

A REVIEW ON – DEVELOPMENT OF ORAL DISINTEGRATING TABLETS**Prasad M. S.*, Somashekhar C. N. and Senthil Kumar G. P.**

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ABSTRACT

Orally disintegrating tablets (ODTs) is one of the popular and widely accepted dosage forms, especially for the pediatric and geriatric patients. These dosage forms are placed in the mouth, allowed to dissolve in the saliva. They release the drug as soon as they come in contact with the saliva, thus avoiding the need for water during administration. They avoid the problem of dysphagia and improve patient compliance. Over the past three decades, orally disintegrating tablets (ODTs) have gained much attention as a preferred alternative to conventional oral dosage forms such as tablets and capsules. ODTs have gained considerable attention as preferred options to conventional tablet and capsule formulations. Various conventional and patented techniques have been employed for the development of ODTs. The techniques render the disintegration of tablet rapidly and dissolve in mouth without chewing or additional water intake. In the present review is focused on the ideal characteristics, formulation by different technologies and evaluation of ODTs are discussed.

KEYWORDS: Oral disintegrating tablet, Advantages and disadvantages, Formulation challenges, Ideal Properties, Approaches for preparation of ODTs, Evaluation.

INTRODUCTION

An extensive diversity of new dosage forms for patients taking the safety of life, ease of medication is being produced by a scientist in pharmaceutical research. Where different dosage forms are available nowadays in market such as tablets, capsule, injections, transdermal patches and etc. Depending upon people compliance and economic consumption of medication they are produced. Where most widely accepted and easy way of drug administration is through oral route of administration.

Oral dosage forms like tablets and capsules possessing great problem of swallowing mainly for pediatrics, geriatrics, and bedridden, nauseous or non-compliant patients.^[1]

Tablets are the unit dosage form containing one or more active ingredients and excipients present in it. Where the tablets can be classified by various conditions like sizes, shapes, thickness, weight and etc. Tablet are classified into pills, caplet, oral disintegrating tablet. Tablets are the most widely used nowadays by patients.^[2]

Over a decade, the demand for development of orally disintegrating dosage has enormously increased as it has significant impact on the patient compliance.

An Orally Disintegrating Tablet (ODT) is a solid dosage form that dissolves in the mouth (either on or beneath the

tongue or in the buccal cavity) without water within 30 seconds or less. In order to achieve tablet disintegration within 30 seconds; superdisintegrants have to be incorporated Crospovidone, croscarmellose sodium, sodium starch glycolate have been used in concentration range of 1- 8%.^[3]

The first ODT form of a drug was approved by the U.S. Food and Drug Administration (FDA) was a Zydis ODT formation of Claritin (loratadine) in December 1996. It was accompanied by a Zydis ODT formulation of clonazepam in December 1997, and a Zydis ODT formulation of Maxalt in June 1998. The US Food and Drug Administration, Center for Drug Evaluation and Research definitions in the Orange Book an ODT as “solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”.^[4]

ODT is also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts.

One survey indicated that about 26% of patients do not get hold of their prescribed medicine as they ran across problems when swallowing conventional tablets. Frequently, the main complaints are the size, surface and taste of the pills. An approximated 35% of the general

population, and an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities, suffer from dysphagia. This disorder is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy.^[5]

Advantages of ODT

1. Easy to administer to the patients who cannot swallow, such as asthma elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
2. Improved patient compliance.
3. Rapid onset of action and may offer an improved bioavailability.
4. Suitable during traveling where water is may not be available.
5. Good mouth feel property helps to change the perception of medication as the bitter pill particularly in pediatric patients.
6. The risk of choking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
7. New job opportunity like product differentiation, product publicity, patent extension and life cycle management.
8. Cost effective.
9. Provides rapid drug delivery of dosage forms.^[6]

Disadvantages of ODT

1. Fast dissolving tablet is hygroscopic in nature so must be kept in dry place.
2. Sometime it possesses mouth feeling.
3. MDT requires special packaging for properly stabilization & safety of stable product.^[7]

Formulation Challenges of ODTs

1. Mechanical strength

ODTs are made of porous or soft molded matrices in order to allow its disintegration in the mouth. This makes tablet friable and handling becomes difficult.

2. Palatability

ODTs are intended to be dissolved in mouth. Most of the drugs have bitter taste and comes in direct contact with the saliva. Hence, maintaining palatability is one of the major formulation challenges in development of ODTs.

3. Aqueous solubility

Drugs that are aqueous in nature are often difficult to formulate since they lead to depression in freezing point and causes formation of glassy solids. These tablets may collapse upon drying. Use of matrix forming excipients like mannitol may prevent such collapse condition.

4. Amount of drug

The amount of drug that can be loaded into each unit dose limits the use of ODTs. For water insoluble drugs, drug dose must be less than 400mg and for soluble drugs it should be less than 60 mg.

5. Hygroscopicity

It poses one of the major challenges in formulating ODTs. Drugs in form of ODTs are hygroscopic in nature and hence need to be protected from humidity.^[8]

Ideal Properties

An ideal ODT should

1. Require no water for oral administration.
2. Have a pleasing mouth feel.
3. Have an acceptable taste masking property.
4. Be harder and less friable.
5. Leave minimal or no residue in mouth after administration.
6. Exhibit low sensitivity to environmental conditions (temperature and humidity).
7. Be portable and easy to transport.^[9]

Approaches For Preparation of ODTs

There are number of approaches employed in the formulation of orally disintegrating dosage forms. They have their own advantages as well as disadvantages. The approaches used to manufacture ODTs are:

1. Conventional Technologies

- a) Freeze Drying.
- b) Tablet Molding.
- c) Sublimation.
- d) Spray Drying.
- e) Mass extrusion.
- f) Direct Compression.

a) Freeze drying

Freeze drying or lyophilization is a process in which solvent is removed from a frozen drug solution or suspension containing structure forming excipients. Tablets formulated by this technique are normally very light and porous in nature which allows their rapid dissolution. Glassy amorphous porous structure of excipients as well as the drug substance produced with freeze drying results in enhanced dissolution. Freeze drying process usually consists of three steps:

1. Material is frozen to bring it below the eutectic point.
2. Primary drying to reduce the moisture around 4% w/w of dry product.
3. Secondary drying to reduce the bound moisture up to required final volume.

The entire freeze-drying process is carried out at non elevated temperature; therefore, nullifying adverse thermal effects that may affect drug stability during processing.

b) Tablet molding

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-

drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.

c) Spray drying

This technique is based upon the use of a particulate support matrix prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. Disintegration and dissolution were further improved by adding effervescent components, i.e. citric acid and sodium bicarbonate. The formulation was finally spray dried to yield a porous powder.

d) Mass-extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

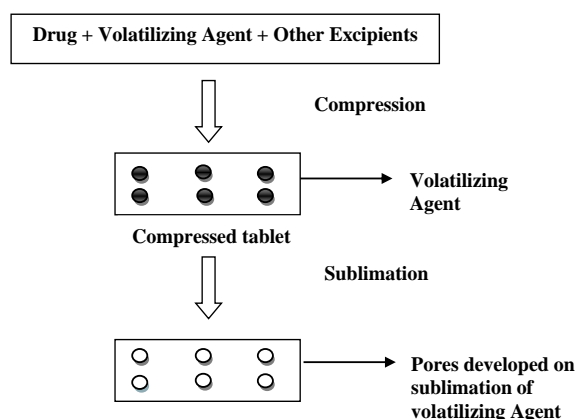
e) Sublimation

Because of low porosity, compressed tablets containing highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in water. Some inert volatile substances like urea, urethane, ammonium carbonate, naphthalene, camphor etc. are added to other

tablet excipients and blend is compressed into tablet. Removal of volatile substances by sublimation generates a porous structure. Additionally, several solvents like cyclo-hexane and benzene etc. can also be used as pore forming agents. Steps involved in sublimation are seen in below figure.

f) Direct compression

This is most popular technique because of its easy implementation and cost-effectiveness. The basic principle involves addition of disintegrants and/or water-soluble excipients and/or effervescent agents. Superdisintegrants in optimum concentration (about 2-5%) are mostly used so as to achieve rapid disintegration along with the good mouth feel.^[10]



Some examples of Superdisintegrants employed in ODT.^[11]

Super disintegrants	Nature	Mechanism of Action	Brand Names
Crosscarmellose	Modified cellulose or Cross-linked cellulose	Wicking due to fibrous structure swelling with minimal gelling.	Ac-Di-Sol Nymce 25 X Nymcel
Crosspovidone	Cross-linked PVP	Water wicking, swelling and possibly some deformation recovery	Kollidon Polyplasdone
Soy polysaccharides	Natural disintegrant		EMCOSOY
Sodium starch glycolate	Modified starch	Rapid and extensive swelling with minimal gelling	Explotab, Primogel
Ion-exchange resin	Resins		Amberlite (IPR 88)
L-HPC	Low hydroxyl propyl cellulose	Both swelling and wicking	

2. Patented Technologies^[12]

ODTs characteristics is generally quick penetration of water into tablet resulting in fast disintegration. Different technologies have been developed on the formulation aspects.

Resulting dosage forms vary on several parameters like mechanical strength, porosity, dose, stability, taste, mouth feel, dissolution rate and overall bioavailability.

Below table represents the list of unique patented technologies, patent owner along with significant advantages.

Patented Technology	Technique Employed	Company Name	Active Ingredient (Brand Names)	Advantage(s)
Zydis	Lyophilization	R.P. Scherer, Corp	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)	Highly porous in nature, quick dissolution, increased bioavailability
Quicksolv	Lyophilization	Janssen Pharma	Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-Tab)	Short disintegration time, good mouth feel

Lyoc	Lyophilization	Farmalyoc	Phloroglucinol Hydrate (Spasfon Lyoc)	Accommodate high dose, disintegrates rapidly
Orasolv	Effervescent disintegrant compression	CIMA Labs, Inc	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt)	Unique taste masking, fast dissolution, require Conventional manufacturing process
Durasolv	Molding	CIMA Labs, Inc.	Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)	Good rigidity
Wowtab	Compression molded tablets	Yamanouchi Pharma Tech.Inc.	Famotidine (Gaster D)	Adequate dissolution rate and hardness
Flashdose	Cotton Candy Process	Fuisz Technology Ltd.	Tramadol HCl (Relivia Flash dose)	Highly porous in nature, pleasant mouthfeel
Flashtab	Effervescent disintegrant microencapsulated drug compression	Prographarm Group	Ibuprofen (Nurofen FlashTab)	Conventional tableting technology required
Ziplets	Molding	Eurand International	Ibuprofen (Cibalgina DueFast)	Sufficient mechanical strength
Oraquick	Micromask taste masking	KV Pharm. Co., Inc.	Hyoscyamine Sulfate ODT	Significant friability, appropriate for thermolabile drugs
Advatab	Microcaps and diffuscap CR Technology	Eurand International	AdvaTab cetirizine, AdvaTab Paracetamol	High drug loading, improved mechanical strength

Evaluation of Oral Disintegrating Tablets

The tablets after manufactured they were evaluated for following parameters.

a) Thickness

Thickness was determined for 20 pre weighed tablets of each batch using a vernier calipers scale and the average thickness was determined in mm.

b) Hardness

Tablet hardness (tablet crushing strength), the force required for breaking a tablet in was determined using Monsanto hardness tester. It was expressed in Kg/cm². Five tablets of each formulation were randomly picked and hardness of each tablet was determined. Then the average hardness value was calculated.

c) Friability

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). 10 tablets were randomly selected and their initial weight was noted. Then tablets were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes. The tablets were taken out the weight was noted again. For conventional tablets the percentage loss in friability should be less than 1% whereas friability values of up to 4% are acceptable for oral disintegrating and chewable tablets.

d) Weight variation test

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications, when not more than 2 tablets are outside the percentage

limit and if no tablet differs by more than 2 times the percentage limits.

e) Wetting time

Wetting time of the mouth dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. It can be measured using the following procedure. Procedure: Five circular tissue papers of 10cm diameter were placed in a Petri dish with 10cm diameter. 10ml of water was added to Petri dish, a tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as wetting time.

f) Water absorption ratio

The weight of the tablet in the above procedure before keeping in to the Petri dish was noted (Wb). The wetted tablet from the Petri dish was taken and re weighed (Wa) using the same. The Water absorption ratio was determined as per the equation. Equation: $R=100(Wa-Wb)/Wb$.

g) In-vitro disintegration time

Disintegration time is the time taken by the tablet to break into smaller particles. The disintegration test is carried out using USP disintegration test apparatus containing a basket rack assembly with six glass tubes which consists of a 10-mesh sieve. The basket is raised and lowered 28-32 times per minute in the medium of 900ml of distilled water, which is maintained at $37\pm 2^{\circ}\text{C}$. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments

through the sieve (# 10) was considered as the disintegration time of the tablet. And the time for disintegration of ODTs were tabulated.

h) Dissolution studies

In vitro dissolution studies for all the fabricated tablets was carried out using USP paddle method at 100 rpm in 900 ml of phosphate buffer Ph 7.4 as dissolution media, maintained at $37 \pm 0.5^\circ$ C. 5 ml aliquot was withdrawn at specified time intervals, filtered through whattman filter paper and assayed spectrophotometrically at 279 nm. An equal volume of fresh medium, which was pre-warmed at 37° C, was replaced in to the dissolution media after each sampling to maintain the constant volume throughout the test.^[13-14]

i) Drug Content

Five tablets were powdered and the blend equivalent to 20 mg of Mefenamic acid was weight and dissolved in 100 ml of phosphate buffer (pH 7.4). Stock solution was

sonicated for 15 minutes. Filter the sample and withdraw 1ml filtrate was taken in 100ml phosphate buffer and analyzed spectrophotometrically at 284 nm. The amount of Mefenamic acid was estimated by using standard calibration curve of drug. Drug content studies were carried out in triplicate.

j) Stability study

Stability of a pharmaceutical preparation can be defined as “the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life”. Stability studies were carried out at room temperature 25-30 OC for a specific time period up to 30 days for selected formulations. For stability study, the tablets were sealed in aluminum packaging coated inside with polyethylene. The tablets were analyzed for drug content uniformity, in-vitro dispersion time, in-vitro disintegration time and in vitro dissolution study for up to 30 days.^[15]

Some ODT products in Indian market

Sl no	Brand Name	Active Ingredients	Company
1	Nimulid-MD	Nimesulide	Panacea Biotech
2	Zyrof meltab	Rofecoxib	Zydus Cadila
3	MOSID-MD	Mosapride Citrate	Torrent Pharmaceuticals
4	Feledine Melt	Piroxicam	Pfizer
5	Maxalt ODT	Famotidine	Merck
6	Remeron Sol Tab	Mirtazapine	Organon
7	Romilast	Montelukast	Ranbaxy
8	Manza BDT	Olanzapine	Orchid
9	Olanexinstab	Olanzapine	Ranbaxy
10	Valus	Valdecoxib	Glenmark
11	Rofaday MT	Rofecoxib	Lupin
12	Torrox MT	Rofecoxib	Torrent

CONCLUSION

Pediatric and geriatric patients are primary concerns, as both the groups find these dosage forms convenient to administer as compared to the conventional dosage forms. Orally disintegrating dosage solved the major problem of non-compliance for pediatrics and geriatrics which occur mainly because of swallowing difficulty. Orally disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. ODTs can be made in several ways and product performance depends upon the drug suitability and excipients selection in the delivery system. More drugs can be formulated as oral disintegrating tablets. Based on conventional techniques and patented techniques they ODTs are developed like Direct compression, Moulding, Zydis, Quicksolv, Lyoc, Orasolv and many more. This dosage form is gaining market share day by day and becoming a better choice of acceptance by pediatrics and geriatrics.

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