International Journal of Research in Pharmacy and Pharmaceutical Sciences
www.pharmacyjournal.in
ISSN: 2455-698X
Received: 03-08-2024, Accepted: 02-09-2024, Published: 17-09-2024
Volume 9, Issue 3, 2024, Page No. 74-80

Nanotechnology-based mucoadhesive drug delivery systems: A comprehensive review

Ranjita Ramesh Shetty[1], Vikram T[2*], Gururaj S Kulkarni[1], Padmaa M Paarakh[3], Muthukumar A[4]
[1] Department of Pharmaceutics, The Oxford College of Pharmacy, Hongsandra, Bangalore, Karnataka, India
[2] Assistant Professor, Department of Pharmaceutics, The Oxfod College of Pharmacy, Hongsandra, Bangalore, Karnataka, India
[3] Department of Pharmacognosy, The Oxford College of Pharmacy, Hongsandra, Bangalore, Karnataka, India
[4] Department of Pharmacology, The Oxford College of Pharmacy, Hongsandra, Bangalore, Karnataka, India

Abstract
Nanotechnology has the potential to revolutionise medicines through novel nanodevices. Nanotechnology is the study of matter at sizes ranging from 1 to 100 nm. Mucoadhesives could improve medication delivery systems. Mucoadhesive polymers could potentially be used to bypass physiological barriers in long term drug delivery. Nanoparticles are frequently employed due to their high drug loading capacity, potent stability, controlled release properties and surface modification for coating and ligand. Mucoadhesive tablets, pellets, films, sponges, suppositories, beads, wafers and hydrogels are some of the dosage forms that can improve mucoadhesion. The formulation base will be choosen based on the anticipated product profile, mode of administration, active pharmaceutical ingredient and the indication being treated. The current review article provides an in-depth discussion of several nanotechnology incorporated drug delivery techniques for improving mucoadhesive dosage forms that may be intended for buccal, sublingual, vaginal, rectal, nasal or gastrointestinal administration.

Keywords: Nanoparticles, mucoadhesives, controlled release, dosage forms, drug loading capacity, drug delivery systems

Introduction
Recently significant emphasis is being paid to localised drug targeting for improved control over systemic drug delivery that involves concentrating a medicine or drug delivery system in a particular part of the body over an extended period of time. Mucoadhesive were initially employed in controlled administration of drugs in the early 1980s. The development of mucoadhesives has sparkled the interest of many scientists towards the possibility of using these polymers to bypass physiological challenges in long term drug delivery. They render the therapy more efficient as well as secure for topical and sytemic conditions [1].
Bioadhesion is defined as any link established between two biological surfaces or a biological and synthetic surface. Bioadhesion denotes to the binding of polymers either natural or synthetic in the field of bioadhesive drug delivery. When a mucus based connection is formed, the words mucoadhesion and biological adhesion may be used simultaneously mucoadhesion occurs when two components, one of the two being in biological in origin remained together for extended periods of time by mucus; with the aid of interfacial forces [2].
Mucoadhesive dosage forms might be intended for buccal, sublingual, vaginal, rectal, nasal or gastrointestinal delivery. Mucoadhesive tablets, pellets, films, sponges, suppositories, beads, wafers, hydrogels are some of the dosage forms that can enhance mucoadhesive properties. The formulation base will be determined depending on the intended product profile, the method of administration, the active pharmaceutical ingredient and the indication being treated.
At times an entirely novel name emerges to describe a developing scientific paradigm. Genetic engineering, biotechnology, combinatorial chemistry these are some of the past terms examples. Nanotechnology is a term frequently used to describe modern scientific and technological initiatives. Nanotechnology often known as nanoscience refers to study at scales of 100nm or less, as it is still developing field.Nanotechnology like other technological advances has the ability to revolutionise therapies and diagnostics through innovative nanodevices [3].
Nanotechnology has become a growing field due to the expanded assistance provided by scientists in the academia business and federal sectors. The National Nanotechnology Initiative describes nanotechnology as the study and modification of matter at a scale of 1 to 100 nm, allowing for innovative applications [4].
The pharmaceutical industry attempts to produce therapeutic compounds that may be given selectively to specific parts of the body, improving their therapeutic effectiveness [5].
The current review article gives a comprehensive review of various nanotechnology incorporated drug delivery systems for improving bioavailability and enhancing therapeutic effect.

Mucus Layer
Mucus ia a highly visco elastic fluid that covers the gastrointestinal, lung, oral, nasal and genital tract epithelial surfaces. Mucus functions as a barrier for bacteria and for dangerous substances, protects the mucosal membranes from dehydration, and mechanical stress.despite the nature and function of the mucus can vary depending on the part of the body.Mucus is composed primarily of water (up to 95%), lipids, small protein molecules and nucleic acids. Although high molecular weight glycoproteins known as mucins (MW from 0.5 KDa to 200 MDa) provide mucus its mechanical and viscoelastic properties [6].
The large macromolecules reffered as mucin posses a complicated extremely segregated structure that consists of polypeptide sections that have either little or no glycosylation distributed in between extremely glycosylated areas. Mucins posses molecular weights that can vary from 200 kD to 20–40 Mda [7].
In biological systems mucin performs variety of functions the majority of which are linked to the movement, security, and protection of internal body surfaces [8].

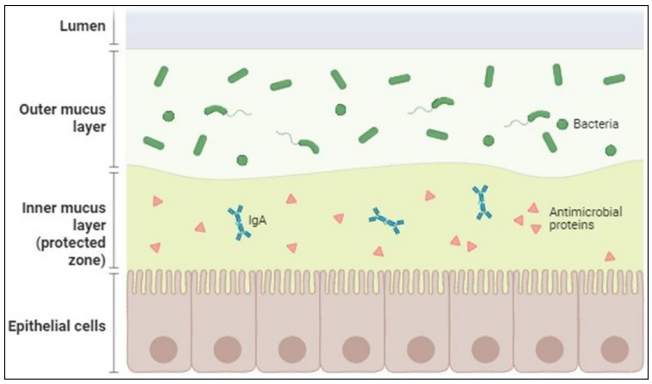

Fig 1: Structure of mucosa

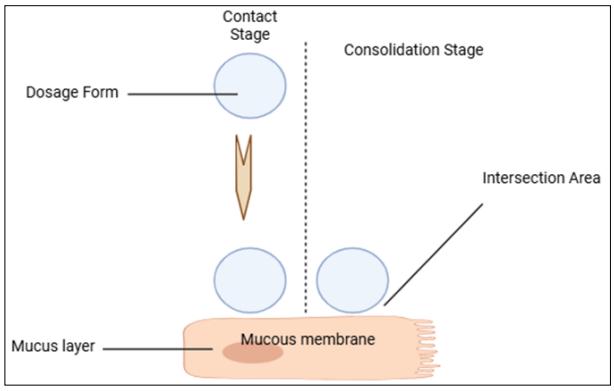

Fig 2: Mechanism of mucoadhesion

Mechanism of mucoadhesion

Mucoadhesion is the method through that a medication and a suitable carrier adhere to the mucosal membrane [9].

There are typically two phases in the mucoadhesion mechanism: the contact stage and the consolidation stage. The formulation spreads and swells during the first stage, that is determined by the interaction between the mucoadhesive and the mucus membrane that makes the beginning of the formulation's deep contact with the mucus layer. This interaction develops between the mucoadhesive and the mucus membrane. Several delivery systems have a mechanical connections over the membrane as in the case of vaginal or ocular formualtions. At other times, such as the nasal route, the aerodynamics of the organ to which the system is deposited promote the delivery.

The presence of moisture stimulates the mucoadhesive materials during the consolidation process. Weak hydrogen and vanderwaals bonds enable the mucoadhesive molecules to bind together when moisture plasticizes the system. Diffusion theory and dehydration theory are two hypothesis that explain the consolidation process [10].

Mucoadhesive polymers

Mucoadhesive delivery techniques are being investigated for the purpose of localizing the active drug to a specific site or locations.in order to prolong the active ingredient's residence period at the intended area, polymers have been a key component of such systems [11].

Mucoadhesive polymers are swellable networks of water soluble or water insoluble polymer bound together by cross linking agents. These polymers are optimally polar to ensure that the mucus is adequately wetted and they are ideally fluid to allow for the mutual adsorption and interpenetration of the mucus and the polymer [12].

Factors affecting Mucoadhesion

Mucoadhesion may be influenced by several factors.

1. Polymer related factors incudes Molecular weight, concentration of active polymer, Flexibility of polymer chains, Swelling, Hydrophilicity.
2. Environment related factors includes pH of Polymer – substrate interface, applied strength.
3. Physiological factors includes Mucin turnover, Disease state.

Table 1: Routes of administration for mucoadhesive based drug delivery systems

Routes of drug administration	Relevant anatomical features	Ref No
Oral	▪ The oral mucosal surface is about 200 cm^2. ▪ The oral mucosa is extensively vascularized. ▪ It is composed of closely compacted epithelial cells, that constitute the upper part to third of the epithelium. ▪ Efficient mucosal delivery requires the elimination of both hydrophylic and hydrophobic barriers.	[13].
Nasal	▪ Total volume of is around 16 to 19 ml. ▪ Total surface area of about 180cm^2. ▪ The nasal cavity is devided into two by the septum, ▪ Each cavity's surface area is around 75 cm^2. ▪ Volume of about 7.5ml. ▪ Epithelial cells of the nasal vestibule consist of stratified, sqamous and keratinized and sebacious glands. ▪ Approximately 1.5-2 litres of mucus is produced every day, ▪ Nasal mucus serves a variety of physiological functions.	[14], [15].
Ocular	▪ Conjuctiva makes up the ocular surface. ▪ It contains numerous glands that secrete fluids that are necessary to keep ocular surface in optimal condition. ▪ The tear film is consist of three layers each about 7mm thick. ▪ It has lipid rich outer layer, that is approximately 0.1mm thick that helps to keep the water content from evaporating.	[16].
Vaginal	▪ Although in the absence of globlet cells and mucin's direct release, the vaginal epithelium is usually considered as a mucosal surface. ▪ The amount of glycogen in epithelial cells, glucose, pH and harmone levels are some of the variables that affect the vaginal ecology.	[17].
Rectal	▪ In adults, the rectum measures around 15-20cm in length and 200-400cm in surface area. ▪ The rectum has neutral pH of 7-8. Average fluid volume of 1-3 milimetres. ▪ Compared to small intestine, the rectum has relatively smaller surface area for absorption, because it doesn't contain villi, microvilli on the luminal surface.	[18].

Nanoparticles

Over the past three decades, the development of nanotechnology has led to numerous advances in the medical sciences, especially in the area of medication delivery. The significance of modern nanotechnology is its capacity to truly contribute to the achievement of site specific, temporal and spatial delievry. The pharmaceutical sector will be severely influenced by the market for nanotechnology and medication delivery system based on it [19].

It is becoming progressively common for readily available items to contain nanoparticles [20].subnanosized colloidal structures, known as nanoparticles, are made of synthetic or semi-synthetic polymers with sizes varying from 10-1000nm [21]. Mesostructures known as nanopaerticles posses certain special characteristics that distinguish them apart from bulk materials and atomic or molecular structures, respectively [22]. In addition, drug that were considered to susceptible to extracellular degradation, such as the enzymatic breakdown of the nucleic acid, or too difficult to penetrate their intracellular target, could possibly be delivered via nanoparticles[23].

Classification of nanoparticles

In general, there are three types of nanoparticles: organic, inorganic and carbon based.

Mucoadhesive dosage forms

Mucoadhesive tablet

Mucoadhesive tablets are tiny, flat and oval dosage forms meant to attach to the mucosal surface, enabling for prolonging the retention at the site of administration and enhanced therapeutic effect.

Mucoadhesive tablets are appropriate to used for controlled release drug delivery. In general, but coupling their mucoadhesive characteristics to tablets has extra benefits such as enhanced absorption and increased bioavailability of drugs because of the high surface to volume ratio that allows for much more contact with the mucus layer. Mucoadhesive tablets can be designed to adhere to any mucosal tissue, including those found in the stomach providing both localised and systemic drug release [24].

Nanoparticles incorporated mucoadhesive tablet shows enhanced drug residence time, and produces targeted and sustained drug delivery.A group of scientist with Denise Murgia *et al*. 2019 [25], developed Bioadhesive matrix tablet containing lipophilic nanoparticles of metronidazole and curcumin for peridontitis treatment. Bacterial infections are one of the most prevelant dissorder that can damage the oral mucosa. Conventional dosage forms may be ineffective due to rapid dissolution and disintegration upon administration. Curcumin possess a significant capacity to penetrate and accumulate in lipophilic membranes. In comparision, metronidazole indicates acceptable solubility in aqueous fluids and because of its partition coefficients it gets distributed in both aqueous and lipophilic domains. The results of this study significantly support the use of this novel matrix tablet to deliver metronidazole and curcumin for the topical treatment of peridontal disease [25].

Pramod Yedurkar et.al 2011 formulated a multiple unit system of mucoadhesive bilayer buccal tablet containing chitosan microspheres containing carvedilol to increase carvedilol bioavailability and therapeutic effectiveness. While overcoming the limitations of traditional therapy the multiple unit system improved carvedilol bioavailabity and prolonged release indicating it has more therapeutic potential for hypertention treatment [26].

Mucoadhesive sponge

Solid dosage forms are frequently used when expanded interaction between medication and mucosa and sustained drug release are desired. The sponges are solid structures producing by diffusing a gas (often air) into a solid matrix. Sponges delivery methods are recently getting a lot of attention when it involves buccal delivery system.

Sponges offer several advantages including an efficient production procedure that relies mostly on freeze drying to take away all included water, resulting in soft stiff structure that has sufficient flexibility. Sponges were developed by freezing the composite hydrogels[27].

It is estimated that there are around 5,00,000 incidences of oral and oropharyngeal cancers worldwide. It includes treatment options as surgery, radiation and chemotherapy either alone or in combination. Aditionally laser ablation, surgery and medication therapy are available for oropharyngeal treatment. However none of them has shown therapeutic effectiveness. An innovative tetrahydrocurcumin incorporated mucoadhesive nanocomposite K/Carrageenan /Xanthum gum sponges has been formulated by Shimaa A. Elbanna et.al 2003 for localised treatment of oral malignant and precancerous lessions. The Developed sponges displayed sustained drug release pattern, therefore which it will be helpful in treating early stages of oral cavity cancer and avoid malignant transformation [28].

Mucoadhesive films

Numerous bioadhesive mucosal dosage forms have been developed including adhesive tablets, gels and more recently films. However when it comes to flexibilty films surpass mucoadhesive tablets. They can also prevent oral gels from having a short residence time with the mucosa, which is easily washed and cleared by saliva. Films may additionally cover the wound area, reducing pain and increasing therapeutic efficiency [29].

Combining mucoadhesive films and nanoparticles could offer high drug dispersion, protection from degrading and control over the release within the system, making it a promising statergy for buccal drug administration. A group of scientists with Nusaiba K. Al-nemrawi *et al*. 2019 [30] formulated insulin chitosan- nanoparticles loaded buccal films.The most promising approach of delivering protein is through buccal administration. The formulation containing nanoparticles and film matrix controlled insulin release, making it stable. The produced films drastically reduced the level of blood glucose in diabetic rats [30].

Concetta Giovino et.al 2012 [31] and research group formulated a insulin loaded PEG-b-PLA nanoparticles embedded with mucoadhesive chitosan based films for buccal drug delivery. These macromolecules offer limited therapeutic benefits due to their instability, lower bioavailability, and shorter half lives. Many of these proteins require numerous injections for them to be therapeutically effective, posing issues with patient compliance. Designing colloidal systems like nanoparticle carriers and microspheres is an effective way to address these disadvantages [31].

Mucoadhesive suppositories

Mucoadhesive suppositories are a form of drug delivery system that adheres to the mucosal surface allowing for extended durability at the point of application along with controlled release for better therapeutic effects. They are frequently used for vaginal or rectal administration.

In general an ordinary suppository causes alienation, pain and even patient rejection, which could lead to patient non-compliance. Moreover the medication may experience the first pass effect, if the solid suppositories proceed to the end of the rectum. Issues with conventional suppository need the development of medication delivery devices capable of minimizing the patient complaints and avoiding hepatic first pass effect [32].

Naoparticles loaded suppositories when placed into the rectal cavity, the nanoparticle-loaded suppositories melt at physiological temperature and release the nanoparticles into the cavity. The mechanism involved can be stated in five steps;

1. Delivering suppositories to the rectal cavity.
2. Dissolution by the rectal fluids.
3. Nanoparticles introduction in fenestrated capillaries.
4. Drugs gets diffused by the nanoparticles.
5. Nanoparticles with mucoadhesive properties may adhere to the mucosa of the rectum for extended periods of time, delivering drugs in a controlled manner [33].

Gulay Buyukkoroglu *et al*. 2016 prepared a formulation of vaginal suppository containing Solid Lipid Nanoparticles (SLNs). There was a need of the paclitaxel formulation for localized and targeted drug delivery inorder to minimize the toxicity and adverse effects. Solid lipid Nanoparticles provide sustained and controlled release of the durgs, The developed dosage forms shows localized delivery of the therapeutic agents to the target site and minimizing systemic drug absorption, thereby reducing the toxicity [34].

Mucoadhesive beads

Mucoadheive beads are tiny, spherical drug delivery sytsems that attach to the mucosal surface, allowing for extended retention at the application site as well as controlled drug release for better therapeutic effects.

Mucoadhesive beads might increase intimate contact with the absorbent areas of the mucosal membrane (i.e mucoadhesion) thereby stomach retention may be prolonged inorder to disperse entrapped drugs in a controlled rate at the absorption site with the objective of providing the optimal therapeutic effect [35].

Gastric carcinoma is the 4th most diagnosed malignancy. Chemotherapy is vital for treating gastric cancer, however it may exhibit limited efficacy, as well as severe systemic adverse effects due to anti tumor medication's irritating properties, quick metabolism, and non selective dispersal. A group of scientists with Nana Chen *et al*. 2019 [36] formulated chitosan coated emodin Nanomicelles loaded mucoadhesive beads to improve the inhibition effect on tumor cells and to prolong the gastric retention time and enhanced the therapeutic effect [36].

Hydrogels

Hydrogels are cross linked polymers that have the ability to swell in water without dissolving. They can be either natural or synthetic in nature. Hydrogel's distinctive structure allows them to resemble biological tissues while maintaining mechanical integrity.When hydrogels are swollen, the flexibility property make them an effective drug delivery system [37].

A group of scientist with Ana Ortega et.al formulated a Lipid core nanocapsules coated with chitosan and filled with curcumin in a thermosensitive hydrogel in order to increase the mucoadhesion. Oral mucosal drug delivery has several limitations like rapid clearance, mucus renewal, limited surface area. The fomualted mucoadhesive hydrogel containing nanocapsules enhances mucoadhesion and act as a statergy to overcome this particular barrier [38].

Emilia Szymanska et.al a scientist created Mucoadhesive hydrogel based on silver nanoparticles and tannic acid improve loal treatrment of HSV infection. During recent years HSV infection prevelence has been increased and there is an increase in the antiviral resistance of the conventional drug. Nanoparticle based hydrogel directly inhibits viral attachment, penetration and post – infection spreading, and producing local treatment of HSV infection and *in vivo* data showed the act of the nanoparticles in preventing the HSV infection [39].

Wafers

Wafers are solid dosage forms with a highly porous structure formed by freeze drying gels or polymeric solutions. Their large surface area and porous structure allow for significant drug loading and water absorption. Wafers have been extensively researched as wound dressing because of their affordable cost of the production and ability to deliver exact doses of medication to the wound site. When applied, they absorb wound exudates and immediately produce a hydrophilic gel to cover and protect the wound bed. This gel moistens the wound, reduces cellular dryness, promotes collagen formation, and angiogenesis and reduces pain.Wafers porous structure allows gas exchange and reduces evaporation of water through wound exudates. Wafers have a longer residence time than semi- solid polymer gels due to their ability to maintain their inflated form over time.

Nanoparticles are biodegradable, biocompatible and non-toxic materials and that have been employed to develop prolonged release drug delivery systems, comprising nanoparticles, microcapsules, microspheres, pellets films and osmotic systems. That enhances therapeutic effect of the drug.

Wounds and physical damage may lead to delayed healing of the skin, increase the risk of inflamation, tissue loss and necrosis. Shabnam Amanat et.al developed cellulose based wafers comprised with resveratrol –loaded nanoparticles was proved to be more effective in promoting wound healing than resveratrol wafer and free water [40].

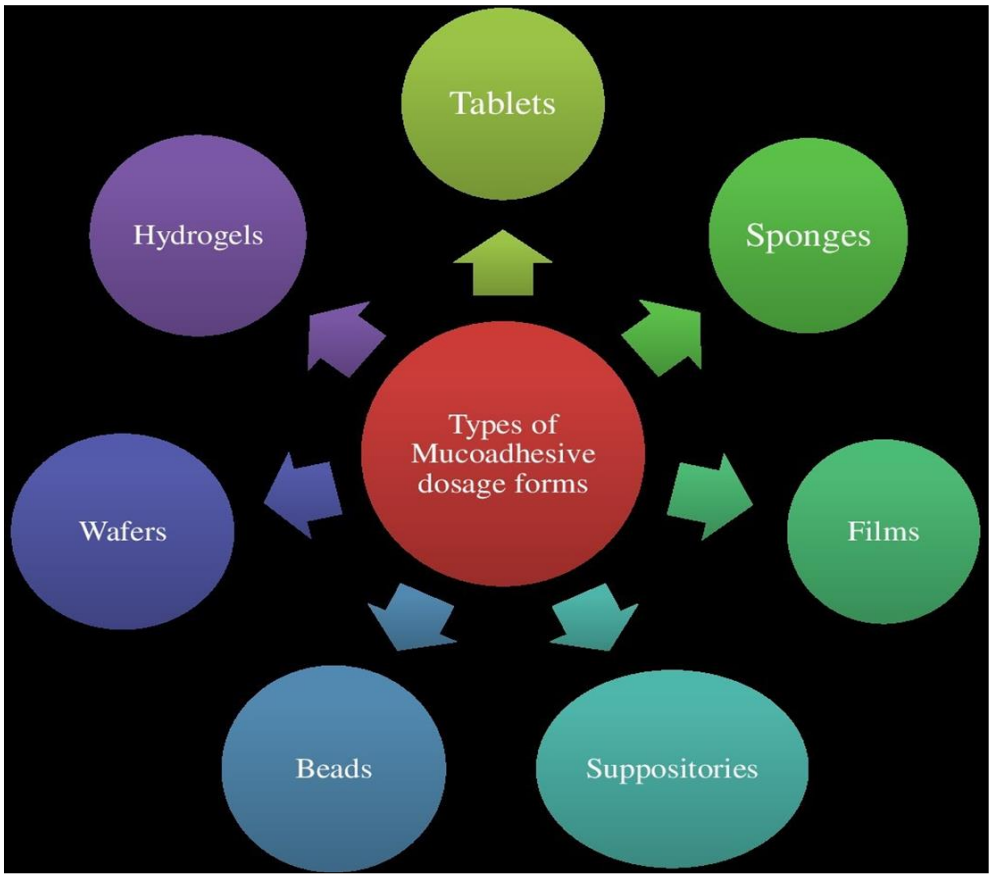

Fig 3: Various types of mucoadhesive dosage forms

Table 2: The effectiveness of combining nanoparticles with mucoadhesive dosage forms

Type of dosage form	Active Pharmaceutical ingredient	Type of Nanoparticles	Key findings	Reference
Tablet	Silymarin	Silymarin nanopartilces	▪ Enhanced permeability of the drug in a controlled way ▪ Improved drug bioavailability	[41]
	Carvedilol	Chitosan Microspheres	▪ Improved bioavailabvility	[26]
Sponges	Curcumin	Solid Lipid Nanoparticles	▪ Provided sustained release over 14-15 hrs. ▪ Study concentration od curcumin thus no need for several dosing.	[42]
Films	Propranolol HCL	Nanoparticles	▪ Improved permeability of propranolol loaded nanoparticles through the buccal mucosa.	[43]
Suppositories	Aspirin	Nanoparticles	▪ Disintegration time and melting point slightly decreased showed sustained release for a period of 24 hrs.	[33]
Beads	Emodin	Nanomicelles	▪ Prolong the gastric retention time and enhanced the therapeutic effect	[36]
Wafers	Resveratrol	Polymeric Nanoparticles	▪ Enhanced therapeutic effect	[40]
Hydrogels	Ibuprofen	Lipid Nanoparticles	▪ Showed sustained release of drug	[44]

References

1. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm,1997:23(5):489-515.
2. Tangri P, Madhav NS. Oral mucoadhesive drug delivery systems: a review. J Biomed Inst,2011:2229:7499.
3. Park K. Nanotechnology: What it can do for drug delivery. J Control Release,2007:120(1-2):1.
4. Koo OM, Rubinstein I, Onyuksel H. Role of nanotechnology in targeted drug delivery and imaging: a concise review. Nanomedicine,2005:1(3):193-212.
5. Kingsley JD, Dou H, Morehead J, Rabinow B, Gendelman HE, Destache CJ. Nanotechnology: a focus on nanoparticles as a drug delivery system. J Neuroimmune Pharmacol,2006:1:340-50.
6. Rondelli V, Di Cola E, Koutsioubas A, Alongi J, Ferruti P, Ranucci E, Brocca P. Mucin thin layers: A model for mucus-covered tissues. Int J Mol Sci,2019:20(15):3712.
7. Svensson O, Arnebrant T. Mucin layers and multilayers—physicochemical properties and applications. Curr Opin Colloid Interface Sci,2010:15(6):395-405.
8. Pettersson T, Dėdinaitė A. Normal and friction forces between mucin and mucin–chitosan layers in absence and presence of SDS. J Colloid Interface Sci,2008:324(1-2):246-56.
9. Khurana SH, Madhav NS, Tangri PR. Mucoadhesive drug delivery: mechanism and methods of evaluation. Int J Pharm Biosci,2011:2(1):458-67.

10. Carvalho FC, Bruschi ML, Evangelista RC, Gremião MP. Mucoadhesive drug delivery systems. Braz J Pharm Sci,2010:46:1-7.
11. Kavitha K, Kumar MR, Singh SJ. Novel mucoadhesive polymers—a review. J Appl Pharm Sci,2011:1(1):37-42.
12. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS, Rao YM. Polymers for mucoadhesive drug delivery system: a current status. Drug Dev Ind Pharm,2008:34(11):1246-66.
13. Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clin Pharmacokinet,2002:41:661-80.
14. Kushwaha SK, Keshari RK, Rai AK. Advances in nasal trans-mucosal drug delivery. J Appl Pharm Sci,2011:1(1):21-8.
15. Ugwoke MI, Agu RU, Verbeke N, Kinget R. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Adv Drug Deliv Rev,2005:57(11):1640-65.
16. Vermani K, Garg S. The scope and potential of vaginal drug delivery. Pharm Sci Technol Today,2000:3(10):359-64.
17. Hua S. Physiological and pharmaceutical considerations for rectal drug formulations. Front Pharmacol,2019:10:489933.
18. Morrison PW, Khutoryanskiy VV. Anatomy of the eye and the role of ocular mucosa in drug delivery. In: Mucoadhesive Materials and Drug Delivery Systems, 2014, 39-60.
19. Saraswathi B, Balaji A, Umashankar MS. Polymers in mucoadhesive drug delivery system—latest updates. Int J Pharm Pharm Sci,2013:5(3):423-30.
20. Pathak Y, Thassu D. Drug delivery nanoparticles formulation and characterization. Informa Healthcare USA, 2009, 1-30.
21. Lewinski N, Colvin V, Drezek R. Cytotoxicity of nanoparticles. Small,2008:4(1):26-49.
22. Sailaja AK, Amareshwar P, Chakravarty P. Formulation of solid lipid nanoparticles and their applications. J Curr Pharm Res,2011:1(2):197.
23. Thurn KT, Brown E, Wu A, Vogt S, Lai B, Maser J, *et al*. Nanoparticles for applications in cellular imaging. Nanoscale Res Lett,2007:2:430-41.
24. Rajput GC, Majmudar FD, Patel JK, Patel KN, Thakor RS, Patel BP, Rajgor NB. Stomach specific mucoadhesive tablets as controlled drug delivery system–A review work. Int J Pharm Biol Res,2010:1(1):30-41.
25. Murgia D, Angellotti G, D'Agostino F, De Caro V. Bioadhesive matrix tablets loaded with lipophilic nanoparticles as vehicles for drugs for periodontitis treatment: Development and characterization. Polymers,2019:11(11):1801.
26. Yedurkar P, Dhiman MK, Petkar K, Sawant K. Mucoadhesive bilayer buccal tablet of carvedilol-loaded chitosan microspheres: *in vitro*, pharmacokinetic and pharmacodynamic investigations. J Microencapsul,2012:29(2):126-37.
27. Freag MS, Saleh WM, Abdallah OY. Exploiting polymer blending approach for fabrication of buccal chitosan-based composite sponges with augmented mucoadhesive characteristics. Eur J Pharm Sci,2018:120:10-9.
28. Elbanna SA, Ebada HM, Abdallah OY, Essawy MM, Abdelhamid HM, Barakat HS. Novel tetrahydrocurcumin integrated mucoadhesive nanocomposite κ-carrageenan/xanthan gum sponges: a strategy for effective local treatment of oral cancerous and precancerous lesions. Drug Deliv,2023:30(1):2254530.
29. Perioli L, Ambrogi V, Angelici F, Ricci M, Giovagnoli S, Capuccella M, *et al*. Development of mucoadhesive patches for buccal administration of ibuprofen. J Control Release,2004:99(1):73-82.
30. Al-Nemrawi NK, Alsharif SS, Alzoubi KH, Alkhatib RQ. Preparation and characterization of insulin chitosan-nanoparticles loaded in buccal films. Pharm Dev Technol,2019:24(8):967-74.
31. Giovino C, Ayensu I, Tetteh J, Boateng JS. Development and characterisation of chitosan films impregnated with insulin loaded PEG-b-PLA nanoparticles (NPs): a potential approach for buccal delivery of macromolecules. Int J Pharm,2012:428(1-2):143-51.
32. Akl MA, Ismael HR, Abd Allah FI, Kassem AA, Samy AM. Tolmetin sodium-loaded thermosensitive mucoadhesive liquid suppositories for rectal delivery: strategy to overcome oral delivery drawbacks. Drug Dev Ind Pharm,2019:45(2):252-64.
33. Ravi Sankar V, Dhachinamoorthi D, Chandra Shekar KB. Formulation and evaluation of novel aspirin nanoparticles loaded suppositories. J Chin Pharm Sci,2013:22:259-67.
34. Büyükköroğlu G, Şenel B, Başaran E, Yenilmez E, Yazan Y. Preparation and *in vitro* evaluation of vaginal formulations including siRNA and paclitaxel-loaded SLNs for cervical cancer. Eur J Pharm Biopharm,2016:109:174-83.
35. Nayak AK, Pal D, Santra K. Development of calcium pectinate-tamarind seed polysaccharide mucoadhesive beads containing metformin HCl. Carbohydr Polym,2014:101:220-30.
36. Chen N, Li Q, Li J, Ren Y, Wu G, Liu Y, *et al*. Development and evaluation of a new gastroretentive drug delivery system: Nanomicelles-loaded floating mucoadhesive beads. J Drug Deliv Sci Technol,2019:51:485-92.
37. Knuth K, Amiji M, Robinson JR. Hydrogel delivery systems for vaginal and oral applications: Formulation and biological considerations. Adv Drug Deliv Rev,1993:11(1-2):137-67.
38. Ortega A, da Silva AB, da Costa LM, Zatta KC, Onzi GR, da Fonseca FN, *et al*. Thermosensitive and mucoadhesive hydrogel containing curcumin-loaded lipid-core nanocapsules coated with chitosan for the treatment of oral squamous cell carcinoma. Drug Deliv Transl Res,2023:13(2):642-57.
39. Szymańska E, Orłowski P, Winnicka K, Tomaszewska E, Bąska P, Celichowski G, *et al*. Multifunctional tannic acid/silver nanoparticle-based mucoadhesive hydrogel for improved local treatment of HSV infection: *In vitro* and *in vivo* studies. Int J Mol Sci,2018:19(2):387.
40. Amanat S, Taymouri S, Varshosaz J, Minaiyan M, Talebi A. Carboxymethyl cellulose-based wafer enriched with resveratrol-loaded nanoparticles for

enhanced wound healing. Drug Deliv Transl Res,2020:10:1241-54.
41. El-Nahas AE, Allam AN, El-Kamel AH. Mucoadhesive buccal tablets containing silymarin Eudragit-loaded nanoparticles: formulation, characterisation and ex vivo permeation. J Microencapsul,2017:34(5):463-74.
42. Hazzah HA, Farid RM, Nasra MM, El-Massik MA, Abdallah OY. Lyophilized sponges loaded with curcumin solid lipid nanoparticles for buccal delivery: Development and characterization. Int J Pharm,2015:492(1-2):248-57.
43. Kraisit P, Limmatvapirat S, Luangtana-Anan M, Sriamornsak P. Buccal administration of mucoadhesive blend films saturated with propranolol loaded nanoparticles. Asian J Pharm Sci,2018:13(1):34-43.
44. Marques AC, Rocha AI, Leal P, Estanqueiro M, Lobo JM. Development and characterization of mucoadhesive buccal gels containing lipid nanoparticles of ibuprofen. Int J Pharm,2017:533(2):455-62.