

A Brief Overview on Fast Dissolving Drug Delivery Systems

Mohd Akhtar Rasool*¹, Mohit Rohitas², Amrish Sharma³ Gautam G. K.⁴

1. Department of Pharmaceutics, Malhotra college of Pharmacy, Bhopal, M.P., India.

Abstract

Recently, fast-dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphagia. Fast-dissolving drug delivery systems may offer a solution for these problems.

Key Words: fast-dissolving drug, conventional dosage form, new drug delivery system.

Introduction

Recent developments in technology have presented viable dosage alternatives for patients who may have difficulty swallowing tablets or liquids. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant. An eight-year-old with allergies could use a more convenient dosage form than antihistamine syrup¹. A schizophrenic patient in the institutional setting can hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic. A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H₂-blocker. Fast-dissolving/disintegrating tablets (FDDTs) are a perfect fit for all of these patients². FDDTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. The target populations for these new fast-dissolving/disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or developmentally disabled patients. Patients with persistent nausea, who are traveling, or who have little or no access to water are also good candidates for FDDTs.

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly.

Fast dissolving drug delivery (FDDTs,) can be achieved by various conventional methods like direct compression, wet granulation, moulding, spray drying, freeze drying, sublimation. In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft- moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel-off blister packaging³⁻⁵.

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under Moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several fast-dissolving drug delivery systems have been developed. Fast-dissolving drug delivery In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving performance, convenience and compliance.

FDDTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form⁶.

The advantage of Fast Dissolving Dosage Forms are increasingly being recognized in both industry and academia.

Advantages of Fast Dissolving Drug Delivery System FDDTs

Fast dissolving technology offers:

- Improved compliance/added convenience
- No water needed
- No chewing needed
- Better taste
- Improved stability

*Corresponding Author

E-mail: mohd81pharma@yahoo.co.in



- Suitable for controlled/sustained release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery and Cost-effective.

Needs

The need for non-invasive delivery systems continues due to patients' poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

The current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of poorly absorbed drugs. Key issues facing the biopharma industry are to improve safety (decreasing gastrointestinal side effects), improve efficacy for organ targeting, and improved compliance via sustained release or easy to swallow dosage forms⁷⁻⁸.

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical companies to survive. This applies to all pharmaceutical companies, regardless of their size. In his book, Jurgen Drews has emphasized that the pharmaceutical industry must accomplish more than it has to date with more modest financial resources⁹.

Pharmaceutical marketing is another reason for the increase in available fast-dissolving/disintegrating products. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast-dissolving/disintegrating tablet formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast-dissolving/disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient populations. Although the cost to manufacture these specialized dosage forms exceeds that of traditional tablets, this additional cost is not being passed on to the consumer.

Characteristics of Fast-Dissolving Tablets:

FDDT, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms. Taste-masking is of critical importance in the formulation of an acceptable FDDT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars and other sweeteners to overwhelm or complement the bitter taste of the drug

Current methods of taste masking in fast dissolving/disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. Most of the FDDT technologies incorporate unique forms of taste masking as well. The primary methods of taste-masking include adsorption onto or complexation with carriers and spray coating of drug particles.¹⁰

INGREDIENTS TO BE USED FOR FDDTs:

Important ingredients that are used in the formulation of FDDT should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients.

Excipients balance the properties of the actives in FDDT. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents¹¹.

Binders keep the composition of these fast-melting tablets together during the compression stage. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–35°C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. The choice of a binder is critical in a fast-dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be used¹².

VARIOUS APPROACHES FOR FAST DISSOLVING TABLET:

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation¹³⁻¹⁵.

Various technologies used in the manufacture of Fast dissolving tablets include

- Freeze –drying or lyophilization
- Tablet Molding
- Direct compression
- Spray drying
- Sublimation

- Taste masking
- Mass extrusion

Comparison of Fast-Dissolving/Disintegrating Technologies

ZYDIS (R.P. SCHERER, INC.)

Novelty	Handling/Storage	Drug Release/Bioavailability
First to market	Do not push tablet through foil	Dissolves in 2 to 10 seconds
Freeze Dried	Do not use dosage form from damaged package	May allow for pre-gastric absorption leading to enhanced bioavailability
	Sensitive to degradation at humidities >65%	

ORASOLV (CIMA LABS, INC.)

Novelty	Handling/Storage	Drug Release/Bioavailability
Unique taste masking	Packaged in patented foil packs	Disintegrates in 5 to 45 seconds depending upon the size of the tablet
Lightly compressed		No significant change in drug bioavailability

DURASOLV (CIMA LABS, INC.)

Novelty	Handling/Storage	Drug Release/Bioavailability
Similar to Orasolv, but with better mechanical strength	Packaged in foil or bottles	Disintegrates in 5 to 45 seconds depending upon the size of the tablet
	If packaged in bottles, avoid exposure to moisture or humidity	No significant change in drug bioavailability

WOWTAB (YAMANOUCHI PHARMA TECHNOLOGIES, INC.)

Novelty	Handling/Storage	Drug Release/Bioavailability
Compressed dosage form	Package in bottles	Disintegrates in 5 to 45 seconds depending upon the size of the tablet
Proprietary taste masking	Avoid exposure to moisture or humidity	No significant change in drug bioavailability
SMOOTHMELT action gives superior mouth feel		

ZYDIS (R.P. Scherer, Inc.)

Zydis, the best known of the fast-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue.⁵ Thirteen products are currently available using Zydis technology.⁴ In the U.S., they include: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt-MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis. On the worldwide market, other Zydis formulations are available for oxazepam, lorazepam, loperamide, and enalapril.

A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.¹⁵

The Zydis formulation utilizes flavors and sweeteners to optimize the taste of the dosage form. In addition, it utilizes microencapsulation with specialized polymers or complexation with ion exchange resins to mask the bitter tasting drug. The combination of lyophilization and taste masking creates a product that is both pleasing to the eye and also to the senses of taste and touch¹⁶⁻¹⁷.

A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pregastric absorption from this formulation. Buccal, pharyngeal and gastric regions are all areas of absorption of the Zydis formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistent bioavailability. While the claimed increase in bioavailability is debatable, it is clear that the major advantage of the Zydis formulation is convenience¹⁸.

There are some disadvantages to the Zydis technology. The process of freeze-drying is a relatively expensive manufacturing process. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher temperatures and humidities. It readily absorbs water, and is very sensitive to degradation at humidities greater than 65%.³ If there is any pinhole or minor damage to the package, the patient may find the lyophilized product has collapsed due to absorption of moisture. As with most other drugs, patients should be advised to avoid storing the Zydis technology in the medicine cabinet in the

bathroom. Patients should use their Zydis formulation within six months of opening the laminated foil pouch and immediately after opening its individual blister packaging.

taste masking may be compromised with high drug doses.

ORASOLV (Cima Labs, Inc.)

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a fast-disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste-masking associated with the OraSolv formulation is two-fold. The unpleasant flavor of a drug is not merely counteracted by sweeteners or flavors; both coating the drug powder and effervescence are means of taste-masking in OraSolv. This technology is frequently used to develop over-the-counter formulations.⁹ The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. For that reason, Cima developed a special handling and packaging system for OraSolv. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. Lyophilization and high degrees of compression, as utilized in OraSolv's primary competitors, may disrupt such a taste masking approach.¹⁸ The OraSolv technology is utilized in six marketed products: four Triaminic Softchew formulations, Temptra FirsTabs, and Remeron SolTab.

DURASOLV (Cima Labs, Inc.)

DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials.

The newest DuraSolv formulation, NuLev, is actually dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such DuraSolv formulations from stock bottles to ensure they are not exposed to high levels of moisture or humidity. Excess handling of tablets can introduce enough moisture to initiate dissolution of the tablet matrix¹⁹.

One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike OraSolv, the structural integrity of any

The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound.¹⁰ DuraSolv is currently available in two products: NuLev and Zomig ZMT²⁰.

WOWTAB (Yamanouchi Pharma Technologies, Inc.)

The WOWTAB fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. It has just recently been introduced into the U.S. The WOWTAB technology utilizes sugar and sugar-like (e.g., mannitol) excipients. The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate. Due to its significant hardness, the WOWTAB formulation is a bit more stable to the environment than the Zydis or OraSolv. It is suitable for both conventional bottle and blister packaging. The taste masking technology utilized in the WOWTAB is proprietary, but claims to offer superior mouthfeel due to the patented SMOOTHMELT action.

The WOWTAB product dissolves quickly in 15 seconds or less. The WOW in WOWTAB signifies the tablet is to be given With Out Water. Two WOWTAB formulations currently on the U.S. market are Benadryl Allergy & Sinus FASTMELT and Children's Benadryl Allergy & Cold FASTMELT^{20,21}.

FLASHDOSE (Fuisz Technologies)

Fuisz Technologies has three oral drug delivery systems that are related to fast dissolution. The first two generations of quick-dissolving tablets, Soft Chew and EZ Chew, require some chewing. However, these paved the way for Fuisz's most recent development, FlashDose. The FlashDose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue.²²

Interestingly, by changing the temperature and other conditions during production, the characteristics of the product can be altered greatly. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making microspheres has been patented by Fuisz, and is known as CEFORM and serves as an alternative method of taste masking.

FLASHTAB (Prographarm Group)

The Flashtab technology is yet another fast-dissolving/disintegrating oral tablet formulation. It utilizes most of the same excipients as in conventional compressed tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in under one minute.²³

ORAQUICK (KV Pharmaceutical Co., Inc.)

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouthfeel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disintegrating technologies makes OraQuick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste-masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives²⁴.

Each technology has a different mechanism, and each fast-dissolving/disintegrating dosage form varies regarding the following :-

- Mechanical strength of final product;
- Drug and dosage form stability;
- Mouth feel;
- Taste;
- Rate of dissolution of drug formulation in saliva;
- Swallowability;
- Rate of absorption from the saliva solution; and
- Overall bioavailability.

COUNSELING POINTS FOR FDDTs

Pharmacists are in the ideal position to become familiar with the different technologies, and educate their patients on what to expect upon taking their first dose. The majority of patients receiving FDDT preparations have little understanding of this new dosage form. Patients may be surprised when tablets begin to dissolve in the mouth. They might expect a faster onset of therapeutic action. Clarification from the pharmacist can avoid any confusion or misunderstanding. As with all dosage form technologies, some patient populations are better served

by their use than others. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs. Similarly, patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations. Although no water is needed to allow the drug to disperse quickly and efficiently, most technologies utilize the body's own salivation. Decreased volume of saliva may slow the rate of dissolution/disintegration and decrease the bioavailability of the product²⁵⁻²⁶.

Although chewable tablets have been on the market for some time, they are not the same as the new FDDTs. Patients for whom chewing is difficult or painful can use these new tablets easily. FDDTs can be used easily in children who have lost their primary teeth, but do not have full use of their permanent teeth.

Patients may mistake fast-dissolving/disintegrating for effervescent tablets. Pharmacists may wish to stress the difference between the use of quick-dissolving and effervescent tablets²⁷.

CONCLUSION

The introduction of fast dissolving dosage forms has solved some of the problems encountered in administration of drugs to the pediatric and elderly patient, which constitutes a large proportion of the world's population. Hence, patient demand and the availability of various technologies have increased the market share of Fast dissolving tablets, which in turn prolongs the patent life of a drug. Keeping in view of the advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more popular.

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