International Journal of Drug Delivery 3 (2011) 171-184
http://www.arjournals.org/index.php/ijdd/index

Review

ISSN: 0975-0215

Buccal Drug Delivery: Past, Present and Future – A Review

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Abstract

The major hindrance for the absorption of a drug taken orally is extensive first pass metabolism or stability problems within the GI environment like instability in gastric pH and complexation with mucosal membrane. These obstacles can be overcome by altering the route of administration as parenteral, transdermal or trasmucosal. Among these trasmucosal has the advantage of ease of administration, patient compliance and are economic too. The mucosa of the buccal cavity is the most easily accessible transmuocosal site. Buccal transmucosal delivery helps to bypass first- pass metabolism by allowing direct access to the systemic circulation through the internal jugular vein. The buccal transmucosal route has been researched for a wide variety of drugs. Several methodologies have been considered so far, to design and manipulate the release properties towards the invention of buccal mucosal delivery systems. This article aims at reviewing the numerous techniques that has been designed till date for optimizing buccal transmucosal drug delivery.

Keywords: complexation; parenteral; transdermal; trasmucosal

Introduction

Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. When the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion. [1]

Mucoadhesion has become an interesting topic for research over the last two decades, for its potential to optimize localized drug delivery, by retaining dosage forms at the site of action or systemic delivery, by retaining a formulation in intimate contact with the absorption site. [2] Mucoadhesive formulations are usually prepared with mucoadhesive polymers. First generation mucoadhesive polymers are hydrophilic in nature, having limited solubility in other solvents, forming high viscous liquid in water and pH sensitive. These characteristics present significant challenges in the formulation development of mucoadhesive formulations. [3-4]

Mucoadhesive polymers have been used to formulate tablets, patches, or microparticles, with the adhesive polymer forming the matrix into which the drug is dispersed, or the barrier through which the drug must diffuse. Mucoadhesive ointments and pastes consist of powdered bioadhesive polymers incorporated into a hydrophobic base. Solutions tend to be viscous due to the nature of the mucoadhesive materials. Other proposed mucoadhesive formulations include gels, vaginal rods, pessaries and suppositories. [5]

Mechanism of mucoadhesion

There are many chemical bonds responsible for the mucoadhesion. Ionic (where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond), covalent

(where electrons are shared, in pairs, between the bonded atoms in order to fill the orbital in both) are the stronger bonds which help the formulation to adhere to the mucosa. The weaker bonds involved in mucoadhesion are hydrogen bonds, Van-der-Waals bonds and other hydrophobic bonds. [6-7] The mechanism by which a mucoadhesive bond is formed will depend on the nature of the mucous membrane and mucoadhesive material, the type of formulation, the attachment process and the subsequent environment of the bond. It is understood that a single mechanism for mucoadhesion cannot be proposed for all the different occasions when adhesion occurs. But, an understanding of these mechanisms in each instance will assist the development of new, enhanced drug delivery systems.

Many theories proposed for mucoadhesion. The most important 'electronic theory' suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. This electron transfer may result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces. The wetting theory considers surface and interfacial energies and is primarily applied to liquid systems. This theory proposes that as a prerequisite for the development of adhesion the liquid should have the ability to spread spontaneously onto a surface. The adsorption theory proposes that hydrogen bonding and van der Waals' forces are the main contributors to the adhesive interaction. As per diffusion theory inter diffusion of polymers chains across an adhesive interface causes adhesion, and is driven by concentration gradient. Other theories proposed for mucoadhesion are the mechanical theory and the fracture theory. [8] Upon adhesion, the drug enters into the systemic circulation by different pathways like passive diffusion (transcellular and or paracellular), carrier mediated transport and endocytosis.

Buccal drug delivery

Difficulties associated with parenteral delivery and poor oral availability provided the impetus for exploring alternative routes for the delivery of such drugs. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. Substantial efforts have recently been focused on placing a drug or drug delivery system in a particular region of the body for extended periods of time. The mucosal layer lines a number of regions of the body including the oral cavity, gastro intestinal tract, the urogenital tract, the airways, the ear, nose and eye. Hence the mucoadhesive drug delivery system can be classified according to its potential site of applications. [9]

The buccal region of oral cavity is an attractive site for the delivery of drugs owing to the ease of the administration. Buccal drug delivery involves the administration of desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. [10]

Based on current understanding of biochemical and physiological aspects of absorption and metabolism of many biotechnologically produced drugs, they cannot be delivered effectively through the conventional oral route. Because after oral administration many drugs are subjected to pre-systemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability. Direct access to the systemic circulation through the external jugular vein by pass the drugs from the hepatic first pass metabolism which may lead to higher bio availability. Further these dosage forms are self administrable, cheap and have superior patient compliance. Unlike oral drug delivery which presents a hostile environment for drugs

especially proteins and peptides due to acid hydrolysis enzymatic degradation, hepatic first pass effect the mucosal lining of buccal tissues provides a much milder environment for drug absorption. In the case of both mucosal and trans-mucosal administration, conventional dosage forms are not able to assure therapeutic drug levels on the mucosa and in the circulation. This is because of the physiological removal mechanisms of the oral cavity (washing effect of saliva and mechanical stress), which take the formulation away from the mucosa, resulting in a too short exposure time and unpredictable distribution of the drug on the site of action/absorption. [4] The advantages that make buccal adhesive drug delivery systems as promising option for continued research are listed in Table 1.

Table 1: Advantages of buccal drug delivery systems.

- Excellent accessibility
- Presence of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms
- Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability
- Low enzymatic activity
- Suitability for drugs or excipients that mildly and reversibly damages or irritates the mucosa
- Painless administration
- Easy drug withdrawal
- Facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation
- Versatility in designing as multidirectional or unidirectional release systems for local or systemic actions etc.

However, low oral mucosal permeability of drugs, the effect of salivary scavenging and accidental swallowing of delivery system; barrier property of buccal mucosa stands as the major limitations in the development of buccal adhesive drug delivery systems. [4]

Design of Formulations for buccal drug delivery

Buccal adhesive drug delivery systems with the size 1–3 cm^2 and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4–6 h. [11]

Pharmaceutical considerations

To develop a safe and effective buccal adhesive drug delivery device great care needs to be exercised. Factors affecting the drug release, penetration through buccal mucosa, organoleptic factors, and effects of other excipients used to improve drug release pattern and absorption, irritation caused at the site of application are to be considered while designing a formulation.

Ideally pharmaceutical buccal adhesive drug delivery systems should contain mucoadhesive agents, penetration enhancers and enzyme inhibitors. Mucoadhesive agents are used to maintain an intimate and prolonged contact of the formulation with the absorption site while penetration enhancers improve the drug permeation across mucosa (trans-mucosal delivery) or into deepest layers of the epithelium (mucosal delivery). The enzyme inhibitors ideally protect the drug from the degradation by means of mucosal enzymes. [12-14]

Buccal adhesive polymers

Mucoadhesive polymers are the important component in the development of buccal delivery systems. These polymers enable retention of dosage form at the buccal mucosal surface and thereby provide intimate contact between the dosage form and the absorbing tissue. These formulations are often water soluble and when in a dry form attract water from the biological surface which in turn leads to a strong interaction between the dosage form and mucosal layer. [15]

The mucoadhesive polymers most commonly used in buccal dry or partially hydrated dosage forms include polyacrylic acid, polyvinyl alcohol (PVA), sodium carboxymethylcellulose (NaCMC), hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium alginate, chitosan and its derivatives, gelatin, carrageenan, lamellar and cubic liquid crystalline phases of glyceryl monooleate (GMO). [16-18] Various copolymers of acrylic acid (acrylic acid polyethylene glycol monomethyl ether copolymer and acrylic acid-2 ethylhexyl acrylate copolymer) have also been used. [4]

Polymer morphology and excipients present are the main components that determine the release kinetics from the polymer matrix. Drug release from a polymeric material takes place either by the diffusion or by polymer degradation or by a combination of the both. Polymer degradation generally takes place by the enzymes or hydrolysis either in the form of bulk erosion or surface erosion. [3-18]

Membrane permeation is the limiting factor for many drugs in the development of buccal adhesive delivery devices. However, examination of penetration route for trans-buccal delivery is important because it is fundamental to select the proper penetration enhancer to improve the drug permeability [19]. The different permeation enhancers that were extensively reviewed and reported in literatures are given in Table 2. [19-23]

Table 2: Different permeation enhancers used in buccal drug delivery.

Class of permeation enhancers	Examples
Thiolated polymers	Chitosan-4-thiobutylamide, chitosan- 4-thiobutylamide/GSH, chitosan-cysteine, Poly (acrylic acid)-homocysteine, polycarbophil-cysteine,polycarbophil-cysteine/GSH, chitosan-4-thioethylamide/GSH, chitosan-4-thioglycholic acid
Surfactants	Sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-lauryl ether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide
Chelators	EDTA, citric acid, sodium salicylate, methoxy salicylates.
Non-surfactants	Unsaturated cyclic ureas.
Fatty acids .	Oleic acid, capric acid, lauric acid, lauric acid/ propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine
Inclusion complexes	Cyclodextrins.
Bile salts .	Sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate
Others	Aprotinin, azone, cyclodextrin, dextran sulfate, menthol, polysorbate 80, sulfoxides and various alkyl glycosides.

However, the relative bioavailability of peptides by the buccal route was still low due to its poor permeation and enzymatic barrier of buccal mucosa but can be improved by the incorporation

of penetration enhancers and/or enzyme inhibitors. Enzyme inhibitors, such as aprotinin, bestatin, puromycin and some bile salts stabilize protein drugs by different mechanisms. [23]

Physiological considerations

Prior to the designing of buccal dosage form physiological factors such as texture of buccal mucosa, thickness of the mucus layer, its turn over time, effect of saliva and other environmental factors are to be considered. Saliva contains certain enzymes (esterases, carbohydrases, phosphatases) that may degrade some drugs. Although saliva secretion facilitates the dissolution of drug, involuntary swallowing of saliva also affects its bioavailability. These disadvantages can be avoided by developing unidirectional release systems with backing layer. This concept may also results in high drug bioavailability. [19-20]

Pharmacological considerations

The general principle of drug absorption holds good for buccal delivery also. Buccal drug absorption depends on the partition coefficient of the drugs. Lipophilic drugs absorb through the transcellular route, where as hydrophilic drugs absorb through the paracellular route. This behavior leads to the assumption that chemical modification may increase drug penetration through buccal mucosa. Increasing nonionized fraction of ionizable drugs increases drug penetration through trans-cellular route. In weakly basic drugs, the decrease in pH increases the ionic fraction of drug but decreases its permeability through buccal mucosa [24-25]. Other pharmacological factors include residence time and local concentration of the drug in the mucosa, the amount of drug transported across the mucosa into the blood. Earlier studies have demonstrated that oral mucosal absorption of amines and acids at constant concentration are proportional to their partition coefficients. Similar dependencies on partition coefficients were obtained from acyclovir, β- adrenoreceptor blocking agents and substituted acetanilide. [24]

Dosage forms

Several buccal adhesive delivery devices were developed at the laboratory scale by many researchers either for local or systemic actions and can be broadly classified in to solid buccal adhesive dosage forms, semi-solid buccal adhesive dosage forms and liquid buccal adhesive dosage forms. The various buccal dosage forms described in the literature are summarized in Table 3 and 4. The most common formulations are tablets and patches.

Table 3: Buccal adhesive tablets described in literatures.

Class of Drug	Bioadhesive polymer	References
NSAIDs		
Ketoprofen	Chitosan and sodium alginate	[26]
Nimesulide		[27]
Calcium channel blockers		
Nifedipine	Chitosan, polycarbophil, Sodium	[28]
Diltiazem	alginate,gellan gum	
	CP 934 and PVP K-30	[29]
Verapamil	HPC-M, CP 934	[30-31]
Beta blockers		
Propranolol	CP, HPMC, PC,SCMC, PAA,	[32]
Propranolol	HPMC, CP 934	[33]
Propranolol	HPMC, PC	[32]
Propranolol	CP-934P, HPMC K4M	[34]
Anti fungal		
Nystain	Carbomer, HPMC	[35]

Clotrimazole	CP 974P, HPMC K4M	[36]
Corticosteroids		
Triamcilone	HPC, CP- 934	[37]
Hydrocortisone Acetate	HPMC (methocelk4m), Carbapol 934P ,Polycarbiphyl	[(38]
Prednisolone	Polycarbophil and CP 934P	[39]
Triamcilone	HPMC, PADH	[40]
Opoid analgesic		
Pentazocine	CP-934P, HPMC	[41]
Buprenorphine	HEMA and Polymeg	[42]
Morphine Sulphate	Carbomer and HPMC	[43]
Proton pump inhibitor		
Omeprazole	Sodium alginate, HPMC, CP-934P, PC	[44]
Omeprazole	Sodiun alginate and HPMC	[45]
COPD		
Nicotine	HPC, CP-934P, PVP	[46]
Nicotine Hydrogen tarterate	Aionic, cationic and nonionic	[47]
Local anaesthetic		
Lidocaine	CP-934, HPC-H	[48]
Anti bacterial		
Metronidazole	CP-934, HPMC	[49]
Anti histamine		
Chlorpheneramine	Hakea gum	[50]
Osteophorosis		
Calcitonin	Hakea gum	[50]
Carminative and laxative		
Citrus oil and Magnesium salt	Cross linked PAA and HPC	[51]
Anti-anxiety drugs		
Buspirone Hcl	CP 974 HPMCK4M	[52]
Anti adrenergic drug		
Ergotamine Tartrate	PVA	[53]
Vasodilator		
Hydralazine Hcl	CP 934 and CMC	[54]
Anti parkinsonism		
Piribedit		[55]
Anti septic and disinfectant		
Cetyl Pyridinium Chloride		[56]

Table 4: Buccal adhesive films described in literature.

Class of Drug	Bioadhesive polymer	References
Biotechnology product		
Plasmid DNA	Noveon, eudragit S-10	[57]
Anti oxidant		
Ipriflavone	PLGA, Chitosan	[58]
Anti septic and disinfectant		
Chlorhexidine Gluconate	Chitosan	[59]
Anti histamine		
Chlorpheneramine maleate	Polyxyethylene	[60]
Opoid analgesic		
Buprenorphine	CP-934, PIB and PIP	[61]
Anti anginal		
Isosorbide dinitrate	HPC, HPMCP	[62]
Local anaesthetic		
Lidocaine	HPC, CP	[63]
Anti fungal		
Miconazole nitrate	SCMC, chitosan, PVA, HEC and HPMC	[64]
Calcium channel blockers		
Nifedipine	Sodium alginate	[65]
Anti viral	[	
Acyclovir	P (AA-co- PEG)]	[66]

Solid buccal adhesive formulations

Solid buccal adhesive formulations achieve bioadhesion via dehydration of the local mucosal surface. They include tablets, micro particles, wafers, lozenges etc. Buccal adhesive tablets that are placed directly onto the mucosal surface for local or systemic drug delivery have been demonstrated to be excellent bioadhesive formulations. Two types of tablets i.e. monolithic and double-layered matrix tablets have been investigated for buccal delivery of drugs. Monolithic tablets consist of a mixture that contains drug and swelling bioadhesive/sustained release polymer. These tablets exhibit a bidirectional release. They can be coated on the outer or on all sides but one face with water impermeable hydrophobic substances to allow a unidirectional drug release for systemic delivery.

Double layered tablets comprise an inner layer based on a bioadhesive polymer and an outer non-bioadhesive layer containing the drug for a bi-directional release but mainly a local action. In the case of systemic action, the drug is loaded into the inner bioadhesive layer whereas the outer layer is inert and acts as a protective layer. Alternatively, the drug is loaded into a controlled release layer and diffuses towards the absorbing mucosa through the bioadhesive layer, whereas a water impermeable layer assures the mono-directional release. [26-29]

Microparticles

Bioadhesive microparticles offer the same advantages as tablets but their physical properties enable them to make intimate contact with a lager mucosal surface area. In addition, they can also be delivered to less accessible sites including the GI tract and upper nasal cavity. [19]

Wafers

A conceptually novel periodontal drug delivery system that is intended for the treatment of microbial infections associated with peridontitis was described elsewhere. . 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. [19]

Lozenges

Bioadhesive lozenges may be used for the delivery of drugs that act topically within the mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. [19]

Semi-solid dosage forms

Gels

Gel forming bioadhesive polymers include crosslinked polyacrylic acid that has been used to adhere to mucosal surfaces for extended periods of time and provide controlled release of drugs.

Patches/films.

Flexible films may be used to deliver drugs directly to a mucosal membrane. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site. Buccal adhesive films are already in use commercially.[19]

Patch systems are the formulations that have received the greatest attention for buccal delivery of drugs. They present a greater patient compliance compared with tablets owing to their physical flexibility that causes only minor discomfort to the patient. Patches are laminated and generally consist of an impermeable backing layer and a drug-containing layer that has mucoadhesive properties and from which the drug is released in a controlled manner**.** [19] **Table 4** explains buccal adhesive films described in literatures.

Liquid dosage forms

Viscous liquids may be used to coat buccal surface either as protectants or as drug vehicles for delivery to the mucosal surface.

A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been recently developed, and it is now in clinical phase II trials.This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth. [19]

Commercially available buccal adhesive drug delivery systems

Recent reports suggest that the market share of buccal adhesive drug delivery systems are increasing in the American and European market with the steady growth rate of above 10%. Some of the commercially available buccal adhesive formulations are listed in Table 5.

Table 5: Commercially available buccal adhesive formulations [19].

Brand Name	Bioadhesive Polymer	Company	Dosage forms
Buccastem	PVP, Xanthum gum, Locust bean gum	Rickitt Benckiser	Tablet
Suscard	HPMC	Forest	Tablet
Gaviscon Liquid	Sodium alginate	Rickitt Benckiser	Oral liquid
Orabase	Pectin,gelatin	Orabase	Pectin,gelatin
Corcodyl gel	HPMC	Glaxosmithkline	Oromucosal Gel
Corlan pellets	Acacia	Celltech	Oromucosal Pellets
Fentanyl Oralet tm		Lexicomp	Lozenge
Miconaczole Lauriad		Bioalliance	Tablet
Emezine TM		BDSI's	

BEMA Fentanyl		BDSI's	
Straint tm SR		Ardana	
Zilactin		Zila	Buccal film
Luborant	Sodium CMC	Antigen	Artificial Saliva
Saliveze	Sodium CMC	Wyvem	Artificial Saliva
Tibozole		Tibotec	Tablet
Aphtach	Hydroxypropyl cellulose Polyacrylic acid	Tejin Ltd	Tablet
Buccastem buccal	Xanthan gum	Reckitt	Tablet
Povidone	Benkner Plc		
Oralin – Gencrex	Unknown	Generex Biotechnology (Phase II trials)	Solution
Lauriad (Phase III trials)	Unknown	BioAlliance Pharma	Tablet
Striant SR buccal	Carbomer 934P Hypromellose Polycarbophil	Ardana Bioscience Ltd	Tablet
Suscard buccal	Hypromellose	Forest Laboratories	Tablet

Delivery of proteins and peptides

The buccal mucosa represents a potentially important site for controlled delivery of macromolecular therapeutic agents, such as peptides and proteins. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. A variety of proteins/peptides with or without penetration enhancer were studied by different scientists using different animal models like dogs, rabbits, rats, pigs and humans. Some of those developments are represented in **Table 6.**

Table 6: Buccal adhesive formulations of proteins/ peptides described in literature.

Protein/peptide drug	Dosage form	Enhancer	Animal model	% increase in bioavailability	references
Buserelin	Patch	SGDC	Pig, rat	12.7%	[67]
Calcitonin	Tablet	No enhancer	Rabbits	37%	[68]
Captropil	Tablet	SGDC	Humans		[69]
Colony stimulating Factor (G-SCF)	Patch	No enhancer	Dogs	Two fold increase in pharmacological action	[70]
Fnalapril	Solution	No enhancer	Human	No significant increase	[71]
Glucose like peptide	Tablet	STC	Human	4 – 23%	[72]
Gonadotropin	Tablet	SC, SDC	Dog	SDC> SC>STC>STDC	[73]

releasing Hormone		STDC, STC			
Inteferorn	Solution	No enhancer	Mice	Marked increase	(74)
Insulin	Liposomes	No enhancer	Rat	No significant increase	[75]
Lisinopril	Solution	No enhancer	Human	No significant increase	[71]
Lutinizing hormone Releasing hormone	Tablet	SDC 5%	Dog	273%	[76]
Octreotide acetate		Azone EDTA,STC	Dog	Azone>SC>EDTA>STC	[77]
Oxytoxin	Patch	No enhancer	Rabbit	Slight increase	[78]
Protrelin (TRH)	Patch	Citric acid Sodium 5-Methoxy salicylate	Human Rats	Increase in plasma thyrotropin concentration	[79]
Recombinant human Interferon alpha B/D Hybrid	Solution	No enhancer	Rabbit,Rat	0.005%	[80]

Future challenges and opportunities

The main impediment to the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption. The relatively recent evolution of recombinant DNA research and modern synthetic and biotechnological methodologies allow the biochemist and chemist to produce vast quantities of variety of peptides and proteins possessing better pharmacological efficacy. However, therapeutic potential of these compounds lies in our ability to design and achieve effective and stable delivery systems. The future challenge of pharmaceutical scientists will not only be polypeptide cloning and synthesis, but also to develop effective non-parenteral delivery of intact proteins and peptides to the systemic circulation. Buccal permeation can be improved by using various classes of transmucosal and transdermal penetration enhancers such as bile salts, surfactants, fatty acids and derivatives, chelators and cyclodextrins. [19]

Researchers are now looking beyond traditional polymer networks to find other innovative drug transport systems. Much of the development of novel materials in controlled release buccal adhesive drug delivery is focusing on the preparation and use of responsive polymeric system using copolymer with desirable hydrophilic/hydrophobic interaction, block or graft copolymers, complexation networks responding via hydrogen or ionic bonding and 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 like inclusion of pH modifiers, enzyme inhibitors, permeation enhances etc. Novel buccal adhesive delivery system, where the drug delivery is directed towards buccal mucosa by protecting the local environment is also gaining interest. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides. Microparticulate bioadhesive

systems are particularly interesting as they offer protection to therapeutic entities as well as the enhanced absorption that result from increased contact time provided by the bioadhesive component. Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa. Successfully developing these novel formulations requires assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials. [19]

Conclusion

The need for research into drug delivery systems extends beyond ways to administer new pharmaceutical therapies. The safety and efficacy of 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 healthcare perspective, finding ways to administer injectable medications is costly and some time leads to serious hazardous effects. Hence inexpensive multiple dose formulations with better bioavailability are needed. Improved methods of drug release through trans-mucosal 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, retentivity, 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 is increasing. The growth rate for transmucosal drug delivery systems is expected to increase 11% annually through 2007. Worldwide market revenues are at $3B with the U.S. at 55%, Europe at 30% and Japan at 10%. [19]

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