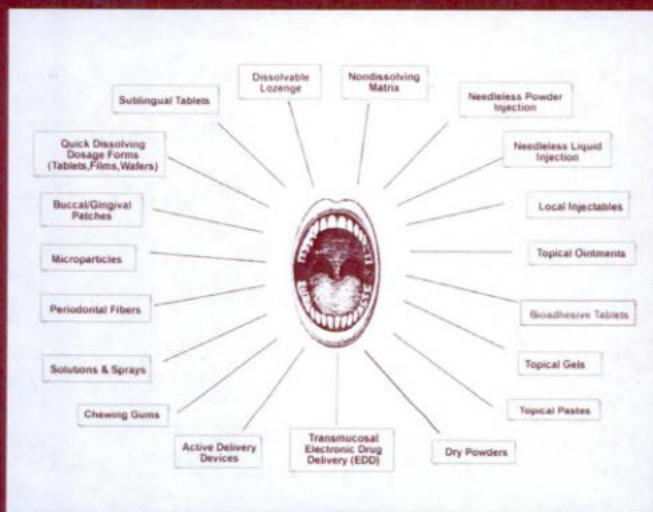


Drug Delivery to the Oral Cavity

Molecules to Market



edited by
Tapash K. Ghosh
William R. Pfister

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Drug Delivery to the Oral Cavity

Molecules to Market

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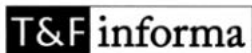
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Quick Dissolving Oral Dosage Forms: Scientific and Regulatory Considerations from a Clinical Pharmacology and Biopharmaceutics Perspective*

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Venkateswar R. Jarugula, Emmanuel O. Fadiran, John P. Hunt,
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I. INTRODUCTION

Over the last three decades, intraoral dosage forms (IODFs) have been evolving as an acceptable, and in some cases as the preferred, alternative to conventional tablets (CTs) and capsules. Quick-dissolving intraoral dosage forms (QODs) are a type of IODFs that have gained much attention recently due to improved patient compliance and ease of administration compared to conventional oral dosage forms (e.g., tablets and capsules). QODs include orally disintegrating tablets (ODTs), the only dosage form of this nature recognized by the FDA listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (i.e., the *Orange Book*)¹ [e.g., Claritin® RediTabs® 24 Hour Non-Drowsy Orally Disintegrating Tablets (loratadine orally disintegrating tablets)].² The European Pharmacopoeia, however, defines a similar term, “orodisperse,” as a tablet that can be placed in the mouth where it disperses rapidly before swallowing.³ The simplest definition of an ODT is a unit dose that disintegrates in the oral cavity. The Center for Drug Evaluation and Research (CDER) defines an ODT to be “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.”⁴ As the majority of the QODs on the market or in different stages of development are in the category of ODTs, the discussion in this chapter primarily focuses on this particular type of dosage form.

Conventional oral dosage forms are administered to the mouth and immediately swallowed intact with water to release the drug for absorption in the stomach and/or intestine (i.e., gastric and postgastric absorption). Potential problems associated with bioavailability (BA) of drug molecules (e.g., stability issues associated within the gastrointestinal tract (GIT) as a chemically hostile environment, gastrointestinal wall, hepatic and gastrointestinal flora metabolism, or variable absorption) can be overcome with a formulation intended for pregastric delivery. To this end, targeted drug delivery to the oral cavity may offer several advantages over the GI and other alternative routes of administration in terms of ease of dosing, enhanced permeability, avoidance of first-pass clearance, better patient acceptability, product life extension, patentability, and increased systemic absorption with certain drugs.⁵⁻¹⁰ However, unless the dosage form is a targeted delivery system such as a buccal tablet or buccal patch, only a minor fraction of the dose is absorbed through the buccal mucosa limiting the main advantage of orally disintegrating dosage forms to convenience of administration and better patient acceptance.

It has long been evident to drug delivery scientists that achieving therapeutically effective plasma levels with intraoral drug delivery systems can be a major challenge. However, nitroglycerin was the first drug shown to be successfully delivered and absorbed from the oral cavity a number of decades ago. Since that

time, many other drug delivery dosage forms administered to the oral mucosa have been commercialized. The development of oral mucosal delivery systems can be distinguished into two periods of innovation. The first period focused on the development of sublingual tablets and solutions. More recently, delivery systems have been refined for oral mucosal delivery by using new technologies and delivery systems such as sprays, mucoadhesive patches, or quick-dissolving solid matrices using advanced manufacturing processes (i.e., lyophilized wafers, solvent cast films, etc.). The second period of drug delivery innovation was spawned over the last decade by the renewed interest in using the highly permeable oral mucosa for targeted delivery of drugs.

Within the United States, the research and development of new unconventional IODFs and their marketing are regulated by legislation or law enacted by the U.S. Congress that is promulgated and enforced by the U.S. Food and Drug Administration (FDA). To assist in the management of the new drug approval process, FDA proposes rules or regulations via the Federal Register,¹¹ which upon finalization are compiled in the U.S. Code of Federal Regulations (CFR) which are also available on the Internet.¹² The relevant CFR sections that address different aspects of clinical pharmacology and biopharmaceutics (CPB) informational needs for supporting a new product's approval are Part 201 of Title 21 (21 CFR 201)¹³ and Part 320 of Title 21 (21 CFR 320)¹⁴ entitled *Labeling* and *Bio-availability and Bioequivalence Requirements*, respectively.

The FDA also publishes guidances that are not legally binding but are intended to provide sponsors with informal guidance and the FDA's current thinking on how regulatory requirements can be satisfied. Currently there are numerous FDA guidances that have been finalized or are in draft that are accessible to the pharmaceutical industry at the FDA's Web site.¹⁵ Official and draft guidances related to this chapter may be found under the general headings of *Clinical Pharmacology*, *Biopharmaceutics*, and *Chemistry*. However, it is noted that currently there is no specific FDA guidance for the types of dosage forms discussed in this chapter. In addition to FDA guidances, there are International Conference on Harmonization (ICH) guidelines prepared jointly by regulatory authorities and pharmaceutical representatives from the European Union, Japan, and the United States.¹⁶ The ICH guidance documents also provide insight as to informational needs (i.e., including the areas of clinical pharmacology and biopharmaceutics) for the drug development process. The ICH guidelines and FDA regulations and guidances complement each other.

The overall approval cycle for any product encompasses multiple disciplines. The intent of this chapter is to review general and specific CPB considerations when developing a new QOD. However, relevant issues pertaining to any IODF in general are also discussed. As some CPB issues overlap with chemistry, manufacturing, and control (CMC) issues mainly in the area of product specifications and in vitro disintegration/dissolution, these considerations are also discussed in this chapter.

II. QUICK-DISSOLVING ORAL DOSAGE FORMS

It is believed that routes of administration that avoid first-pass metabolism may lead to better clinical safety and efficacy predominantly due to lower doses leading to production of a lower amount of potentially toxic metabolites. It has been demonstrated that administration of morphine by routes that avoided first-pass metabolism resulted in lower metabolite production.¹⁷ An increase in the area under the plasma drug concentration time curve (AUC) and $C_{\max}$ for an ODT may be explained in part by avoidance of first-pass metabolism and significant buccal absorption as it has been reported that a lower dose of Zelpar® Zydis® (1.25 mg Zydis® selegiline) is equivalent to a 10 mg selegiline CT.¹⁸ Moreover, because of the lower dose, Zelpar® Zydis® produces less selegiline metabolites (N-desmethylselegiline, methamphetamine, and amphetamine), especially amphetamine metabolites (approximately thirteenfold less) which are linked to side effects of insomnia and cardiac arrhythmias.

Difference in metabolism via the buccal route compared to metabolism in the GIT has also been demonstrated for verapamil. Observed higher $C_{\max}$ and AUC for verapamil and lower $C_{\max}$ and AUC for norverapamil (major metabolite) from a buccal formulation with half a dose of verapamil than that in the CT shows that the buccal drug product might be more desirable than the conventional one in a clinical setting.¹⁹ However, not all compounds can be absorbed through the oral mucosa because pregastric absorption depends on the appropriate physico-chemical characteristics of the drug. For example, it has been found that sublingual administration of salbutamol tablets has no clinical benefit over conventional oral delivery and buccal absorption of salbutamol was found to be negligible.²⁰

The ideal characteristics of a drug for pregastric absorption include: less than 20 mg dose; small to moderate MW; good solubility in water/saliva; partially nonionized at the pH of oral cavity (approximate pH 6.8); ability to diffuse and partition into the epithelium of the upper GI tract ($\log P > 1$, or preferably >2); and ability to diffuse and partition into the blood.^{18,21}

Table 14.1 provides a description of the various IODFs compiled from the approved labeling of a variety of products based on different drug delivery technologies and the *CDER Data Standards Manual*.⁴ Some of these dosage forms are synonymous. The majority of the products mentioned in Table 14.1 are designed to rapidly disintegrate or dissolve in the oral cavity, and other dosage forms are slow- or controlled-release in nature (i.e., sublingual tablets, gums, and patches). Rapidly disintegrating dosage forms release the drug substance for immediate absorption through the buccal mucosa (although insignificant in most cases) followed by subsequent absorption from different segments of the gastrointestinal tract.

However, there is at least one product (Prevacid® SoluTab®) that disintegrates rapidly in the oral cavity and releases coated microgranules from which the drug substance is not absorbed at all from the buccal mucosa, and upon swallowing releases the drug substance in the GIT in a delayed fashion. However,

Table 14.1 Description of Different Intraoral Dosage Forms

Dosage Form	Description of Dosage Form
Freeze-dried wafer	A quick-dissolving thin matrix containing a medicinal agent that needs no water to aid in swallowing. This is a unique freeze-dried dosage form that when placed in the mouth disintegrates instantaneously, releasing the drug which dissolves or disperses in the saliva. The saliva is then swallowed and the drug is absorbed across the gastrointestinal (GI) tract.
Orally disintegrating tablet (ODT)	A solid dosage form containing medicinal substances that disintegrates rapidly, usually within a matter of minutes to seconds, when placed upon the tongue, releasing the drug which dissolves or disperses in the saliva. The saliva is then swallowed and the drug is absorbed across the GI tract.
Quick-dissolving tablet Fast-dissolving tablet Rapid-dissolving tablet Mouth-dissolving tablet Fast-melting tablet Quick-melting tablet	An oral tablet that requires no intake of liquid. The dosage form dissolves in less than a few minutes when placed in the mouth (i.e., faster than a lozenge). The active ingredients are absorbed into the body through the mucous membranes of the mouth into the bloodstream, bypassing the digestive system where they can be inactivated by the stomach acids and enzymes.
Orodispersing tablet	A tablet that can be placed in the mouth where it disperses rapidly before swallowing.
Rapid disintegrating tablet Rapid dispersing tablet	This dosage form is placed in the patient’s mouth and the saliva rapidly dissolves the tablet, releasing the active ingredient (either as coated granules or as solubilized drug), which is swallowed in a liquid form.
Buccal gum Chewing gum	A nondissolving polymer matrix modified release dosage form containing the drug and other excipients that must be chewed but not swallowed to promote release of the drug from the dosage form in the oral cavity. The gum is removed from the mouth and disposed of following use.
Buccal patch Gingival patch Odontal patch	A nondissolving thin matrix modified-release dosage form composed of one or more polymer films or layers containing the drug and/or other excipients. The patch may contain a mucoadhesive polymer layer which bonds to the oral mucosa, gingiva, or teeth for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release). The patch is removed from the mouth and disposed of after a specified time.

Table 14.1 Description of Different Intraoral Dosage Forms (continued)

Dosage Form	Description of Dosage Form
Buccal tablet	A modified-release dosage form that dissolves in the mouth, releasing the drug which is intended to be absorbed through the mucosal lining of the mouth without the aid of water, and should not be swallowed whole. The tablet slowly dissolves once placed in the upper or lower cheek pouch (buccal pouch) between the gum and the side of the cheek. It is recommended not to eat, drink, chew, or smoke while the tablet is dissolving. Patients are also instructed to rinse the mouth and brush the teeth after dissolution to remove the taste, if necessary.
Sublingual tablet	A fast-dissolving, usually small flat tablet intended to be inserted beneath the tongue, where the tablet slowly dissolves and active ingredient is absorbed directly through the oral mucosa. The tablet must not be chewed.
Spray	A unit actuation pump or aerosol spray in a gas or solvent carrier vehicle for rapid drug absorption by the buccal mucosa.
Quick-dissolving film Quick-dissolving wafer	A fast-dissolving polymer film embedded with drug that melts and dissolves in the saliva of the oral cavity quickly and completely, releasing the drug for absorption through the oral mucosa. A fraction of the drug will be swallowed with the saliva and absorbed along the length of the GI tract.

both of these types of dosage forms are considered as immediate-release (IR) dosage forms from the standpoint of releasing the drug substance or coated microgranules instantaneously in the oral cavity. There are dosage forms mentioned in Table 14.1 (such as buccal tablets, patches, and gums) that are designed to release the drug in a slow and controlled manner when first placed in the oral cavity, and therefore they are categorized as modified-release (MR) dosage forms. However, MR dosage forms are not within the scope of discussion of this chapter.

A list of selected ODT products marketed in the United States along with the associated technologies upon which they are based are summarized in Table 14.2. Most of these ODTs are over-the-counter (OTC) line extensions of CTs developed for life-cycle management with improved patient convenience, which can be taken with or without water.²² A human pharmacokinetic (PK) study comparing apomorphine Zydis® versus subcutaneous injection showed that the Zydis® formulation provides comparable plasma levels of apomorphine and therefore may even be used as an alternate route of administration for apomorphine.¹⁸ Market research studies have shown that a significant number of consumers prefer

Table 14.2 Summary of Selected ODT Products

Technologies (Innovator)	Type of Dosage Form	Marketer	Drug	Indication	Products on the U.S. Market
DuraSolv® OraSolv® (CIMA)	Compressed tablet	Wyeth Schwarz Pharma Organon Bristol-Myers Squibb	Loratadine Hyoscyamine Sulfate Mirtazapine Acetaminophen	Allergy Irritable bowel Depression Analgesic	Alavert™ NuLev® Remeron® SolTabs™ Temptra® Quicklets/ Temptra® FirsTabs Triaminic® Softchews® (several formulations) Zomig Rapidmelt™ Excedrin® QuickTabs™
Flashtab® (Ethyparm)	Compressed tablet	Novartis	Pseudoephedrine HCl (other actives)	Pediatric cough & cold	
WOWTAB® (Yamanouchi)	Compression molded tablet	AstraZeneca Bristol-Myers Squibb	Zolmitriptan Acetaminophen	Migraine Headache	
Zydis® (Cardinal Health)	Freeze-dried wafers	Pfizer Schering	Caffeine Diphenhydramine Citrate Pseudoephedrine HCl	Allergy & sinus	Benadryl® Fastmelt®
			Loratadine	Allergy	Claritin® Reditabs®
			Rizatriptan Benzoate	Migraine	Maxalt-MLT®
			Ondansetron	Nausea & vomiting	Zofran ODT®
			Olanzapine	Schizophrenia	Zyprexa® Zydis®
			Clonazepam	Seizures	Klonopin® Wafers
Other	Tablet	TAP Pharm. Inc.	Lansoprazole	Duodenal ulcers	Prevacid® SoluTab®

ODTs to the CT or liquid counterpart products.²³ This may, in part, be due to the pleasant taste and variations of flavors available with the ODTs.

III. ADVANTAGES AND LIMITATIONS OF ORALLY DISINTEGRATING TABLETS

The administration of ODTs may not inherently result in a faster therapeutic onset, but can circumvent problems such as difficulty in swallowing traditional solid oral dosage forms such as tablets and capsules, particularly by pediatric and geriatric patients. The driving force in developing an ODT or other QODs may include one or more of the following advantages.

Patient compliance: To allow patients to easily swallow the dosage form anytime, anywhere, for systemic absorption via rapid dissolution or disintegration in the oral cavity

Patient convenience: To enhance convenience to the patients in carrying and administering these dosage forms especially when traveling by designing them to be taken without water

Rapid absorption and onset of action: To produce rapid absorption and faster onset of therapeutic efficacy mainly from the rapid disintegrating/dissolving dosage forms, presumably due to rapid disintegration, dissolution, and absorption (i.e., antianginal therapy)

Avoidance of first-pass effect: To improve bioavailability owing to partial avoidance of first-pass metabolism resulting from at least partial absorption through the buccal mucosa

Elimination of water/improved stability: To provide an alternative to liquid dosage forms (i.e., syrups, solutions, dispersions) and thereby improve physical/chemical stability of the drug

Product life-cycle management: To extend product life cycle by product differentiation by providing alternative formulations of the conventional oral products

Although one or more of the advantages mentioned above may be desired in the product labeling of a particular ODT, the planned clinical studies should support each claim. In contrast to the advantages, many ODTs have limitations in terms of the amount of drug that can be incorporated in each unit dose. For lyophilized dosage forms, the drug dose must generally be less than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. Also, due to the nature of ODTs, special packaging is needed for products that are fragile, which may add to the cost.²⁴

IV. CLINICAL PHARMACOLOGY CONSIDERATIONS

Dosage forms intended to dissolve in the oral cavity may also be designed to favorably alter delivery of a drug. Avoidance of first-pass metabolism may be demonstrated by information comparing a difference in the drug and metabolite

profiles when given as ODTs versus a conventional dosage form. Standard single and multiple dose pharmacokinetic studies may help to characterize absorption of active and metabolites as well as the bioavailability. Studies to evaluate taste, tolerability to the oral cavity, and toxicity (i.e., mucosal irritation, stinging, etc.) should be carried out. Depending on the proposed indication, clinical safety and efficacy data may also be needed to support the approval of a QOD.

The published information on clinical pharmacology requirements for approval of ODTs is limited at this time for products that are either a pharmaceutical alternative (PA) or pharmaceutical equivalent (PE) to a CT. Based on available information, the following CP information appears relevant depending upon the label claims made by the sponsor in the application for approval of an ODT, and should be considered for characterization of the product.

A. In Vivo Assessment

If the safety and efficacy of a drug in a CT has already been established and the product is already approved for a specific indication, and the purpose of the ODT is to make another dosage form with equal dosage strength to improve patient compliance only, then the primary CP requirement will be to establish bioequivalence (BE) between the ODT and the CT. The design of a BE study should consider sample size in view of variability in absorption of the ODT through the oral mucosa due to the inter- and intraindividual differences in salivary output and variable physiologic conditions of the oral cavity. However, considering the nature of the dosage form, time to reach maximum plasma levels ($T_{\max}$) may be an important PK parameter. On the other hand, if the ODT is being developed with a different dosage strength for similar exposure, bioavailability, exposure-response, and/or clinical studies should be conducted. Also, if the ODT is targeted for a new molecular entity (NME), all of the CP studies for developing a new drug will be required. The following examples are provided to address the general BE issues.²⁵⁻²⁸

1. ODT is generally bioequivalent with the CD as exemplified by the fact that 4 and 8 mg doses of either Zofran® (ondansetron) Oral Solution or Zofran® ODT Orally Disintegrating Tablets are bioequivalent to corresponding doses of Zofran® Tablets.²⁵ Therefore, in this case, no clinical safety or efficacy study was conducted on this new ODT.
2. Contrary to the usual expectation that drugs from an ODT will be absorbed faster than a CT with a shorter $T_{\max}$, it has been found that the AUC and maximum plasma concentration ($C_{\max}$) of rizatriptan were similar following administration of Maxalt® Tablets and Maxalt-MLT® Orally Disintegrating Tablets, but the rate of absorption was somewhat slower with Maxalt-MLT® ($T_{\max}$ ranged from 1.6 to 2.5 hours) as compared to Maxalt® Tablets ($T_{\max}$ ranged between 1 and 1.5 hours).²⁶ Another example is zolmitriptan in which the AUC and $C_{\max}$ of zolmitriptan were similar following administration of Zomig® Tablets and

Zomig-ZMT[®] Orally Disintegrating Tablets, but the $T_{\max}$ was longer with Zomig-ZMT[®] (median $T_{\max}$ of 3 hours for the ODT compared with 1.5 hours for the Zomig[®] Tablets).²⁷ In both of these examples, the apparent rate of absorption was found to be slower with a longer $T_{\max}$ with the ODT as compared to the conventional tablet.

3. AUC, $C_{\max}$, and $T_{\max}$ may differ between a CT and an ODT dosage form. If these parameters are different for an ODT compared to the CT, the ODT dose may need to be adjusted accordingly. For example, Zelapar[™] (selegiline HCl) ODT (not approved in the United States) dissolves instantly in the mouth and provides therapeutic levels of selegiline in Parkinson patients with one eighth of the usual daily dose.²⁸

In light of the preceding examples and general understanding of these dosage forms, the following section describes general CP considerations for development of an ODT.

1. Bioequivalence

Generally the PK profiles between CT and ODT with the same dosage strength are similar and may demonstrate pharmaceutical equivalents (PE). However, if there is any change in PK parameters such as AUC, $C_{\max}$, trough plasma concentration (C_{trough}), and $T_{\max}$ with the ODT compared to CT, the sponsor may need to demonstrate or justify that there are no safety- and efficacy-related issues associated with these factors for the proposed indication(s). A hypothetical comparison of PK profiles between a CT and an ODT is shown in Figure 14.1.

2. Water Effect

As for patient convenience, ODTs can be administered without water; the effect of water intake on bioavailability should be studied. In light of the directions given to patients for most of the approved ODTs, which do not require the patients to take the dosage form with water, the following study design may be considered to evaluate BE as well as the effect of water: three-way design where ODT is administered with and without water and the reference listed drug (RLD) is administered with water under fasting conditions. The hypothesis of the above study design is that the ODT administered with and without water will be bioequivalent to each other and to the RLD administered with water. A typical profile of a BA study comparing a CT and ODT when taken with or without water is shown in Figure 14.2. Generally the profiles are similar. However, if the results show any difference, the clinical relevance of the differences will need to be evaluated.

3. Food Effect

Food generally has a similar effect on drug absorption following administration of an ODT or a CT. However, the effect of food intake may need to be addressed

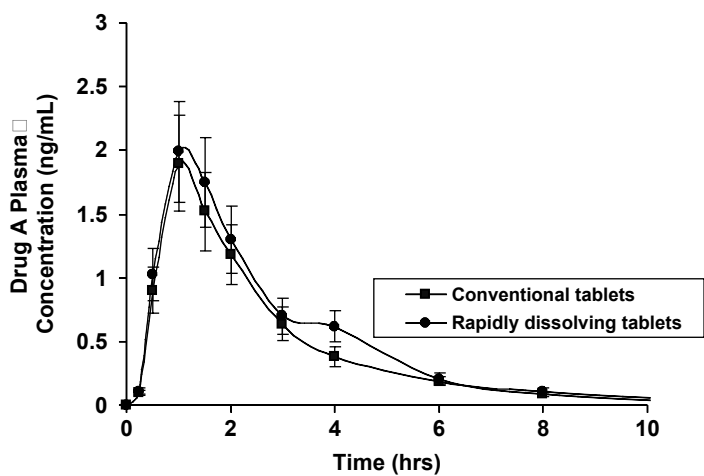


Figure 14.1 Comparative human plasma pharmacokinetic profiles of drug A following administration of either conventional or orally disintegrating tablets.

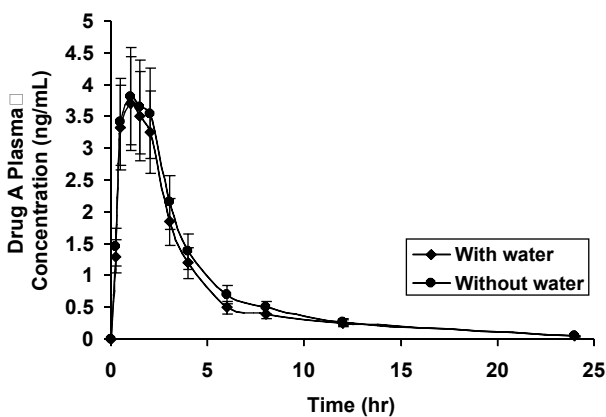


Figure 14.2 Comparative human plasma pharmacokinetic profiles of drug A following administration of orally disintegrating tablet with or without water.

particularly when the drug in an ODT disintegrates in the mouth and the resulting solution/suspension is swallowed rendering a significant fraction of the drug available for absorption in the GIT. This is particularly important for drugs having a documented significant effect of food on absorption, efficacy, or safety. A typical profile showing the effect of food on retarding absorption and altering the bio-availability of a drug in an ODT is shown in Figure 14.3. The following scenarios may be worthwhile to consider in this context.

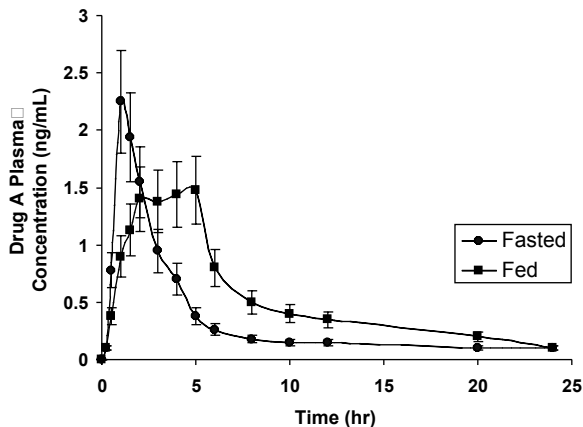


Figure 14.3 Comparative human plasma pharmacokinetic profiles of drug A following administration of an ODT with or without food.

- If food has not affected the BA of the active drug in the CT, similar lack of food effect may be expected with an ODT. Therefore, the sponsor may choose not to conduct any food effect study with the ODT as long as absorption and metabolism remain unchanged from the CT.
- If food does affect BA of the active drug in the CT, then the sponsor should conduct a food effect study on the ODT as per FDA guidance on food effect studies.²⁹ Given the nature and label instructions of the dosage form, ODTs should be administered without water in the food effect study.

In addition, the following CP information may need to be addressed in the development of an ODT on a case-by-case basis. However, not all are needed or applicable to every ODT.

- Contribution of oral (i.e., local site within the oral cavity, e.g., buccal, sublingual, etc.) absorption to drug bioavailability.
- Taste characteristics of the dosage form (compliance/adherence).
- Interactions with drugs that influence production of saliva (e.g., anticholinergics).
- Effect of chewing or swallowing an ODT on the PK of the drug.
- Local (buccal) mucosa irritation.
- Effect of the volume and ingestion of saliva on drug bioavailability. The effects of saliva (volume, pH, etc.) on drug BA from an ODT are not well understood.

V. BIOPHARMACEUTICS CONSIDERATIONS

To be formulated as a lyophilized ODT, the drug molecules should have certain characteristics that include but are not limited to:²⁴

- Relative water insolubility with fine particle size and good aqueous stability.
- Drug loading for water insoluble drugs less than 400 mg.
- Upper limit for water soluble drug loading of about 60 mg.
- Appropriate particle size is ~50 microns as sedimentation is possible with large particles.

The major challenge with ODTs lies in establishing product specifications in terms of in vitro assessments. The considerations in establishing in vitro specifications for ODTs are discussed below.

A. In Vitro Assessment

Most sponsors have used in vitro dissolution time as the release specification for ODTs similar to CTs. Given the nature and mode of action of ODTs and in line with the ICH Q6A guidance document, there is an ongoing initiative to address whether a dissolution test can be replaced by a disintegration test for these dosage forms.³⁰ According to this guidance, if the disintegration test is shown to be an equal or better discriminating test compared to the dissolution test, then the disintegration test may be considered in lieu of the dissolution test. However, it remains to be determined whether a disintegration test by itself is adequate from a biopharmaceutics perspective. To further address this issue, the following points should be considered.

- Disintegration time does not necessarily correlate with dissolution time, even for soluble drugs. Factors attributed to excipients, lubricants, agglomeration, particle size, and dosage form (coated or delayed release drug products) can delay drug dissolution and may have little apparent effects on disintegration.
- Short of in vivo studies, the characterization of a product's dissolution profile is the best quality control test that may correlate with the drug's in vivo bioavailability.
- A disintegration test cannot detect chemical degradation of a drug, whereas a dissolution test can.

If it is decided that a disintegration test alone is adequate from a biopharmaceutics point of view, then the following issues and questions remain to be addressed.

- What medium (e.g., water vs. simulated saliva) should be used for a disintegration test?
- At what temperature should the test be conducted?

- What volume of medium should be used?
- What type of apparatus and mechanical condition should be used for that purpose?
- What should be an appropriate disintegration time specification?

However, if it is decided that a disintegration test alone is not adequate from a biopharmaceutics point of view, and a dissolution test is also needed, then the issues similar to the above would need to be addressed for selecting a dissolution method.

Another factor that may or may not have any clinical relevance but may be a valuable tool in early development is the consideration of *in vivo* (on the tongue) disintegration time. However, the utility of this information is debatable.³¹

B. In Vitro Dissolution Methodology, Requirements, and Challenges

Dissolution testing is a very important tool in drug development and quality control. Initially developed for immediate-release solid oral dosage forms, the application of dissolution testing in recent years has widened to a variety of modified-release and “novel” or “special” dosage forms such as suspensions, ODTs, chewable tablets, chewing gums, transdermal patches, semisolid topical preparations, suppositories, implants, injectable microparticulate formulations, and liposomes. The ultimate goal of these *in vitro* tests for ODTs is analogous to that for conventional solid oral dosage forms, that is, to use the test for the biopharmaceutical characterization of the drug product, and as a tool to assure batch-to-batch consistency in product quality within a defined set of specifications.

ODTs create an *in situ* suspension by disintegrating typically within one minute or less in the mouth. Taste masking (i.e., drug coating) is very often an essential feature of ODTs, and thus can also be the rate-determining mechanism for dissolution/release. *In vitro* dissolution testing of ODT should follow the principles of conventional solid oral dosage forms (i.e., tablets, capsules, or suspensions). A suitable method using an appropriate apparatus needs to be developed before the method is finalized, validated, and accepted for developing release specifications. Due to the different characteristics of ODTs and their sites and modes of application, it is essential that apparatus selection, composition of the dissolution medium, agitation (i.e., flow rate or stirring speed), and temperature be given appropriate consideration during method development and validation. In some cases, the method used in the early phases of product/formulation development could be different from the final test procedure utilized for control of product quality.

A single-point specification is considered appropriate for ODTs with fast dissolution properties. If taste masking is a key aspect of the dosage form by use of polymer coating, a multipoint profile in a neutral pH medium with early points of analysis (e.g., ≤ 5 min) may be recommended. It is to be noted that this early

time point in the profile is intended to address the taste-masking properties of the formulation and may not have any relevance to the product's biopharmaceutical properties. Such a dissolution criterion (typical example: ≤ 10 percent dissolved in 5 min) would largely depend on the taste intensity of the drug and may enable the *in vitro* evaluation of the taste-masking properties while avoiding organoleptic measurements.

If a separate quality control assessment is deemed necessary from the biopharmaceutics point of view, that test should attempt to mimic *in vivo* conditions. The purpose of this assessment is to predict the performance of the ODTs *in vivo* and to establish an *in vitro/in vivo* correlation, if possible. This test may or may not have utility in predicting batch-to-batch product uniformity. Due to instantaneous disintegration/dissolution of most of the ODTs, the sponsor may need to consider which is the more appropriate test to use (i.e., a dissolution test, a disintegration test, or both). Whichever test is used, it should take into account salivary volume, physiologic pH, and temperature of the oral cavity. Therefore, instead of traditional compendial apparatuses, this test may be performed in temperature-controlled test tubes with or without mechanical stirring to determine whether the dosage units dissolve/disintegrate in accordance to patient expectations (as in labeling). If product performance can be characterized by disintegration and dissolution, measures to capture those parameters should be addressed by appropriately designing sampling times. This will help to accurately characterize a disintegration time and/or dissolution profile for the product, and to set appropriate biopharmaceutical specifications. For intraoral products that are intended for rapid drug release, dissolution specifications (typically not less than 80 percent drug dissolved) are usually set within 15 minutes.

Compendial methods (CM) should be used as a first approach in drug development. Alternative methods should be considered only when it has been shown that compendial methods do not provide meaningful data for a new dosage form. In instances where a compendial (e.g., USP, Ph. Eur., and Ph. Jap.) method is employed for *in vitro* drug release testing, the experimental test conditions, qualifications, and validation steps should conform to those discussed in the FIP (International Pharmaceutical Federation) and FDA guidelines on dissolution testing.³² A disintegration test may be used in lieu of a dissolution test for an ODT if it is shown to be an optimally discriminating method.³⁰ Procedures similar to dissolution should also be followed for disintegration method development. Although there is a method for determination of disintegration time in the United States Pharmacopoeia (USP) for conventional hard tablets (Method <701> for troches or lozenges),³³ it may not be appropriate for use with ODTs, and modified methods may be required.³² Use of validated dissolution methods may then be used to demonstrate equivalence between ODTs as an alternative to conducting bioequivalence studies. Validated *in vitro* dissolution tests may in some instances be used as an alternative to conducting *in vivo* BA and BE studies for IR solid oral dosage forms based on the Biopharmaceutics Classification System (BCS), and are outlined in a Guidance Document.³⁴

VI. GENERAL REGULATORY ISSUES AND CONSIDERATIONS

The developmental steps for an ODT or a QOD in general should be similar to any other new dosage form provided the active ingredient in the ODT is already approved in a CD (e.g., tablets or capsules) for a specific indication. In the absence of any separate therapeutic claim, a comparative BA or BE study between the ODT and the reference-listed CD may be required. Information on the design of a BA or BE study can be found in 21 CFR 320 and in the FDA guidance entitled *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations*.³⁵ Bioequivalence by definition is established if the maximum plasma concentration and area under the plasma concentration time curve (systemic exposure) are comparable between the two dosage forms as per the criteria set forth in the general BA/BE guidance (90 percent confidence interval of geometric mean ratio of AUC and $C_{\max}$ of test/reference should fall within 80 to 125 percent). Sometimes ODT may result in a different exposure than CD. In this case, it would be important to know what the exposure–response relationships are in order to understand the meaning of differences in exposure. However, if a different therapeutic claim is made for an ODT over the reference-listed conventional product, the new formulation needs to be supported by clinical safety and efficacy information. The exposure–response relationship should be considered in finding the optimal dose.

In addition to a comparative BA or BE study, local and systemic tolerability and irritation/toxicity in the oral cavity with the use of an ODT may need to be adequately evaluated in preclinical and clinical studies.

VII. SUMMARY

The pediatric, geriatric, and psychiatric populations are the primary targets for ODTs. The future potential for ODTs is promising because of the availability of technologies and strong patient demand. Several ODT products have been commercialized, and the market size for ODTs will surely continue to expand. By paying close attention to the advances in technologies, pharmaceutical professionals should take advantage of this new dosage form.³⁶

To develop an ODT, the following clinical pharmacology and biopharmaceutics areas may need to be addressed: site of absorption (buccal, sublingual, etc.), extent of absorption through oral cavity, involvement of metabolizing enzyme systems (including transporters), net effect of all these on BA, effects of intrinsic and extrinsic factors on drug PK and PK/PD, physicochemical characteristics of the drug, formulation effect, and BCS classification. Taken collectively, the clinical development of an ODT should include a complete characterization of the drug in terms of absorption characteristics, metabolism pathways, and formulation effects. Furthermore, consideration should be given to explore parameters that can be used as predictors of in vivo performance of the ODT and also parameters that can be used to determine/ensure product quality. Categorizations

of ODTs and QODs, in general, into a new dosage form along with guidance documents may assist sponsors in designing the appropriate preclinical, clinical, and biopharmaceutical studies to support marketing applications. Many of these issues were recently discussed in a symposium on this topic.¹⁸

An important issue that remains to be addressed is harmonization of definitions of ODT. It remains to be decided whether it is necessary to perform in vivo disintegration tests in addition to in vitro dissolution or disintegration tests. As the disintegration time of an ODT is generally less than 60 seconds, it is expected that the in vivo disintegration time will not correlate with the in vivo drug plasma concentration profiles. However, both in vitro as well as in vivo disintegration times may be useful as objective measures to determine whether a dosage form can be classified as an ODT, and this area needs to be explored in the future. Given the rapid dissolution characteristics of the ODTs and the recent developments of the BCS for drug molecules, the BCS may be useful in defining regulatory requirements for developing an ODT or any QOD in the future.

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