Considerations in Developing Sublingual Tablets—An Overview

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This review highlights relevant physicochemical drug properties and formulation design considerations critical to quality and performance of the sublingual tablets.

The oral mucosal lining offers a preferable route for the local and systemic administration of certain drugs and for the treatment of some diseases (see **Table I**) (1). This route has several distinct advantages over the enteral and parenteral routes of drug delivery due to its rich blood supply, rapid onset of action, enhanced bioavailability, avoidance of the first pass and food effects, increased patient compliance, and ease of self-medication. Over the years, a number of products taking advantage of oral mucosal drug delivery have been introduced in the market.

Oral mucosal drug absorption is governed by (a) the permeability of the oral mucous membrane and the anatomy of the underlying tissues, (b) the physicochemical properties of the drugs, and (c) the formulation design. The focus of this review is on the latter two points, as an understanding of these elements enables the selection of drug candidates suitable for oral mucosal delivery and optimizes drug delivery.

Table I: Drugs available as sublingual tablets.

Drug	**Manufacturer**
Nitroglycerin (Nitrostat)	Pfizer
Isosorbide dinitrate	Multiple manufacturers
Fentanyl citrate (Abstral)	Galena Biopharma
Buprenorphine hydrochloride	Multiple manufacturers
Ergotamine tartrate (Ergomar)	Rosedale Therapeutic
Ergoloid mesylates	Watson
Asenapine (Saphris)	Merck Sharp & Dohme
Buprenorphine hydrochloride and naloxone hydrochloride	Multiple manufacturers
Zolpidem tartrate (Intermezzo)	Purdue Pharma

Anatomical structure of the oral mucosa

The oral cavity has four distinct regions that can absorb drugs-the sublingual, buccal, gingival, and palatal regions. These regions differ from one another in histological structure and biochemical composition of the mucosal membrane, and their ability to retain the dosage form long enough to allow complete drug absorption. The sublingual membrane on the floor of the mouth under the tongue and the buccal membrane lining the cheeks are commonly used for systemic drug delivery.

The mucosal lining consists of three distinct layers. The outermost layer is the epithelial membrane, which consists of stratified squamous epithelial cells and has a protective barrier function. The innermost layer of the epithelial membrane is called the basement membrane that replenishes the epithelium. Below the epithelium lies the lamina propria followed by the submucosa. The lamina propria is a hydrated and less dense layer of connective tissue containing collagen and elastic fibers. The oral submucosa is also richly supplied with blood vessels.

Following absorption through the mucous membrane in the sublingual region, the drug instantly diffuses into venous blood. The venous blood from the sublingual region of the oral cavity drains into a common trunk, which then drains via the internal jugular vein, the subclavian vein, and the brachiocephalic vein directly into the superior vena cava (2, 3). Thus, venous return from these regions enters the systemic circulation, bypassing the pre-systemic drug elimination, unlike in oral administration. Direct drainage into systemic circulation results in immediate systemic availability of the drug and rapid onset of action. It should be noted that smoking, which causes vasoconstriction, may affect drug absorption.

Permeability of the oral mucosa and drug absorption

The salivary glands present in the oral cavity secrete saliva that has a pH of 5.5-7.0. Saliva consists of proteins and carbohydrate complexes called mucus and enzymes such as amylase and carboxylesterase. Mucus is negatively charged at the physiological pH, forming a cohesive gelatinous film on all oral cavity surfaces. This cohesiveness permits mucoadhesion of the drug to the epithelial tissue leading to drug absorption (4, 5).

The epithelial membrane is 100–200 μm thick in the sublingual region and 500–600 μm thick in the buccal region (6). The epithelial membrane in both regions is non-keratinized. The permeability of the mucosa varies from region to region in the oral cavity depending on thickness and degree of keratinization of the epithelial membrane (7).

Membrane-coating granules deposited at the apical surfaces of the epithelial cells and neutral lipids, such as ceramides and acylceramides, impart a barrier function to keratinized epithelium resulting in decreased permeability. Conversely, cholesterol, cholesterol esters, and glucosyl ceramides in the non-keratinized epithelial cells of the sublingual and buccal regions render it permeable to drug absorption (8).

The profuse blood supply, combined with the relative thinness and higher permeability of the sublingual mucosa, permits rapid absorption and desirable bioavailability of certain drugs following sublingual administration. Thus, the sublingual mucosa is a suitable site for achieving a clinically effective drug concentration in a shorter period of time when rapid onset of action is desired. For this reason, rapidly dissolving sublingual tablets are highly effective for the emergency treatment of angina, breakthrough cancer pain, or migraine.

It should be noted that the sublingual region is constantly washed by saliva and by movements of the tongue, and thus is not suitable for the prolonged retention of a drug-delivery system. On the other hand, the buccal mucosa is not continuously affected by saliva or by tongue movements and is suitable for prolonged retention of dosage forms such as mucoadhesive sustained drug-delivery systems.

Commercially available sublingual tablets

Presently, a small number of commercially available drugs use the sublingual mucosa for drug administration. These drugs are used for the emergency treatment of angina pectoris, hypertensive crises, breakthrough cancer pain, and migraine. The buccal route has been exploited for hormone replacement therapy. **Table I** lists some of the approved drugs that are available as sublingual tablets (9).

Potential drug candidates for oromucosal delivery

The literature is full of studies that have demonstrated the enhanced potential of several drugs when administered via oromucosal route. However, this potential has not been fully utilized commercially in developing drugs for oromucosal delivery. The following examples illustrate superior therapeutic management when drugs were administered via the oromucosal route as compared to oral administration.

In a comparative effectiveness study of sublingual captopril, nifedipine, and prazosin, it was reported that sublingual captopril may be a better alternative to sublingual nifedipine in treating hypertensive emergencies based on less side effects (10). Another study has shown that sublingually administered captopril and nifedipine are effective in the treatment of hypertensive emergencies; however, for severe forms of hypertension, this study recommends sublingual nifedipine (11).

Sublingual administration of verapamil has exhibited significantly higher maximum plasma concentration of the drug (C_{max}), a faster absorption rate, and greater bioavailability as compared to its oral administration (12). It has also been shown to produce a rapid and significant reduction in ventricular rate (13). Sublingual administration of furosemide was shown to offer a therapeutic advantage over the oral route of administration (14).

Oromucosal administration of midazolam was compared with the rectal administration of diazepam for the emergency treatment of acute febrile and afebrile (epileptic) seizures in children (15). Oromucosal midazolam was found to be more effective than the rectal diazepam.

The sublingual tablets of buprenorphine and naloxone have shown useful results for the treatment of opiate addiction (16). The study has proposed office-based treatment of addiction using sublingual administration of these drugs.

Zolmitriptan is used for the treatment of migraine and cluster headaches. A sublingual formulation of zolmitriptan exhibited faster absorption and higher drug exposure as compared to subcutaneous injection and is expected to be highly efficient for the emergency treatment of these conditions (17).

In a randomized, double-blind clinical trial, comparing 40 mg of sublingual piroxicam with a 75 mg intramuscular injection of diclofenac for the emergency treatment of acute renal colic, sublingual piroxicam was found as effective as the intramuscular diclofenac (18).

Self-injected epinephrine is used for the treatment of anaphylaxis. In a study, sublingual epinephrine resulted in rapid absorption and higher peak plasma concentration in animal models when compared to self-injected epinephrine. The study proposed sublingual epinephrine as an alternative to self-injected epinephrine (19, 20).

Estrogens in menopausal women with cardiovascular disease have been shown to produce coronary and peripheral vasodilation, reduction of vascular resistance, and improvement of endothelial function. Sublingual estrogens have exhibited faster drug absorption (i.e., shorter T_{max} higher C_{max}) than orally administered forms (21, 22).

The sublingual administration of vaccines may be used against various infectious diseases. Preclinical studies have found that sublingual vaccines can be highly immunogenic and may protect against influenza virus and Helicobacter pylori (23–25).

Development of sublingual tablet formulations

For optimal sublingual formulation development, it is necessary to understand the mechanism of drug absorption, physicochemical and mechanical properties of the drug, function of the excipients in the formulation, and taste-masking techniques for better patient compliance.

Mechanism of mucosal drug absorption. Following sublingual administration, the drugs are absorbed across the mucous membrane by one of the following mechanisms:

- Passive diffusion
- Active or carrier-mediated transport
- Endocytosis.

Although the process of passive diffusion is spontaneous, the rate of diffusion is dependent on the molecular weight and solubility of the drug, concentration gradient, temperature, the surface area of the membrane, and the proximity of the molecule to the membrane. When a drug exists in its unionized form in saliva, it is absorbed by passive diffusion. Physical models have been proposed to describe drug absorption from saliva through the lipid bilayer of the mucous membrane into systemic circulation (26–29). The rate of drug absorption across the mucous membrane is directly related to its partition coefficient (30). Some compounds, such as glutamic acid, L-ascorbic acid, nicotinic acid, and thiamine, are transported via a carrier-mediated process (31–34).

Lipids present in the oral mucous membrane offer the main barrier to the permeability of hydrophilic drugs. On the other hand, well-hydrated connective tissues provide resistance to lipophilic drugs. Thus, the potential transport path across the oral mucous membrane may be either polar or non-polar. Non-polar molecules cross through the lipid regions of the epithelium, while polar molecules travel through ionic channels present in the intercellular spaces of the epithelium, or aqueous pores present in the epithelial cells. For this reason, an understanding of a drug's lipophilic or hydrophilic nature during the developmental stage of the drug product appears to be the most useful index for evaluating its suitability for absorption across the oral mucosa.

Physicochemical properties of drugs. Table II lists the physicochemical properties of some commercially available drugs administered sublingually. These properties of the drugs facilitate their absorption by passive diffusion through the oral mucosa. Partition coefficients and ionization constants of several drugs are described in the literature (35–38).

Table II:
Physicochemical properties of sublingually administered drugs.

Drug

Molecular weight

Largest dose**

Water solubility

pKa

Log P

Nitroglycerin

227

0.6 mg

1.8 mg/ml

-5.6

0.94

Fentanyl citrate

336*

0.8 mg

0.025 mg/ml (citrate)

8.4

2.9

Buprenorphine

467.6

2–8 mg

Insoluble in water

8.24, 10.0

4.9

Asenapine maleate

285.8*

10 mg

3.7 mg/mL

8.6

4.9

Nicotine

162.234

4 mg

Slightly soluble

8.21

0.99

Ergotamine tartrate

583.68*

2 mg

Insoluble in water

6.3

* Molecular weight of the base.
**Largest dose for sublingual tablet.

For efficient absorption through the oral mucosa, the drug must be hydrophobic enough to partition into the lipid bilayer, but not so hydrophobic such that once it is in the bilayer, it will not partition out again. Satisfactory oral absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5. As the log P value increases beyond 5, the solubility in saliva is usually not enough to provide adequate concentration for diffusion through the lipid bilayer (39). According to the diffusive model of absorption, the flux across the lipid bilayer is directly proportional to the concentration gradient. Therefore, lower solubility in saliva results in lower absorption rates and vice versa. In general, a drug formulated for sublingual or buccal administration should have a molecular weight of less than 500 (as free base) to facilitate its diffusion (39).

Because drugs diffuse through the lipid bilayer in the unionized form, based on the pH-partition theory, the pKa of drugs also plays a crucial role in drug transport across the oral mucous membrane. It is important to note that the oral cavity, unlike the gastrointestinal tract, has a narrow range of pH, usually from 5.6 to 7.6. Thus, a basic drug administered as a salt, predominantly exists as a free unionized base if the pH is raised above its pKa value and this increase in the unionized fraction of a drug increases its bioavailability (40). For this reason, the inclusion of a suitable buffer in the formulation of an ionizable drug makes it possible to control the pH of aqueous saliva in a range most appropriate for the optimal absorption of such drugs. Drugs that do not contain ionizable groups are not affected by changes in pH.

Unlike the gastrointestinal tract, the absorptive surface of the oral cavity is much smaller; therefore, large doses cannot be administered via this route. Thus, only potent drugs, which require small doses to obtain the desired therapeutic effect, can be administered from this route. In addition to these critical drug attributes, it is highly desired that drugs for oromucosal delivery be adequately taste masked. Otherwise, it is difficult to achieve patient compliance.

Characteristics of sublingual tablets. In view of the short residence time in the mouth, rapid disintegration and dissolution is crucial for drug absorption following administration of sublingual tablets. For this reason, sublingual tablet formulations should be designed to disintegrate and dissolve rapidly in saliva, without the aid of water to achieve this objective.

The physical and mechanical characteristics of a tablet, such as size, hardness, porosity, and wettability, affect its disintegration time. A smaller tablet size, with low hardness and high porosity, disintegrates more rapidly than a larger or harder tablet. However, a tablet with a high porosity and low hardness is more friable, and this presents problems in tablet packaging and handling. During development, all approaches to increase the mechanical strength of tablets should be studied, without compromising disintegration and dissolution.

The amount and type of disintegrants also play a significant role in achieving rapid disintegration. Effervescent agents have been used to facilitate disintegration (41). The inclusion of water-soluble excipients, such as saccharides, helps in achieving rapid dissolution by enhancing the wettability of the tablet matrix. Moreover, the manufacturing process and critical process parameters also affect disintegration and dissolution of sublingual tablets.

Following sublingual administration, the patient is advised to abstain from swallowing the tablet and avoid eating, drinking, or chewing to facilitate drug absorption through the oral mucosa. Even swallowing saliva is to be avoided, to prevent ingestion through the gastrointestinal tract where drug absorption may be inefficient. Because these aspects pose some inconvenience to the patient, they should be taken into account at the product development stage to improve patient compliance.

Some drugs may have a bitter or unpleasant taste. When such drugs are dissolved in the saliva for mucosal absorption, they may also interact with the taste buds in the mouth and produce the bitter, unpleasant taste, and may not be acceptable to patients. Patient acceptability of formulations is improved by various physicochemical approaches that prevent the interaction of drugs with taste buds and thus eliminate the negative sensory response (42–46). Sweeteners, flavors, and other taste-masking agents are essential components for formulations containing drugs with an unpleasant taste. Sugar-based excipients quickly dissolve in saliva and produce endothermic heat of dissolution. They create a pleasant feeling in the mouth and are most suitable for sublingual tablets along with other flavors. The coating of bitter drugs is not an option for drugs to be dissolved in saliva.

Sublingual tablets promote rapid absorption and higher bioavailability with an almost instant onset of action. If the dissolution of the drug is incomplete, contact time is short, and/or permeation is too low, part of the dose may be swallowed and consequently not absorbed through the oral mucosa, with subsequent effects on bioavailability. Many sublingual tablets may be compromised by the possibility of the patient swallowing the active drug substance before it has been released and absorbed via the oral mucosa into the systemic circulation.

A sublingual tablet designed to promote the retention of the active drug substance under the tongue, to prevent its swallowing, and to minimize inter and intra individual variability, has been reported. This approach made use of ordered mixtures of fine drug particles and bio-adhesive material attached to coarser excipient carrier particles. Tablets composed of these units have the potential to rapidly disintegrate and release the units, which adhere to the sublingual mucosa, and thus prolong the contact time at the absorption site (47–48). Directly compressible sublingual tablets developed using this approach led to the bio-adhesive retention of the drug in the oral cavity and optimal exposure of drug substance to the dissolving fluids in the mouth, which resulted in complete and rapid sublingual absorption.

Manufacturing sublingual tablets-Technology platforms

Although several technologies are available to manufacture sublingual tablets, usually compression molding, direct compression, and freeze drying have been commonly used for commercial manufacture of sublingual tablets. The compression molding process has been used since the early nineteenth century for the preparation of nitroglycerin tablets. Presently, the direct compression and freeze-drying methods are commonly exploited for commercial manufacture of sublingual tablets.

Compression molding. Tablets manufactured by the compression molding process exhibit rapid disintegration and dissolution, which is usually within 5–10 seconds. These tablets pose special challenges during handling and shipping, because of the poor mechanical strength, and may require special packaging (49, 50). Alternatively, the mechanical strength of the tablets may be enhanced by employing a suitable binder. However, the binder level should be optimized to avoid any deleterious effects on disintegration and dissolution of the tablets.

The formulations for the compression molding process typically contain soluble excipients to impart quick and complete dissolution, and taste modifiers for patient compliance (51). Molded tablets have also been prepared directly from a molten matrix, in which the drug is dissolved or dispersed (heat molding), or by evaporating the solvent from a drug solution or suspension at room pressure (no vacuum lyophilization) (52).

The compression molding process involves moistening of the formulation blend with a solvent (usually hydro-alcoholic), followed by molding into tablets under low pressure. The moist tablets are finally dried (53). The lower compression pressure employed for molding and drying of the moist tablet produces a highly porous tablet structure with enhanced dissolution. The choice, ratio, and amount of granulating solvents are critical to the physicochemical characteristics, performance, and stability of the tablets, and should be optimized (54, 55). Several patented technologies are also available for commercial manufacture of compression molded tablets.

Takeda (Osaka, Japan) has developed a mixture containing a combination of starches and sugars. This mixture, after blending with the drug and wetting with a suitable amount of water, can be compression molded. The tablets manufactured from this proprietary mixture are reported to have sufficient mechanical strength and exhibit rapid disintegration (56).

Novartis Consumer Health (Basel, Switzerland) has filed a patent application for tablets prepared by dispensing the drug solution or suspension into molds, evaporating the solvent from the molds by heating under reduced pressure, or microwave radiation, and then sealing the dried units directly in the mold (57).

Nippon Shinyaku (Kyoto, Japan) compression-molds and dries a kneaded mixture containing drug and a water-soluble sugar. This process is claimed to impart sufficient physicochemical stability to the tablet, good appearance, and dissolution time of less than 30 seconds in the oral cavity (58).

Direct compression. The direct compression method is commonly used for commercial manufacture of sublingual tablets. It is a simple and cost-effective process, as it employs ingredients that can be mixed well and do not require further granulation steps prior to lubrication and compression. Sublingual tablets manufactured by the direct compression method exhibit good mechanical strength and acceptably fast disintegration (59).

The directly compressible sublingual tablet formulation contains directly compressible soluble excipients, a super disintegrant, and lubricant. It may also contain microcrystalline cellulose, dry binder, buffers, surface-active agents, sweeteners, and flavors. Sugar-based excipients are widely used as bulking agents because of their high aqueous solubility, sweetness, pleasant feeling in the mouth, and good taste-masking. Nearly all sublingual formulations incorporate some saccharide-based material (60). The choice of a suitable disintegrant and its amount are critical for achieving a fast disintegration and dissolution rate. Sometimes effervescent agents are used to increase disintegration and dissolution of sublingual tablets.

Several novel approaches of incorporating disintegrants and other soluble and/or insoluble excipients to obtain rapid dissolution and adequate mechanical strength are reported. One example is the Flashtab technology of multiparticulate actives (coated crystals and uncoated or coated microgranules) (61). In these tablets, the simultaneous presence of a disintegrant with a high swelling or disintegrating force, defined as “disintegrating agent,” and a substance with a low swelling force (starch, cellulose, and direct-compression sugar), defined as “swelling agent,” was claimed as the key factor for the rapid disintegration of a tablet. The tablet manufactured by this technology is reported to have adequate mechanical strength (62).

Daiichi (Tokyo, Japan) developed a fast disintegrating composition of moderate strength, using a combination of starch or cellulose, and one or more water-soluble saccharides (63). Erythritol was found to be the best sugar for this type of formulation, showing rapid disintegration that was negligibly affected by tablet hardness, good tolerability and sweetening, and a refreshing mouth sensation because of its endothermic heat of dissolution.

Freeze drying. The process of freeze drying (lyophilization) is expensive, time-consuming, and produces tablets of poor mechanical strength. For these reasons, it is not commonly used to manufacture sublingual tablets. However, it does have advantages over the other processes, as the tablets made by this process have high porosity, and when placed under the tongue disintegrate and dissolve instantly. It is a process of choice for products that are unstable or are heat sensitive.

The process involves lowering the temperature of the product in an aqueous medium to below freezing, followed by applying a high-pressure vacuum. To extract the water in the form of a vapor, which is collected as ice on a condenser, a gradual temperature rise is applied during the drying process. The product temperature at the ice sublimation interface and the formulation collapse temperature are critical to obtain a freeze-dried cake of quality structure. This process retains the physical structure and preserves the material for storage or transport.

The resulting tablets are usually light and have highly porous structures that allow rapid dissolution or disintegration. The freeze-drying process may result in a product with an amorphous structure, leading to an enhanced dissolution rate. However, tablets manufactured by freeze drying process have poor stability at a higher temperature and humidity (64).

Considerations critical to product quality

To develop a sublingual tablet that can elicit the desired physicochemical and mechanical properties of the drug product at the site of absorption, it is important to understand, control, and monitor the following critical to quality attributes: particle size of API, wetting time, disintegration and dissolution, content uniformity, hardness, friability, size and weight variation, stability, texture and taste masking, etc.

Most of these tests are universal quality determinants of conventional tablet dosage forms and are equally relevant for sublingual tablets. However, the disease management and conditions of use for sublingual tablets require a very short residence time in the oral cavity. This critical determinant particularly calls for very rapid disintegration, dissolution, and absorption of the product resulting in quick onset of action.

The drugs that are administered sublingually generally have low solubility. Therefore, to enhance dissolution, it is crucial to reduce and control the particle size of the API. This attribute is important in the case of all drugs with low solubility. However, a tighter control on particle size of API is desirable in sublingual drug products to maintain the reproducible quality and performance of the drug product in view of the limited window of dissolution and absorption time.

The conditions prevailing in the oral cavity for disintegration and dissolution of sublingual tablets are markedly different from the tablets that are orally ingested. For this reason, the compendial disintegration and dissolution test methods are not suitable for testing sublingual tablets. It is important to note that compendial methods for disintegration and dissolution tests were developed to test the in-vitro performance of tablets developed for disintegration and dissolution in the stomach following oral ingestion. Other specialized tablets, such as modified-release or enteric-coated tablets, may also partly release the drug in the stomach. In contrast, sublingual tablets are designed to completely disintegrate and dissolve in the oral cavity under the tongue.

To address this critical difference, researchers have proposed various approaches to test disintegration and dissolution of sublingual tablets. These approaches employ physiological conditions of the oral cavity as a guide in testing disintegration and dissolution of sublingual tablets.

One such disintegration method employs a 10-cm diameter Petri dish filled with 10 mL of water that contains eosin, a water-soluble dye. A 10-cm diameter circular tissue paper is placed in the Petri dish. The tablet is carefully placed in the center of the dish and the time for the tablet to completely disintegrate into fine particles is noted as the disintegration time (65). This method has been used widely to test the ability of the sublingual tablets to disintegrate and dissolve in a minimal amount of water, which is more representative of the moisture available under the conditions of use.

Another popular ***in-vitro*** method involves a texture analyzer (TA) instrument to accurately determine the disintegration time. In this method, a tablet under constant force is immersed in a defined volume of water. The time for the tablet to disintegrate is determined by measuring the distance the probe travels into the tablet. The time-distance profiles generated by the TA software enable the calculation of the beginning and end of disintegration time. The influences of the applied force, the volume of water, and water temperature were found to be critical experimental conditions (66–68).

The wetting test, designed by Bi et al., compares favorably with the conditions prevailing in the sublingual region of humans and animals (69). Other authors employed physiological conditions of the oral cavity by using different pieces of equipment (70–72).

The palatability of a sublingual formulation, especially those containing APIs that have an unpleasant taste, is another critical factor for patient compliance as the drug product disintegrates, dissolves, and is absorbed in the oral cavity. Various taste-modifying techniques are reported in the literature including sweeteners, flavoring agents, inclusion and molecular complexes, granulation, salt formation, pro-drug, viscosity modifiers, solid dispersions, and the use of lipoproteins among others (73).

To address this critical patient compliance concern, suitable taste-masking strategies should be studied in the product development stage and incorporated in the product design. The technologies that are reported in the literature for the evaluation of taste include the electronic tongue, measurement of frog taste nerve response, the spectrophotometric method, and a human taste panel (74–76).

Conclusion

The scientific principles employed and the knowledge gained during the product and process development for the manufacture of a sublingual drug product that is fit for its intended use should be provided in the appropriate quality section of ICH M4Q (R1) of the application submitted to FDA (77). As the quality of the drug product cannot be adequately ensured merely by in-process and finished-product testing, critical to quality

controls for raw material, process and equipment, packaging, fitness of test method, and risk analysis should be discussed following the principle highlighted in ICH Q8 (R2), Q9, and Q10 and presented in the submission to FDA. The proposed specification to ensure the quality of the sublingual tablet should be based on the ICH quality guidances, with adequate justification and supportive data (78).

Where applicable, qualification data should be provided in the application to support the use of excipients not used previously in the FDA-approved product. The objective of the drug product is to ensure that the drug available to the consumer is not only safe and effective, but has also been properly manufactured and packaged to meet the established quality target product profile over its intended shelf life. A well-developed product will effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes, critical process parameters and patient needs to meet the tablet quality attributes as discussed in the article.

In conclusion, this review demonstrates that there are a number of commercially available sublingual formulations manufactured using various technologies. The publically available information on sublingual tablets implies that this dosage form has good potential to enhance drug delivery in treating a number of indications. In most reported cases, it has been shown that the sublingual dosage form not only improves the patient's compliance, but also reduces the time for the onset of the drug action, and increases the bioavailability of drugs as compared to conventional tablets.

References

1. H. Zhang, J. Zhang, and J.B. Streisand, Clin. *Pharmacokinet*. 41 (9) 661-680 (2002).
2. K.L. Moore, A.F. Dalley, and Anne M.R. Agur, Eds. *Clinically Oriented Anatomy* (Lippincott Williams & Wilkins, Philadelphia, PA, 6th ed., 2009), p. 944.
3. C.A. Squier and P.W. Wertz, "Structure and function of the oral mucosa and implications for drug delivery," in *Oral Mucosal Drug Delivery*, M.J. Tathbone Ed. (Marcel Dekker, New York, NY, 1996) pp.1-26.
4. W.M. Edgar, *Br. Dent. J.* 172 (8) 305-312 (1992).
5. M.J. Rathbone, B.K. Drummond, and I.G. Tucker, *Adv. Drug Deliv. Rev.* 13 (1-2) 1-22 (1994).
6. S.Y. Chen, C.A. Squier, in *The Structure and Function of Oral Mucosa*, J. Meyer, C.A. Squier, and S.J. Gerson, Eds. (Pergamon, Oxford, 1984) pp.7-30.
7. W.R. Galey, H.K. Lonsdale, and S. Nacht, *J. Invest. Dermatol. 67*, 713-717 (1976).
8. D. Harris and J.R. Robinson, *J. Pharm. Sci.* 81, 1-10 (1992).
9. FDA,Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, accessed Oct. 2, 2014.
10. S.G. Wu et al., *Nephron*. 65 (2) 284-7 (1993).
11. G. Guerrera et al., *Minerva Cardioangiologica*. 38 (1-2) 37-44 (1990).
12. D.N. John et al., *Br. J. Clin. Pharmacol*. 33 (6) 623-627 (1992).
13. S. Fort et al., *Br. J. Clin. Pharmacol*. 37 (5) 460-463 (1994).
14. L. Haegeli et al., *Br. J. Clin. Pharmacol*. 64 (6) 804-809 (2007).
15. J. McIntyre et al., *The Lancet* 366 (9481) 205-210 (2005).
16. P.J. Fudala et al., *N. Engl. J. Med*. 349 (10) 949-958 (2003).
17. Z. Bayrak et al., *Eur. J. Pharm. Biopharm*. 78 (3) 499-505 (2011).
18. A. Supervia et al., *Br. J. Urol.* 81 (1) 27-30 (1998).
19. M.M. Rawas-Qalaji, F.E. Simons, and K.J. Simons, *J. Allergy Clin. Immunol.* 117 (2) 398-403 (2006).
20. X. Gu, K.J. Simons, and F.E.R. Simons, *Biopharm. Drug Dispos*. 23 (5) 213-216 (2002).
21. M. Volterrani et al., *Am. J. Med*. 99, 119-122 (1995).
22. T.M. Price et al., *Obstet. Gynecol.* 89 (3) 340-345 (1997).
23. G. K. Pedersen et al., *PLoS ONE* 6 (11) e26973 (2011) doi:10.1371/journal.pone.0026973.
24. J.H. Song et al., *Proc. Natl. Acad. Sci.* USA. 105 (5) 1644-1649 (2008).
25. S. Raghavan et al., *Infect. Immun*. 78 (10) 4251-4260 (2010).
26. A.H. Beckett and R.D. Hossie, "Buccal absorption of drugs," in *Handbook of experimental pharmacology*, B.B. Brodie and JR Gillette Eds. (Springer-Verlag, Berlin, 1971), pp. 25-46.
27. A.H. Beckett, R.N. Boyes, and E.J. Triggs, *J. Pharm. Pharmacol.* 20 (2) 92-97 (1968).
28. N.F.H. Ho and W.I. Higuch, *J. Pharm. Sci.* 60 (4) 537-541 (1971).
29. K.R.M. Vora, W.I. Higuch, and N.F.H. Ho, *J. Pharm. Sci.* 61 (11) 1785-1791 (1972).
30. L.S. Schanker, *Adv. Drug. Res*. 1, 71-106 (1964).
31. F. Sadoogh-Abasian and D.F. Evered, *Br. J. Nutr*. 42 (1) 15-20 (1979).
32. D.F. Evered and J.V. Vadgama, *Biochem. Soc. Trans*. 9 (1) 132-133 (1981).
33. D.F. Evered, F. Sadoogh-Abasian and P.O. Patel, *Life Sci*. 27, 1649-1661 (1980).
34. D.F. Evered and C. Mallett, *Life Sci*. 32, 1355-1358 (1983).
35. S.D. Roy and G. Flynn, *Pharm. Research*, 6 (2) 147-151 (1989).
36. S. Bredenberg et al., *Eur. J. Pharm. Sci.* 20 (3) 327-334 (2003).
37. S. Riahi et al., *J. Chinese Chemical Soc.* 55 (2) 345-355 (2008).
38. N.Y. Li, Y. Li and J.W. Gorrod, *Med. Sci. Res.* 20, 901-902 (1992).
39. C.A. Lipinski et al., *Adv. Drug Deliv. Rev*. 46, 3-26 (2001).
40. A.M. Al-Ghananeem, A.H. Malkawi, and P.A. Crooks, *AAPS PharmSciTech*. 7 (1) Article 23 (2006).
41. F. Wehling, S. Schuehle and N. Madamala/Cima Labs Inc., "Effervescent Dosage Form with Microparticles," US Patent 5178878 (1993).
42. C. Kumaresan, Pharmainfo.net. (Sept. 9, 2008).

43. J.P. Reo and J.K. Fredrickson, *Am. Pharm. Rev*. 5 (4) 8-14 (2002).
44. R. Kannuri, T. Challa, and H. Chamarthi, *Int. J. Pharm & Ind. Res*. 1 (3) 200-210 (2011).
45. A.M. Morella, I.H. Pitman, G.W. Heinicke, "Taste masked liquid suspensions," US patent 6197348 (2001).
46. D. Sharma et al., *Int. Res. J. Pharmacy*. 3 (4) 108-116 (2012).
47. S. Bredenberg et al., *Eur. J. Pharm. Sci*. 20 (3) 327-334 (2003).
48. S. Bredenberg and C. Nyström, *J. Pharm. Pharmacol*. 55 (2) 169 -177 (2003).
49. K.G. Van Scoik, "Solid pharmaceutical dosage in tablet triturate form and method of producing same," US patent 5,082,667 (1992).
50. L. Dobetti, "Fast disintegrating tablets," US Patent 6,596,311 (2003).
51. M. Okada, Y. Ikeda, K. Ono, T. Kurazumi, S. Kasai and K. Imamori, "Quickly soluble solid oral preparations," US Patent 6,455,053 (2002).
52. L. Dobetti, Pharm Technol. *Drug Deliv. Suppl*. 44-50 (2001).
53. J.W. Conine and M.J. Pikal, "Special Tablets," in *Pharmaceutical Dosage Forms: Tablets*, H. A. Lieberman, L. Lachman and J.B. Schwartz, Eds. (Marcel Dekker, New York, NY, 1989), pp. 338-339.
54. I.A. Chaudry and R.E. *King, J. Pharm. Sci*. 61 (7) 1121-1125 (1972).
55. F.W. Goodhart et al., *J. Pharm. Sci*. 65 (10), 1466- 1471 (1976).
56. T. Makino, M. Yamada, and J. Kikuta/Takeda Chemical Industries, "Fast Dissolving Tablet and Its Production," EU Patent 0,553,777 A2 (1993).
57. P. Humber-Droz, M. Seidel, and R. Martani/Novartis Consumer Health, "Fast Disintegrating Oral Dosage Form," PCT Patent WO 97/38679-A1 (1997).
58. K. Nakamichi, S. Izumi, and H. Yasuura / Nippon Shinyaku Company Ltd., "Fast Soluble Tablets," EU Patent 0,627,218 A1 (1994).
59. Z. Bayrak, C. Tas, U. Tasdemir, H. Erol, C.K. Ozkan, A. Savaser and Y. Ozkan, *Eur. J. Pharm. Biopharm*. *78* (3) 499-505 (2011).
60. R-K Chang et al., *Pharm. Technol*. 24 (6) 52-58 (2000).
61. M.D. Costanzo, "Flashtab and T-Mask Technologies," in *Proceedings of the 7th International Glatt Symposium* (1997), pp. 1-9.
62. G. Cousin, E. Bruna, and E. Gendrot/Laboratories Prographarm, "Rapidly Disintegratable Multiparticular Tablet," US Patent 5,464,632 (1995).
63. T. Murakami et al., *Proc. Intl Symp. Control. Rel. Bioact. Mater*. 26, 855-856 (1999).
64. W. Habib, R.K. Khankari and J. Hontz, *Crit. Rev. Ther. Drug Carrier Sys*. 17, 61-72 (2000).
65. J.S. Ferran et al., "Orally Disintegrating Tablets and Process for Obtaining Them," WO 103629 (2003).
66. G. Abdelbary et al., *Int. J. Pharm*. 292 (1-2), 29-41 (2005).
67. S.K. el-Arini and S.D. Clas, *Pharm. Dev. Technol*. 7 (3), 361-371 (2002).
68. P.J. Dor and J.A. Fix, *Pharm. Dev. Technol*. 5 (4), 575-577 (2000).
69. Y. Bi et al., *Chem. Pharm. Bull*. 44 (11) 2121-2127 (1996).
70. N. Narang and S. Jyoti, Int. *J. Pharm. Pharm*. Sci. 3 (2), 18-22 (2011).
71. J.H. Park et al., *Pharm. Tech*. 32 (8), 54-58 (2008).
72. M.M. Rawas-Qalaji et al., *AAPS PharmSciTech*. 7 (2), E72-E78 (2006).
73. S. Deepak et al., *Int. Res. J. Pharmacy* 3 (4), 108-116 (2012).
74. K. Woertz et al., *Int. J. Pharm*. 417 (1-2), 256-271 (2011).
75. Y. Katsuragi, M. Kashiwayanagi and K. Kurihara, *Brain Res. Protoc*. 1 (3), 292-298 (Aug 1997).
76. S. Kamalpreet and V.R. Kapoor, Ind. *J. Pharm. Sci*. 72 (2), 211-215 (2010).
77. FDA, Guidance for Industry, *Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions* (Rockville, MD, February 2008).
78. FDA, International Conference on Harmonization-Quality, accessed Oct. 2, 2014.

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