Expert Opinion

1. Introduction
2. Taste of the drug
3. Swallowing difficulties
4. Intraoral dosage forms
5. Number of doses
6. Inconvenient time for dose
7. Multiple drugs
8. Other routes of drug delivery
9. Conclusions
10. Expert opinion

Formulation approaches in enhancement of patient compliance to oral drug therapy

Aliasgar Shahiwala
Dubai Pharmacy College, Pharmaceutics and Pharmacy Practice, Dubai, UAE

Introduction: Disease management of outdoor patients is mainly affected by patient compliance to the drug therapy, which in turn is governed by patient convenience. Failure to follow through with a treatment decision is one of the biggest causes of unsuccessful medical care. At present, different formulation options are available for various drugs, and hence, the decision is based on the most convenient dosage form for the patient, along with optimum therapeutic benefits.
Areas covered: This paper reviews various available formulation approaches, in the hope of improving patient convenience, compliance and the overall outcome of oral drug therapy.
Expert opinion: While parenterals are valued for their speed and efficiency of delivery, these systems generally score low on patient satisfaction surveys. The oral route is the preferred route for drug delivery, although it renders multiple obstacles to formulate a patient-convenient platform, such as unfavorable taste and swallowing difficulties. Transdermal drug delivery also provides high patient satisfaction, but is effective only for the delivery of smaller, lipophilic molecules. The increasing development of biopharmaceutical therapies renders an increasing number of challenges for formulation scientists to develop a more patient-convenient means of drug delivery.

Keywords: intraoral drug delivery, patient compliance, patient convenience, taste masking

Expert Opin. Drug Deliv. (2011) 8(11):1521-1529

1. Introduction

Compliance, which is also known as adherence, concordance or capacitance, in drug therapy describes the extent to which a patient properly follows the medical advice. Ignoring or not following through with a treatment decision is called noncompliance or nonadherence and it is one of the biggest causes of unsuccessful medical care. There are many reasons for noncompliance, but the main ones are denial of the problem, the cost of the treatment, the difficulty of the dosing regimen, the unpleasant outcomes or side effects of the treatment, lack of trust, apathy and previous bad experience [1,2]. Compliance has become a major problem, mostly for children and elderly people. It was found that only 5% of the children suffering from otitis media fully complied with the treatment regimen [3]. In giardiasis treatments (metronidazole, tinidazole and furazolidone), 50% of the pediatric study population resisted taking the medication and spillage was common (32%) [4]. In geriatric population, studies of compliance reveals varying rates of noncompliance, up to 60%, depending on the study and the definition of noncompliance [5]. Compliance is very important in case of anti-infective drugs because of the need to maintain therapeutic blood concentrations [4], since emergence of resistant bacterial strains is a serious outcome of antibiotic noncompliance [6]. Antibiotics often have a bad taste that is likely to compromise compliance in children [6]. Compliance is also an issue

10.1517/17425247.2011.628311 © 2011 Informa UK, Ltd. ISSN 1742-5247

in the treatment of chronic conditions such as asthma [7] and the prevention of rejection after transplants in children [8].

Recently, various sophisticated delivery systems have been developed including needleless injections, transdermal patches, oral transmucosal delivery systems, nasal delivery formulations, pulmonary formulations, site-specific gastrointestinal delivery systems and controlled, sustained and pulsatile release formulations and it is evident that the ultimate aim of all these formulation efforts is to improve patient convenience of self-medication. Patient convenience leads to improved compliance with the prescribed dosing regimen and, as a consequence, to optimal drug therapy.

In recent years, direct-to-consumer marketing of pharmaceuticals, including prescription drugs, has created a new "empowered" patient whose needs must be addressed in the development of pharmaceuticals. Patient-friendly dosage forms that offer ease of administration and convenience are needed to satisfy the empowered patient. The factors affecting the patient compliance are depicted in **Figure 1**. A large percentage of the medicines that doctors prescribe orally is not taken not because of the medicine's unwanted side effects, but because medicines taste bad, are difficult to swallow, of multiple doses/day, of the inconvenient time of dose (midnight or early morning) or too many drugs. This review mainly focuses on different formulation approaches to counteract these problems in detail.

2. Taste of the drug

Taste of a drug and drug product is an important parameter as it directly relates to the patient acceptability, compliance, and prescribing practice of various oral formulations [9]. Taste-masking technologies are important for obtaining high patient compliance and drug therapy efficiency, since many oral-delivery drugs have unpleasant qualities such as bitterness, sourness, or saltiness, or that cause oral numbness [10-14]. Taste masking of bitter drugs has become a commercially motivated activity for the huge success of the product [15]. Pharmaceutical industry is investing a lot of time, money and resources in the development of good palatable products because pleasant tasting products not only enhance patient compliance but also provide a competitive advantage when a therapeutic category is crowded with lots of similar products like anti-infectives and provide brand recognition to combat private-label competition [16].

Several approaches namely sensory, barrier, chemical and complexation have been tried to mask the unpleasant taste of formulation. Commonly used techniques for taste masking are use of flavors, coating of drug particles with inert materials, formation of inclusion complexes, molecular complexes of drug with other chemicals, microencapsulation, multiple emulsions, prodrugs, use of liposomes, dispersion coating and an ion exchange resin approach [17].There are many publications, but an extensive review on practical taste masking approaches is published in *Expert Opinion On Drug Delivery* [17].

3. Swallowing difficulties

A constant problem in the treatment of patients is their inability or unwillingness to swallow solid dosage forms. This problem is most frequently encountered in children and elderly. The problem is, however, not uncommon in healthy adults as well. Although this problem may seem innocuous or idiosyncratic, the fact remains that the inability or unwillingness of some people to take certain dosage forms can severely compromise the patient's compliance with a prescribed treatment protocol. Moreover, due to embarrassment, many patients are unwilling to tell their doctor of their problem to enable the doctor to consider other drugs and/or alternative vehicles. Of course, such a lack of compliance can delay treatment or cure.

From the consumer's side, alternate dosage forms also have significant disadvantages in terms of convenience. For example, effervescent tablets which are intended to be dissolved in a glass of liquid require the provision of a glass of liquid and a waiting period sufficient to allow the tablet to completely dissolve. Often, these dosage forms leave an objectionable scum which must be wiped out of the glass. Oral route is known to be the most preferred and patient-convenient means of drug administration. Most of the drugs are being taken in the form of tablets and capsules by almost all patients, including adult, pediatric and geriatric patients. However, around 26 – 50% of patients find it difficult to swallow tablets and hard gelatin capsules [18]. These patients mainly include elderly (who have difficulties taking conventional oral dosage forms because of hand tremors and dysphagia), pediatric patients (who are often fearful of taking solid oral dosage forms owing to their underdeveloped muscular and nervous systems) [19] and others which include the mentally ill, developmentally disabled, patients who are uncooperative, on reduced liquid-intake plans or nauseated, and travelers who may not have access to water [20,21].

The traditional alternative for swallowing difficulties is formulating a drug substance in a liquid dosage form. However, liquid dosage forms have a number of limitations like need of measuring, bulkiness, physical, chemical and microbial stability issues, spoilage, inaccurate dosing and organoleptic properties of drug and drug formulation. All these limitations can be overcome by intraoral dosage forms.

As a site for drug delivery, oral cavity (intraoral route) offers advantages over the conventional gastrointestinal route, parenteral and other mucosal routes of drug administration. Absorption from oral mucosa has special significance for drugs, despite the fact that the surface area is small. Venous drainage from the mouth is to the superior vena cava; thus significantly protecting the drug from rapid first pass metabolism by the liver. The rate of absorption through the mucous membrane is rapid. Another advantage of absorption from the oral mucosal membrane is the elimination of the effect of food intake on the rate and on the resulting concentration of the pharmacological agent during

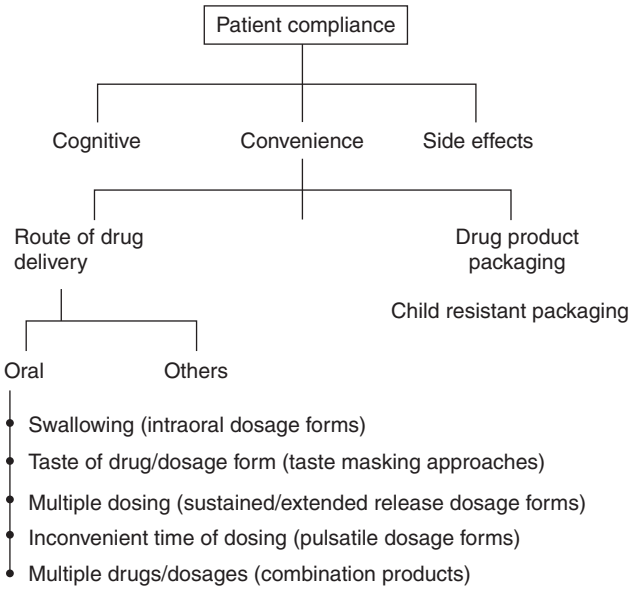

Figure 1. Factors affecting patient compliance. (•) highlights possible approaches to overcome the compliance barrier.

the absorption process. The exposure of the active agent to the low pHs of the stomach is also avoided. Intraoral delivery also allows termination of delivery when required [22]. Patient compliance, rapid onset of action and ease of administration are the key factors that guide the selection of oral cavity as a route for drug administration. Thus, intraoral drug delivery has become an important route of drug administration. Dissolution within oral cavity also permits intraoral absorption, thus bypassing presystemic metabolism. Solid intraoral dosage forms offer advantages such as disintegration without water, rapid onset of action, ease of transportability, ease of handling, pleasant taste, and improved patient compliance. Advantages and limitations of intraoral dosage forms are listed in **Table 1**.

4. Intraoral dosage forms

Intraoral dosage forms are mainly unit solid dosage forms intended to be either dissolved or finely dispersed and release the medicament in the oral cavity. Oral mucosa favors rapid drug absorption because it has a very thin epithelium without stratum corneum and very rich vascularity [23]. However, the absorption through the oral mucosa depends on the nature of drug molecule and time of contact of drug molecule with oral mucosa. The released drug in the oral cavity has alternatively been introduced to the gastrointestinal tract in either dissolved or finely dispersed form in saliva and is readily bioavailable [24]. Moreover, as the gastric mucosa is not directly exposed to high concentrations of the drug in the solid state, it reduces the risk of intolerance or erosion. Intraoral administration of drugs is possible anywhere anytime without simultaneous intake of water, which promotes very high patient compliance. Furthermore, the treatment can be terminated at any time by expelling the dosage form. Moreover, they are having pleasant organoleptic properties, does not draw any attention to the medication, though it is medicated and therefore it does not stigmatize the patient.

Various intraoral dosage forms include mouth dissolving/disintegrating tablets (MDT), mouth dissolving films/strips (MDF), medicated chewing gums (MCG) and medicated lozenges (MLO). Few examples of these products are listed in **Table 2**. Lozenges are also known as candies and lollipops (with stick). We have not included specialized buccoadhesive and sustained release dosage forms and other dosage forms like gargles and ointments (for local treatment of mouth disorders) as they are for a different purpose rather to improve the patient's convenience. Intraoral dosage forms can be classified depending on the time of their stay in oral cavity. MDT and MDF are of short duration as they stay in the oral cavity for 5 – 30 seconds, while MCG and MLO are of comparatively long duration of 5 – 30 minutes in oral cavity. MDT is of shortest duration while MCG is longest duration.

Most fast dissolving drug delivery systems are in the form of tablets [25]. Orally disintegrating tablet has become a popular dosage form, capturing a market value of $1.1 billion worldwide [26,27], which has increased tremendously by now. WOWTAB® (Yamanouchi Pharma Technologies, Norman, USA, compressed tablet, disintegrates in 15 s), Zydis® (Cardinal Health, Dublin, USA, freeze-dried tablet, disintegrates in 10 s), Orasolv® (Cima Labs, Eden Prairie, USA, effervescent tablet, disintegrates in 60 s) and Shearform® (thin fiber matrix, disintegrates in 10 s) are some of the fast dissolving technologies that are in the form of tablets. The basic approach used in the development of MDT is the use of super disintegrants like croscarmellose sodium, sodium starch glycolate, and crospovidone which help in the instantaneous disintegration of tablet when placed on the tongue, thereby releasing the drug in saliva.

The bioavailability of a water-insoluble drug such as piroxicam in Zydis tablets is similar to a standard capsule dosage form, while bioavailability of a water-soluble, low-dose, and low-molecular-weight drug such as selegiline was improved with the Zydis formulation as lower doses of selegiline Zydis tablets provide blood concentration and therapeutic activities equivalent to standard oral tablets [28,29]. Extensive clinical testing of OraSolv-based products has been carried out, especially in children. OraSolv multivitamin tablets were compared with conventional pediatric multivitamins in children. Children were asked to state their preference. The OraSolv multivitamin tablets were favored by 89% of the children [30,31]. In another study, OraSolv 40 mg famotidine tablet was compared with a standard, commercially available famotidine tablet and 75% of subjects preferred OraSolv tablet.

The complete bitter-taste masking of drugs is an extremely important factor in the formulation of oral disintegrating

Table 1. Advantages and drawbacks of intraoral dosage forms.

Advantages of intraoral dosage forms
Improved patient compliance
Rapid onset of action and may offer an improved bioavailability
Patient having difficulty swallowing tablets can easily have this type of dosage form
Useful for pediatric, geriatric and psychiatric patients
Suitable during traveling where water may not be available
Gives accurate dosing as compared to liquids
Good physical, chemical and microbial stability
Free of need of measuring, an essential drawback in liquids
Does not stigmatize the patient
Cost effective
Leave minimum residue
Limitations of intraoral dosage forms
Organoleptic property of the drug should be favorable
Variability in the absorption from the oral cavity
Not all classes of drugs are suitable
Dose of the drug should be less
Specialized technology for manufacturing

tablets (ODT) and the palatability of ODT is a critical factor in ensuring patient compliance [32,33].

In addition, developing a formulation for ODT in which taste is masked, and drug release is improved, is a major challenge. Anti-malarial drugs have extremely unpleasant bitter taste due to the presence of quinine moiety [34]. In one study, the bitter taste of the mefloquine hydrochloride was completely masked by encapsulation in microparticles with Eudragit E (an acid soluble polymer), while allowing the complete release of MFL under the acidic conditions of stomach (pH 1.2). Masking of bitter taste of the β-Artemether is an extremely important factor in the formulation of rapidly disintegrating tablets to ensure patient compliance [35,36]. Primaquine phosphate (PRM), another antimalarial drug has an extremely unpleasant bitter taste. The complete taste masking of artemether (ARM) and PRM with improved dissolution is achieved by solid dispersion technique using hydrophilic polymer glycyrrhizin [37,38].

MDFs can be defined as a dosage form that employs a water-dissolving polymer (generally a hydrocolloid, which may be a bioadhesive polymer), which allows the dosage form to quickly wet, adhere, and dissolve to release the drug when placed on the tongue or in the oral cavity [39]. They are also known as fast-dispersing, mouth dissolving, orally disintegrating, fast melting, and quick-dissolving films [40]. Compared with oral dispersible tablets, MDFs are easy to handle, store and carry. The risk of destroying the dosage form during the removal from its pouch/blister is reduced. Till date, the commercial launch of MDF is primarily in OTC products addressing therapeutic categories such as cough/cold, sore throat and antacid/gas relief as well as a number of nutritional supplement applications. However, it is finding increased use as a delivery system for prescription drugs as well. Recently, the US Food and Drug Administration (FDA) has approved Zuplenz® (ondansetron) oral soluble film as a prescription medication for the prevention of postoperative, highly and moderately emetogenic cancer chemotherapy-induced, and radiotherapy-induced nausea and vomiting. Ondansetron is also a drug of choice for the prevention of post-operative nausea and vomiting. Ondansetron Rapidfilm®, a patented technology is an orodispersible pharmaceutical form, made suitable, particularly for patients with difficulties in swallowing conventional tablets, for example pediatric patients, elderly people and patients with oral chemotherapy- and/or radiotherapy-induced mucositis [41,42]. Considering the target population, the Ondansetron Rapidfilm is especially designed for higher patient compliance. Patients on chemotherapy treatment may have intense nausea that makes difficult the administration of conventional tablets with water, especially those with head and neck or esophageal cancers. Authors have concluded that the Rapidfilm delivery system, by alleviating the administration by the end-user and by allowing patients to take their medication anytime and anyplace under all circumstances, can result in higher convenience for several applications.

In another study, authors prepared fast dissolving oral thin film containing dexamethasone [43]. There were no significant differences in pharmacokinetic parameters obtained from rats with oral administration of dexamethasone suspension and those with topical application of the film to the oral cavity. Therefore, the present fast-disintegrating oral film containing dexamethasone is considered to be potentially useful for cancer patients with disturbance in eating and swallowing who receive radiotherapy and/or high- to moderate emetogenic anticancer drugs.

Medicated chewing gums and medicated lozenges are retained in oral cavity comparatively for a longer duration and hence they have the added ability to promote production of saliva, which helps in dry mouth conditions and acts as a lubricant soothing the sore throat [44]. Sensorial aspects of treatment can also play an important role in promoting patient compliance with treatment by providing additional benefits to the sufferer. This could be as simple as a pleasant or refreshing flavor that, in it, may enhance the demulcent soothing effects of the product [45] or a stimulating cooling or comforting warming sensation, which complements the overall benefits of a particular treatment. The first medicated gum approved for prescription use FDA was Nicorette® nicotine gum [46]. Prior to marketing in the United States the FDA required a thorough abuse liability assessment to examine whether the enhanced palatability of nicotine through gum-based formulation would increase its abuse liability or not [47]. In this study, mint- and orange-flavored gum did not increase abuse liability, but was effective in reducing craving. Another inherent benefit of chewing gum is it satisfies the psychological component of smoking as a suitable smoking substitute which is not there in case of other routes of nicotine delivery. In comparison to other intraoral dosage forms, in case of MCG the active ingredient remains in contact with the oral cavity for a longer period of time during chewing and it is forced through the oral mucosa to a larger extent.

Table 2. Examples of currently marketed intraoral dosage forms.

Mouth dissolving/Dispersible tablets	Mouth dissolving films	Medicated chewing gums	Medicated lozenges
Excedrin® (acetaminophen, caffeine) Claritin®, Dimetapp®, Alavert® (loratadine) Propulsid® (cisapride) Risperdal® (risperidone) Zolmig® (Zolmitriptan) Gaster D® (famotidine)	Zuplenz® (ondansetron) Benadryl®, Theraflu®, Triaminic® (diphenhydramine) Gas-X® (simethicone) Subutex® (buprenorphine)	Stay alert® (caffeine) Endekay® (vitamin C) Aspergum® (aspirin) Fluogum® (fluoride) Nicorette® (nicotine) Trawel gum® (dimenhydrinate) Hexit® (chlorhexidine)	Strepsils® (amylmetacresol and dichlorobenzyl alcohol) Niquitin CQ®, Nicorette® (Nicotine) Vicks® (dextromethorphan) Strefen® (flurbiprofen)

In doing so, a larger portion of the drug is made available for rapid absorption without a first-pass effect to the general circulation [48]. Also, the gastrointestinal tract suffers much less from the unwanted effects of excipients as gum does not reach the stomach. More details on MCG as drug delivery system and its manufacturing can be found in our review article published earlier [49].

Lozenges are specifically useful in the treatment of acute sore throat. Medicated throat lozenges have the added advantage over sprays and gargles of being slow-releasing, and therefore continually delivering the active ingredients to the affected areas of the throat, over a prolonged period of time. Over-the-counter throat lozenges (Strepsils®) containing amylmetacresol and 2,4-dichlorobenzyl alcohol which possess both antibacterial [50,51] and antiviral activity against many of the infectious causes of sore throat in the relief of acute sore throat, have demonstrated the added benefit of sensorial optimization in meeting patients' needs. Oral transmucosal fentanyl citrate (OTFC) is a solid dosage form of fentanyl that consists of fentanyl incorporated into a sweetened lozenge on a stick. When consumed, a portion of fentanyl is absorbed through the oral mucosa and the rest is swallowed and absorbed through the GI tract. OTFC gained regulatory approval in 1993 for use as a premedication before surgery and painful procedures (not requiring general anesthesia) in both children and adults [52-56].

5. Number of doses

Drug delivery in conventional dosage forms often suffers from the drawbacks of repeated drug administration and large fluctuations in drug blood levels. Due to the short half-life of many drugs, they are prescribed in multiple doses per day like b.i.d. (twice a day), t.i.d. (three times a day) or q.i.d. (four times a day). It is evident that as the number of doses per day increases, there are more chances to miss a dose and hence leads to noncompliance to the drug therapy. This situation is more realized in case of chronic diseases like high blood pressure, diabetes, tuberculosis, cancer, AIDs and so on. To counter this problem, the best approach is to formulate the short half lives of drug into sustained and controlled release dosage forms. Sustained-or controlled delivery systems reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. The main objective of peroral controlled release drug delivery systems is to maintain therapeutically effective plasma drug concentration levels for a longer duration, thereby reducing the dosing frequency and to minimize the plasma drug concentration fluctuations at steady state by delivering drug in a controlled and a reproducible manner. Drug delivery rate, duration of delivery and the dosing interval are the target features for controlled drug delivery system. Various approaches are used like matrix system, reservoir system, and complexation (resin-drug complexes are widely used for sustained release). Due to the advance technology, these formulations can be modified to release the drug for a long period at specific gastrointestinal segment. For example, floating systems can provide the sustained release of the drugs which are meant to be absorbed through the stomach or locally acting on stomach. Zero-order drug release is also possible by formulating a drug into osmotic systems. Once-a-day drugs are also in the market. The further details on sustained and controlled drug delivery can be found in almost all the text books related to pharmaceutics and pharmaceutical technology.

The rate of drug delivery assumes even greater importance in the instances where pharmacodynamic effects (especially adverse effects) can be correlated to drug delivery rate. For example, Kleinbloesem *et al.* [57,58] reported nifedipine to show pharmacodynamic differences at different delivery rates (the slower the delivery rate, the less the reflex tachycardia).

Study was conducted in three different countries (United States, United Kingdom and France) to determine the effect of dose frequency on compliance and persistence with bisphosphonate therapy in postmenopausal women [59]. Rates of compliance and persistence in large representative samples of postmenopausal women from the United States, the United Kingdom, and France were significantly greater in women prescribed a weekly regimen of a bisphosphonate than in women prescribed a daily regimen. The authors have concluded that dosing frequency may be an important

factor to consider in improving compliance and persistence among patients treated with bisphosphonates.

6. Inconvenient time for dose

The dependence of several diseases and body function on circadian rhythm is well known. Particular rhythms in the onset and extent of symptoms were observed in diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesterolemia, and hypertension [60]. Most of the symptoms were at peak either during midnight or early morning, which leads to great deal of patient inconvenience and noncompliance. For such chronopathological conditions, chronotherapeutic systems play an important role, because these formulations take into account probable time-dependent variation in the risk or symptoms of disease. Such systems are designed to enable a pulsatile release of drug after a predetermined off-release period (lag time) which mimics the chronopathological symptoms [61,62]. Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The detailed reviews have been published to cover drug delivery approaches according to chrono-pharmacological requirements of the body [63,64].

7. Multiple drugs

Compared to 1940s, average life span of people has dramatically increased from 50 to 75 years. Age drastically increases the number of patients with multiple diseases, which in turn changes the need for medicines. More individualized and combination treatment options are particularly critical for this population, and pharma companies must increase the speed of innovation to match these changing needs. Various products like antihypertensives and diuretics are often given in combination. Pharmaceutical companies are turning toward fixed-dose combination products to diffuse the impact of generic competition, revitalize established brands, fill gaps in product pipelines, and enhance patient compliance. Conditions treated with combination therapy include tuberculosis, leprosy, cancer, malaria and HIV/AIDS. One major benefit of combination therapies is that they reduce the development of drug resistance, since a pathogen or tumor is less likely to have resistance to multiple drugs simultaneously. Fixed-dose combination products usually result in fewer prescriptions and are less expensive than buying the medications separately. Also, patients need to take fewer pills which leads to an increase in compliance, resulting in better health outcomes.

Combination therapy, lower case–fatality ratios, slower development of resistance and consequently, less money needed for the development of new drugs.

8. Other routes of drug delivery

Recently, other routes of drug delivery have explored for needle-free systemic drug delivery with self-medication options like nasal, transdermal, pulmonary, rectal, intrauterine. Amongst these, transdermal drug delivery has attained much more attention because of ease of application, traditional (people use to apply topical dosage forms since ages) and the large surface area available for application. While there are many advantages to delivering drugs through the skin via existing technology have traditionally been limited to the delivery of smaller, lipophilic molecules that can passively diffuse through the skin at rates sufficient for therapeutic effect. Therefore, only few products such as fentanyl, selegiline, sumatriptan, nicotine, contraceptives and nitroglycerin have found their way to market.

Recent trend toward developing biopharmaceuticals over classic small molecules has projected that by 2014, 6 of the top 10 pharmaceutical products will be biologics [65].

This trend has created new challenges in finding delivery methods (as oral route is naturally inappropriate for biologics) that meet both the bioavailability and efficiency requirements of the therapy, as well as the needs of patients, who are seeking noninvasive, convenient and comfortable self-administration options. Given the limitations imposed on transdermal systemic drug delivery by the barrier properties of the stratum corneum, new technologies have attempted to completely bypass this obstacle by either the creation of a physical conduit (micro needles) or direct powder delivery via compressed gas [66]. In addition to traditional dermal and transdermal delivery formulations such as creams, ointments, gels, and patches, several other systems have been evaluated.

Scientists are working on other novel formulations since long, made use of sprays, foams, multiple emulsions, microemulsions, liposomes, transfersomes, niosomes, ethosomes, cyclodextrins, glycospheres, dermal membrane structures, and microsponges[67-69]. However, successful marketed preparation using these technologies has yet to be realized.

9. Conclusions

Patient convenience is a deciding step in compliance to the drug therapy and ultimate outcome of the therapy. As discussed, patient convenience can only be achieved by designing right kinds of formulation to suit patient needs and comfort. Various formulation options available have made drug therapy a pleasant experience.

10. Expert opinion

While parenterals are valued for speed and efficiency of delivery, these systems generally score low on patient satisfaction surveys. The oral route is inevitably a preferred route for drug delivery, though it renders multiple obstacles to formulate

a patient-convenient platform. Depending on the type of patient inconvenience, like unfavorable taste of drug and dosage forms, swallowing difficulties, multiple drugs and dosages, inconvenient time of dosing, the best option available needs to be worked upon as discussed. Conversely, transdermal drug delivery provides high patient satisfaction, second only to oral delivery, but is effective only for delivery of smaller, lipophilic molecules. The trends in the pharmaceutical industry of increasing development of biopharmaceutical therapies render more challenges for formulation scientists to develop a patient-convenient drug delivery.

Declaration of interest

The author states no conflict of interest and has received no payment in the preparation of this manuscript.

Bibliography

1. Ngoh LN. Health literacy: a barrier to pharmacist-patient communication and medication adherence. J Am Pharm Assoc 2009;49(5):e132-46
2. Elliott RA, Marriott JL. Standardized assessment of patients' capacity to manage medications: a systematic review of published instruments. BMC Geriatr 2009;9:27
3. Mattar ME, Markello J, Yaffe SJ. Pharmaceutic factors affecting pediatric compliance. Pediatrics 1975;55:101-8
4. Boreham PFL, Benrimoj S, Ong M, et al. A compliance study in pediatric patients receiving treatment for giardiasis. Aust J Hosp Pharm 1986;16:138-42
5. Fincham JE. Patient compliance in the ambulatory elderly: a review of the literature. J Geriatr Drug Ther 1988;2(4):31-52
6. Goldfarb J, Patel J, Wormser G. Antimicrobial flavors: a consideration in drug compliance. Drug Ther 1986;2:59-71
7. Weinstein AG. Clinical management strategies to maintain drug compliance in asthmatic children. Ann Allergy Asthma Immunol 1995;74:304-10
8. Fennell RS, Foulkes L-M, Boggs SR. Family-based program to promote medication compliance in renal transplant children. Transplant Proc 1994;26:102-3
9. Nunn T, Williams J. Formulation of medicines for children. Br J Clin Pharmacol 2005;59(6):674-6
10. Kumazawa T, Nomura T, Kurihara K. Liposomes as model for taste cells: receptor sites for bitter substances including N–C S substances and mechanism of membrane potential changes. Biochemistry 1988;27:1239-44
11. Sugao H, Yamazaki S, Shiozawa H, Yano K. Taste masking of bitter drug powder without loss of bioavailability by heat treatment of wax-coated microparticles. J Pharm Sci 1998;87:96-100
12. Hashimoto Y, Tanaka M, Kishimoto H, et al. Preparation, characterization and taste-masking properties of polyvinylacetal diethylaminoacetate microspheres containing trimebutine. J Pharm Pharmacol 2002;54:1323-8
13. Nanda A, Kandarapu R, Garg S. An update on taste masking technologies for oral pharmaceuticals. Indian J Pharm Sci 2002;64:10-17
14. Keast RSJ, Breslin PAS. Bitterness suppression with zinc sulfate and Nacclamate: a model of combined peripheral and central neural approaches to flavor modification. Pharm Res 2005;22:1970-7
15. Fu Y, Yang S, Jeong SH, et al. Critical reviews™ in therapeutic drug carrier systems. Crit Rev Ther Drug 2004;21(6):433-75; Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies
16. Kleinert HD, Baker WR, Stein HH. Ion exchange resin complexes: an approach to mask the taste of bitter drugs. Pharm Technol 1993;17:30
17. Douroumis D. Practical approaches of taste masking technologies in oral solid forms. Expert Opin Drug Deliv 2007;4(4):417-26
18. Anderson O, Zweidorff OK, Hjelde T. Problems when swallowing tablets. A questionnaire study from general practice [in Norwegian]. Tidsskr Nor Laegeforen 1995;20:947-9
19. Slowson M, Slowson S. What to do when patients cannot swallow their medications. Pharm Times 1985;51:90-6
20. Lindgren S, Janzon L. Dysphagia: prevalence of swallowing complaints and clinical findings. Med Clin N Am 1993;77:3-5
21. Chang RK, Guo X, Burnside BA. Fast-dissolving tablets. Pharm Technol 2000;24(6):52-8
22. Rathbone MJ, Drummond BK, Tucker IG. The oral cavity as a site for systemic drug delivery. Adv Drug Deliv Rev 1994;13:1-22
23. Rhodus NL, Schuh MJ. Effects of pilocarpine on salivary flow in patients with Sj€ogren's syndrome. Oral Surg Oral Med Oral Pathol 1991;72:545-9
24. Gmunder CB, Li W, Ream R, et al. Sildenafil chewing gum formulations and methods of using the same. US6592850B2; 2003
25. Liang AC, Chen LH. Fast-dissolving intraoral drug delivery systems. Expert Opin Ther Patents 2001;11(6):981-6
26. Brown D. Orally disintegrating tablets: taste over speed. Drug Deliv Technol 2003;3(6):58; 61.13
27. Ghosh TK, Pfister WR. Drug delivery to the oral cavity: molecules to market. Marcel Dekker, Inc.; New York: 2005
28. Seager H. Drug delivery products and Zydis® fast dissolving dosage form. Presented at the British Pharmaceutical Conference; September 1997; Scarborough
29. Yarwood R. Oral fast dissolving dosage form technologies. Presented at IBC symposium on drug delivery systems; July 17 - 18, 1997; San Francisco
30. Wehling F, Schuehle S. Base coated acid particles and effervescent formulations incorporating same. US5503846, 1993
31. Wehling F, Schuehle S, Madamala N. Pediatric effervescent dosage. US5223264, 1991
32. Fu Y, Yang S, Jeong SH, et al. Orally fast disintegrating tablets: developments, technologies, tastemasking and clinical studies. Crit Rev Ther Drug Carrier Syst 2004;21:433-76

33. Khan S, Kataria P, Nakhat P, Yeole P. Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapidly disintegrating tablets. AAPS PharmSciTech 2007;8:article 46
34. William N. Anti-infective. In: Gennaro AR, editors. Remington's: the Science and Practice of Pharmacy. Volume 2 Lippincott Williams and Wilkins; Philadelphia, PA: 1547
35. Khan S, Kataria P, Nakhat P, Yeole P. Taste masking of ondensetron hydrochloride by polymer carrier system and formulation of rapidly disintegrating tablets. AAPS PharmSciTech 2007;8:article 46
36. Fu Y, Yang S, Jeong SH, et al. Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. Crit Rev Ther Drug Carrier Syst 2004;21:433-76
37. Shah PP, Mashru RC. Development and evaluation of artemether taste masked rapid disintegrating tablets with improved dissolution using solid dispersion technique. AAPS PharmSciTech 2008;9:494-500
38. Shah PP, Rajashree C. Mashru formulation and evaluation of primaquine phosphate taste-masked rapidly disintegrating tablet. J Pharm Pharmacol 2008;60:1279-85
39. Dinge A, Nagarsenker M. Formulation and evaluation of fast dissolving films for delivery of Triclosan to the oral cavity. AAPS PharmSciTech 2008;9(2):349-56
40. Saigal N, Baboota S, Ahuja A, Ali J. Fast-dissolving Intraoral drug delivery systems. Expert Opin Ther Patents 2008;18(7):769-78
41. Habib W, Khankari R, Hontz J. Fast dissolve delivery system. Crit Rev Ther Drug Carrier Syst 2000;17:61-72
42. Biradar SS, Bhagavati ST, Kuppuasad IJ. Fast dissolving drug delivery systems: a brief overview. Internet J Pharmacol 2006;4:2
43. Shimoda H, Taniguchi K, Nishimura M, et al. Preparation of a fast dissolving oral thin film containing dexamethasone: a possible application to antiemesis during cancer chemotherapy. Eur J Pharm Biopharm 2009;73(3):361-5
44. Kelly F. Something for a sore throat please. Aust Pharm 2008;27:394-7
45. Hartung-Brooks L. Sore throat. On Contin Pract 1990;17:2-6
46. Fincham JE. Smoking cessation products, Chapter 36. In: Covington TR, editor. Handbook of Nonprescription Drugs. American Pharmaceutical Association; Washington, DC: 1996. p. 715-23
47. Houtsmuller EJ, Fant RV, Eissenberg TE, et al. Flavor® improvement does not increase abuse liability of nicotine chewing gum. Pharmacol Biochem Behav 2002;72(3):559-68
48. Christrup LL, Davis SS, Frier M, et al. Deposition of a model substance, 99mTcE-HIDA, in the oral cavity after administration of lozenges, chewing gum and sublingual tablets. Int J Pharm 1990;66:169-74
49. Chaudhri S, Shahiwala A. Medicated chewing gums: a promising drug delivery system. Expert Opin Drug Deliv 2010;7(7):871-85
50. Richards RME, Cowie G, McCague GJ. In vivo investigations of the antibacterial activity of lozenges and mouthwashes on the aerobic bacterial flora of the mouth and throat. Pharm J 1989;6:58-63
51. Richards RME, Xing DKL. In vitro evaluation of the antimicrobial activities of selected lozenges. J Pharm Sci 1993;82:1218-20
52. Stanley TH, Hague BH, Mock DL, et al. Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers. Anaesth Analg 1989;69:21
53. Streisand JB, Stanley TH, Hague B, et al. Oral transmucosal fentanyl citrate premedication in children. Anaesth Analg 1989;69:28
54. Friesen RH, Lockhart CH. Oral transmucosal fentanyl citrate for preanesthetic medication of pediatric day surgery patients with and without droperidol as a prophylactic anti-emetic. Anesthesiology 1992;76:46
55. Feld LH, Champeau MW, van Steennis CA, et al. Preanesthetic medication in children: A comparison of oral transmucosal fentanyl citrate versus placebo. Anesthesiology 1989;71:374
56. Goldstein-Dresner MC, Davis PJ, Kretchman E, et al. Double-blind comparison of oral transmucosal fentanyl citrate with oral meperidine, diazepam, and atropine as preanesthetic medication in children with congenital heart disease. Anesthesiology 1991;74:28
57. Kleinbloesem CH, van Brummelen P, van de Linde JA, et al. Nifedipine: kinetics and dynamics in healthy subjects. Clin Pharmacol Ther 1984;35:742-9
58. Kleinbloesem CH, van Brummelen P, Danhof M, et al. Rate of increase in plasma concentration of nifedipine as a major determinant of its haemodynamic effects in man. Clin Pharmacol Ther 1987;41:407-12
59. Cramer JA, Lynch NO, Gaudin A-F, et al. The effect of dosing frequency on compliance and persistence with bisphosphonate therapy in postmenopausal women: a comparison of Studies in the United States, the United Kingdom, and France. Clin Ther 2006;28(10):1686-94
60. Ritschel WA, Forusz H. Chronopharmacology: a review of drugs studies. Methods Find Exp Clin Pharmacol 1994;16(1):57-75
61. Lemmer B. Chronobiology, drug-delivery, and chronotherapeutics. Adv Drug Deliv Rev 2007;59:825-7
62. Smolensky MH, Peppas NA. Chronobiology, drug delivery and chronotherapeutics. Adv Drug Deliv Rev 2007;59:828-51
63. Lemmer B. Chronopharmacology and controlled drug release. Expert Opin Drug Deliv 2005;2(4):667-81
64. Mandal AS, Biswas N, Karim KM, et al. Drug delivery system based on chronobiology–A review. J Control Release 2010;147(3):314-25
65. Janice M. Reichert trends in US approvals: new biopharmaceuticals and vaccines. Trends Biotechnol 2006;24(7):293-8
66. Walters KA. Drug delivery: topical and transdermal routes. In: Swarbrick J, editor. Encyclopedia of Pharmaceutical Technology. 3rd edition. Volume 1 Informa healthcare; New York: p. 1311-25, 2007
67. Rogers K. Controlled release technology and delivery systems. Cosmet Toilet 1999;114(5):53-60

68. Touitou E, Dayan N, Bergelson L, et al. Ethosomes-novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release 2000;65:403-18

69. Tao L. Skin delivery from lipid vesicles. Cosmet Toilet 2000;115(4):43-50

Affiliation

Aliasgar Shahiwala MPharm PhD
Associate Professor,
Dubai Pharmacy College, Pharmaceutics and Pharmacy Practice, P.O.Box 19099,
Dubai, UAE;
E-mail: alishahiwala@gmail.com