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A review on oral disintegrating tablets: aboon in the world of pharmaceuticals

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ABSTRACT

DDS-Drug delivery systems are getting progressively modern as pharma scientists acquires a clearer insight of the physico-biochemical boundaries appropriate to their performance. In the last four decades, orally dissolving/disintegrating tablets(ODTs) have acquired significant consideration as a desirable alternate option because of improved patient compliance in contrast to conventional capsules and tablets. ODTs are solid dosage forms containing therapeutic ingredients that disintegrate rapidly within seconds in the oral cavity leaving an easy to swallow residue. orally dissolving/disintegrating tablets advancements addressing numerous medicine and patient necessities, varying from improved life cycle management to appropriate administer dose of medicine for pediatric, mental and geriatric patients with dysphagia. The main object of the present review was centered on to explain the evolution, processing technology, formulation attributes, evaluation parameters, advantages, limitations and global market status of ODT's and future potential prospects.

Keywords: Drug delivery systems (DDS), Orally disintegrating tablets(ODTs), Current research.

INTRODUCTION

Orally disintegrating tablets (ODT's) are advanced drug delivery systems which are administered through oral route to disintegrate in the oral cavity [1].ODT technology was first developed by RP Scherer in the 1980s by the Zydis technology named after its invention, and the first products reached patients in the early 1990s. The first drug incorporated in this technology was loratidine (an anti-histaminic or anti- allergic) and sold under brand name *Claritin* and some other drugs include clonazepam and rizatriptan. The before mentioned drugs were formulated and released into market in 1996,1997 and 1998.

Now-a-days, most of the industries choosing ODT technology for its enormous advantages and greater patient compliance.This is the most common approach used to overcome the problems associated with the common oral dosage forms like tablets and capsules. ODT's have potential impact on the patient compliance compared to routine dosage forms like tablets and capsules. ODTs are also known as the orodispersible tablets, quick melts, mouth dissolving tablets, rapid dissolving tablets, and fast

disintegrating tablets. ODT's helps in overcoming the problems associated with the conventional dosage forms by avoiding the step of swallowing a solid mass [2][3][4]. ODT's dissolved very rapidly in the saliva of mouth and allowed to swallow without need of water[5].

The regulatory bodies explains ODT's

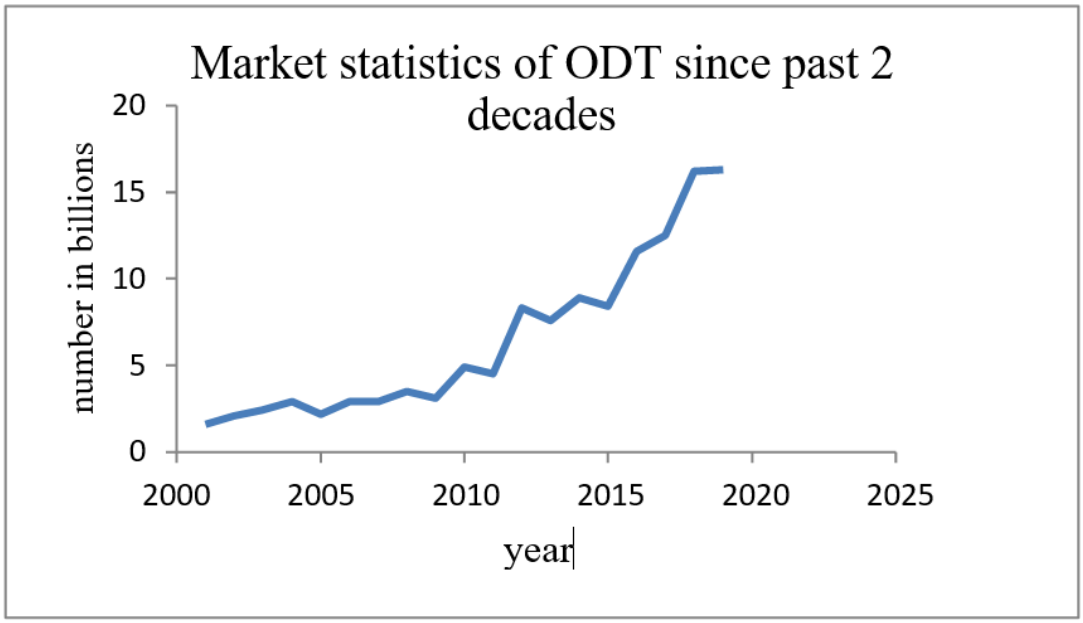
European pharmacopoeia used the word orodispersible tablet as it is intended to keep the dosage form in the oral cavity and it should be disintegrate rapidly i.e. within 3 minutes and to be dissolved in saliva for swallowing without water[6]. The USFDA defined "the ODT as the solid unit dosage form containing the medical substance which can disintegrate rapidly, usually in a matter of seconds when placed on tongue". This is there as on that why many marketed ODT formulations have the disintegration time from few seconds to a single minute.

These ODT's are very useful for the group of population who are unable to swallow especially the kids, travellers and the older people [7]. According to a global survey in 2010 almost 70% patients desired to have the ODTs for their medication over the solid oral and liquid dosage forms due its special feature of easy administration without water

After the drug gets dissolved in saliva it starts travel down through GIT where it gets absorbed either through oesophagus or pharynx or from the other parts of GIT. Generally the dissolution and the absorption are the major parameters to affect the onset of action. Because of this rapid dissolving and the easy absorption of the drug from the ODT the bioavailability of the drug will get increased compared to other conventional oral dosage forms. ODT's are also given sublingually, then it roglycerine (treats anginapectoris) sublingual tablets, which were then very easily disintegrates in oral cavity and absorbed directly into blood vessels presented under the tongue.

Ideal Properties of the ODTs

Rapid disintegration, Rapid dissolution in saliva, Pleasant taste, Avoidance of water to administer dose, Minute or no residue in oral cavity, High drug loading and rapid onset of action, Easy to chew, Easy to manufacture with the existing procedure, Acceptable stability during shipping & storage, It Should be cost effective and with Compatible taste with different age groups and with the active pharmaceutical ingredient (API), Less sensitive to environmental changes. Statistical reviews show the gradual increase of ODT sale from past two decades in the global market. It shows an average of 3 billion USD between 2000 and 2005 and from then the sale increases gradually till a decade with some fluctuations and in the last five years the sale reached the extreme point of 17 billion USD approximately. On basis of market analysis from business analysts, it is predicted that the sale can be increased to 25 billion USD in 2025 and the above reports shows the need and demand for ODT formulations in the patient population.



Properties to prefer ODTs over conventional tablets

Enhanced compliance, Better stability, improved and better taste, avoidance of chewing and swallowing the dosage form, problem of choking due to conventional tablets and capsules can be avoided especially in paediatric and geriatric patients[19]. Ease of administration for mentally sick, aged, bed ridden, stroke patients, renal failure patients and for kids[20]. And these are also preferred for rapid drug therapy. These are very suitable forthe patients with oesophageal problems. ODT's does not leave any residue and gives good feel to the buccal region. Research shows ODT's have improved bioavailability[21].The usage of ODT's were limited due to their fragile nature, highly hygroscopic[22], require special pack aging restriction of eating and drinking difficult to achieve dose uniformity may have chances to leave unpleasant taste and/or grittiness in mouth[23]

ODTs can be developed by using different methods by considering the changes in parameters can be explained as... the mechanical strength can be varied depending on the method used, swallowing ability can also be changed, change dissolution of API in saliva[24], ultimately the said changes can alter the bioavailability of the drug, changes in the taste and the mouth feel, alteration of Stability[25].

There are several methods for manufacturing ODT's, but some important methods areLyophilization/Freeze drying, Spray drying, Tablet molding, Sublimation, Mass Extrusion, Direct Compression, Cotton candy process, Nanonization, Nanocrystal technology, Fast dissolving films, Melt granulation, Effervescent method etc.

Whereas the process of Lyophilization involves the water sublimation from the frozen product to produce amorphous and porous products[26]. Generally the amorphous compounds will disintegrate and dissolve faster rather than the crystalline compounds[27]. The tablets formulated using the lyophilization process will form the porous matrix which allows the saliva to enter rapidly into the tablet for disintegration of the tablet when placed in mouth. The API entrapped matrix contains the rapidly soluble polymer along with the other ingredients or excepients like antioxidants, colours, flavours, suspend ingagents, wetting agents which can improve the final quality of the product. Preferably the API used for the lyophilization process should be tasteless, small particle size, low dose[28], physically and chemically stable and water insoluble.

Typical freeze drying process involves three steps:

- Freezing the material mixture which can be formulated as ODT
- Primary drying to get the moisture content 4% W/W of the dry product

Secondary drying to attain the bound moisture content to the desired level[29]

The ODTs formulates using lyophilisation process will have less tendency to resist the changes in temperature, humidity and other environmental conditions which can directly or indirectly affects the product stability.

While in Spray drying the name itself indicating the mechanism that the material can be dried by spraying the hot gas on to the material, this method will be useful especially for the thermo sensitive materials. The usage of spray driers is getting increased in food, pharmaceutical and biochemical industries[30]. As the process involves the rapid evaporation of solvents it can produce the fine powder highly porous matrix[31] which can able to dissolve rapidly. The method of formulating ODT is based on the supporting matrix which is prepared by the spray drying the aqueous phase containing supporting matrix generally hydrolysed or unhydrolysed gelatine. As the supporting matrix is highly porous in nature along with that sodium starch glycolate and/or cross carmellose sodium as disintegrating agent, Mannitol as bulking agent and in few cases citric acid and sodium bicarbonate can also be used to get rapid disintegration and dissolution[32].The Matrixa long with the excepients and API together compressed as tablet. The ODT containing spray dried granules are having the disintegration time less than 30 sec[33].

Tablet molding involves either solvent method or heat method. The process of solvent method involves the API and the excepients are getting wetted by the solvent followed by the molding of the mixture into tablets under low pressure. Usually the pressure used in compression molding is less than the pressure applied in routine tablet compression process. The molded tablets are allowed to dry under normal air. Due to the usage of lower pressure during compression the molded tablets will have the porous structure which can enhance drug release[34]. But to increase the dissolution rate the dry power should passthrough thefine screen before wetting. Heat method in volves the drying of suspension containing the gel base (Usually agar),sugars (Usually Mannitol or lactose). Usually the suspension used to pour into

blister packing wells and allowed to dry at 30°C under vacuum[35].

Even though the ODT containing highly solubilising components sometimes it is unable to release the API rapidly due to the less porosity in the matrix used for the preparation of ODT. Sublimation is one of the techniques used to make the matrix porous. Sublimation is the process in which the solid will directly converted to vapour state by avoiding the liquid state[36]. In this technique the volatile ingredients will be incorporated during the compression and they can be removed from the tablet by sublimation. Due to removal of this volatile components from the tablet by sublimation the matrix become porous which allows the solvent to penetrate rapidly there by faster disintegration of the tablet[37]. The disintegration time for the ODTs manufactured by this technique was found to be less than 30 sec.

Examples of subliming agents are camphor, urea,benzoic acid, naphthalene, adipic acid, myristic acid, urea, urethane, capric acid, ammonium bicarbonate, ammonium carbonate, hexamethylenetetramine, thymol, menthol, and palmiticacid etc. Generally these compounds are converted into vapours from 40°C to 60°C[38].

Mass Extrusion is a technology which involves the expulsion of softened active blend mass through the extruder to get the cylinder of the product followed by even segments of the product with help of heated blade to formulate tablet. Solvent mixture containing the water soluble polyethylene glycol and methanol can be used for softening the active blend mass[39]. The process of mass extrusion can also be used for the coating of the API with bitter and unpleasant taste and the Direct compression is a process in which the API and excepients are compressed together without any granulation technique. It is the simplest and convenient technique for tablet formulation. Direct compression isthe cost effective method due to avoidance of multiple steps like granulation, milling etc. For employing direct compression process the API should posses good flow properties to prevents segregation, cloggingin hopper and to attain dose uniformity[40]. For providing pleasant taste, faster disintegration andotherpropertiesofODTsthistechniqueneedsspecial gradeofexcepientslike super disintegrants, bulking agents like sorbitol and other sweeteners which can provide both bulk in ess and taste masking. Along with super disintegrants and sweeteners flavouring agents, preservatives and some effervescent agents like citric acid and sodium bicarbonate to accelerate disintegration[41]. All the excepients used in this technique should posses good flow properties, desired particle size, wettability and water absorption capacity to provide desired disintegration time followed by therapeutic effect.

Cotton candy process is known as the cotton floss process. The process produces the floss like crystalline structures which looks like cotton candy by utilising the unique spinning technology. In this process of cotton candy the formation of polysaccharide matrix followed by the flash melting and spinning. The formed matrix subjected for milling an blending with API and other ingredients followed by compression as ODT.High doses of drug can be incorporated into the ODT by using this method. Formulation of thermo sensitive APIs as ODT is risky with this process[42].

Nanonization technology involves the size reduction of the API to nano size for achieving desired the rapeutic effect. As the size of particle reduces the problem of agglomeration will occur which can be prevented by adsorbing the nano sized crystals or nanoparticles on to the stabilizers[43]. These stabilizers along with API can be compressed as ODTs along with other excepients. Nanonization will help to incorporate the APIs with poor water solubility, help to get faster disintegration and/or dissolution followed by improved absorption due to the nano size of particles leads to the dose reduction due to improved bioavailability[44].

Nanocrystal technology can be employed for the potent APIs with lower dose Due to less number of steps and negligible wastage of API[45].It consists of colloidal dispersions of API and water soluble ingredients filled in blister pockets and subjected for lyophilization.

Fast dissolving films can be prepared by using technique which involves the formation of film which melts and dissolves rapidly when keeps in mouth. This method involves the non-aqueous solvent containing the API along with the film forming agents like hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, hydroxypropyl cellulose, pullulanetc[46]. And other excepients includes taste masking agents, flavour ingagents, preservatives etc. Film will be formed upon evaporating the non-aqueous solvent. Coated microparticles of API can be incorporated into the film for bitter API. Poorly water soluble drugs can also be incorporated into the film.

The process of melt granulation doesn't involve any organic or aqueous solvent. It is the processin which the agglomerating the API and excepients in ameltable binder. Generally hydrophilic waxy binder will be used in this technique to provide sufficient mechanical strength and to get desired physical resistance. The binder used should have the property

to dissolve rapidly without leaving any residue when placed in mouth[47].

ODTs formulated by effervescent method can release drug due to evolution of CO_2. For this effervescent method effervescent agents like sodium bicarbonate and citric acid or tartaric acid can be used at a concentration of 12% w/w, super disintegrants like sodium starch glycolate, cross carmellose sodium, pre-gelatinized starch can be used. To remove the residual moisture from sodium bicarbonate and tartaric acid subjected to the preheating about 80°C and mixed properly with other excepients followed by compression[48].

Excepients plays a major role in the formulation of ODTs which can affect the performance and stability of the dosage form. Generally ODTs contains at least one disintegrant, a lubricant, a diluent and if required a flavouring agent, a sweetening agent to improve the Organoleptic properties[49].

The main property for an ODT is the ability to disintegrate rapidly to dissolve and show its therapeutic action. The role of disintegrants is to make the dosage form disintegrate into smaller particles and there by further decrease in size followed by drug release. Comparatively the super disintegrants can able to disintegrate and dissolve quickly rather than the routine disintegrants[50]. Sodium starch glycolate, microcrystalline cellulose, calcium carboxy methyl cellulose, cross povidone, pregelatinized starch, modified corn starch, cross carmellose sodium are the few examples of super disintegrants.

Factors like flow properties, dissolution in saliva, pleasance of mouth feel, friability and compacting properties can have a greater impact on selection of super disintegrants for ODT formulations. Super disintegrants can provide the disintegration by either of the mechanisms like particle- particle repulsive forces, swelling, wicking and due to deformation[51]

Most of the APIs will have the unpleasant or disagreeable taste which will affect the patient compliance especially in paediatric patients. The concept of ODT is to provide the therapeutic action for the patients without leaving any bitter or unpleasant taste in mouth. This can be achieved by using sugar based excepients called as sweeteners[52]. As the majority of APIs are bitter in taste, it is necessary to use the taste masking agents. Generally xylitol, mannitol, sucrose, dextrose and other sweeteners are used as taste masking agents.

Generally binders are used to keep the materials together during compression and to provide sufficient strength for the ODT to be stable during transportation and packaging. Commonly using binders are povidones, acrylic polymers, polyvinyl alcohols and cellulosic polymers[53]. The addition of binder should impart the smooth texture and appearance to the ODT and the binders selected should able to melt at body temperature to provide rapid release. Selection of binder will decide the integrity and stability of the ODT[54]. Some best examples of binders are cellulose derivatives (ethyl cellulose, hydroxy propyl cellulose and hydroxy methyl cellulose) and acrylic polymers (Eudragit E, Eudragit NE, Eudragit RL and RS)

Surface active agents **c**an improve the solubility of the ODT by decreasing the interfacial tension**.** Sodium dodecyl sulphate and sodium lauryl sulphate are the couple of examples for surface active agents[55].

Flavours like clove oil, citrus oil, vanilla and peppermint oil and colours like red iron oxides, sunset yellow are preferable to improve patient compliance. Along with the above excipients lubricants, fillers and some other excipients can also be used depends in the need.

Pre-compression parameters should be evaluated for the ODT's before going to compression to ensure the flow properties of blend.

Angle of reposeis performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula:

$$\theta = \tan^{-1} H/R$$

Where, θ=angle of repose H=height of powder cone, R=radius of powder cone

Bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of about 50 $cm^3$of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in $cm^3$of the sample contained in the cylinder. Bulk density can also determined by bulk density apparatus by using same process without manual tapping. It was calculated by using equation given below:

$$Df = M / Vp$$

Where, Df = bulk density
M = weight of sample in grams

Vp = final volume of powder in cm^3

Tapped densitys the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Do = M/Vp$$

Compressibility Index or Carr's index is an indication of the compressibility of a powder. This is calculated by the formula

$$C = \frac{(\rho b - \rho t)}{\rho b} \times 100$$

Where, ρb is the bulk density, ρt is the tapped density

A Carr's index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Carr's index	Properties
5-15	Excellent
12-16	Good
18-21	Fair to Passable
2-35	Poor
33-38	Very Poor
>40	Very Very Poor

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner's ratio is calculated by the formula

$$H=\rho b/b$$

Where, ρbis the bulk density, ρbis the tapped bulk density

After compression the following parameters should be evaluated for the finished product. Micrometer screw gauge or varniercalipers will be used to determine the tablet 56 diameter and tablet thickness. Average values of 5 tablets from each batch will be reported.Generally the values will be reported in mm. Hardness will directly indicate the crushing strength of the tablet which will affect 32 the performance of the ODT by affecting the disintegration time. Hardness of the tablets 33 can be measured by using Monsanto hardness tester, Pfizer or Erweka hardness tester 57. Weight variation test will be very useful to understand the uniform distribution of API in tablets. To determine weight uniformity weight of 20 tablets will be measured. Limits for weight variation as per IP&BP are in the following table.

Average tablet weight		% Deviation
(IP&BP)	USP	
Less than 80 mg	Less than 130 mg	±10.0
80 mg to 250 mg	130 mg to 325 mg	±7.5
More than 250 mg	More than 325 mg	±5.0

Content uniformity will helps us to understand about the amount of API present in each unit and the uniformity of API distribution among the batch. Content uniformity will be required for the dosage units which contain API less than 25 mg or less than 25% of one unit. This is based on the value of assay of API in individual units. Content uniformity will be performed on randomly selected 10 units . 58 Friability is an important parameter which directly indicates the mechanical strength of tablet and its ability to withstand the stress occurs during handling, packing and transportation. Friability will be determined using Roche Friabilator. 10 tablets from each batch will keep into the Friabilator and will be operated for 4 min. or up to 100 revolutions at 25 revolutions per minute. Friability will be expressed in %. The following is the formula for calculation of friability.59

$$F= [(W1-W2)/W1]x100$$

Where,

F= Percent Friability

W1= Initial weight of the tablets 13

W2 = final weigh of the tablets after 100 revolutions or 4 min.

Friability less than 1% will be accepted

Wetting time is one of the parameter to understand the disintegration behaviour of the tablet when placed in mouth. Wetting time of the tablet will be measured by the simple procedure keeping circular tissue papers of (12*10.75cm) folded twice in petridish having inner diameter 9 cm. 10 mL of

either water with eosin or pH 6.8 phosphate buffer will be added to the petridish and keep a tablet carefully tissue paper and the time required for 19 complete wetting of tablet will be noted as wetting time of the tablet. Lesser the wetting time will indicate the faster disintegration[60].

Initial and final weights of the tablet will be noted during the study of wetting time. The following formula will be used to calculate the water absorption ratio60.

$$R = \{(Wa-Wb)/Wb\}X100$$

Where, R= Water absorption ratio
Wb= Weight of the tablet before keeping on tissue paper
Wa= Weight of the tablet after wetting time study

In-vitro disintegration testing: Previously the disintegration time (DT) for ODT was performed by the same like 27 conventional method. As per European Pharmacopoeia the ODT should disintegrate without leaving any residue on bottom mesh of the apparatus in less than 3 minutes. But it is very difficult to correlate this DT with in-vivo performance of the ODT due to very less 6 volume of saliva in mouth. Later many methods were proposed to determine DT. Among those the Charge Couple Device (CCD) camera or the texture analyser is the one to determine DT. Along with this recently a modified disintegration apparatus is used which consists of a wired basket with 3*2 cm (Height*Diameter) and a #10 mesh is placed at the top of the beaker containing 900 ml of simulated saliva. The equipment will have a heater to maintain temperature at 37°C. Now the basket will be placed in a position that it contains only 6ml of saliva and it is operated at 25RPM. Along with all these techniques a simple method using 6 ml of simulated saliva in a measuring cylinder and place a tablet in it 60.

In-vitro dissolution testing: Dissolution of ODT should be faster comparatively other conventional tablets. For measurement of dissolution USP type-II dissolution apparatus will be used at 37°C and 50-100 rpm. 0.1NHCl, pH 4.5 and pH 6.8 buffers should be used for dissolution testing 60.

Current marketed ODT products

API	Therapeutic action	Brand name	Manufacturer
Olazepine	Psychotropic	Zyperxa®	Eli Lilly
Olandansetron	Antiemetic	Zofran® ODT	Galaxo Smith
klineRizatritpan benzoate	Migrane	Maxalt® -MLT®	Merck
Femotidene	Anti-ulcer	Pepeid® ODT	Merck
Loratadine	Antihistamine	Claritin®RediTabs®	Scherig corporation
Piroxicam	NSAIDs	Feldene Melt®	Pfizer
Resperidone	Schizophrenia	Resperdal® MTabTM	Janssen

CONCLUSION

Quick-dispersing oral drug delivery systems are defined as oral drug delivery systems that when placed in the mouth dissolve or disintegrate within a few seconds to a few minutes and do not require water to aid swallowing. The FDT dosage forms are ideal for many groups of patients including geriatrics, pediatrics, and those people who have difficulty swallowing. An important benefit of FDT dosage forms is the ability to provide the advantages of a liquid medication in the form of a solid preparation. This feature enables the patient to take the doseas directed at any time without water and inconvenience. There is clear medical need and clinical benefits provided by these technologies and products.

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