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Review Article

ADVANCES IN NONINVASIVE DRUG DELIVERY SYSTEMS OF OPIOIDS: FORMULATIONS AND CLINICAL PERSPECTIVE

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ABSTRACT

Opioid continues as the main pharmacological treatment for severe acute pain. Extensive first-pass metabolism is the major limitation of opioid delivery by oral route. Thus, the parenteral route has been the only option for the delivery of opioids before the beginning of the 21st century. However, as the delivery through parenteral route is associated with limitation of being invasive, a strong need for developing non-invasive delivery systems has been felt among the drug delivery scientists. Since mucosal surfaces are rich in blood supply and provide rapid drug transport to the systemic circulation, this delivery system has been explored to enhance opioid bioavailability by avoiding their degradation through first-pass hepatic metabolism. Oral transmucosal delivery such as buccal and sublingual has progressed far beyond the use of traditional dosage forms developed with novel approaches emerging continuously. This review provides updated information about the use of opioids for the treatment of severe pain with special emphasis on the work done by various scientists on formulation development of opioid analgesics, especially by buccal and sublingual route for delivery of opioids along with their clinical perspective. Particular attention is given to new approaches enhancing bioavailability of opioids by these routes.

Keywords: Opioids, Buccal, Oral drug, Sublingual delivery of opioids.

INTRODUCTION

Pain a direct response to an untoward event associated with tissue damage such as injury, inflammation or cancer, but severe pain can arise independently of any predisposing cause and can persist for a long period even after the precipitating injury has healed [1]. Pain management is a branch of medicine for easing the suffering and improving quality of life of those living with pain and is one of the most important therapeutic priority [1]. Opioid analgesics are drug of choice for management of both acute and chronic severe pain. These drugs are used successfully in long-term care strategy for patients with chronic cancer pain and thus play an important role in pain management [2]. Morphine is the first line of treatment and all the narcotic analgesics are compared to it [2].

Most opioid analgesics are although well absorbed when given orally, however, because of the first-pass effect; their oral bioavailability is poor, and thus, the oral dose of the opioid needs to be higher than the parenteral dose to elicit a therapeutic effect. Therefore, most of the available formulations are parenteral. However, parenteral formulations have their own limitations mainly because of their invasive nature. These need skilled person for injecting the medicine. Therefore, it is easier to administer these medications to hospitalized patients but compliance becomes an issue for out-patients. Because of the sterility condition, the cost of production of these parenteral is also high as compared to other dosage forms. Owing to these inherent limitations of parenteral formulations, and opioids being the first line of treatment in many therapeutic indications, a considerable amount of research is carried out to formulate non-invasive delivery systems of opioid analgesics with improved bioavailability.

The present work reviews the advancements in the delivery of opioids using non-invasive routes. The work critically analyzes the various strategies, technologies and research approaches used by various researchers in order to improve the delivery by transmucosal route, i.e., in a non-invasive manner.

Oral drug delivery of opioids

Oral drug delivery is the most popular and convenient drug delivery system among the healthcare professional and patients. It provides maximum surface area for drug absorption as compared to buccal or sublingual route. It is mostly preferred over parenteral delivery systems as it does not need a skilled person for injecting the medicine. In addition, oral formulations are highly cost-effective as compared to parenteral formulations which require strict standards of sterility during production. The main problem associated with oral drug delivery of opioid analgesics is the first pass biotransformation of opioids in the liver. All opioid analgesics when given orally they get absorbed via the gastric and duodenal mucosa and transported to the liver via the portal venous system, where it undergo, "first pass metabolism" before it enters the systemic circulation. This has a major impact on the amount of drug available in the systemic circulation [3]. Hence, the oral formulations of opioid analgesic are less available in market as compared to opioids parental, sublingual and buccal formulations as shown in Table 1. Certain work has been reported on controlled release oral opioid formulations, whereby attempts to control the release of opioids have been made using polymeric microparticles [4] and *in situ* gel formation approach [5]. No studies are reported in literature to improve the bioavailability of these formulations and their advantages over the existing oral formulations.

A common problem with the use of opioids is the non-medical use of prescription opioids. For this reason, regulatory agencies encourage pharma companies to make their formulations abuse resistant. Oxycodone is widely used opioid analgesic for the management of moderate to severe pain. Oxycodone has very short half-life (4.5 hrs), necessitating the need of high dose frequency. Zamloot *et al.* developed oral extended release oxycodone capsule, in abuse deterrent viscoelastic matrix. The viscosity of the formulation was such that it can't be filled in syringes or evaporated to get the residue and injected for abuse purpose. The technology was named as Oradur® [6]. This technology deter the most common methods of tampering that would lead to rapid release of the complete opioid content including crushing and swallowing or

Table 1: Marketed formulations of opioid analgesics

Opioid analgesics	Marketed dosage form	Route of administration	Company	Bioavailability (%)
Hydromorphan HCl	Tablet (dilaudid)	Oral	Purdue Pharm Prods	21 [75]
	Tablet (exalgo)			
	Injectable (dilaudid)	Parental		100
Oxicodone HCl	Tablet (oxycontin)	Oral	Purdue Pharm Prods	60-80 [76]
	Capsule	Oral	Glenmark Generics Inl	60-87 [77]
Fentanyl citrate	Injectable	Parental	Hospira	100
	Tablet (Fentora®)	Buccal, sublingual	Cephalon	65 [78,79]
	Spray (Lazanda®)	Nasal	Depomed Inc.	85 [80]
	Film (Onsolis®)	Buccal	Meda pharms	71% (51% via buccal mucosa and 20% via GIT) [81]
	Patch (Duragesic®)	Transdermal	Janssen Pharmaceuticals Inc.	50 [82]
	Tablet (Abstral™)	Sublingual	Galena Biopharma	54 [83,84]
	Spray (Subsys®)	Sublingual	Insys Therapeutics Inc	76 [85-89]
Buprenorphine hydrochloride	Injectable (Buprenex®)	Parental	Reckitt Benchiser	100
	Tablet	Sublingual	Roxane	50 [90]
Buprenorphine HCL and naloxone HCL	Film (Bunavail®)	Buccal	Biodelivery Sci Intl	59 [27,28,33,34,91]
	Tablet (Suboxone®)	Sublingual	Reckitt Benchiser	50 [48]
	Film (Suboxone®)			59 [56-58]
Butorphanol tartrate	Injectable	Parental	Hospira, Bedfort	100
	Spray	Nasal	Mylan, Novex	60-70 [92]
Pentazocine lactate	Injectable (Talwin®)	Parental	Hospira	100
Nalbuphine hydrochloride	Injectable	Parental	Hospira	100
Sufentanil citrate	Injectable	Parental	Hospira, Akorn, Hikma Maple	100
Alfentanil hydrochloride	Injectable	Parental	Hospira, Akorn	100
Remifentanil hydrochloride	Injectable	Parental	Mylan Institutional	100
Meperidine HCL	Injectable (Demerol®)	Parental	Hospira	100
	Tablet (Demerol®)	Oral	Sanofi Aventis US	40-60 [93]
Morphine sulphate	Capsule (Avinza®)	Oral	Ligand Pharmaceuticals Incorporated	<40 [94]

HCL: Hydrochloride, GIT: Gastrointestinal tract

crushing for subsequent snorting, extracting, injection, or volatilization (i.e. to promote smoking or inhalation). In the aqueous medium or in gastrointestinal tract (GIT), the fluid matrix transform from the viscous state to a matrix with predominantly elastic properties that controls the rate of drug release and resists drug extraction. Oxycodone developed using this technology is sold under the brand name of Remoxy® [6]. Friedmann *et al*. evaluated the long-term safety, tolerability and efficacy of Remoxy® in patients with chronic pain related to osteoarthritis. The study revealed that frequency of oxycodone administration could be reduced to twice daily with Remoxy® extended release capsule [7].

The inherent problems of poor bioavailability of opioids due to first pass metabolism can't be possibly solved by administering opioids orally. Thus, more research efforts have been featured on delivering these molecules through transmucosal surfaces, e.g., buccal or sublingual. Research in these areas is discussed in the following sections.

Buccal drug delivery of opioids

From the various available transmucosal sites, buccal cavity mucosa is the most convenient and easily approachable site for delivering the therapeutic agents for both local as well as systemic delivery. As the mucosa has a rich blood supply, so it is relatively permeable to therapeutic agents and systemic effects achieved by administering the drugs through buccal route [8]. This route avoids the first pass effect, which results in dose reduction as compared to oral dose [8,9]. The lipophilicity of the molecule governs the rate of absorption. More lipophilic molecules get absorbed faster. For buccal administration, different dosage forms used are tablets, lozenges, pills, gels, and patches [10]. This system has high patient acceptance as compared to the other non-oral routes of administration of drugs as the drug administration is convenient. The patient can afford to have a longer residence time of a buccal system. Smaller is the size of system, better is the compliance. The formulations are made mucoadhesive so that they can stay longer at the delivery site resulting in improved bioavailability. The saliva in the mouth plays a key role in the dissolution and release of drugs from this delivery system. The contact area between buccal mucosa and formulation is limited in buccal delivery system, thus, formulation requires longer residence time to meet the complete dissolution of the drug. Following section discusses the developments in the buccal delivery systems of opioids.

Morphine, a gold standard of pain relief has been formulated into buccoadhesive tablet and evaluated for its bioavailability across the buccal membrane. This buccoadhesive tablet composed of hydroxypropylmethyl cellulose and carbomer as bioadhesive compounds and evaluated for *in vivo* absorption which revealed about 30% of drug absorption through buccal route [11]. Later Aiache formulated a bioadhesive buccal tablet system formulated using milk protein derivatives and reported enhanced bioavailability [12]. The studies were carried out in 12 healthy volunteers, and bioavailability of bioadhesive tablet was compared with morphine solution retained in the oral cavity for 10 minutes and morphine oral extended release tablets. It was found that bioavailability of bioadhesive buccal system was comparable to oral controlled release system. Although it was not superior to morphine oral controlled release tablets, it has advantage that during an emergency the buccal bioadhesive system can be easily removed to stop the drug delivery [13].

Fentanyl citrate a synthetic opioid analgesic is about 80-100 times more potent than morphine because of its lipophilicity. It gets absorbed quickly from the gut but is extensively metabolized due to first pass effect. Hence, the bioavailability of oral medication is much poorer than parenteral systems. The lipophilic nature of fentanyl citrate has been exploited in formulating its buccal delivery systems [14]. Fentanyl lozenges (Actiq™, Oralet™, Cephalon) have been developed as lollipop formulation where fentanyl citrate was loaded on a stick meant for chewing by keeping in the area between gum and lower lip. It dissolves slowly there and gets absorbed through transmucosal route [15,16]. These lozenges are very useful for breakthrough pain relief in opioid tolerant patients and for "incident-pain" analgesia especially in

children [17]. Randomized, placebo-controlled, blinded clinical trials carried out on children between the age group of 3-18 years showed that it is a rapid, safe and nonthreatening approach to sedation and analgesia for painful procedures in children [18]. A total of 48 children were selected for study underwent bone marrow aspiration or lumbar puncture and were randomly administered with either a placebo or fentanyl citrate lollipop. The lollipop was removed after 20 minutes or before if the patient fell asleep after complete consumption. 30 minutes after being given the lollipop, the patients were evaluated for their vital signs and oxygen saturation for every 10 minutes during and after administration of a lollipop for 1 hr. The lollipop formulation was very well accepted among the children.

Effervescent tablets of fentanyl citrate have also shown promising efficacy for the delivery of fentanyl citrate. The fentanyl buccal tablet (FBT) received the approval from USFDA in 2006 and from the European Commission in 2008 and is marketed under the trade names such as Effentora® and Fentora® [16]. For the development of an effervescent tablet a proprietary OraVescent™ technology has been used to produce an effervescent reaction that results in modifications in pH of microenvironment at the site of administration [19]. The pH modification is executed in such a way that initially acidic pH is created which increases solubility of fentanyl in the buccal cavity. The pH is then raised by the carbonates present in the formulation to increase the nonionic fraction that is favorable for absorption. Darwish *et al*. carried out the pharmacokinetic study of "Fentora®" and found that fentanyl was rapidly absorbed in healthy adult volunteers with T_{max} of about 35-45 minutes resulting in an average onset of analgesia of about 15 minutes compared to oral hydrocodone or oxycodone, which was approximately 45 minutes [14,20]. This proved superiority of FBT over oral hydrocodone and oxycodone. Manco *et al*. reported the significant efficacy of FBT in breakthrough cancer pain. These studies were carried out in opioid tolerant patients [21]. Kosugi *et al*. then carried out a randomized, double-blind, placebo-controlled study of FBT for breakthrough cancer pain in cancer patients. The analgesic onset of action was within 15 minutes and the treatment was well tolerated [22]. Similarly, the efficacy and safety of FBT was evaluated in 102 opioid tolerant adult patients with chronic neuropathic pain. This study confirmed a rapid onset of action of about 10 minutes with better effectivity and tolerability of FBT for the treatment of breakthrough pain [23]. Jandhyala *et al*. also studied the efficacy of FBT in opioids tolerant adult cancer patients with breakthrough cancer pain. These studies revealed that although the fentanyl preparation provides superior pain relief versus placebo in the first 30 minutes, FBT exhibits an 83% of superior pain relieving efficacy [24]. Fine *et al*. further studied the long-term safety and tolerability of FBT for the treatment of breakthrough pain in opioid tolerant patients with chronic pain [25]. Since 2006, the FBT is well accepted as buccal mode of therapy for the treatment of breakthrough cancer pain.

With advent of thin-film technology in pharmaceuticals, buccal delivery of opioids through thin films was also explored. Opioid drugs such as fentanyl, buprenorphine alone and in combination with naloxone have been developed and are available in market. The buccal films of fentanyl citrate available in market (Onsolis®) are based on patented BioErodible MucoAdhesive technology [26-28]. In fact, this is the first prescription product in thin-film technology platform marketed since 2009 [29]. These films consist of two layers, one is bioadhesive containing fentanyl and other is inactive layer that acts as backing membrane. The bioadhesive layer control the release of fentanyl from the film, while the backing membrane maintains the flow toward the buccal membrane and prevents the drug from going to gut for inactivation. This system increases the total bioavailability of fentanyl to 48% as compared to 22% by oral route. In the same line of development, Consuelo *et al*. developed the bioadhesive film of fentanyl made with polyvinylpyrrolidone (PVP) of two different molecular weights: PVP K30 and PVP K90 as bioadhesive polymers and evaluated the *ex vivo* fentanyl permeability using pig esophageal model. The transport rates achieved from the PVP films suggest that a buccal system of only 1-2 cm^2 in surface area could meet a therapeutic effect equivalent to a 10 cm^2 transdermal patch, with a much shorter lag time [30]. Rauck *et al*. carried out randomized double-blind, placebo-controlled study of fentanyl buccal soluble film for breakthrough pain in cancer patients. This clinical study reveals that these fentanyl films were effective for control of breakthrough pain in patients receiving opioid therapy and were well tolerated in the oral cavity without any adverse effect [31].

Buprenorphine, a partial opioid receptor agonist, was also successfully added to this technology platform and showed a significant increase in bioavailability. The buccal film of buprenorphine available in market (Bunavail®) consists of opioid antagonist naloxone to prevent the parental abuse of the formulation. These films consist of two layers with selected pH; one is mucoadhesive layer containing buprenorphine with pH between 4 and 6 using buffering agent which maximizes absorption of buprenorphine and other is baking layer containing naloxone with pH between 4-4.8, which prevents absorption of naloxone [27,28,32,33]. This system increases the total bioavailability of buprenorphine to more than 40% in healthy subjects [33]. Bai *et al*. carried out the pharmacokinetic study of buprenorphine buccal film formulation in healthy volunteers. These studies revealed that the bioavailability of buprenorphine was about 46-51% from its buccal formulation in healthy human volunteers [34].

Sullivan and Webster carried out a 12 weeks conversion study of buccal film formulation of buprenorphine-naloxone for the treatment of opioid dependent adults [35]. A total of 249 subjects (mean age 38.7 years, 65.9% male) converted from buprenorphine naloxone sublingual tablet or film (SLBN) to a single daily dose of buprenorphine naloxone buccal film (BBN), and 79.1% completed the 12 weeks conversion study. The study data showed better acceptability of patients toward BBN since many patients accepted a single dose of BBN better instead of SLBN [35]. In this study, all the patients were undergoing treatment for opioid dependence.

Controlled delivery buccal patches of buprenorphine have been developed using polyisobutylene, polyisoprene, and carbopol 934P as bioadhesive polymer. Nearly 75% of the buprenorphine released after *in vitro* evaluation studies from the buccal patches following 24 hrs incubation period [36]. Thus, buccal route can offer a good non-invasive route for administration of opioids. No clinical studies are reported for this controlled release system.

Buccal disks are additional drug delivery system employed for buccal administration. These are mucoadhesive in nature and thicker than films but thinner than tablets. These are about 8-12 mm in diameter and about 2-5 mm in thickness and prepared using either compression or mold casting. Literature reports the studies on the formulation of buccal disks, but not many reports are there on its clinical efficacy. Han *et al*. studied the release of nalbuphine prodrug from mucoadhesive buccal disks. The buccal disks were prepared by compressing carbopol 934, hydroxypropyl cellulose and drug in a tablet compression machine. A backing layer of ethyl cellulose was applied on one side of this disk. Carbopol was studied as a mucoadhesive polymer, and the aim was to meet constant release of nalbuphine from these disks using various ratios of carbopol and hydroxypropyl cellulose. Five different prodrugs of nalbuphine were formulated into these disks. The findings suggested that release rate of nalbuphine could be controlled by solubility and amount of prodrug used. As expected, more hydrophilic prodrug showed faster release. A ratio of 90 mg carbopol and 30 mg hydroxypropyl cellulose was found to give consistent release of nalbuphine along with mucoadhesivity [37]. Gelatin was explored as mucoadhesive agent by Parodi *et al*., for formulating oxycodone loaded buccal disks [38]. Gelatin along with glycerol, sorbitol and drug was casted into disks using molds. The thickness of the film and amount of drug present was found to affect the mucoadhesion ability of the disk. The pharmacokinetics of these gelled disks was then evaluated in nine healthy volunteers. It showed that the oxycodone loaded disks have C_{max} and $AUC_{0-\infty}$, similar to conventional oral tablets but t_{max} was greater (about 3.7 hrs). Thus,

this formulation could be used as a controlled release dosage form for the delivery of oxycodone for inducing complete remission from the cancer pain. The studies showed that oxycodone 10 mg buccal disks could be given every 12 hrs compared to oxycodone 10 mg tablets given every 4-5 hrs [38]. Such controlled release buccal disks offer twice a day dosing regimen and thus, are a useful alternative to oral tablets, which are required to be taken 4-5 times a day. The limitation of these buccal disks is its thickness. Because of the thickness, it is inconvenient to keep them in the oral cavity for longer periods and hence is not patient friendly. Due to this limitation, these formulations despite being clinically effective could not make their way to the market.

In the world of digitalization, scientists are exploring the use of electronic devices for administration of drugs through various routes of administration. Using iontophoretic techniques drugs present in liquid dosage forms can be delivered in a controlled way through skin or mucosa [39,40]. Iontophoresis is introduction of ions of soluble salts into these surfaces of body with an electric current [41]. Taking advantage of this technology, Campisi *et al*. [42] developed a buccal drug delivery system for naltrexone. Naltrexone, although gets completely absorbed from GI but metabolized extensively by first-pass metabolism requiring the need of high dosage if given by oral route. The system was studied in pigs and naltrexone was found to appear in plasma within 5-10 minutes of administration and peak blood levels were obtained at around 90 minutes. After 6 hrs, the naltrexone levels delivered via iontophoresis were compared with intravenous (IV) delivery. Iontophoretic mechanism showed higher blood levels [42]. Such studies showed that iontophoretic technology has the potential to control the delivery and release of drugs. The formulation was found to show no signs of flogosis or tissue damage as studied by histology. Hence, buccal delivery by intraoral electronic device could be potentially used for inducing long-lasting, continuous and controlled blood levels of opioids, avoiding spikes of drug plasma levels which are typically observed in the case of IV route. Giannola *et al*. used this technology for improving the drug delivery across the buccal mucosa *in vivo* by making use of an electrical enhancement which carried out by direct current iontophoresis [43]. The various drugs used by the scientist for these iontophoretic techniques were monocationic salts with a molecular weight in the range of 303-378: Atenolol hydrochloride (HCl), naltrexone HCl and galantamine hydrobromide [43].

Thus, this iontophoretic technology is in the growing stages for used by buccal and another transmucosal route of drug delivery systems for treatment in chronic disease conditions.

Sublingual drug delivery of opioids

The sublingual epithelium is relatively thin as compared to buccal epithelium and has rich supply of blood vessels. This site of administration has been explored widely for absorption of drug molecules that undergo extensive first-pass metabolism. Molecules delivered by this route are also protected from acidic and enzymatic degradation of GIT. Drugs get absorbed by passive diffusion via sublingual mucosa [44]. Thus, this system provides a rapid onset of action as compared to orally ingested tablet [45]. This route of administration has been extensively used for the delivery of opioids since 1996.

Buprenorphine in sublingual tablet formulation (Subutex™) is approved for use in France since 1996 for the treatment of opioid addicts [10]. In the United States, it got approved in 2003 [46]. But because of the high abuse potential associated with Subutex™ an abuse-resistant formulation of buprenorphine was developed by adding opioid antagonist naloxone in 4:1 ratio. This formulation is currently been marketed only in the United States under the brand name of Suboxone™ and Zubsolv® [47]. Suboxone™ tablets consist of soluble excipients such as lactose, mannitol, dextrose, sucrose along with granulating and disintegrating agent such as starch and binding agents such as povidone or hydroxypropyl methyl cellulose. Lubricating agent used was magnesium stearate [48]. Abuse potential of this formulation is very low.

In Zubsolv® sublingual tablets micro particles of buprenorphine are present on the surface of water-soluble carrier particles made up of mannitol and citric acid. Size of micro particles is relatively small with respect to carrier particles which are larger in size. The citric acid carrier particles, maintains the pH around 4.0-6.5 for about 3 minutes at the site of administration which facilitates dissolution of buprenorphine micro particles and helps in the absorption of buprenorphine across the sublingual mucosa. Another carrier particles present in the formulation consists of opioid antagonist naloxone. These carrier particles are further mixed with particles of mucoadhesive promoting agent consisting of a polymer from cellulose derivatives which swells when brought in contact with the saliva and thus helps in adhering the formulation to mucosal tissue [49-53]. Both formulations are abuse deterrent but the additional advantage of Zubsolv® over Suboxone™ has been its mucoadhesive ability, faster disintegration, and better taste masking. This was proved in an open-label, two-period, randomized sequence, crossover study performed in 60 male and female healthy volunteers to compare bioavailability of buprenorphine and naloxone in Zubsolv® and Suboxone™ sublingual tablets [54]. The study revealed that Buprenorphine exposure was equivalent in Zubsolv® and Suboxone® tablets, whereas the sublingual dissolve time was significantly shorter for Zubsolv® than Suboxone® tablets and were similar to Suboxone® films. The Zubsolv® formulation was found to show higher subjective ratings for taste and acceptability than Suboxone® formulation.

Based on the Zubsolve™ concept, Bredenberg *et al*. developed bioadhesive sublingual tablets of fentanyl citrate, consisting of carrier particles partially covered with fine dry particles of the drug and a bioadhesive component [55]. These tablets were evaluated for the plasma concentrations of fentanyl and the results revealed that the bioadhesive component present in formulation prevented the fentanyl from being swallowed, without hindering its release and absorption. The onset of action by this formulation was 10 minutes only. Thus, sublingual dosage forms hold the potential for desired rapid onset of action.

Although, the combined use of opioid agonist and antagonist was successful in reducing the abuse potential of buprenorphine, however, such combinations in tablet dosage form still have the potential for abuse. In some instances, the patient administered with the drug may store the tablet in his mouth without swallowing it and later extract the agonist from the tablet and inject the drug into an individual's body. This necessitates for providing a dosage form that cannot be easily removed from the mouth once it's administered [56]. Zubsolve® being mucoadhesive and fast dissolving in nature was free from this problem. This limitation was associated with Suboxone™ sublingual tablets, which was overcome by formulating the same concept in thin-film dosage form. These thin films when placed in mouth were difficult to remove and hence could not be stored in mouth for further abuse. Such sublingual film formulation is currently marketed in the US market under the brand name of Suboxone®. These films consist of mucoadhesive water-soluble polymer polyethylene oxide which is combined with a hydrophilic cellulosic polymer [56-60]. Pharmacokinetic studies revealed that Suboxone® film has a bioequivalent release profile as compared to a Suboxone® tablet which contains about 2 times the amount of buprenorphine [56]. Further literature also reveals that sublingual bioavailability of many opioids is in the range of 5% to 50% indicating that these molecules can't cross the mucosal barrier easily, hence, scientist is now working in an area to improve bioavailability of these opioid analgesics across the sublingual mucosa using various approaches. Yeola *et al*. made use of a film-forming polymer pullulan with a plasticizer polyethylene glycol 400 and developed a clear and transparent sublingual film of buprenorphine and it's *in vivo* bioavailability studies were done in rabbits. This study revealed a 10% increase in relative bioavailability of the film formulation with respect

Fig. 1: Zalviso™ handheld sufentanil sublingual micro tablet system with security tether and radio-frequency identification thumb tag for single patient identification

to tablet formulation and having a rapid T_{max} of 0.08 hrs for film while 0.15 hr for tablet [59]. Thus, the sublingual film may offer an even less divertible [60], more quickly administered and more childproof version than the conventional buprenorphine naloxone tablet [61]. These films are more patient convenient [62] being available in unit-dose packaging, ability to track dose of the medication is there. More importantly, the film formulation may reduce safety concerns and risk of diversion, which is particularly relevant in regard to the risk of intoxication in children [63]. In the USA, the number of children exposed to buprenorphine has grown exponentially over the past decade [64]. Recent data show a lower risk of intoxications with the novel buprenorphine film in children [65]. Thus, the present technology could be a promising alternative to conventional drug delivery systems for breakthrough pain management.

Sublingual spray is an additional delivery system sprayed underneath the tongue for absorption of drug across the sublingual mucosa. Opioid drug such as fentanyl is available in the market under the brand name of Subsys®. This unit dose non-propellant sublingual fentanyl formulation consists of dehydrated alcohol, propylene glycol, xylitol, and L-menthol [66-68]. Pariek *et al*. carried out the randomized 3-way crossover pharmacokinetic study to compare the rate of absorption and systemic bioavailability between fentanyl sublingual spray (FSS) and oral transmucosal fentanyl citrate (OTFC). This study comprised of 29 healthy volunteers between the age group of 30-35 years who received single dose of FSS, OTFC and IV fentanyl citrate separated by washout period of 7-day. This study design concluded that absorption of fentanyl was faster and bioavailability was greater with FSS than with OTFC [69]. Such an enhanced bioavailability with sublingual spray formulation is very much needed for cancer pain management.

Nowadays, new modalities have been developed that provide systemic opioid analgesia via patient-administered systems that are less invasive and have simplified the dosage regimens. A novel sublingual patient administered system, ZALVISO™ (AcelRx Pharmaceuticals, Redwood City, CA, USA), is a pre-programed, handheld system which delivers a 15 mcg sufentanil microtablet under the tongue with a 20 minutes lockout [70]. The micro tablet is a 3 mm diameter, 0.75 mm thick dosage form intended to minimize the taste and salivation when placed sublingually, which in turn reduces swallowing of solubilized drug and maximizes sublingual transmucosal drug uptake. Forty microtablets (approximately a 2 days supply) are placed in a disposable cartridge which is inserted into a secure bedside device with a fixed timed lockout and other safety features, as well as radio-frequency identification on the patient's thumb to allow single-user identification (Fig. 1). Six successful Phase 2 and 3 clinical trials of ZALVISO™ system for the relief of pain in both major orthopedic and major abdominal surgery post-operative settings has been completed [71]. In these clinical studies, the use of sublingual sufentanil microtablets exhibited rapid onset of analgesia superior to both placebo and intravenously administered patient-controlled analgesia morphine by 1 hr after initiating use [72]. ZALVISO™ (sufentanil sublingual microtablet system) is currently under review by FDA for the management of moderate to severe acute pain [70].

Marketed buccal, sublingual and oral dosage forms of opioid analgesics [47,73,74]

POSSIBILITIES FOR FUTURE RESEARCH

Colloidal dosage forms including liposomes, niosomes, nanoparticles, nanocapsules, and microemulsions are widely investigated as drug carriers. However, only few studies have been reported to investigate their potential via oral mucosal drug delivery. Looking toward the potential of colloidal systems as oral mucosal delivery systems, three major features are of interest. First having a very large specific surface of those systems is likely to favor a large contact between the dosage form and the oral mucosa. Second, immobilization of particles on the mucosal surface could be obtained by adsorption or adhesion phenomenon. As a result, a high drug concentration might be obtained at the oral mucosal surface. Third, entrapped drug could be protected from saliva, which is of importance for drug subject to degradation in this fluid.

CONCLUSION

Due to ease of access and avoidance of the hepatic first pass metabolism, oral transmucosal drug delivery of opioid analgesics offers promising alternative to overcome the limitations of parenteral and conventional oral drug delivery system. The buccal and sublingual routes, in particular, present favorable opportunities and many formulation approaches are explored for delivery through these routes. The results are evident by the availability of many buccal and sublingual marketed formulations of opioids. Oral transmucosal dosage forms will continue as an exciting research focus for improving the drug delivery of opioid analgesics as this route does not have limitations of both oral and parenteral like poor bioavailability and inconvenient administration, respectively.

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