International Journal of Advanced Pharmaceutical Sciences, Volume 1, Issue 08, Page 86-104
ISSN:2456-8147

RECENT ADVANCES IN MUCOADHESIVE BUCCAL DRUG DELIVERY SYSTEM AND ITS MARKETED SCOPE AND OPPORTUNITIES

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An open access journal

Supporting Information:

Received: 22 July 2018
Accepted: 31 July 2018
Published: 07 August 2018

Competing Interests:
The authors have declared that no competing interests exist.

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ABSTRACT

Extensive efforts have been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drug but also for better compliance of systemic drug delivery. Mucoadhesive characteristics are a factor of both the bioadhesive polymer and the medium in which the polymer will reside. Buccal dosage forms can be of Matrix or Reservoir types. However, this route could become a significant means for the delivery of a range of active agents in the coming years, if the barriers to buccal drug delivery are overcome. Mucoadhesive drug delivery system prolong the residence time of the dosage form at the site of application or absorption and facilitate an intimate contact of the dosage form with the underline absorption surface and thus contribute to improved and better therapeutic performance of the drug.

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. The objective of this article is to review buccal drug delivery by discussing the structure and enviorment of the oral mucosa and highlighting the mechanism of drug permeation and methodology in evaluating buccal formulations. This review also highlights a brief description of advantages, limitations of buccal drug delivery and theories of bioadhesion, mucoadhesive polymer, mechanism of buccal absorption along with mucoadhesive dosage form, factors affecting mucoadhesion.

Keywords: Mucosa, Mucoadhesion, Mucoadhesive Polymers, Mucoadhesive Drug Delivery System.

Introduction

Conventional dosage forms for delivery of drugs via the oral mucosa include solutions, erodible or chewable, buccal or sublingual tablets and capsules. Unfortunately, a major portion of the drug in these systems may be unavailable due to involuntary swallowing and a very short residence time, because of mastication, speech etc. and hence sustained release is usually not within the scope of such formulations. In recent years, significant interest has been shown in the development of novel bioadhesive dosage forms for mucosal delivery of drugs that attempt to overcome these limitations. Drug absorption into the oral mucosa is mainly via passive diffusion into the lipoidal membrane. Compounds with partition coefficient in the range 40-2000 and pKa2-10 are considered optimal to be absorbed through buccal mucosa. Compounds administered by buccal route include steroids, barbiturates, papain, and trypsin etc. Drugs can be absorbed from the oral cavity through the oral mucosa either by sublingual or buccal route [1]. Absorption of therapeutic agents from these routes overcomes premature drug degradation within the gastrointestinal tract as well as active drug loss due to first-pass hepatic metabolism that may be associated with oral route of administration [4]. In general, rapid absorption from these routes is observed because of the thin mucus membrane and rich blood supply. After absorption, drug is transported through the deep lingual vein or facial vein which then drains into the general circulation via the jugular vein, bypassing the liver and thereby sparing the drug from first-pass metabolism.

Since sublingual administration of drugs interferes with eating, drinking and talking, this route is generally considered unsuitable for prolonged administration. On the other hand, the duration of buccal drug administration can be prolonged with saliva activated adhesive polymers without the problems of sublingual administration [1,3].

In recent years, significant interest has been shown in the development of novel bioadhesive dosage forms for mucosal delivery of drugs that attempt to overcome these limitations A bioadhesive dosage form necessitates the use of mucoadhesive polymers to adhere to mucosa and withstand salivation, tongue movement and swallowing for significant period of time [3]. High molecular weight polymers are generally used for bioadhesion. Hydrogen bonding due to

hydrophilic groups such as -COOH or -OH plays an important role in bioadhesion [4]. The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS) of existing drug molecule to maximize their effect in terms of therapeutic action and patient protection. Mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in a high drug flux through the absorbing tissue. In addition, mucoadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce the overall dosage required and to minimize the side effects that may be caused by the systemic administration of the drugs.

Advantages of Mucoadhesive Buccal Drug Delivery Systems

1. Ease of administration.
2. Termination of therapy is easy.
3. Permits localization of drug to the oral cavity for a prolonged period of time.
4. Can be administered to unconscious patients.
5. Offers an excellent route, for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
6. A significant reduction in dose can be achieved thereby reducing dose related side effects.
7. Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route.
8. Drugs which show poor bioavailability via the oral route can be administered conveniently.
9. It offers a passive system of drug absorption and does not require any activation.
10. The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.
11. Systemic absorption is rapid.
12. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents etc.
13. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.

Limitation of Buccal Drug Administration [1,5,6,7, 8]:

Drug administration via buccal mucosa has certain limitations.

1. Drugs, which irritate the oral mucosa, have a bitter or unpleasant taste, odour; cannot be administered by this route.

2. Drugs, which are unstable at buccal pH cannot be administered by this route.

3. Only drugs with small dose requirements can be administered.

4. Drugs may swallow with saliva and loses the advantages of buccal route.

5. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.

7. Swallowing of the formulation by the patient may be possible.

8. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by the swelling and hydration of the bioadhesive polymers.

Marketed Scope and Opportunities

Novel drug delivery systems are becoming one of the most important fields in the modern pharmaceutical formulation technology. Several techniques are employed to design the sustained or controlled drug delivery systems. Studies on mucoadhesive systems have focused on a broad array of aspects. It is a growth area whose goal is the development of new devices and more "intelligent" polymers, as well as the creation of new methodologies that can better elucidate the mucoadhesion phenomenon. With the great influx of new molecules stemming from drug research, mucoadhesive systems may play an increasing role in the development of new pharmaceuticals.

The advantages are tremendous which make further study in this field extremely important. The formulation of these drug delivery systems depends on the developments of suitable polymers with excellent mucosal adhesive properties, stability and biocompatibility. The buccal cavity provides a highly vascular mucous membrane site for the administration of drugs. The epithelial lining of the oral cavity differs both in type (keratinized and non-keratinized) and thickness in different areas, and the differences give rise to regional variations in permeability to drugs. So

far, the oral mucosa has been utilized for the delivery of small drug molecules, since their adsorption occurs more reproducibly and rapidly. The main advantages of the buccal route of administration over the traditional per oral route are that drug degradation in the stomach is avoided, first-pass metabolism is avoided, and therapeutic drug levels of drug can be achieved rapidly. Clearly these advantages are presently clinically relevant for only a limited number of drugs. However, with the recent developments of new formulation types, such as mucoadhesive preparations and the use of peptides as drugs, this number may increase in the future. Mucoadhesive drug delivery systems available in the market include attach tablet (Triamcinolone acetonide), suradrin tablet (Nitroglycerin), Buccostem tablet (prochlormperazine maleate). Salcoat powder sprays (Beclomethazone dipropionate). Rhinocort powder spray (Beclomethazone Dipropionate) and sucralfate (Aluminum hydroxide). Though there are only a few mucoadhesive formulations available currently, it can be concluded that drug delivery using mucoadhesive formulations offers a great potential both for systemic and local use in the near future.

Mucoadhesive drug delivery systems, are gaining popularity day by day in the global pharma industry and a burning area of further research and development. Extensive research efforts throughout the world have resulted in significant advances in understanding the various aspects of mucoadhesion. The research on mucoadhesives, however, is still in its early stage, and further advances need to be made for the successful translation of the concept into practical application in controlled drug delivery system (CDDS). There is no doubt that mucoadhesion has moved into a new area with these new specific targeting compounds (lectins, thiomers, etc.) with researchers and drug companies looking further into potential involvement of more smaller complex molecules, proteins and peptides, and DNA for future technological advancement in the ever-evolving drug delivery arena.

Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract are avoided.

The area is well suited for a retentive device and appears to be acceptable to the patient. 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. Novel buccal delivery such as soluble thin films, mucoadhesive films and rapid mist spray offers newer route of delivery for the generics that has lesser patient's compliances. This report will provide detailed analysis on buccal delivery systems in broader pharma market in finding companies and technologies and complexities involved in developing this unique high potential delivery system [9]

Rationalist approach of MBDDS towards different diseases

Cardio vascular disease

Hypertension, one of the major cardiovascular diseases, needs a lifelong therapy to remain under control. Most of the antihypertensive drugs like carvedilol, metoprolol, propranolol, isosorbide mononitrate etc. have low oral bioavailability and smaller half-life. Two main reasons for low bioavailability are poor aqueous solubility and high first pass metabolism. The buccal mucoadhesive route of drug delivery provides direct access to the systemic circulation through the internal jugular vein by passing the first pass metabolism, leading to high bioavailability.

The dose of carvedilol, a model antihypertensive drug, is 25 mg twice a day; however, a lower effective dose is reported to be approximately 3.125 mg. Thus, by increasing the contact time and avoiding the first pass metabolism, a lower amount of drug can effectively produce the normal dose effect.

Again, by sustaining the drug release, the frequent administration of drug can be avoided, thereby increasing the patient compliance [11], [12].

Fungal/microbial infections

Oral candidiasis is an opportunistic fungal infection caused by Candida albicans. These yeast infections are usually treated locally by application of gels or suspensions. Release of drugs from these preparations involves an initial burst of activity whose level rapidly

declines to sub therapeutic concentrations. Thus, systemic antifungals such as fluconazole are usually preferred for treating oral candidiasis. The oral dose of fluconazole for the treatment of oral candidiasis (100 mg/day for 1 or 2 weeks) results in notable side effects varying from headache, nausea to liver dysfunction, and hepatic failure. Furthermore, oral fluconazole is reported to interact with a number of medications, including oral hypoglycemics, coumarin-type anticoagulants, cyclosporins, terfenadine, theophylline, phenytoin, rifampin, and astemizole. The pathogenic yeasts in oral candidiasis are usually detected in the superficial layers of the oral mucosa. Thus, the effectiveness of the systemic fluconazole may be partially topical through its concentration in oral fluids. The reported topical efficacy of fluconazole together with the adverse effects and drug interaction of systemic fluconazole justifies the design of MBDDS containing a small dose of fluconazole to increase the contact between the drug and the pathogenic yeast for a long time[13],[14].

Migraine

Migraines are thought to occur when certain blood vessels in the brain become swollen (dilated). Drugs used for the treatment include the "triptan" group, comprising of sumatriptan, zolmitriptan, and rizatriptan. These drugs work by helping blood vessels in the brain to return to normal size. It may also block pain signals in the brain. The model drug, sumatriptan is administered orally, in doses of 25, 50 or 100 mg as a single dose, nasally in doses of 10 mg or 20 mg and also subcutaneously as two 6-mg doses over 24 hours. Nasal route and subcutaneous route have their own limitations, like lower retention time for nasal solution and inability of self- administration for injectables, respectively [15],[16].

This justifies a need to develop an effective formulation, which allows the drug to directly enter the systemic circulation, bypassing the first-pass metabolism, thereby increasing bioavailability of sumatriptan succinate. Buccal mucosal route is one such alternative.

Nausea and vomiting

Ondansetron HCl, chosen as a model drug for treating postoperative nausea and vomiting associated with emetogenic cancer chemotherapy, possesses certain characteristics that a drug should have to get absorbed through buccal mucosa viz., biphasic solubility and low

molecular weight. Moreover, the primary route of ondansetron clearance is by hepatic phase I metabolism, so its bioavailability may be improved when delivered through the buccal mucosal route. Patients may have frequent vomiting following chemotherapy and they may be unable to swallow a tablet to prevent vomiting. It justifies the need to develop a buccal patch/film of ondansetron hydrochloride, which increases patient compliance. Its bioavailability when administered by oral route is only 50% to 60% and its dose is low i.e., 4-8 mg; hence, it can be conveniently loaded onto a patch [17],[18].

Clinical/Therapeutic Approach

Cardio vascular diseases

Carvedilol is a non-selective beta-adrenergic antagonist used in the treatment of hypertension and stable angina pectoris. Yamsani et al. proposed the utilization of carvedilol mucoadhesive tablets for the treatment of hypertension. In this hydrophilic polymer formulation, hydroxypropyl methylcellulose (HPMC K4M and K15M) and Carbopol 934 (CP 934) were used to obtain controlled and zero order release. Studies revealed that increasing the concentration of the polymer in the formulations showed a sustained effect on carvedilol release. The rapidly hydrating polymer dominated in controlling the release of carvedilol from the buccal tablets [19].

Buccoadhesive patch of PRO-HCl was developed by the same workers using the hydrophobic polymer Eudragit L-100 as the base matrix. A stability study of optimized Eudragit patches was done in natural human saliva; it was found that both drug and buccal patches were stable in human saliva [20]

Antimicrobial therapy

The clinical treatment of oral candidosis (a common pathological condition of the oral cavity) using conventional pharmaceutical dosage forms-such as solutions, gels, suspensions, and mouthwashes-is usually not very effective, mainly because drugs are quickly removed from the oral cavity. These tablets released nystatin quickly from the lactose layer and then in a sustained way, during approximately 6 hours, from the polymeric

layer [21].Chlorhexidine diacetate was used by Giunchedi et al. to formulate buccal tablets based on chitosan microspheres [24].

Anti-inflammatory therapy

Inflammatory processes are one of the major reasons for oral cavity diseases [25]. This problem is managed with topical administration of various nonsteroidal, anti-inflammatory drugs, like flurbiprofen, flufenamic acid, ibuprofen etc. Designed sustained-release mucoadhesive bilayered tablets, using mixtures of mucoadhesive polymers and an inorganic matrix (hydrotalcite), for topical administration of flurbiprofen in the oral cavity. The optimized formulation, loaded with 20 mg of the drug, showed the best results, producing good anti-inflammatory sustained release in the buccal cavity for 12 hours and thus a reduction in daily drug dosage (40 mg /vs. 70 mg)[25].

This justifies a need to develop an effective formulation, which allows the drug to directly enter the systemic circulation, bypassing the first-pass metabolism, thereby increasing bioavailability of sumatriptan succinate. Buccal mucosal route is one such alternative.

Antiemetics Ondansetron hydrochloride is a 5HT3 serotonin antagonist used in the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy [28],[29]. As administering drug by buccal route avoids hepatic first-pass metabolism, delivery of ondansetron to the systemic circulation via the buccal route would improve its bioavailability. The stability of drug in the optimized adhesive tablet was tested for 6 h in natural human saliva; both the drug and device were found to be stable in natural human saliva [30].

Muscle relaxants

Tizanidine hydrochloride is an imidazoline derivative which acts as agonist on centrally located α2 receptors and this leads to myotonolytic effects on skeletal muscle. Shanker et al. formulated and evaluated bioadhesive buccal tablets of tizanidine using bioadhesive polymers such as HPMC K4M, SCMC alone, and a combination of these two polymers, in an attempt to avoid first-pass effect and provide for prolonged release of the drugThe degree

of swelling indicated that the rate of swelling is directly proportional to SCMC content and inversely proportional to HPMC K4M content [32].

Protein and hormone delivery

The delivery of peptide drugs across the buccal mucosa is more convenient and safer than other delivery approaches. It is shown that the buccal administration of drugs has some advantages, such as low enzymatic activity compared with the gastro intestinal track, and tolerance to potential sensitizers [33]–[34]. Insulin was used by Cui et al. as a model protein and its release behavior from bilaminated films was evaluated. The insulin loaded bilaminated film showed a pronounced hypoglycemic effect following buccal administration to healthy rats, achieving a 17% pharmacological availability compared.

Oral mucosa [31,32,33] The total area of the oral cavity is 100cm^2. One third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The main role of oral mucosa is protection of tissue underlying. Oral epithelium proliferation time is 5-6 days. Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regionsOral cavity proper which extends from teeth and gums back to the faucets (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

Functions of Oral Cavity

• It helps in chewing, mastication and mixing of food stuff.

• It is Helps to lubricate the food material and bolus.

• To identify the ingested material by taste buds of tongue.

• To initiate the carbohydrate and fat metabolism.

• As a portal for intake of food material and water.

• To aid in speech and breathing process.

Overview of Buccal Mucosa

The oral mucosa is composed of an outermost layer called stratified squamous epithelium and below a basement membrane; a lamina propria followed by the sabmucosa as the inner most layer. It also contains many sensory receptors including the taste receptors of the tongue. The blood epithelium is classified as non keratinized tissues. It is penetrated by tall and conical shaped connective tissues. These tissues which are referred to as lamina propria, consist of colagen fibers a supporting layer of connective tissues, blood vessel and smooth muscles. The epithelium may consist of a single layer (stomach, small and large intestine, bronchi) or multiple layers (esophagus, vagina). The upper layer contains goblet cells, which secrete mucus components directly onto the epithelial surface. Specialized glands producing components of the mucous layer may also be located beneath the epithelium.

Methods to increase drug delivery via buccal route:

1. Permeation enhancers

The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances that facilitate the permeation through buccal mucosa are referred as absorption enhancers. As most of the absorption enhancers were originally designed for increase the absorption of drug and improved efficacy and reduced toxicity. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism.

Mechanism

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows:

• Changing mucus rheology**:** Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

• Increasing the fluidity of lipid bilayer membrane**:** The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Acting on the components at tight junctions**:** Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption. Some examples of permeation enhancers Lauryl ether, Phosphatidylcholine, Aprotinin, Azone Polysorbate 80, Benzalkonium chloride

2. Prodrug

Nalbuphine and naloxone bitter drugs when administered to dogs via buccal mucosa causes excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in

prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds.

3. pH:

The in vitro permeability of acyclovir was found to be pH dependent with an increase in flux and permeability

Factors influencing drug absorption from the oral cavity

As the oral mucosa is a highly vascular tissue, the main factors that influence drug absorption from the mouth are:

a) The permeability of the oral mucosa to the drug.

b) Physicochemical characteristics of the drug and

c) Miscellaneous factors

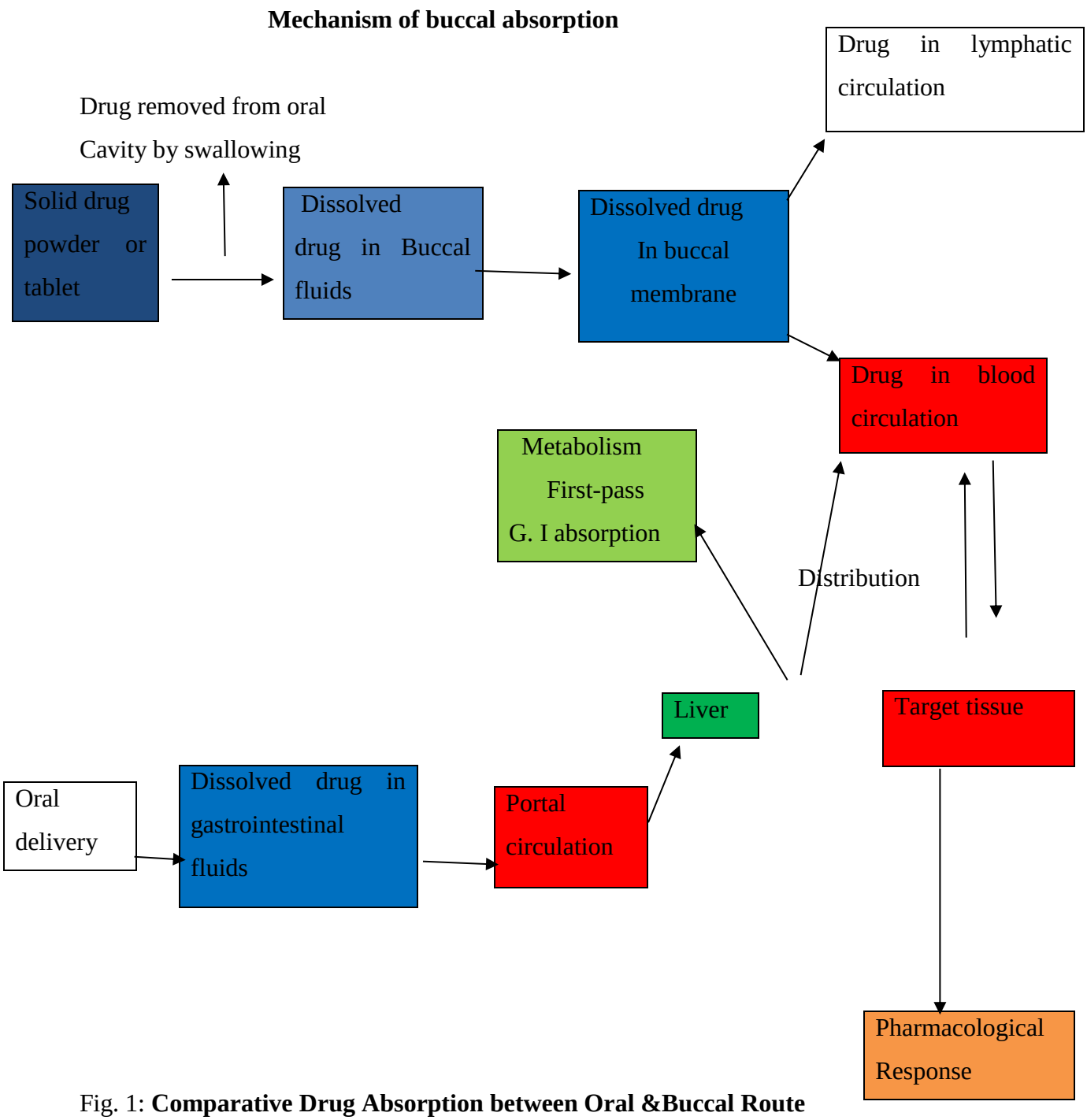

Fig. 1: **Comparative Drug Absorption between Oral &Buccal Route**

Different Buccal Mucoadhesive Dosage Forms [28,29]

Even though the mucoadhesive buccal drug delivery offers some distinct advantages, the ideal candidate for designing such formulations is always limited due to several factors. One of the important factors is size limitation. For an effective and comfortable buccal drug delivery system, the quantity of drug moiety enclosed should be reasonably small, ideally 25 mg or less is more appropriate for buccal drug delivery 2. The drug shaving a short biological half-life can be formulated as buccal drug delivery and thus offering a sustained, prolonged and controlled delivery of drug from the designed dosage form. The different type of buccal drug delivery system includes, adhesive tablets, adhesive gels, adhesive patches, adhesive ointments, adhesive powders and buccal chewing gums etc.

A. Mucoadhesive buccal films

These are mainly referred to transparent drug loaded films which are intended to be placed in the buccal mucosa because of its adhesive character. Buccal films can be more preferred over other dosage forms because of its flexibility and comfortness.

The mucoadhesive buccal patches can be of two types

a) Matrix type

Drug, adhesive and additives mixed together and this mixture is then designed in the form of patches.

b) Reservoir type

Drug and additives should be separated from the additives. Depending on the presence or absence of a backing membrane, the release from the patch is unidirectional or bi-directional.

B. Mucoadhesive buccal tablets

These are similar to conventional tablets, but they have the property of mucoadhesion, and instead of swallowing, they held in between cheeks and gums. These tablets are sufficiently dissolved by the medium, provided from locations where they are placed. But the dissolution of tablet should be slowing order to ensure a sustained and controlled release. A care should be given to ensure the controlled dissolution of such dosage forms. Hence the adhesive tablet does not contain any disintegrants. tablets which are intended to adhere with the

buccal cavity and gets softened due to the production of saliva continuously in the mouth and which ensures the complete drug release in the systemic circulation through the blood capillaries in the buccal cavity and thereby by-passes the hepatic metabolism. .

C. Semi solid buccal mucoadhesive dosage form

Gels and ointments as semisolid dosage form for mucoadhesive drug delivery marches out significant approaches throughout the oral mucosa The major advantage with these systems is that they shows a plastic rheological behavior, and thus offer a prolonged residence time with the surface application.

D. Buccal chewing gum

Medicated chewing gum is particularly used in the treatment of oral cavity and in nicotine replacement therapy.. Buccal patches are preferred as best mucoadhesive buccal drug delivery system because of its flexibility and patient comfort.

E. Microparticles

Have more advantages than tablet. The physical properties of microspheres enable to make them closely contact with a large mucosal surface. They can also be delivered to less accessible sites like GI track and nasal cavity and they cause less local irritation at the site of adhesion but the success of these microspheres is limited due to their short residence time at site of absorption.

F. Wafers

A novel periodontal drug delivery system. This is used for the treatment of microbial infection. Surface layers possessing adhesive properties, while the bulk layer consists of antimicrobial agents, biodegradable polymers, matrix polymer.

G. Lozenges

Are used as topically within mouth including antimicrobials, corticosteroids, local anaesthetics, antibiotics and antifungals. In lozenges multiple daily dosing required because the release of drug in oral cavity is initially high and then rapidly decline.

Conclusion

Mucoadhesive drug delivery system utilize the property of bioadhesion of certain water soluble polymer which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for an extended period of time. Development of novel mucoadhesive delivery systems are being undertaken so as to understand the various mechanism of mucoadhesion and improved permeation of active agents. Many potential mucoadhesive systems are being investigated which may find their way into the market in near future. The idea of bioadhesive began with the clear need to localize a drug at a certain site in the GI tract. Therefore a primary objective of using bioadhesive systems orally would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing.

This review concludes that the mucoadhesive drug delivery system was found to be a better alternative to the conventional oral route. It is a unique alternative to conventional drugs by virtue of its ability in overcoming hepatic metabolism, reduction in dose, frequencies and enhancing bioavailability. This delivery system will shows a controlled release of drug; ease of application and the formulation and evaluation of such systems does not have any complication. So we can expect that the mucoadhesive system may be one of the important dosage form in the future pharmaceutical and health care sector.

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