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Review Article

BUCCAL DRUG DELIVERY SYSTEM: HISTORY AND RECENT DEVELOPMENTS

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ABSTRACT

Being an alternate method of systemic drug delivery, oral mucosal drug delivery proves to be advantageous over both injectable and enteral methods. Because of the mucosal surface usually being rich in blood supply, it enhances drug bioavailability, thereby enabling rapid drug transport to the systemic circulation. Moreover, in most cases, it avoids degradation by first-pass hepatic metabolism. The drug absorption takes place faster as it is in contact with the absorption surface. The drug delivery system helps the drug to remain at the same place of application longer for once or twice daily dosing. For some drugs, the alternate way of administration results in novel methods of action as opposed to the above-said procedure. The characteristics of the oral mucosa as well as physicochemical properties of the drug pose as a hindrance to the oral mucosal administration of some drugs. Commercial availability of drug is restricted, although most of the drugs are qualitatively assessed for oral transmucosal delivery. The clinical benefit produced by an oral transmucosal dosage form is good even though the production of this dosage form is expensive. Transmucosal products are the recent drug delivery strategies. Delivery through transmucosal products benefits the absorption 4 times than that of the skin. Considering the availability of products, only some drugs are used for oral transmucosal delivery. Hence, new drugs have to be processed and developed to meet the limited transmucosal drug delivery. The present paper intends to emphasize the importance of oral transmucosal drug delivery and also highlights on the latest advancement in the field.

Keywords: Buccal mucosa, Buccal drug delivery, Buccoadhesive dosage forms, Bioadhesive polymer, Transmucosal.

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INTRODUCTION

Buccal drug delivery system

When administration is considered, the oral cavity can be cited as one of the best sites for the delivery of drugs. Mucosal and transmucosal (local effect and systemic effect, respectively) drug administration can be achieved through this route. The effect of the former is such that a site-specific release of the drug on the mucosa is achieved, and in the latter, the drug reaches the systemic circulation by the way of mucosal barrier and gets absorbed. The vascularization is high in oral mucosa, and enzymatic activity is minimal as that of nasal, intestinal, and rectal mucosa. On account of irritation and impairment, the oral mucosa is less sensitive than the nasal epithelium. In transmucosal drug administration, the sublingual and buccal mucosa work as absorption sites that has two curative goals. The sublingual process is made use of in the treatment of acute disorders. Since it has a high permeability across the mucosa, it is generally administered for the delivery of drugs. When a continuous release of the active substance becomes necessary as in the case of chronic disorders, the buccal process is generally employed. However, the sublingual process has pitfalls. The activity of the tongue hampers the contact of the dosage form with the mucosa, further worsened by the surface being incessantly washed by saliva [1]. Buccal process is more suitable for the placement of control release system which the patient also receives well. When compared to sublingual, buccal mucosa is flush and has a surface which is immovable. These features make it a befitting site for controlled drug delivery in miscellaneous chronic systemic treatments.

Need for buccal drug delivery system

The sublingual process has been a research subject for the past several years, but concern over buccal drug delivery is much more recent that happens to be concurrent with the biotechnological advances. It made peptides to be available for curative uses without delay. Degradation and low absorption hinder the administration of hydrophilic high molecular weight drugs such as peptides (e.g., insulin, cyclosporine A, etc.) through the oral process. Here, buccal process turns out to be effective. Drugs having short half-lives (e.g., midazolam) necessitate repeated injections which, in turn, result in poor patient compliance. This parenteral administration is then most favored for such drugs and it also involves high production and control costs. In humans, the permeation of drugs through the buccal epithelium is said to associate both the transcellular and paracellular routes. The large surface area represented by buccal mucosa (23% of the total surface of the oral mucosa including the tongue) makes it more fit for systemic drug delivery. Buccal mucosa is made up of several layers of different cells as is shown in Fig. 1.

Advantages

Among the advantages of the buccal drug delivery system, the crucial one is the direct access to the systemic circulation through the internal jugular vein that bypasses drugs (e.g., propranolol hydrochloride, nifedipine, etc.) from the hepatic first-pass metabolism. This results in high bioavailability, low enzymatic activity, and suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa. Other benefits include painless administration, easy drug withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation, and versatility in designing multidirectional or unidirectional release systems for local or systemic actions. Moreover, the drug delivery system can be localized, applied, and removed easily due to its easy access to the membrane sites. In addition, there is a good potential for prolonged delivery through the mucosal cavity [2]. Bioadhesive polymers have prolonged contact time with the tissues which enable them to significantly improve the performance of many drugs.

Drug selection

The physicochemical properties of the drugs play a critical role in the drug selection for oral transmucosal delivery. Drugs must have unique physicochemical properties that are a proper balance between solubility and lipophilicity to deliver them transmucosally. Even

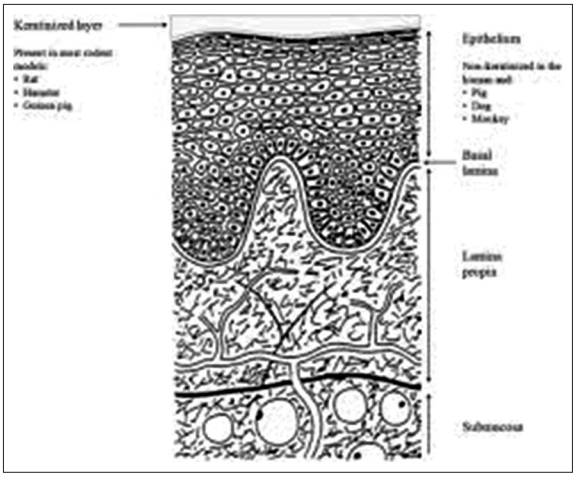

Fig. 1: Cross-section of buccal mucosa

though the drug has a favorable condition for oral mucosal delivery, only a few milligrams of drug can permeate it. No new classes of drugs are scientifically developed recently for oral transmucosal delivery because of the economic impulse flourishing the development of new drug formulations. For an effective transmucosal delivery to take place, in addition to the necessary physicochemical properties of the drug, there must also be a significant clinical advantage. Hence, drugs used for oral transmucosal delivery are limited to the existing products (e.g., nitroglycerine, prochlorperazine, metronidazole, etc.). Consequently, there should be a drastic change in the selection and development process of new drugs. Many products in the market, however, have shown unique properties and advantages of this delivery route (e.g., fentanyl citrate, buprenorphine hydrochloride, prochlorperazine, etc.).

To develop more drugs that are suitable for delivery routes other than oral and parenteral administration, the focus of the future will be to involve drug delivery and formulation by scientists early in the drug selection process [3]. Drugs such as buprenorphine, testosterone, nifedipine, and several peptides, such as insulin, thyrotropin-releasing hormone, and oxytocin, have been successively delivered through the buccal route.

The present review intends to illustrate the potential of buccal route in drug delivery, discussing the recent ways in which the technologies could improve the future treatment of mucosal and systemic disease by making use of the full advantages of the properties of the oral mucosa that makes it an ideal drug delivery site.

FORMULATIONS

History of buccal drug delivery development

Back in 1947, when attempts were made to formulate a penicillin drug delivery system for delivering the bioactive agent to the oral mucosa using gum tragacanth, dental adhesive powders for the use of mucoadhesive polymers were used for the development of pharmaceutical formulations. Improved results were reported when carboxy methyl cellulose (CMC) and petrolatum were used for the development of formulation. Subsequent research resulted in the development of a mucoadhesive delivery vehicle which consisted of finely ground sodium CMC (SCMC), pectin, and gelatin. The formulation was later marketed as Orahesive^{R}. Another formulation which entered into the clinical trials is Orabase^{R} which is a blend of polymethylene/mineral oil base. This was followed by the development of a system where polyethylene sheet was laminated with a blend of SCMC and polyisobutylene which provided an added advantage of protecting the mucoadhesive layer by the polyethylene backing from the physical interference of the external environment [4-8].

Over the years, various other polymers, for example, sodium alginate, SCMS, guar gum, hydroxy ethyl cellulose, karya gum, methyl cellulose, polyethylene glycol, and tragacanth have been found to exhibit mucoadhesive properties. During the 1980s, poly acrylic acid, hydroxypropyl cellulose, and SCMC were widely explored for the development of formulations having mucoadhesive properties. Since then, the use of acrylate polymers for the development of mucoadhesive formulations has increased many folds. Various authors have investigated the mucoadhesive properties of different polymers with varying molecular architecture [8,9]. After rigorous research, the researchers are of the view that a polymer will exhibit sufficient mucoadhesive property if it can form strong intermolecular hydrogen bonding with the mucosal layer, penetration of the polymer into the mucus network, easy wetting of mucosal layer, and high molecular weight of the polymer chain. The ideal character of a mucoadhesive polymer matrix includes the rapid adherence to the mucosal layer without any change in the physical property of the delivery matrix, minimum interference to the release of the active agent, biodegradable without producing any toxic byproducts, inhibits the enzymes present at the delivery site, and enhances the penetration of the active agent [10,11].

Research on buccal adhesive drug delivery systems

Several buccal adhesive delivery devices were developed at the laboratory scale by many researchers either for local or systemic actions. They are broadly classified into:

- Solid buccal adhesive dosage forms
- Semi-solid buccal adhesive dosage forms
- Liquid buccal adhesive dosage forms.

Solid buccal adhesive dosage forms

Dry formulations achieve bioadhesion via dehydration of the local mucosal surface.

Tablets

Several bioadhesive tablet formulations were developed in recent years either for local or systemic drug delivery. Tablets are placed directly on to the mucosal surface. These tablets adhere to the buccal mucosa in the presence of saliva. They are designed to release the drug either unidirectionally targeting buccal mucosa or multidirectionally into the saliva. Table 1 shows some of the research done so far in the development of buccal adhesive tablets. Tablets are demonstrated to be excellent bioadhesive formulations. Due to the size of the tablets, intimate contact with the mucosal surface is limited.

Microparticles

These are typically delivered as an aqueous suspension but can also be applied by aerosol or incorporated into a paste or ointment. Microparticles can make intimate contact with a larger mucosal surface area and can be delivered to less acceptable sites including the gastrointestinal tract (GIT) and upper nasal cavity. Its small size reduces the local irritation at the site of adhesion and the uncomfortable sensation of the foreign objects within the oral cavity. The major disadvantage is that the dose of drug retains on the buccal mucosa and therefore it may not be consistent relative to a single-unit dosage form such as buccal tablet or patch.

Wafers

Wafers are used in novel periodontal drug delivery system [43] that is intended for the treatment of microbial infections associated with periodontitis. The delivery system is a composite wafer with surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers, and matrix polymers. The advantage being less obtrusive and more acceptable to the patients due to thin nature and flexibility. Limitation include susceptible to overhydration and loss of the adhesive properties due to relative thin nature of the film.

Lozenges

Bioadhesive lozenges may be used for the delivery of drugs that act typically within the mouth including antimicrobials, corticosteroids,

local anesthetics, antibiotics, and antifungals [44]. The main advantage of the use of slow release bioadhesive lozenges is the prolonged drug release with improved patient compliance and limitation include high initial drug release in the oral cavity which rapidly decline to subtherapeutic level.

Semi-solid buccal adhesive dosage forms

Gels

Gel-forming bioadhesive polymers include cross-linked poly acrylic acid that has been used to adhere to mucosal surfaces for extended period of time and provide controlled release of drugs. Gels have been widely used in the delivery of drugs to the oral cavity [45]. Gels have the ability to form intimate contact with the mucosal membrane and thus there will be a rapid release of the drug at the absorption site. They are unable to deliver a measured dose of drug to the site. They are therefore of limited use for drugs with narrow therapeutic window.

Patches/films

These may be used to deliver drugs directly to a mucosal membrane. Buccal adhesive films and patches are already commercially (e.g., zilactin) used for the therapy of canker sores, cold sores, and lip sores. These are shown in Table 2.

Liquid buccal adhesive dosage forms

Solution, suspension, and gel-forming liquids

Viscous liquids may be used to coat buccal surface either as protectants or as drug vehicles for delivery to the mucosal surface. Traditionally, pharmaceutically acceptable polymers are used to enhance the viscosity of products to aid their retention in the oral cavity. They are used in the preparation of artificial saliva for the treatment of dry mouth. A major drawback is that they are not readily retained or targeted to the buccal mucosa and can deliver relatively uncontrolled amounts of drug throughout the oral cavity.

Delivery of proteins and peptides

The buccal mucosa represents a potentially important site for controlled delivery of macromolecular therapeutic agents such as peptides and protein drugs. It has some unique advantages such as the avoidance of hepatic first-pass metabolism, acidity, and protease activity encountered in the GIT.

Another interesting advantage is its tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers. A variety of proteins/peptides with or without penetration enhancer were studied by different scientists. Some of these developments are shown in Table 3.

Challenges in buccal drug delivery development

The environment of the oral cavity presents some significant challenges for systemic drug delivery. The drug needs to be released from the formulation to the delivery site (e.g., buccal or sublingual area) and should pass through the mucosal layers to enter the systemic circulation. Certain physiological aspects of the oral cavity play significant roles in the process, including pH, fluid volume, enzyme activity, and the permeability of the oral mucosa. For drug delivery systems designed for extended release in the oral cavity (e.g., mucoadhesive systems), the structure and turnover of the mucosal surface are also the determinants of performance. Table 4 shows a comparison of the physiological characteristics of the buccal mucosa with the mucosa of GIT.

The principal physiological environment of the oral cavity, in terms of pH, fluid volume, and composition is shaped by the secretion of the saliva. Saliva is secreted by three major salivary glands (parotid, submaxillary, and sublingual) and minor salivary or buccal glands situated in or immediately below the mucosa. The parotid and submaxillary glands secrete watery secretion, whereas the sublingual glands produce mainly viscous saliva with limited enzyme activity. The main functions of saliva are to lubricate the oral cavity, to facilitate swallowing, and to prevent demineralization of the teeth. It also allows carbohydrate digestion and regulates oral microbial flora by maintaining the oral pH and enzyme activity [75,76]. The daily total salivary secretion volume

Table 1: Buccal adhesive tablets

Drug	Bioadhesive polymer	References
Ketoprofen	Chitosan and sodium alginate	[12]
Nifedipine	Chitosan, polycarbophil, sodium alginate, gellan gum	[13]
Propranolol	CP, HPMC, PC, SCMC, PAA	[14]
Propranolol	HPMC, CP 934	[15]
Propranolol	HPMC, PC	[14]
Diltiazem	CP, HPMC, PC, SCMC, PAA	[16]
Diltiazem	CP 934, PVP K-30	[17]
Metoclopramide	CP, HPMC, PC, SCMC, PAA	[18]
Nystatin	Carbomer, HPMC	[19]
Verapamil	HPC-M, CP 934	[20]
Triamcinolone	HPC, CP 934	[21]
Triamcinolone	HPMC, PADH	[22]
Lidocaine	CP 934, HPC-H	[23]
Metronidazole	CP 934, HPMC	[24]
Sodium fluoride	Modified starch, PAA	[25]
Miconazole	Modified starch, CP 934	[26]
Pentazocine	CP 934P, HPMC	[27]
Chlorpheniramine	Hakea gum	[28]
Calcitonin	Hakea gum	[28]
Omeprazole	Sodium alginate, HPMC, CP 934P, PC	[29]
Nicotine	HPC, CP 934P, PVP	[30]
Clotrimazole	CP 974P, HPMC K4M	[31]
Nicotine hydrogen tartrate	Anionic, cationic and nonionic	[32]
Citrus oil and magnesium salt	Cross linked PAA and HPC	[33]
Buspirone HCl	CP 974, HPMC K4M	[34]
Omeprazole	Sodium alginate and HPMC	[35]
Hydrocortisone acetate	HPMC, CP 934P, polycarbophyl	[36]
Ergotamine tartrate	PVA	[37]
Hydralazine HCl	CP 934P and CMC	[38]
Prednisolone	Polycarbophil and CP 934P	[39]
Buprenorphine	HEMA and Polymeg	[40]
Morphine sulphate	Carbomer and HPMC	[41]
Propranolol	CP 934P, HPMC K4M	[42]

CP: Carbopol, HPMC: Hydroxypropyl methyl cellulose, PC: Polycarbophyl, SCMC: Sodium carboxy methyl cellulose, PAA: Polyacrylic acid, HPC: Hydroxypropyl cellulose, PVP: Poly vinyl pyrrolidone, PADH: Polyacrylic acid dimethyl hexadiene, PVA: Polyvinyl alcohol

Table 2: Buccal adhesive patches/films

Drug	Bioadhesive polymer	References
Plasmid DNA	Noveon, eudragit S-100	[46]
B-galactosidase	Noveon, eudragit S-100	[46]
Ipriflavone	PLGA, chitosan	[47]
Chlorhexidine gluconate	Chitosan	[48]
Chlorpheniramine maleate	Polyoxyethylene	[49]
Protirelin	HEC, HPC, PVP, PVA	[50,51]
Buprenorphine	CP 934, PIB and PIA	[52]
Isosorbide dinitrate	HPC, HPMCP	[53]
Lidocaine	HPC, CP	[54]
Miconazole nitrate	SCMC, chitosan, PVA, HEC and HPMC	[55]
Nifedipine	Sodium alginate	[56]
Acyclovir	PAA-CO-PEG	[57]

CP: Carbopol, HPMC: Hydroxypropyl methyl cellulose, PC: Polycarbophil, SCMC: Sodium carboxy methyl cellulose, PVP: Polyvinyl pyrrolidone, PLGA: Poly lactide co-glycolide, HPMCP: Hydroxypropyl methyl cellulosepthalate, PIB: Polyisobutylene, PIP: Polyisoprene, HPC: Hydroxypropyl cellulose, HEC: Hydroxyethylcellulose, PVA: Polyvinyl alcohol

is in between 0.5 and 2.0 L. However, the volume of saliva constantly present in the mouth is around 1.1 ml, thus providing relatively low fluid volume available for drug release from delivery systems compared to the GIT. This challenge can be overcome if the oral cavity offers relatively consistent and friendly physiological condition for drug delivery which is maintained by the continuous secretion of saliva. Compared to secretions of the GIT, saliva is a relatively mobile fluid with less mucin, limited enzymatic activity, and virtually no proteases. Saliva is a weak buffer with a pH around 5.5-7.0. This may slightly increase depending on the high flow rate because of the higher concentration of the sodium and bicarbonate. This challenge can be overcome by the limited enzymatic activity of the saliva.

Saliva provides a water-rich environment of the oral cavity which can be favorable for drug release from delivery system, especially those based on hydrophilic polymers. However, saliva flow decides the time span of the released drug at the delivery site. This flow can lead to premature swallowing of the drug before effective absorption occurs through the oral mucosa, and it is a well-acceptable concept known as "saliva washout." However, this challenge can be overcome by the volume of saliva constantly present in the mouth which is around 1.1 ml.

Drug permeability through the oral mucosa (e.g., buccal/sublingual) represents another major physiological barrier for oral transmucosal drug delivery. The oral mucosal thickness varies depending on the site as does the composition of the epithelium. The characteristics of the different regions of interest in the oral activity are shown in Table 5. The mucosa of areas subjected to mechanical stress (the gingiva and hard palate) is keratinized similar to the epidermis. The mucosa of the soft palate, sublingual, and buccal region, however, is not keratinized. The keratinized epithelia contain neutral lipids such as ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water in contrast to non-keratinized epithelia, such as the floor of the mouth, and the buccal epithelia do not contain acylceramides and only have small amounts of ceramides [82]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia [83,84].

Within the oral mucosa, the main penetration barrier exists in the outermost quarter to one-third of the epithelium [85,86]. The relative impermeability of the oral mucosa is due to intercellular materials derived from the so-called membrane-coating granules (MCGs) [1]. They are found in both keratinized and non-keratinized epithelia [87]. The MCGs discharge their contents into the intercellular space to ensure epithelial cohesion in the superficial layers and this discharge forms a barrier to the permeability of various compounds. This challenge can be overcome by the buccal and sublingual routes which are the focus for drug delivery via the oral mucosa because of the higher overall

Table 3: Buccal adhesive formulations for proteins/peptides

Protein/peptide drug	Dosage form	Enhancer	% increase in bioavailability	References
Buserelin	Patch	SGDC	12.7%	[58]
Calcitonin	Tablet	No enhancer	37%	[59]
Captopril	Tablet	SGDC	No significant increase	[60]
Colony stimulating factor (G-SCF)	Patch	No enhancer	Two-fold increase in pharmacological action	[61]
Enalapril	Solution	No enhancer	No significant increase	[62]
Glucagon-like peptide	Tablet	STC	4-23%	[63]
Gonadotropin-releasing hormone	Tablet	SC, SDC, STC, STDC	SDC>SC>STC>STDC	[64]
Interferon	Solution	No enhancer	Marked increase	[65]
Insulin	Liposomes	No enhancer	No significant increase	[66]
Lisinopril	Solution	No enhancer	No significant increase	[62]
Luteinizing-releasing hormone	Tablet	SDC 5%	237%	[67]
Octreotide acetate	Tablet	Azone, SC, EDTA, STC	Azone>SC>EDTA>STC	[68]
Oxytocin	Patch	No enhancer	Slight increase	[69]
Protirelin (TRH)	Patch	Citric acid, sodium 5-methoxysalicylate	Increase in plasma thyrotropin concentration	[51]
Recombinant human interferon alpha B/D hybrid	Solution	No enhancer	0.005%	[70]

SGDC: Sodium glycodeoxycholate, STC: Sodium taurocholate, SC: Sealer color, SDC: Sodium deoxycholate, STDC: Sodium taurodeoxycholic acid, EDTA: Ethylene diaminetetra acetate

Table 4: Comparison of different mucosae [71-74]

Absorption site	Estimated surface area	Percent total surface area	Local pH	Mean fluid volume (ml)	Relative enzyme activity	Relative drug absorption capacity
Oral cavity	100 cm^2 (0.01 m^2)	0.01	5.8-7.6	0.9	Moderate	Moderate
Stomach	0.1-0.2 m^2	0.20	1.0-3.0	118	High	Moderate
Small intestine	100 m^2	98.76	5.0-7.0	212	High	High
Large intestine	0.5-1.0 m^2	0.99	6.0-7.4	187	Moderate	Low
Rectum	200-400 cm^2 (0.04 m^2)	0.04	7.0-7.4	-	Low	Low

Table 5: Characteristics of oral mucosa

Tissue	Structure	Thickness (µm) [77]	Turnover time (days) [78]	Surface area (cm^2±SD) [79]	Permeability [80]	Residence time [80]	Blood flow* [81]
Buccal	NK	500-600	5-7	50.2±2.9	Intermediate	Intermediate	20.3
Sublingual	NK	100-200	20	26.5±4.2	Very good	Poor	12.2
Gingival	K	200	-	-	Poor	Intermediate	19.5
Palatal	K	250	24	20.1±1.9	Poor	Very good	7.0

*In rhesus monkeys (ml/min/100 g tissue). NK: Non keratinized tissue, K: Keratinized tissue

permeability compared to the other mucosa of the mouth. The effective permeability coefficient values reported in the literature across the buccal mucosa for different molecules range from a lower limit of 2.2 × 10 cm/s for dextran 4000 across rabbit buccal membrane to an upper limit of 1.5 × 10 cm/s for both benzylamine and amphetamine across rabbit and dog buccal mucosa, respectively [1]. The oral mucosa is believed to be 4-4000 times more permeable than that of the skin [86]. The permeability of water through the buccal mucosa was approximately 10 times higher than the floor of the mouth. The permeability was approximately 20 times higher than the skin.

The drugs are transported through the buccal epithelium by passive diffusion across lipid membranes via either paracellular or transcellular pathways.

Recent advances in buccal drug delivery system

Vaccination against debilitating infectious diseases has proven remarkable in the prevention of these diseases and has contributed significantly to an increase in life expectancy, especially in children in many parts of the world. To have adequate mucosal protection, there are several factors that can influence the effectiveness of vaccines. The most critical factor in mucosal vaccine effectiveness is the route of administration and potential for the antigen to be processed by the antigen-presenting immune cells, such as macrophages and dendritic cells. At present, most vaccines are administered via the parenteral route or via other invasive routes. Invasive mode of vaccine administration can trigger the systemic immune response, but may not essentially provide adequate mucosal immune protection. On the other hand, effective mucosal vaccines will not only elicit superior local immune protection, but has been shown to trigger systemic response analogous to that of parenterally delivered vaccine. As such, it is critically important to examine the development of mucosal vaccination strategies that can effectively trigger systemic as well as mucosal immunity [83]. Mucosal vaccines have currently been investigated using a broad spectrum of nanocarrier systems such as multiple emulsions, liposomes, polymeric nanoparticles, dendrimers, and immunostimulating complex. More importantly, mucosal delivery of nanocarrier antigens and vaccines can trigger immunization at different mucosal barriers which is the body's imperative first-line defense in addition to systemic immune response. From the future perspective, development of vaccines using combined strategic approach such as nanocarriers delivered by mucosal route of delivery can play a major role in the treatment of infectious diseases.

CONCLUSION

The need for research on drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of the current treatments may be improved if their delivery rates, biodegradation, and site-specific targeting can be predicted, monitored, and controlled. From both a financial and global health care perspective, finding ways to administer injectable medications is costly and sometimes leads to serious hazardous effects. Hence, inexpensive multiple dose formulations with better bioavailability are needed. Improved methods of drug release through transmucosal and transdermal methods would be of great significance, as by such routes, the pain factor associated with parenteral routes of drug administration can be totally eliminated. Buccal adhesive systems offer innumerable advantages in terms of accessibility, administration and withdrawal, retentively, low enzymatic activity, economy, and high patient compliance. Since the introduction of Orabase^{R} in 1947, when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa, the market share of bioadhesive drug delivery systems has increased.

Adhesion of buccal adhesive drug delivery devices to mucosal membranes leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drugs. In addition, buccal adhesive dosage forms have been used to target local disorders at the mucosal surface (e.g., mouth ulcers) to reduce the overall dosage required and to minimize side effects that may be caused by systemic administration of drugs. Researchers are now looking beyond the traditional polymer networks to find other innovative drug transport systems. Much of the development of novel materials in controlled release buccal adhesive drug delivery focuses on the preparation and use of responsive polymeric system especially co polymer with desirable hydrophilic/hydrophobic interaction; block or graft co polymers; complexation networks responding via hydrogen and ionic bonding as well as new biodegradable polymers especially from natural edible sources. At the current global scenario, scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of orally less inefficient drugs by manipulating the formulation strategies such as inclusion of pH modifiers, enzyme inhibitors, and permeation enhancers. Novel buccal adhesive delivery system, where the drug delivery is directed toward buccal mucosa by protecting the local environment, is also gaining interest. Currently, solid dosage forms, liquids, and gels applied to the oral cavity are commercially successful.

Mucosal (local) and transmucosal (systemic) delivery of drugs via the buccal route is still very challenging. The main obstacles arise from the limited absorption area and from the barrier properties of the mucosa, particularly in the case of drugs intended for a transmucosal delivery. Moreover, the effective physiological removal mechanisms of the oral cavity, which take the formulation away from the absorption site, are factors that have to be considered in the design of buccal drug delivery systems, notably in the case of local delivery.

The strategies studied to overcome such obstacles include the use of materials that combine mucoadhesive, enzyme inhibitory and penetration enhancer properties, and the design of novel formulations. This favors an intimate and prolonged contact of the drug with the absorption mucosa besides improving patient compliance. An important aspect to be considered concerns the mechanisms by which the materials employed interacts with the biological substrate. The study of the mechanisms of interaction between the formulations and the mucosa is fundamental to the design and development of new materials with improved performances.

The most interesting areas for future research lie in finding a delivery method suitable for delivering new biological therapies including antibodies, peptides, and gene therapy across the oral mucosa. These new therapies, if could be delivered to the appropriate sites in a self-administered way, could dramatically change the way many diseases both systemic and oral are treated. If gene therapy research can be transferred from strong results in laboratories into a clinically safe and effective treatment suitable for use in the oral mucosa, oral keratinocytes could be genetically engineered to synthesize insulin for diabetes mellitus or therapeutic hormones or peptides for other diseases.

The oral mucosa's accessibility, high blood supply, by-pass of the hepatic first-pass metabolism, quick recovery time after damage, and permeability profile make it an attractive and interesting area for topical drug delivery research. With the appropriate technologies and delivery techniques, the oral mucosa could in the future be utilized for the treatment of many diseases both mucosal and systemic, and the catalog of drugs which can be delivered via the mucosa could be greatly increased. Further advances in mucobuccal adhesive technology and sustained local drug release also have the potential for reducing the systemic side effects from ingested or injected therapies, where an oral mucosal disease is the target of therapy.

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