Dosage Form Design and Patient Compliance: Exploring Orally Disintegrating Tablets as a Patient-Centric Solution

How easy-to-use, convenient dosage forms play an important role in improving patients' engagement with treatment regimens

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INTRODUCTION

Poor compliance with a medication regimen reduces treatment effectiveness for the patient and has a significant impact on overall healthcare costs. Some of the common factors influencing compliance are the disease being treated, patient age and the therapy regimen itself. Therefore, when developing dosage forms, it is important to consider specific patient challenges for different diseases. This article explores the needs of different patient groups, identifies frequent issues leading to non-compliance, looks at the role of orally disintegrating tablets (ODTs) in helping improve patient compliance and provides examples of improving the delivery profile of the drug.

PATIENT POPULATIONS AND DYSPHAGIA

A significant issue across all age groups is dysphagia, defined as a patient's difficulty with or inability to swallow. This disorder is associated with the risk of choking and aspiration of food and liquids into the lungs. A 1999 report by the Agency for Health Care Policy and research estimated that one-third of patients with dysphagia develop pneumonia and about 60,000 people die annually from associated complications [1].

Dysphagia has many causes and may arise as the result of a variety of conditions. Epidemiological findings suggest its prevalence to be as high as one in five in people above the age of 50. Studies have reported its occurrence in 61% of this age group admitted to acute trauma centers, 41% of those in rehabilitation settings, 30 to 75% of people in nursing homes and 25 to 30% of patients admitted to hospitals [1].

Looking at the other end of the age spectrum, there is a need for age-appropriate pediatric formulations in the hospital setting. Sixty seven percent of the oral prescriptions dispensed in the pediatric ICU were considered suitable as determined by a recent study from the Netherlands; the issue is most prevalent with neonates and infants in the ICU as only forty two percent of their oral prescriptions were considered patient-appropriate [2].

For younger pediatric patients, oral formulations that are easy to swallow and allow for dosing flexibility are preferred. As the pediatric population ages, traditional oral solid dosage forms become more acceptable; however, an important key to compliance is to both ensure ease of administration and provide sufficient taste masking for bitter APIs.

The neonate's gastrointestinal (GI) tract is still developing, and as a result, some patients may struggle with certain excipients and foods. In older pediatric groups, a study to determine tablet acceptability in children aged 4 to 8 years and 9 to 12 years indicated tablet size was the most significant issue and that taste, texture, and smell are also dosage form factors to consider [3]. **FIGURE 1** provides a summary of the appropriateness of oral dosage forms in pediatric populations ranging from neonates to teenagers [4].

The target product profile (TPP) for both the pediatric and older age groups described above are similar in that both require formulations that are easy to swallow, dose, handle and offer good palatability. In addition, flexible dosing capabilities are especially important for pediatric patients. Specific dosing devices, such as droppers, tend to be available for the very young, but less so for older patients. Straightforward, user-friendly instructions are desirable for both age groups.

TREATMENT COMPLIANCE IMPACTS BOTH PATIENT HEALTH AND HEALTHCARE COSTS

Looking at treatment compliance rates in five common chronic conditions—cancer, cardiovascular disease, rheumatoid arthritis, diabetes and asthma—reveals large variations in compliance rates [5]. Non-compliance is affected by factors such as health literacy, prior beliefs, memory, dosing regimen complexity and polypharmacy. Interpersonal factors such as the patient-physician relationship, trust issues, and the patient's support group also play a role, as do cultural influences [6].

FIGURE 1: Age-appropriate formulations for pediatric patients. The figure was adapted from [4].

	Preterm	Term	Infants/ Toddlers	Child Preschool	Child School	Teenager
Drops	2	4	5	5	3	2
Liquid	2	2	5	5	3	2
Multiparticulate	1	2	2	4	4	5
Tablet			1	3	4	5
Chew Tablet			1	3	5	5
"Melt" Tablet		1	4	4	5	5

5 Dosage Form of Choice 4 Preferred 3 Acceptable 2 Acceptable, has challenges 1 Not appropriate

The economic cost of medication non-compliance in the U.S. may be as much as $100B - $200B annually. In addition, around 10% of hospitalizations of elderly patients are attributed to non-compliance and may involve up to three extra medical visits per year and an additional $2,000 of costs per person per year. When looking at the cost of non-compliance, inpatient costs represented the greatest proportion of costs contributing to total healthcare costs for cardiovascular disease, diabetes mellitus, osteoporosis, mental health, epilepsy and Parkinson's disease patients. For example, estimates show that improvements in diabetes medication compliance could lead to estimated annual cost savings of between $0.6B and $1.16B [7].

Clearly, non-compliance is extremely detrimental in both monetary terms and with respect to an individual patient's treatment outcomes. Strategies for improving patient compliance must therefore be tailored to the varying needs of the patient as described above with the dosage form of the medicine playing a significant role. In addition, development of pharmaceutical product line extensions should be undertaken with compliance in mind, looking to improve ease of use and dosing flexibility, and to address issues of swallowability, taste and cost.

ORALLY DISINTEGRATION TABLETS AS A PATIENT-CENTRIC SOLUTION

ODTs can provide support in many ways for improving patient engagement in their treatment programs. For example, appearance is a critical aspect of medicines and an attractive dosage form that is easy to swallow can foster patient compliance. The convenience of the ODT also means the patient can take their medication more subtly, something that could be important if they experience a perceived stigma about their condition. Rapid disintegration, a good mouthfeel and pleasant taste are significant factors in the acceptability of ODT dosage forms.

ODTs lend themselves to the usual taste masking strategies of flavors and sweeteners, and for more bitter compounds, there are technologies where the bitter drug binds to the resins to form non-bitter drug-resin complexes due to ion exchange reactions.

With respect to drug delivery and pharmacokinetics, ODTs are generally equivalent to other oral solid dosage forms, but for drugs with suitable characteristics, they open the possibility of pre-gastric absorption. With this comes the potential to reduce the dose and side-effects, again, an important aspect of patient preference and therefore compliance.

There are two main techniques for making ODT — loosely compressed tablets and lyophilized tablets. Although both ODTs have the common characteristic of rapid disintegration, their physical attributes may vary. For example, loosely compressed tablets are easier to handle and can be packaged in blister packs or bottles due to their higher mechanical strength, in comparison to lyophilized ODTs that can be packaged only in unit-dose blisters due to their higher friability.

When considering ODTs, it is important to ensure a pleasant patient experience during dosing. The results of a recent study, shown in **FIGURE 2**, indicate considerable variation between different manufacturers and types of ODTs, particularly in terms of disintegration rate and mouthfeel. Nevertheless, ODT technology improves the patient experience, as illustrated in the following case studies.

Case Study 1 - Migraine patients prefer rizatriptan ODT

In this study, patients taking rizatriptan administered as an ODT were asked if they would prefer to take the migraine medication as a tablet with water or an ODT without water. Of the 368 patients that expressed a formulation preference, 75 to 83% said they would prefer to take their medicine as an ODT rather than as a tablet [8]. In a separate study, patients with a preference for the ODT dosage form felt it to be faster acting and soothing [9].

Case Study 2 - Buprenorphine/naloxone ODT is preferred to tablet or film for sublingual administration

Opioid dependence therapy often involves the use of buprenorphine/naloxone sublingual films or tablets, where the tablet may take up to 10 minutes to dissolve and carries the risk of patients developing ulcers under the tongue.

FIGURE 2: Because Speed Matters. When compared to competitor ODTs, Zydis® ODT technology has a faster disintegration rate and smoother mouthfeel.

The Requirements for an ODT is to have **fast dispersion rates**

May enable pre-gastric absorption – **rapid onset of action** and improved product safety

Rapid dissolution enables effective **buccal and sub-lingual delivery**

	Zydis® ODT	Competitor 1	Competitor 2	Competitor 3
Technology	Unique Lyophilized ODT	Lyophilized	Loose Compressed Tablet	Loose Compressed Tablet
Disintegration Rate	2.9s	> 1 min	15.7s	18.3s
Mouth Feel	Smooth	Paste like	Gritty/chalky	Gritty/chalky

In a comparison of ODT, tablet and film formulations of buprenorphine/naloxone for sublingual administration, Fischer, A., *et al.* [10] found that approximately 77% of healthy volunteers preferred the sublingual ODT to the sublingual tablet, while almost 89% preferred the sublingual ODT to the sublingual film.

Case Study 3 - Patients with allergic conditions prefer ODTs

In a study of 7,686 patients with either allergic rhinitis or dermatitis, participants were given a placebo ODT, and their dosage form preferences were recorded. Ninety-three percent of participants said they would choose an ODT formulation and 88% would actively look to switch their current medication to the ODT format [11].

Case Study 4 - Patients with dysphagia found ODT easier to swallow

The study group was made up of patients either with dysphagia, resulting from neurological problems such as a stroke or a particular disease, such as cancer of the throat [12]. Participants in the single-subject design, crossover study were randomly given either a conventional compressed tablet or an ODT. Results indicated that 75% of participants found the ODT easier to swallow. Only 17% of those taking the ODT requested water, compared with 39% of those taking the compressed tablet. It was noted that 53% of patients did not like to take the conventional tablet without water, while only 11% reported the same for the ODT. These results support the hypothesis that ODTs help improve compliance in patients with dysphagia. Overall, the studies described suggest that when an ODT is available, patients prefer that format, and this was clearly the case for patients living with dysphagia.

IMPROVING THE DELIVERY PROFILE

Beyond the patient preference and swallowability benefits, the ODT format can be used to help improve the drug delivery profile of a given API. An optimally designed ODT formulation can lead to a rapid onset of action, use lower doses, and improve tolerability. Rapid API release from the formulation

FIGURE 3: Wide Range of ODT Applications

Dysphagia	Affects 35% of the general population
Pediatric Application	25-45% of typically developing children demonstrate swallowing problems
Geriatric Population	30-40% of elderly institutionalized patients suffer from dysphagia
Compliance Issues	Institutionalized patients (e.g., schizophrenia, psychosis); CNS disorders (e.g., epilepsy, Parkinson's, Alzheimer's)
Fast Onset	Treatment for nausea, migraine, pain, fever, heartburn, insomnia
Ease of Use	Travel, lack of access to (sterile/potable) water
Market Differentiator	OTC and LCM - Line extensions in response to patent expiration and generic challenge
Biologic	Sub-lingual/Buccal peptides, allergens and immunological vaccines delivery

is especially important for sublingual immunotherapy applications where the active ingredient needs to be released at the oral mucosae before the dose is washed away by saliva or any ingested liquids. The case studies below showcase how the ODT format can help improve the delivery profile.

Rapid onset of action

Ebastine ODT, an allergy treatment, was given to 100 patients. When asked, 85% of participants rated it as "fast" or "very fast" in terms of the speed with which it worked and 77% said it was faster than their usual tablet. Ebastine was also studied in terms of convenience, taste, mouthfeel and sensation. Ninety-four percent of patients reported the ODT formulation was more convenient than other medications and overall, ebastine ODT was preferred by 83% of patients [13].

Rapid release of active ingredients

A study to examine the effects of formulation on in vitro disintegration and release kinetics compared a loosely compressed tablet of house dust mite allergens with a Zydis ODT formulation. Both the 10,000 Japanese allergy unit (JAU) and 20,000 JAU ODTs disintegrated within one second when placed in buffer while the 19,000 and 57,000 JAU compressed tablets took 27 and 45 seconds, respectfully. Both of the Zydis ODTs achieved complete *in vitro* release of allergens in 30 seconds as seen by a plateau in the allegen concentration curve versus the 57,000 JAU compressed tablet, which achieved only partial release at 30 seconds and continued to release allergens throughout the ten minute experiment. The rapid release of API enabled a reduced dosage of the drug in the Zydis formulation and supports lower lingual hold times which may lead to an improved patient experience [14].

Reduced first pass metabolites

An ODT of the Parkinson's treatment selegiline was developed, and its performance compared to a standard tablet. Uptake of this drug via the gastrointestinal tract resulted in high first-pass metabolism that led to low bioavailability and the production of metabolites that included amphetamines. When taken in the evening, the presence of amphetamines can result in sleep issues. Using an ODT that enabled buccal absorption gave higher blood concentrations of the drug and meant the dosage could be significantly reduced from 10mg in the standard tablet to 1.25mg in the ODT, with a consequent reduction in metabolite levels. This allowed patients the option to take the medication in the evening without significantly disrupting their sleep [15].

CONCLUSION

Many factors influence patient compliance during drug treatment. Taking into account the patient's condition, dosage forms can play a critical role, particularly in delivering ease of use and dosing flexibility, along with addressing concerns about dysphagia and taste. Convenient, fast-disintegrating ODT formulations make medicines easy to swallow, often without water, and are amenable to taste-masking strategies. In addition, the rapid release achieved and the possibility of pre-gastric absorption can improve efficacy and lower doses. In the studies presented, patients expressed a strong preference for this format. Whether you are considering an ODT to address patient compliance or improve your product delivery profile, the Zydis technology can help enhance the value of your investment and accelerate your product's potential.

For more information, watch the webinar: Dosage Form Design and Patient Compliance–Exploring ODTs as a Patient-centric Solution

ABOUT CATALENT

Catalent is the global leader in enabling pharma, biotech, and consumer health partners to optimize product development, launch, and full life-cycle supply for patients. With broad, deep-scale and expertise in development sciences, delivery technologies, and multimodality manufacturing, Catalent is a preferred partner for personalized medicines, blockbuster drugs and consumer

health brand extensions. Catalent helps accelerate over 1,000+ partner programs and annually launches over 150 new products, and its flexible manufacturing platforms at 50+ global sites supply over 70 billion doses of nearly 7,000 products to over 1,000 customers. Catalent is headquartered in Somerset, New Jersey.

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