

## ORALLY DISINTEGRATING DOSAGE FORMS: BREAKTHROUGH SOLUTION FOR NON-COMPLIANCE

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### ABSTRACT

The objective of this review is to discuss the emergence of orally disintegrating dosage forms as a breakthrough solution for non-compliance. Orally disintegrating dosage forms come in two types, namely orally disintegrating tablet (ODT) and orally disintegrating film (ODF). This article discusses non-compliance issue in general, development of orally disintegrating dosage forms (ODT and ODF), their characteristics, advantages, formulation challenges, manufacturing methods, examples of patented technology of ODT, examples of ODF product, taste masking technologies, patients' acceptance and preference, and lastly counseling. Orally disintegrating dosage forms were originally developed in 1970s to circumvent the problem of swallowing tablet. Over the last few decades, these dosage forms are viewed as an alternative to conventional oral dosage forms. Orally disintegrating dosage forms are aimed to disintegrate rapidly on the tongue, can be taken at anywhere and anytime without the need of drinking water, and the bitter taste of the drug is masked. Orally disintegrating dosage forms are proposed as a solution to the non-compliance problems of patients who are on chronic treatment, have fear of choking in swallowing, on travel, mentally retarded, psychic, bed-ridden and suffer from dysphagic condition.

**Keywords:** Orally disintegrating dosage forms, Orally disintegrating tablet, Orally disintegrating film, Non-compliance.

### INTRODUCTION

Non-compliance has always been identified as a major health care issue that causes therapeutic failure and increase in health care cost. It is a significant challenge in public health sector today [1-2]. Non-compliance is defined as the degree to which a patient does not carry out the clinical recommendations of a treating physician [3]. In US, it is estimated that 50% to 70% of patients do not take prescribed medication properly. It is reported that non-compliance issue tends to worsen in long term drug therapy [4]. Statistics showed that approximately 50% of patients on long-term therapy did not comply to the prescribed treatment [4]. Patients with long term treatment reported that they either never start or they stopped therapy completely within the first year. The reason is that long-term therapy normally involves complex drug regimens and may alter existing living patterns. Taj and Khan (2005) reported that the cost of treatment, discomfort with treatment and long term therapy, were common reasons for non-compliance [5]. Nikolaus *et al.* (1996) reported that 16.4% of patients did not comply to the prescribed medication due to forgetfulness [6]. Only a minority continued taking drugs as prescribed. The consequences of non-compliance are increase in health care cost, lack of disease control and increase in hospital admission or readmission [7]. Approximately 125,000 people with treatable ailments died each year in US due to non-compliance. Hospital cost due to patient non-compliance was estimated at \$8.5 billion annually [8]. Nokolous *et al.* (1996) recommended strategy to improve compliance, which included simplifying treatment regimens, using reminder packaging, and developing more patient-friendly modes of drug administration [6].

### Oral drug delivery system

Oral delivery remains the most popular route of drug delivery [9]. It is because oral drug delivery system has the key advantage of convenient administration. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available due to its convenience of self administration, compactness and simple manufacturing process. Moreover, drug is found to be more stable in solid dosage form than liquid dosage form. However, many patients experience the fear of swallowing tablets and capsules. Some patients have experienced choking while swallowing tablets or capsules of large size. As a result, they do not take their medications as prescribed and non-compliance issues arise. Honda and Nakano (1998) conducted a survey and found that half of the patients experienced difficulty in taking solid medications, such as tablets and capsules, which resulted in a high incidence of non-compliance and ineffective therapy [10]. Majority of patients

who are found to be non-compliance to the treatment are paediatric and geriatric populations [11]. The mentally retarded and uncooperative, nauseated or on reduced liquid-intake/diet patients, have difficulties swallowing these dosage forms. Patients who travel or have no access to water are similarly affected [12].

### Orally disintegrating dosage forms

Over the last few decades, pharmaceutical industries put in a lot of effort to innovate on drug delivery systems. A patient friendly, economical and yet effective drug delivery system, is needed to provide a solution to the non-compliance issue. One of the novel inventions is oral disintegrating dosage form, namely orally disintegrating tablet (ODT) and orally disintegrating film (ODF). The demand for orally disintegrating dosage form has increased markedly since 1970, as it has significant impact on the patient compliance [13].

### Orally disintegrating tablet

#### Definition and background

ODT is a patient friendly dosage form which disintegrates rapidly when placed upon the tongue without the need of drinking water. So, it offers solution to patients who have difficulty in swallowing conventional solid tablets. ODT is different from chewable tablets. Patients especially the geriatrics for whom chewing is difficult, can consume ODT tablets easily. Development of ODT is undoubtedly good news to pediatric and geriatric patients along with hospitalized patients and patients with nausea, vomiting, and motion sickness. ODT is suitable for children who have lost their primary teeth and do not have full use of their permanent teeth [14]. ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population [9].

Recently, British Pharmacopoeia (2009) used the term orodispersible tablet for tablets that dispersed readily and within 3 min in mouth before swallowing [15]. United States Food and Drug Administration (2003) defined ODT as a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue [16].

#### Characteristics of ODT

Bradoo (2001) listed a few ideal characteristics that an ODT should have [17]:

- a.) Disintegrate in mouth in a matter of seconds.

- b.) Taken without water
- c.) Employ effective taste masking technique
- d.) Pleasant mouth feel.
- e.) Robust and less friable
- f.) Stable
- g.) Simple manufacturing method which can use conventional processing and packaging equipments

#### Advantages of ODT

Kuchekar *et al.* (2003) listed some advantages of ODT over other dosage forms [18]:

- a.) Reduced risk of choking
- b.) Eliminated fear of swallowing tablets.
- c.) Convenient in administration as water is not a must.
- d.) Accurate and precise dosing as compared to liquid dosage forms.
- e.) Rapid disintegration leads to fast dissolution, rate of absorption and earlier onset of drug action.
- f.) Improved patient compliance especially for geriatric, paediatric, disabled and bedridden patients.

#### Manufacturing methods of ODT

Some of the manufacturing methods of ODT are described below:

##### (a) Freeze-drying

This method is suitable for thermolabile drugs, since it does not employ heat in the manufacturing process. It is a process in which water is sublimated from the product after freezing. The product prepared using this method is highly porous and has a very high specific surface area, which dissolves rapidly when in contact with water [11, 19-20]. The disadvantages of this method besides producing fragile products, are the use of high cost equipment and complex processing steps, which limit the use of this method [18].

##### (b) Tablet moulding

Tablet moulding method uses water-soluble ingredients so that the tablets dissolve completely and rapidly. Moulding process includes moistening, dissolving, or dispersing of drug with a solvent. The powder blend is then moulded into tablets under pressure lower than that used in conventional tablet compression. Air drying process removes the solvent in the tablet. As a result, moulded tablets are very porous and less compact than compressed tablets. The ODT possesses porous structure that improves dissolution [20-21].

##### (c) Sublimation

Sublimation is a manufacturing method which produces porous ODT with fast disintegration. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate and camphor) are mixed with other tablet ingredients and the mixture is compressed into tablets. When the volatile materials are sublimated, an ODT with porous structures is produced [19]. Kizumi *et al.* (1997) developed ODT utilizing camphor as subliming material. Camphor was sublimated in vacuum at 80°C for 30 min after preparation of tablets. Hence, the tablet produced is highly porous with fast disintegration time [22].

##### (d) Spray drying

Spray drying technique produces highly porous and fine powders as the processing solvent is evaporated during this process. However, this method is not suitable for heat sensitive drugs. ODT manufactured using this method disintegrates within 20 seconds when immersed in an aqueous medium. Allen and Wang (1993) reported an example of ODT manufactured using this method [23]. Hydrolyzed and non-hydrolyzed gelatin were used as supporting matrix, mannitol as bulking agent, sodium starch glycolate as superdisintegrant, citric acid and sodium bicarbonate as disintegration and dissolution enhancers [19].

##### (e) Mass extrusion

Mass extrusion involves softening of the active blend using a solvent mixture of water-soluble polyethylene glycol and methanol, and subsequent expulsion of soft mass through an extruder. The product is cut into even segment using heating blade. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste [20].

##### (f) Direct compression

Direct compression is the easiest and conventional way to manufacture ODT. The advantages of this method are low manufacturing cost, the use of conventional equipments and limited number of processing steps. However, the disintegration and dissolution of the ODT are slower due to the more compacted and less porous ODT formed. The disintegration of ODT manufactured using this method was dependent on superdisintegrant, water soluble excipients and effervescent agents [19-20].

##### (g) Phase transition

Two sugar alcohols, one with high and one with low melting points are used to manufacture ODT. The ODT is compressed then heated at a temperature between the melting points of the two sugar alcohols. The tablet hardness was increased after heating process, due to increase of inter-particle or the bonding surface area in the tablets induced by phase transition of lower melting point sugar alcohol [24].

#### Examples of patented ODT technologies

There are various ODT technologies that have been patented by various pharmaceutical companies. Table 1 shows some of the patented ODT technologies [25].

**Table 1: Examples of patented ODT technology**

Technology	Manufacturing method	Patent owner
Zydis	Lyophilization	R.P. Scherer Inc.
Quicksolv	Lyophilization	Janseen Pharmaceutica
Lyoc	Lyophilization	Farmlyoc
Flashtab	Multiparticulate compressed tablet	Ethypharm
Orasolv	Compressed tablet	Cima Labs Inc.
Durasolv	Compressed tablet	Cima Labs Inc.
Rapi Tab	Compressed tablet	Schwarz Pharma
WOWTAB	Compressed molded tablet	Yamanouchi Pharma Technologies, Inc.
Fast melt	Molding	Elan Corp
Ziplets	Molding	Eurand
Flashdose	Cotton candy process	Fuisz Technology Ltd.
Adva Tab	Combination of Microcaps and Diffucap technologies	Eurand

#### Orally disintegrating film (ODF)

ODF is an ultra-thin and flexible strip of postage stamp size film, with an active pharmaceutical ingredient or combination of active pharmaceutical ingredients, which disintegrate within a minute when in contact with water. ODF is intended to be placed on patient's tongue. When wetted by saliva, the film rapidly hydrates and disintegrates to release the active ingredient for mucosal absorption or gastrointestinal absorption after swallowing. ODF starts to gain recognition as a consumer friendly dosage form since the early 21st century, with the introduction and widespread use of Listerine pocket strips, a new launch in the mouthwash range [26]. However, it is a challenge to incorporate bitter molecules into this kind of dosage form.

#### Characteristics of ODF

Dixit and Puthli (2009) listed some of the characteristics of ideal ODF:

- a.) Ultra thin
- b.) Post stamp size
- c.) Fast disintegration upon contact with water
- d.) Flexible and not fragile

e.) Taste masked [27]

#### Advantages of ODF

This dosage form enjoys some distinct advantages over other oral dosage forms such as:

(a) Large surface area

ODF is an ultra thin and postage size film. The large surface area leads to fast disintegration and dissolution in the oral cavity.

(b) Taken without water

ODF is easy to swallow without the need of water. The dosage form can be consumed at any place and at any time.

(c) Solution for specific group of patients

It is suitable for patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders, who are unable to swallow large quantity of water.

(d) Accuracy of dose

Compared to liquid formulations, solid formulations enjoy the advantage of more accurate dose.

(e) Stability of drug molecule

Drug molecule is more stable in solid dosage forms compared to liquid dosage forms.

(f) Flexibility of film

Some ODTs are fragile and brittle, which warrant special packaging for protection during storage and transportation. The ODF is a flexible film and not as fragile as the ODT.

(g) Rapid onset of action

ODF disintegrates and releases the active ingredient rapidly when placed upon the tongue. Hence, a rapid onset of action is expected [28].

(h) Barrier to generic entry

From the industry point of view, ODF is considered as an alternative for conventional oral products, that affords a barrier to generic entry.

(i) Revenue

From the marketing point of view, a patented ODF technology is beneficial and would help the company to gain more revenue.

(j) Solution to non-compliance issue

From the health care provider's point of view, ODF will help to solve the non-compliance issue. Hence, the health care cost could be reduced [27].

#### Manufacturing method of ODF

(a) Hot melt extrusion

The active ingredient and other excipients are mixed in dry state and subjected to heating process. The mixture is extruded in a molten state. The formed films are then cooled and cut into the desired size [28]. In this method, solvent system is not used. Other advantages of this method are simple preparation process and more uniform dispersion because of intense mixing. It is also a suitable method for insoluble drugs. However, this method might not be suitable for thermolabile drug, as the drug may degrade under high temperature used in the process [29].

(b) Solvent casting method

Solvent casting method is the most common preparation method for ODF. It involves the mixing of active pharmaceutical ingredient and strip forming excipients together, in a suitable solvent system. The water soluble polymer is first dissolved in water to form a viscous solution. Heating process is included at this stage to aid the dissolution of materials in the solvent system. Drugs and other

ingredients are mixed in another smaller portion of solvent. Both portions are then mixed together with high stirring speed to ensure uniformity. The air bubbles can be removed by vacuum. Entrapped air may produce uneven films. Once this mixture is mixed uniformly, the film casting process is performed where the desired mass of mixture is casted onto suitable mould. The mixture is then dried to remove the solvent. In small scale production, film strips are usually casted using applicators. Once the films are dried, it is cut into suitable shape and size. The commonly available sizes of films are 3 x 2 cm<sup>2</sup> and 2 x 2 cm<sup>2</sup>. The film is then subjected to packing. The packaging should give sufficient mechanical protection to prevent the film from damage during transportation, handling and storage. Aluminium foils are ideal and most preferred for film packaging [30].

#### Examples of patented ODF product

There are various ODF products that have been patented. Table 2 shows some of the ODF products [25].

Table 2: Examples of ODF products in the market

Product	Drugs	Manufacturer
Theraflu Thin Strips Long Acting Cough	Dextromethorphan	Novartis
Theraflu Thin Strips Multi-Symptom	Diphenhydramine	Novartis
ThaminicThin Strips Long Acting Cough	Dextromethorphan	Novartis
Triaminic Thin Strips Cough & Runny Nose	Diphenhydramine	Novartis
Gas-X Thin Strip Anti Gas	Simethicone	Novartis
Little Colds Sore Throat Strips	Pectin (from vitamin C)	Prestige Brands
Suppress Cough Strips	Dextromethorphan	InnoZen
Suppress Herbal Cough Relief Strips	Menthol	InnoZen
Chlorasptic Relief Strips	Benzocaine; menthol	Prestige Brands

#### Taste masking

Taste refers to a perception arising from the stimulation of taste buds present on the surface of the tongue. Human can distinguish the components of taste: sourness, saltiness, sweetness and bitterness [31]. Taste masking technology is used in the development of orally disintegrating dosage forms, as majority of drugs are bitter in nature. When the dosage form disintegrates in the mouth, the taste bud is exposed to the bitter drug.

#### Challenges in developing orally disintegrating dosage forms

Development of the dosage forms have never been an easy task. Habib *et al.* (2000) listed some of the potential challenges in developing orally disintegrating formulations [32]:

(a) Mechanical strength and disintegration time

In order to allow ODT to disintegrate in the oral cavity, most of the ODT are made of either very porous tablet structure or compressed into tablets with very low compression force. As a result, the ODTs are friable, brittle, difficult to handle, and often require specialized peel-off blister packing to protect the product. It is very likely that such fragile tablets tend to break during packing, transporting or handling by the patients. Likewise, ODF is a very thin film. ODF is designed in such a way so that rapid disintegration is achieved. However, the film might be fragile due to low thickness. On the other hand, increasing the mechanical strength delays the disintegration time.

(b) Taste masking

Many drugs are bitter in taste. It is not acceptable if ODT / ODF disintegrate and the bitter substances dissolve in saliva and leave a bad taste. Poor taste will seriously affect patient compliance and acceptance for the dosage form. Effective taste masking technique which can mask the bitter taste of the drugs must be used so that the taste of the drug is not felt in the oral cavity. ODT / ODF with good taste might increase the acceptance of patients and hence resolving non-compliance issue.

## (c) Mouth feel

The ODTs / ODFs disintegrate in the oral cavity. Hence, mouth feel is another critical factor which affects the acceptance of the dosage form. ODTs / ODFs which disintegrate into larger particles in the oral cavity leave a poor mouth feel on the tongue. The particles generated after disintegration of the ODT / ODF should be as small as possible. The addition of flavours and cooling agents, like menthol, improves the mouth feel.

## (d) Stability

Most of the ODT / ODF are hygroscopic in nature due to the ingredient used and cannot maintain physical integrity under normal condition of temperature and relative humidity. Hence, special packaging is needed to protect the product from humidity.

## (e) Cost

ODT / ODF that are packed in specialized packaging might increase the production cost. Manufacturing of Zydis and Orasolv that require special technologies and equipments, increases the cost to a remarkable extent [32].

**Patients' preference and compliance**

Orally disintegrating dosage forms are more preferred by majority of patients compared to conventional tablets. Danilevičiūtė *et al.* (2009) conducted a study on the efficacy, tolerability and preference of mirtazapine orally disintegrating tablets in depressed patients [33]. The survey revealed that majority of patients (80%) preferred ODT than the conventional tablet. In another study, Dowson and Almqvist (2005) conducted a survey on the convenience of, and patient preference for zolmitriptan orally disintegrating tablet [34]. The results revealed that 90% of patients preferred ODT than conventional tablet. Unlike conventional tablet, zolmitriptan ODT can be taken wherever and whenever migraine occurred. Paul *et al.* (2005) conducted a multicenter, open-label, sequential study comparing preferences for carbidopa-levodopa orally disintegrating tablets and conventional tablets in 60 Parkinson's disease patients [35]. The findings showed that 45% of the study subjects preferred ODT, 35% had no preference and 20% preferred the conventional tablets. The factors contributing to patient preference for ODT are summarized in Table 3 [35]. The high acceptance and preference rate by majority of patients, indicated that orally disintegrating dosage forms had potential in improving patients' compliance towards medication.

**Table 3: Reasons cited for preference and percentage of patients**

Reasons cited for preference	Percentage of patients
Greater access to medication	50%
Easier to perform daily activity	47%
Reduced concern about swallowing medications	45%
Use for nighttime dosing	42%
Less self-conscious about use in public	42%

**Counselling**

Orally disintegrating dosage forms might be new to patients. Health care providers play an important role in educating their patients on the administration of this kind of dosage forms. Clarification from the pharmacist may avoid any misunderstanding or confusion [25]. Some general counselling points are summarised as below:

- Although ODT / ODF can be taken without water, it is advisable to take with water to avoid decrease in disintegration time / dissolution of the dosage form, which could affect the bioavailability of the product.
- ODTs are different from chewable tablets. They are not meant to be chewed. The dosage form will disintegrates with the aid of saliva or water [36].
- ODTs are not effervescent tablet. They are not meant to dissolve in glass of water for drinking.

(d) ODT and ODF are not sweets or candies. Keep them away from the reach of children.

(e) ODT and ODF are susceptible to degradation via temperature and humidity. Keep the product in air tight container.

(f) Avoid from direct sunlight and heating. Store in condition as recommended by the manufacturer.

**CONCLUSION**

Orally disintegrating dosage forms might serve as a better solution to improve patients' compliance in health care setting. Studies have shown the value and potential of orally disintegrating dosage forms in solving non-compliance issue, especially for patients who are on long term medication, fear of choking, bed-ridden, mentally retarded as well as pediatric and geriatric patients. In addition, these dosage forms have managed to garner strong patient acceptance and preference. Therefore, these dosage forms have great potential to replace the current oral dosage forms in the very near future.

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