this is shaped by the secretion of saliva. Saliva is secreted by the parotid,sublingual and submandibular glands which is used for the lubrication of the oral cavity, helps in swallowing and prevents demineralization of the teeth also helps in the regulating the oral microbial flora by maintaining the oral pH and enzyme activity[11,12]. The saliva provides a rich environment for the oral cavity which can be useful for drug release from delivery systems especially those with hydrophillic polymers.Also the saliva flow dictates the time span of the released drug at the delivery site which could lead to a “saliva wash out” the premature swallowing of the drug before effective absorption [13]. Drug permeability is also another major barrier for oral transmucosal drug delivery because the oral mucosa is of varied thickness in different regions.The keratinized epithelium contains ceramides and acylceramides which have a sort of barrier like function [14]. The relative impermeability of the oral mucosa could be due to Membrane coating granules(MCGs).The cells of the epithelia are surrounded by a ground substance called mucus,most of it is made up of water and macromolecular components called mucin..These mucin form a three dimensional network and help in cell-cell adhesion.This layer plays a role in mucoadhesion for drug systems and hence extend the dosage form at the delivery site [15]

Characteristics of the Nanoparticles:

The advantage of nanoparticles is it’s modifiable size,its large enough to prevent leakage into the blood capillaries but small enough to escape capture by macrophages in the reticuloendothelial system.The size of the nanoparticle will be around 100 nm to reach targetted tissues by passing through vascular structures. The surface characteristics play an important part determining the life span and duration in circulation.Ideally they should have a hydrophillic surface to prevent macrophage capture.This is achieved by coating the surface of the nanoparticles with a hydrophillic polymer or forming them from block copolymers with hydrophillic and hydrophobic domains [16,17].

Nanomedicine formulations depends on the choice of suitable polymeric systems having maximum encapsulation,bioavailibilty and retention time.Biodegradable polymeric nanoparticles are preferred since they provide sustained release,subcellular size and biocompatibilty [18].The drug molecules either bound to surface as nanosphere or encapsulated inside as nanocapsules.The nanocapsules consists of vehicular systems with a polymeric shell and inner core.The nanospheres consist of a polymeric matrix [19,20].

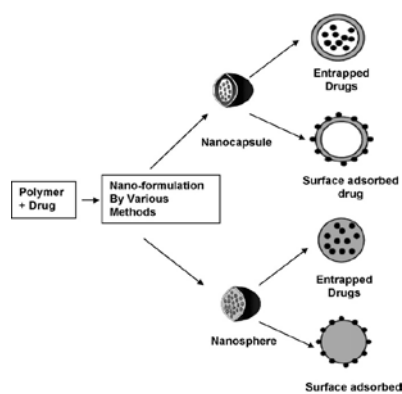


Figure - 3 showing The nanoparticle classification according to structural organization.

PLGA (poly-D,L-lactide-co-glycolide) is the most successful biodegradable system since it undergoes hydrolysis in the body to produce a biodegradable metabolite monomer, lactic acid and glycolic acid, therefore showing least systemic toxicity. These nanoparticles are prepared by emulsification-diffusion, solvent emulsion-evaporation, interfacial deposition and nanoprecipitation method.

These particles are used to develop the proteins and peptides nanomedicines, nano-vaccines, nanoparticles based gene delivery system, nano antigen and growth factors[5].

Mechanism of action:

The drug transport mechanism involves two main types of pathways: (1) Transcellular and (2) paracellular pathways. Transcellular transport is done by transcytosis: a process by which particles are taken up by the cell. It starts with endocytosis that happens at the cell apical membrane, then the particles move through the cells and released at the basolateral pole[21]. Paracellular is a major pathway, across the stratified epithelium via intercellular spaces. It is a passive process as a result of diffusion under the control of tight junctions which acts as a rate limiting barrier for permeation of ions and large substances [22]. It is studied that the lipid matrix of the extracellular space plays an important role in the barrier function of the paracellular pathway with particles that are hydrophilic and have a high molecular weight [23]. Two other types of transport are the Carrier-mediated transport and Receptor-mediated transport.

In carrier-mediated transport the drugs are transferred across the cell membrane and released through the basal surface into circulation and this process is utilized by small hydrophilic molecules. Active absorption requires the uptake of the drug molecules by the carriers, they recognize target molecules through membrane receptors and transport them even against the concentration gradient [21]. The lipid solubility and the molecular weight of the diffusant influence the absorption potential of the oral mucosa. The absorption increases when the carrier pH of the nanoparticle is lowered [24].

In receptor-mediated transport, the drugs act as receptor specific ligand for surface attached receptors or as a

receptor for surface attached ligands[25]. This method is used to increase the oral bioavailability of protein drugs. Portal blood represents the major pathway for the orally administered drugs with the hydrophilic ligands carried to the liver via the portal vein and the lipophilic ligands cross the epithelial barrier to the interstitial lymphatics which deliver the drug to vena cava skipping the hepatic first pass metabolism [26,27].

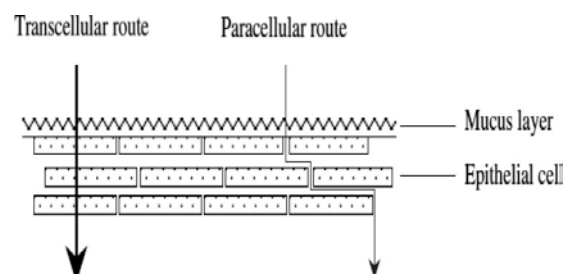


Figure 4 showing the representation of penetration routes

Applications of nanoparticles through oral transmucosal delivery systems:

The nanoparticles have shown it has many benefits in drug delivery, so its applications in oral transmucosal routes are slowly being introduced into the markets. It's been used for cytotoxic drugs, muscle relaxants, antihypertensives, analgesics, steroids, vitamins, sedative and hypnotics, antibiotics, chemotherapeutic agents and prostaglandins, most of them were studied in vitro than in vivo [28].

Some of the drugs using this mechanism are explained below:

Oral Nystatin:

Oral candidiasis is a prevalent fungal infection of the oral cavity caused by *Candida albicans*. It poses a chronic systemic threat to patients with diabetes mellitus and immunocompromised. Nystatin was usually given as an antifungal drug to treat candidiasis by producing pores in the fungal cell membrane that increases the cell permeability that leads to the lysis of the fungal cell. Oral nystatin has poor absorption in the gut, so it's being investigated to be delivered through the buccal mucosa for better bioavailability by encapsulating the Nystatin with alginate microspheres, chitosan and hydrogels [29]. Studies have demonstrated that the Nystatin nanoparticles were not seen in the systemic circulation and the quantity of the drug seen in the mucosa was enough to ensure fungicidal effects against candidiasis without causing tissue necrosis[30].

Chlorhexidine:

Chlorhexidine is a topical antimicrobial agent by binding the cationic molecule to the negatively charged bacterial cell wall causing a bactericidal effect, it is used in the prevention of ventilator-associated pneumonia, oral candidiasis and microbial lichenoid infections. Chlorhexidine loaded into chitosan proved increased antimicrobial activity. Tests conducted on the saliva containing Chlorhexidine demonstrated this fact [31] and also its delivery through oral transmucosal drug system shows increased local dosage[32].

Curcumin:

Curcumin is a component of turmeric which has many benefits such as anti inflammatory, hypoglycemic, antioxidant, antimicrobial activities and many more. But its application clinically has been limited due to poor solubility, rapid hydrolysis, rapid metabolism and systemic elimination. Therefore curcumin nanoparticles delivered through the mucosal route increases its therapeuticality and bioavailability [33], Curcumin solid lipid nanoparticles are used to treat oral mucosal infections and it was evaluated that curcumin shows high efficacy and stability enhancement [34].

Fluoxetine:

Fluoxetine is an anti depressant drug used to treat various psychological disorders such as Obsessive compulsive disorder, bulimia nervosa etc. The drug is encapsulated into poly methyl vinyl ether nanoparticles. The delivery of Fluoxetine through oral transmucosal route indicated better drug efficacy, extended release of the drug, increase bioavailability and reduced side effects [35].

Metronidazole:

Metronidazole is an antibiotic and anti protozoal drug. Studies are being conducted to enclose this drug with pectins or Chitin to form better delivery systems than conventional systems, to increase efficacy and outcomes [36].

Addition of such drugs in oral products such as toothpastes, oral rinses and mouth gargles are also being studied in the laboratories [37, 38].

CONCLUSION:

Nanoparticles have made a significant impact in the field of medicine as nanoparticles in oral transmucosal drug delivery systems are proving to be a great strategy for the delivery of various drugs that have poor bioavailability. They provide more advantages than the other routes. These drug delivery reduce the drug dosage frequency, reduced toxicity and will be more patient friendly without many side effects. These particles will provide precise treatment by having targeted delivery and controlled release. With further research and development, these tiny particles will create massive impact on medicine in the following years to come.

REFERENCES:

- Sevda Senel, Merve Cansiz, Michael J. Rathbone. Text Book of Buccal delivery of Biopharmaceuticals: Vaccines and Allergens. Mucosal Delivery of Biopharmaceuticals. Springer, Boston, MA. 2014:149-168.
- Hao Zhang, James Zhang, James B. Streisand. Oral Mucosal drug delivery: Clinical Pharmacokinetics and Therapeutic Applications. Clinical Pharmacokinetics. Aug 2002; 41, 9:661-680.
- Nookala Venkata Sathesh Madhav, Ravindra Semwal, Deepak Kumar, Semwal, Ruchi B Semwal-Recent trends in oral transmucosal drug delivery systems: emphasis on the soft palatal route. Expert Opinion on Drug delivery. Apr 2012; 9(6):629-647.
- Wim H De Jong, Paul JA Borm-Drug delivery and nanoparticles: Application and hazards. International Journal of Nanomedicine. 2008; 3(2): 133-149.
- Avnesh Kumari, Sudesh Kumar Yadav, Subhash C. Yadav-Biodegradable polymeric nanoparticles based drug delivery systems. Colloids and Surfaces B: Biointerfaces. 2011; 75:1-18.
- F. Alexis, et al. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol. Pharm. 2008; 5(4):505-515.
- L. Zhang, F. X. Gu, J. M. Chan, A. Z. Wang, R. S. Langer, O. C. Farokhzad-Nanoparticles in Medicine: Therapeutic Applications and Developments. Clinical Pharmacology & Therapeutics. May 2008; 83(5):761-769
- CA Squier, MW Hill. Oral Mucosa. In: Ten Cate AR, editor. Oral histology: development, structure and function. St. Louis (MO): CV Mosby; 1989:341-381.
- Roed-Peterson B, Renstrup G. A Topographical classification of the oral mucosa suitable for electronic data processing. Its application to 560 leukoplakias. Acta Odontol Scand 1969; 27:681-695.
- CA Squier, Mary J Kremer. Biology of oral mucosa and esophagus. Journal of the National Cancer Institute Monographs. 2001; 29: 7-15.
- J.L Herrera, M.F Lyons, L.F. Johnson. Saliva: its role in health and disease. J. Clin. Gastroenterol. 1988; 10:569-578.
- B.L. Slomiany, V.L. Murty, J. Piotrowski, A. Slomiany. Salivary mucins in oral mucosal degeneration. Gen. Pharm. 1996; 27:761-771.
- V.F Patel, Fang Liu, Marc B. Brown. Advances in oral transmucosal drug delivery. Journal of Controlled release. 30 July 2011; 153(2):106-116.
- C.A. Squier, P.W. Wertz. Structure and function of the oral mucosa and implications for drug delivery. Oral Mucosal Drug Delivery. 1996; 74, Marcel Dekker, Inc. New York: 1-26.
- R.B. Gandhi, J.R. Robinson. Oral cavity as a site for bio adhesive drug delivery. Adv. Drug delivery. 1994; 13:43-74.
- Kwangjae Cho, Xu Wang, Shuming Nie, Zhuo Chen, Dong M. Shin- Therapeutic Nanoparticles for drug delivery in Cancer. Clin Cancer Res 2008; 14(5):1310-1316.
- Moghimi SM, Szebeni J-Stealth liposomes and long circulating nanoparticles: critical issues in pharmacokinetics, opsonization and protein binding properties. Prog Lipid Res 2003; 42:463-378
- J. Panyam, V. Labhasetwar. Biodegradable nanoparticles for drug and gene delivery to cells and tissues. Adv. Drug Deliv. Rev. 2003; 55(3):329-347
- L. Brannon-Peppas-Recent advances on the use of biodegradable microparticles and nanoparticles in controlled drug delivery. Int. J. Pharm. 1995; 116:1-9.
- W. Tiyaboonachi. Chitosan nanoparticles promising system for drug delivery. Naresuan University J. 2003; 11:193-209.
- Yeonhee Yun, Yong Woo Cho, Kinam Park-Nanoparticles for oral delivery: Targeted nanoparticles with peptidic ligands for oral protein delivery. Adv Drug Deliv. Rev 2013; 15; 65(6):822-832
- Madara JL-Regulation of movement of solutes across tight junctions. Annu Rev Physiol. 1998; 60:143-159
- Rathbone MJ, Tucker IG. Mechanisms, barriers and pathways of oral mucosal drug permeation. Adv. Drug Del. Rev. 1993; 13:1-22
- Nielsen HM, Rassing MR. TR146 cells grown on filters as a model of human buccal epithelium. Permeability enhancement by different pH value, different osmolality value and bile salts. Int. J. Pharm. 1999; 185:215-225.
- Russell-Jones GJ-The potential use of receptor-mediated endocytosis for oral drug delivery. Adv Drug Deliv Rev. 1996; 20:83-97.
- Charman WN, Porter CJH-Lipophilic prodrugs designed for intestinal lymphatic transport. Adv Drug Deliv. Rev 1996; 19:149-169
- P Chinna Reddy, K.S.C Chaitanya, Y. Madhusudan Rao-A review on bioadhesive buccal drug delivery systems: current status formulation and evaluation methods. Daru. 2011; 19(6):385-403.
- Max Donbrow-Part 1. Advances in production technology and characterization of microcapsules, microspheres and nanoparticles. Microcapsules and Nanoparticles in Medicine and Pharmacy. 1991
- Martin MJ, Calpena AC, Fernandez F, Mallandrich M, Galvez P, Clares B-Development of alginate microspheres as Nystatin carriers for oral mucosa drug delivery. Carbohydr Poly. 2015 Mar 6; 117:140-9.
- Maria J. Martin, Ana C. Calpena, Francisco Fernandez, Mireia Mallandrich, Patricia Gálvez, Beatriz Clares-Development of alginate microspheres as nystatin carriers for oral mucosa drug delivery. Carbohydrate Polymers. March. 2015; 117:140-149.
- Bruno Sarmenro, Jose Das Neves. Text book of Chitosan-based systems for biopharmaceuticals: Delivery, Targeting and Polymer Therapeutics. Wiley & sons; 10.1002/9781119962977.

32. S Garner, ME Barbour-Nanoparticles for controlled delivery and sustained release of chlorhexidine in the oral environment. *Oral Diseases*.2015;21(5):641-644.
33. Leticia Mazzarino,Christophe Travelet,Sonia Ortega-Murillo,Issei Otsuka,Isabelle Pignot-Paintrand,Elenara Lemos-Senna,Redouane-Elaboration of Chitosan-coated nanoparticles loaded with curcumin for mucoadhesive applications.*Journal of Colloid and Interface Science*. 2012;370:58-66.
34. Heba A Hazzah,Ragwa M Farid,Maha MA Nasra,Walaa A Hazzah,Magda A.El-Massik,Ossama Y Abdallah-Gelucire-Based Nanoparticles for Curcumin targeting to oral mucosa preparation, characterization and antimicrobial activity assessment.2015;104,11:3913-24.
35. Abhay S.Sapre,Rajesh K.Parikh-Design of buccal mucoadhesive ,nanoparticles based delivery system of fluoxetine- JPSBR.2012;2(3):148-161.
36. Toril Andersen,Zeljka Vanic,Natasa Skalko-Basnet-Pectosomes and Chitosomes for the delivery of Metronidazole:The one pot preparation method. *Pharmaceutics* 5.3 (2013): 445–456.
37. Doron Steinberg, Michael Friedman-Dental drug delivery devices: Local and sustained release application. *Critical RevTherDrugCarrier*.1999;16 (5):5-10.
38. Arvind Venkatesh, Jaiganesh Ramamurthy. Local drug delivery systems in the treatment of periodontitis-An Overview. *Int J Pharm Pharm Sci*. 2012;1,1:30-37.