BUCCAL DRUG DELIVERY SYSTEM: HISTORY AND RECENT DEVELOPMENTS

ARUN JL1*, RANI S2, MANOJ KUMAR P3

1Department of Pharmaceutics, The Dale View College of Pharmacy and Research Centre, Thiruvananthapuram - 695 575, Kerala, India.
2Department of Pharmacology, Annamalai University, Chidambaram - 608 002, Tamil Nadu, India. 3Department of Pharmaceutical Chemistry, The Dale View College of Pharmacy and Research Centre, Thiruvananthapuram - 695 575, Kerala, India.

Email: ajil01979@gmail.com

Received: 11 July 2016, Revised and Accepted: 25 July 2016

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 have 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

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.

© 2016 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/) DOI: http://dx.doi.org/10.22159/ajpcr.2016.v9i6.14041

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 have 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
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 acrylic 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 [14]. 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, pharmacologically 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, gelan gum |[13]       |
| Propranolol   | CP, HPMC, PC, SCMC, PAA                    |[14]       |
| Propranolol   | HPMC, CP 934                              |[15]       |
| Propranolol   | HPMC, PC                                  |[14]       |
| Dilatiazem    | CP, HPMC, PC, SCMC, PAA                    |[17]       |
| Metolopronamide | CP, HPMC, PC, SCMC, PAA                  |[18]       |
| Nystatin      | Carbomer, HPMC                             |[19]       |
| Verapamil     | HPMC, CP 934                              |[20]       |
| Triamcinolone | HPMC, CP 934                              |[21]       |
| Triamcinolone | HPMC, PADH                                 |[22]       |
| Lidojaine     | CP 934, HPC-H                             |[23]       |
| Metronidazole | CP 934, HPMC                               |[24]       |
| Sodium fluoride | Modified starch, PAA                     |[25]       |
| Miconazole    | Modified starch, CP 934                    |[26]       |
| Pentazocine   | CP 934 P, HPMC                             |[27]       |
| Chlorpheniramine | Hakegum                                   |[28]       |
| Calcitonin    | Hakegum                                   |[28]       |
| Omeprazole    | Sodium alinate, HPMC, CP 934 P, PC         |[29]       |
| Nicotine      | HPC, CP 934 P, PVP                         |[30]       |
| Clotrimazole  | CP 974 P, HPMC K4M                         |[31]       |
| Nicotine hydrogen tartrate | Anionic, cationic and nonionic |[32] |
| Citrus oil and magnesium salt | Cross linked PAA and HPC |[33] |
| Busproprone HCl | CP 974 P, HPMC K4M                     |[34]       |
| Omeprazole    | Sodium alinate and HPMC                    |[35]       |
| Hydrocortisone | HPMC, CP 934 P, acetate                   |[36]       |
| Ergotamine tartrate | PVA                                        |[37]       |
| Hydralazine HCl | CP 934 P and CMC                      |[38]       |
| Prednisolone  | Polycarbophil and CP 934 P                |[39]       |
| Buprenorphine | HEMA and Polyneg                          |[40]       |
| Morphine sulphate | Carbomer and HPMC                     |[41]       |
| Propranolol   | CP 934 P, HPMC K4M                         |[42]       |

**Table 2: Buccal adhesive patches/films**

| Drug          | Bioadhesive polymer                        |References |
|---------------|--------------------------------------------|-----------|
| Plasmid DNA   | Noveon, eudragit S-100                     |[46]       |
| B-galactosidase | Noveon, eudragit S-100                  |[46]       |
| Ipratropium   | PLGA, chitosan                            |[47]       |
| Chlorhexidine gluconate | Chitosan                   |[48]       |
| Chlorpheniramine | Polyoxyethylene                         |[49]       |
| Maleate       | HEC, HPC, PVP, PVA                        |[50,51]    |
| Propranolol   | CP 934 P, PIB and PIA                     |[52]       |
| Isosorbide dinitrate | HPC, HPMC                        |[53]       |
| Lidojaine     | HPC, CP                                   |[54]       |
| Miconazole     | SCMC, chitosan, PAA, HEC and HPMC          |[55]       |
| Nifedipine    | Sodium alinate                            |[56]       |
| Aycloviro     | PAA-CO-PEG                                 |[57]       |

CP: Carbopol, HPMC: Hydroxypropyl methyl cellulose, PC: Polycarbophil, SCMC: Sodium carboxy methyl cellulose, PAA: Polycrylic acid, HPC: Hydroxypropyl cellulose, PVP: Polyvinylpyridilone, PDAH: Polycrylic acid dimethyl hexadiene, PVA: Polyvinyl alcohol
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 permeability of the oral cavity 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 varies greatly which is due to the state of rest, activities like swallowing, and volume of saliva. Estimated surface area of the outermost quarter to one-third of epithelium that contains MCGs is 0.04 m². This can be overcome by increasing the oral fluid volume 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.

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 permeability of the oral cavity 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.
permethylation compared to the other mucosa of the mouth. The effective permethylation 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 × 1000 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, retaining, low enzymatic activity, economy, and high patient compliance. Since the introduction of Orabase® 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; complexion 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 efficient 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.

REFERENCES

1. Gandhi RB, Robinson JR. Oral cavity as a site for biosynthetic drug delivery, Adv Drug Deliv Rev 1994;13(1-2):43-74.
2. Semalty A, Semalty M, Singh R, Saraf SK, Saraf S. Properties and formulation of oral drug delivery systems of protein and peptides. Adv Drug Deliv Rev 1994;13(1-2):43-74.
3. Acharya RN, Baker JL, U.S. 20016210699; 2001.
40

Arun et al.

Asian J Pharm Clin Res, Vol 9, Issue 6, 2016, 36-42
29. Choi HG, Kim CK. Development of omeprazole buccal adhesive

tablets. J Control Release 2004;98(3):405-12.

30. Alur HH, Pather SI, Mitra AK, Johnston TP. Transmucosal

delivery – A promising option for orally less efficient drugs. J Control

31. Nagai T, Machida Y. Buccal delivery systems using hydrogels. Adv

32. Nagai T, Nagai M, Kawamura S, Takeo K. Buccal drug delivery system

33. Dinsheet SP, Ahuja AA. Preparation and evaluation of buccal

tablets containing water-soluble drugs. Drug

34. Senel S, Ikinci G, Kas S, Yousefi-Rad A, Sargon MF, Hincal AA.

35. Choi H, Jung J, Yong CS, Rhee C, Lee M, Han J, et al. Formulation and

36. Ceschel GC, Maffei P, Lombardi Borgia S, Ronchi C. Development and

37. Tsutsumi K, Obata Y, Nagai T, Loftsson T, Takayama K. Buccal

38. Dinsheet SP, Ahuja AA. Preparation and evaluation of buccal

tablets containing nystatin. AAPS PharmSciTech 2002;3:E22.

39. Rafiee-Tehrani M, Jazayeri T, Toliyat B, Bayati K, Khalkhali K, Shimami K, et al. Development and in-vitro evaluation of novel

40. Iacopetta BL, Pappas BS, Shami K, et al. Evaluation of novel

41. Cui Z, Mumper RJ. Bilayer films for mucosal (genetic) immunization

42. Codd JE, Desay PB. Formulation, development and in-vitro evaluation of a novel bioadhesive lozenge containing a synergistic combination of

43. Bromberg LE, Buxton DK, Friden PM. Novel periodontal drug
delivery system for treatment of periodontitis. J Control Release 2001;71(3):251-9.

44. Perugini P, Genta I, Conti B, Modena T, Pavanetto F. Periodontal

delivery of iripilumab: New chitosan/PLGA film delivery system for a lipolipidic drug. J Int Pharmacol 2003:252(1-2):1-9.

45. Anders R, Merckle H. Evaluation of laminated mucoadhesive patches for buccal drug delivery. Int J Pharm 1989;497:43-97.

46. Anders R, Merkle HP, Schurr W, Ziegler R. Buccal absorption of

47. Pham H, Mercier-Lourcy L, Merke K, et al. Adhesive

48. Senel S, Icikoglu S, Kas S, Youshi-Rad A, Sargon M, Hzncal A. Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. J Int Pharmacol 2000:193(2):197-203.

49. Faridi M, Agha M, Ebrahimi M, et al. Evaluation of bioadhesive

50. Anders R, Merkle H. Evaluation of laminated mucoadhesive patches for buccal drug delivery. J Int Pharmacol 1989;197:43-97.

51. Anders R, Merkle HP, Schurr W, Ziegler R. Buccal absorption of

52. Codd JE, Desay PB. Formulation, development and in-vitro evaluation of a novel bioadhesive lozenge containing a synergistic combination of

53. Torreri D, Goldman D, Saquie R, Madan PL. Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations. AAPS PharmSci 1999;1:1-8.

54. Anders R, Merkle H. Evaluation of laminated mucoadhesive patches for buccal drug delivery. J Int Pharmacol 1989;49:231-40.

55. Anders R, Merkle HP, Schurr W, Ziegler R. Buccal absorption of

56. Save T, Shah MU, Ghande AR, Venkatachalam P. Comparative study of buccal bioadhesive formulations and sublingual capsules of nifedipine. J Int Pharmacol 1994;46(3):192-5.

57. Shojaei AH, Li X. Mechanisms of buccal mucoadhesive novel

copolymers of acrylic acid and polyethylene glycol monomethyl ether. J Controlled Release 1997;47:151-61.

58. Hooestraete AJ, Verheijden JC, Pijpers A, Leengroda L, Verheijden JH,
Junginger HE, et al. *In vivo* buccal delivery of the peptide drug buserilin with glycodeoxycholate as an absorption enhancer in pigs. Pharm Res 1996;13:1233-7.

59. Alur H, Beal JD, Pather SI, Mitra AK, Johnston JP. Evaluation of a novel, natural oligosaccharide gum as a sustained-release and mucoadhesive component of calctionin buccal tablets. J Pharm Sci 1999;88(12):6376-81.

60. Guttiar MK, Larsson H, Heiber SJ, Junejans OT, Mitra AK, Johnston JP. Potential therapeutic levels of glucagon-like peptide 1 achieved in humans by a buccal tablet. Diabetes Care 1996;19(8):43-8.

61. Ito Y, Nakane S, Lee Y, Kakimoto M, Chien Y. Oramucosal delivery of LHRH: Pharmacokinetic studies of controlled and enhanced transmucosal permeation. Pharm Dev Technol 1996;1(3):251-9.

62. Merkle HP, Wolany GJ. Bioadhesion Method. J Control Release 1992;21:155-64.

63. Li C, Bhatt PP, Johnston TP. Transmucosal delivery of oxytocin to rabbits using a mucoadhesive buccal patch. Pharm Dev Technol 1997;2(3):265-74.

64. Bayley D, Temple C, Clay V, Steward A, Lowther N. The transmucosal absorption of recombinant human interferon-alpha B/D hybrid in the rat and rabbit. J Pharm Pharmacol 1995;47:721-4.

65. Defelippis MR. Overcoming the challenges of noninvasive proteins and peptides delivery. Am Pharm Rev 2003;6:21-30.

66. Martin del valle EM, Galan MA, Carbonell RG. Drug delivery technologies: The way forward in the new decade. Ind Eng Chem Res 2009;48:2475-86.

67. Gotch F, Nadell J, Edelman IS. Gastrointestinal water and electrolytes. IV. The equilibration of Deuterium oxide in gastrointestinal contents and the proportion of total body water (T.B.W) in the gastrointestinal tract. J Clin Invest 1957;36:289-96.

68. Cummings DH, Banwell JG, Segal I, Coleman N, Englyst HN, MacFarlane GT. The amount and composition of large bowel contents in man. Gastroenterology 1990;98:A408.

69. Herrera JL, Lyons MF, Johnson LF. Saliva: Its role in health and disease. J Clin Gastroenterol 1988;10(5):569-78.

70. Slomiany BL, Murtz VL, Piotrowski J, Slomiansy A. Salivary mucus in oral mucosal defense. Gen Pharmacol 1996;27(5):761-71.

71. Alur H, Beal JD, Pather SI, Mitra AK, Johnston JP. Evaluation of a novel, natural oligosaccharide gum as a sustained-release and mucoadhesive component of calctionin buccal tablets. J Pharm Sci 1999;88(12):6376-81.