Available online on 15.06.2021 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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Review Article

Orodispersible Tablets: A Compendious Review

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A B S T R A C T

In recent times, there has been an enhanced demand for more patient compliant dosage forms. Oral route has been the gold standard in the administration of medications due to its safety, good patient compliance, ease of ingestion, pain avoidance and versatility. Dysphagia poses a problem especially in geriatric and paediatric patients. Mentally retarded patients, institutionalized patients and those travelling without access to water face a challenge as well. Orodispersible tablets are solid unit dosage form which when placed in the oral cavity swiftly disintergrates or dissolves without the need of water. ODT technology helps overcome the above mentioned challenges. Literature on ODT, their formulation and evaluation, challenges, manufacturing techniques along with patented technologies are reviewed in this article.

Keywords: ODT's, oral disintegrating tablets, superdisintegrants, dysphagia, MOA of superdisintegrants, ODT preparation, evaluation, patented technologies.

A R T I C L E I N F O: Received 19 Jan 2021; Review Complete; 20 March 2021 Accepted; 08 May 2021 Available online 15 June. 2021

Cite this article as:

Roshan K, Keerthy H.S, Orodispersible Tablets: A Compendious Review, Asian Journal of Pharmaceutical Research and Development. 2021; 9(3):66-75. **DOI:** http://dx.doi.org/10.22270/ajprd.v9i3.947

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INTRODUCTION.

The best route for the administration of therapeutic agents has always been the oral route. It's the most preferred, desired and most widely used route compared to all other routes of administration. Furthermore, oral medicine is commonly known to be the first way to pursue the discovery and growth of new drug entities[1]. The tablet is one of the most utilized form due to their ease of processing, convenience, accurate dosing, patient compliance and stability. Swallowing could pose a problem in all age groups (Dysphagia), especially paediatric and geriatric patients along with institutionalized patients, patients suffering with nausea, vomiting and motion sickness[2]. A novel drug delivery system has been developed in oral delivery called as Orodispersible tablets (mouth melt tablets) to help overcome these obstacles[3].

Orodispersible tablets when placed in the oral cavity swiftly melts in saliva without the need of water and disperses rapidly before swallowing. In cases like this, Bio-availability is significantly more than that seen from typical tablet type of dosage[4].

ODT's are also known as mouth dissolving tablets, melt-in-mouth tablets, fast dissolving tablets, rapid melts, porous tablets and quick dissolving tablets[5].

The Unites States Food and Drug Administration (USFDA) have defined ODT as "A solid dosage form containing medicinal substance or therapeutic agent which disintegrates usually within a matter of seconds when placed upon the tongue". Generally, the disintegration time for ODT varies from few seconds to around a minute [6].

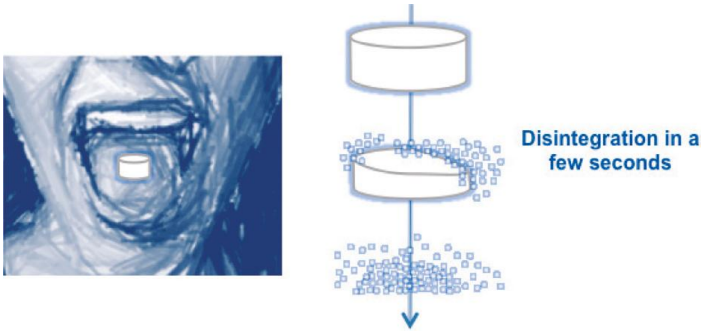


Figure 1:Representing the administration of Orodispersible tablets and the simulation of rapid disintegration in the oral cavity.

Ideal Properties of Orodispersible tablets[7,8,9].

Orodispersible tablets,

1. Does not require water or substitute liquid to swallow.
2. Rapidly dissolves and disintegrates in saliva within a matter of seconds.
3. Have a pleasant taste and mouth feel.
4. Easily transportable and mobile.
5. Leave no/negligible residue in the mouth after administration.
6. Be able to manufacture in a simple conventional way with low cost.
7. Withstand environmental conditions like humidity, temperature etc.

Salient features of Orodispersible tablets[10, 11, 12].

1. Ease of administration to patients who have difficulty in swallowing a tablet or who refuse to swallow tablets, such as paediatric, geriatric and psychiatric patients.
2. Precise dosing to achieve desired and optimum therapeutic effect with the least possible adverse reactions.
3. Hassle free and convenient method of administration when compared to liquid orals.
4. For patients who are travelling and have no access to water, Orodispersible tablets has a distinctly handy characteristic feature where the tablet can be swallowed without water which is a highly convenient feature.
5. Paediatric patients are often fussy and refuse to take pills. It can become a daunting task to treat them. The good mouth feel and taste of ODT's change the view on medication as "bitter pill" and makes treatment easier.
6. Fast disintegration, rapid dissolution and rapid absorption of drug produces swift onset of action.
7. When drugs pass down the mouth, pharynx, oesophagus and reaches the stomach certain drugs are absorbed from these physiological areas, in cases like these the bioavailability of the drugs is increased.
8. Orodispersible tablets provides accurate dosing and also opens a window of absorption pre-gastric.

Advantages of ODT's[13, 14, 15].

1. Improved patient compliance and convenience.
2. No water or liquid required.
3. Taste masking of bitter and unpleasant drugs.
4. Ease of administration for patients who are mentally ill, uncooperative and disabled.
5. Leaves negligible or no residue in the mouth after ingestion.
6. Sweetened and delightful taste with a pleasurable mouth feel.
7. High drug loading.
8. Improved bioavailability.
9. Adaptable and suitable to be manufactured in existing processes.
10. Low cost, lower production, packaging and distribution cost when compared to the current commercially available medications.
11. ODT technology is versatile and can be used for the development of enhanced veterinary medicines, Rx medicines, OTC and line extensions.
12. The new novel method allows incorporation of microencapsulated drugs for increased bioavailability, immediate release &/or controlled release and flexibility of dosing.
13. Superior therapeutic benefits.
14. Improved safety from physical obstruction and choking in oral administration of conventional dosage form.
15. Amalgamated advantage of stability of solid dosage form and bioavailability of liquid dosage form.

Disadvantages[16, 17].

1. Rapi-melt tablets are hygroscopic in nature and have to be stored in cool dry place.
2. Special packaging is required to correctly stabilize and protect the stable ODT's.
3. If not correctly formulated it may leave an unpleasant taste and unsettling feeling in the oral cavity.
4. Have to be careful in handling because the mechanical strength of that tablets are relatively low.

Challenges in formulating Oral Disintegration tablets.

The development of a new novel drug delivery system always poses few challenges which overcome the existing conventional drug delivery system but has obstacles of its own. They are,

Disintegration time and mechanical strength:

ODTs are typically formulated to acquire disintegration time. It's less than a minute. Maintaining a good mechanical strength to achieve this property could pose a daunting challenge. Majority of these rapi-melt tablets are fragile and fracture or break during packing, transport and even while administration. It's a known fact that increase in mechanical strength in turn delays the disintegration time. A successful balance between these two criteria is therefore always necessary [18].

Taste masking:

Most of the drugs compounds are bitter in taste. If these bitter compounds are formulated into ODT's, when they disintegrate in the oral cavity will cause serious patient compliance issues and significant negative impact. So effective taste masking of the bitter drugs must be done so that the taste of the drug is not felt in the oral cavity. A variety of strategies are developed to mask the bitter taste of most products, including the development of pellets by extrusion, spheronization or bulk extrusion, drug coating with a taste masking polymer, spray drying of drug dispersed in a polymeric solution, drug complexation by inclusion of cyclodextrin, drug-resinate complex formation, drug microencapsulation by polymer. All of these approaches help overcome these hindrances [19].

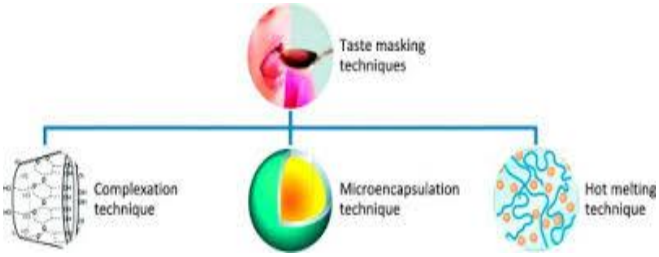


Figure 2: Representing techniques involved in taste masking.

Effect of external environmental conditions:

ODT should show little to no sensitivity to environmental conditions like humidity, moisture and temperature because the formulations contains ingredients which are meant to dissolve in minimum quantity of water[20].

Mouth feel / tactile sensation:

Particles produced after ODTs have been disintegrated should be as small as possible and not large as they produce an uncomfortable sensation. ODT should completely disperse with saliva and leave no residue in the mouth. Incorporation of flavours and cooling agents like menthol enhances the oral feel [21].

Cost:

The technologies used for ODTs should be appropriate as regards the cost of the finished product. Methods like Zydis and Orasolv that require special technologies and specific packaging increase the cost to a remarkable extent.

Aqueous solubility:

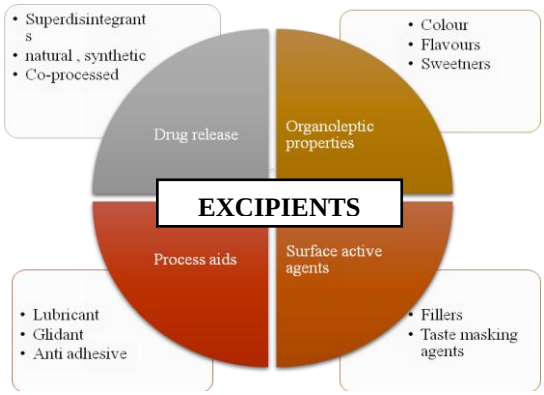
Water-soluble drugs form eutectic mixtures, resulting in freezing point depression and the formation of a glassy solid that can crumble after drying due to lack of support structure during the sublimation process. Such collapse can be avoided by using a number of matrix-forming excipients, such as mannitol, which can cause crystallinity and impart rigidity to the amorphous composite [21].

Excipients used for the formulation of ODT's.

The role of excipients play a major role in the design and formulation of Orodispersible tablets. Excipients balance the properties of the activities in oral disintegrating tablets. A thorough understanding of the chemistry and mechanism of these excipients is needed to prevent interaction and inhibition between their activities. The aspect of cost has to be addressed by the formulator. When the excipients are added in the formulation they impart desired organoleptic properties and improved efficiency of the product. Excipients can be used for a broad range of activities.

Bulking agents:

Bulking agents are crucial in the formulation of ODT's since they contribute functions of a diluent, filler and reduce cost. Bulking agents enhance the characteristics of texture and enhance the disintegration in mouth. The suggested bulking agents for the delivery should be more sugar-based such as mannitol, polydextrose, lacitol, DCL (directly compressible lactose) and starch hydrolysate for aqueous solubility. Mannitol specifically has high aqueous solubility and good sensory perception. Bulking agents are added in the final composition range of 10 to 90% by weight[22].



Emulsifying agents:

Emulsifying agents are major excipients in the formulation of oral disintegrating tablets as they aid in the swift disintegration and release of drug without chewing, swallowing or water. Furthermore, incorporation of emulsifying agents proves to be useful in stabilizing immiscible blends and enhancing the bioavailability. Alkyl sulfates, propylene glycol esters, lecithin, sucrose esters etc. are some of the widely used emulsifiers. They are used in the range of 0.05% to 15% by weight of the final composition.

Lubricants:

Lubricants though not an essential component, helps in the manufacturing process. Lubricants prevents the adherence of powder blend to the die cavity during the process of punching. Lubricants overcome the grittiness and helps in the transport of drug from mouth along the oesophagus till it reaches the stomach. Different hydrophilic and hydrophobic lubricants are used based on the nature and property of the drug used in the formulation[23].

Sweeteners and flavours:

Flavours and sweeteners make products more palatable and appealing to patients. The use of these ingredients tends to overcome the bitterness and undesirable taste of certain active ingredients. Both natural and synthetic flavours can be used to enhance the organoleptic properties of fast-melting tablets. Formulators can choose from a wide variety of sweeteners like sugar, dextrose and fructose as well as synthetic/ non-nutritive sweeteners like aspartame, sodium saccharin, sugar alcohols and sucralose. The inclusion of sweeteners adds both good flavour and the bulk to the formulation [24].

Surface acting agents:

Sodium lauryl sulphate, polyoxyethylene sorbitan fatty acids esters (tweens), sodium doecyl sulphate, sorbitan fatty

acid esters (span), polyoxyethylene sterates etc., are used are surfactants in ODT's[25].

Colours:

FDA approved colours are permitted in the formulation. Examples are sunset yellow, amaranth etc.[25].

Drug:

For the optimal ODT technology, the properties of the drug should not greatly impact the properties of the pill. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of the drug can significantly affect the characteristics of the final formulation such as tablet strength and disintegration. ODT technology should be flexible enough to handle unique properties of each drug.

Table 1: Drugs promising to be incorporated in orodispersible tablets

SR. NO	CLASS OF DRUG	EXAMPLES
1	Analgesics and Anti-inflammatory Agents	Indomethacin, Aspirin, Diclofenac sodium, Ketoprofen, Ibuprofen, Mefenamic acid, Dexamethasone, Hydrocortisone, Prednisolone, Azulene, Phenacetin, Isopropylantipyrin, Acetaminophen, Benzydamine hydrochloride, Phenylbutazone, Flufenamic acid, Sodium salicylate, Choline salicylate, Sasapyrine, Clofezone , Etodolac, Naproxen, Oxyphenbutazone, Piroxicam
2	Anti-coagulants	Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.
3	Anti-arrhythmic Agents	Amiodarone, Disopyramide, Flecainide Acetate, Quinidine Sulphate.
4	Anti-bacterial Agents	Ciprofloxacin, Tetracycline, Erythromycin, Rifampicin, Penicillin, Doxycycline, Nalidixic acid, Trimethoprim, Sulphacetamide, Sulphadiazine.
5	Anti-fungal Agents	Amphotericin, Butoconazole Nitrate, Clotrimazole, Econazole Nitrate, Fluconazole, Fiucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Terbinafine, Terconazole, Tioconazole, Undecenoic Acid
6	Anti-depressants	Trimipramine maleate, Nortriptyline · HCl, Trazodone · HCl, Amoxapine, Mianserin · HCl
7	Hypoglycemic agents	Glibenclamide, Glipizide, Tolbutamide, Tolazamide, Gliclazide, Chlorpropamide
8	Anti-hypertensive Agents	Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem,Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidil, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin, Reserpine, Terazosin
9	Anthelmintics	Albendazole, Mebendazole, Thiabendazole, Livermectin, Praziquantel, Pyrantel embonate, Dichlorophen
10	Anti-malarials	Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine
11	Anti-gout Agents	Allopurinol, Probenecid, Sulphinpyrazone
12	β-blockers	Acebutolol, Atenolol, Labetalol, Metoptolol, Oxprenolol, Pindolol, Propranolol
13	Anti-protozoal Agents	Clioquinol, Diloxanide, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, tinidazole,benznidazole
14	Anti-epileptics	Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Phensuximide, Primidone, Sulthiame, Valproic Acid
15	Anti-migraine Agents	Dihydroergotamine, Ergotamine, Methysergide, Pizotifen,Sumatriptan
16	Anti-thyroid Agents	Carbimazole, Propylthiouracil
17	Anti-neoplastic Agents and Immunosuppressants	Aminoglutethimide, Chlorambucil, Cyclosporin, Estramustine, Etoposide, Melphalan, 5-MP,Methotrexate, Mitomycin, Mitotane, Procarbazine, Tamoxifen.
18	Diuretics	Acetazolarnide, Amiloride, Bendrofluazide, Bumetanide, Chlorothiazide, Chlorthalidone, Ethacrynic Acid,Frusemide, Metolazone, Spironolactone, Triamterene
19	Lipid regulating Agents	Bezafibrate, Clofibrate, Fenofibrate, Gemfibrozil, Probucol
20	Corticosteroids	Beclomethasone, Betamethasone, Budesonide, Cortisone, Desoxymethasone, Dexamethasone, Fludrocortisone, Flunisolide, Flucortolone, Fluticasone Propionate, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone
21	Oral Vaccines	Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, Measles, Lyme Disease.
22	Nitrates and Other Anti-anginal Agents	Amyl Nitrate, Glyceryl Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrate
23	Gastro-intestinal Agents	Bisacodyl, Cimetidine, Cisapride, Diphenoxylate, Domperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole, Ondansetron, Ranitidine ,granisetron · HCl
24	Anti-parkinsonian Agents	Bromocriptine Mesylate, Lysuride Maleate
25	Antiulcer agents	Ranitidine, Sulpiride, Cetraxate hydrochloride, Gefarnate, Irsogladine maleate, Cimetidine, Lanitidine hydrochloride, Famotidine, Nizatidine or Roxatidine acetate hydrochloride

Ideal properties of a drug to be formulated asODT[26].

1. The drug should be partially unionized at buccal pH.
2. Drug should permeate through oral mucosa tissues.
3. Molecular weight should be in the range of small to moderate.
4. Good solubility & stability in saliva and water.
5. Drug should not be very bitter.
6. Low dose.
7. Ability to diffuse and partition in the upper GIT epithelium.

Ill-suited for,

1. Drugs with very short half-life.
2. Drugs having regular and frequent dosing.
3. Drugs with very bitter or intolerable taste.
4. Drugs which require controlled or sustained release.

Superdisintergrants:[27,28]

Disintegrating agents overpower the cohesive strength provided during compression, thereby helping to dissolve the tablet and increasing the surface area for dissolution. Several newer agents have been synthesized that are more efficient at lower concentrations with greater mechanical strength and disintegrating efficiency. These agents are called 'Superdisintegrants'. Superdisintegrants play a major role in achieving the desired rapid melt / oral disintegration of tablets.

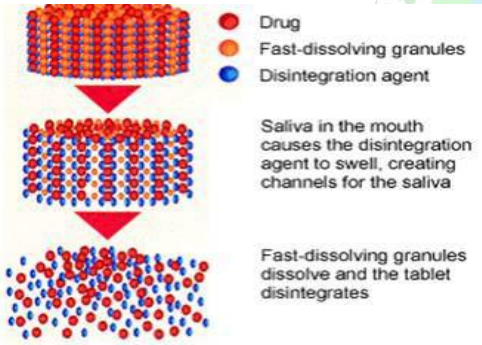


Figure 3: Representing basic mechanism of superdisintegrants.

Superdisintegrants are classified into two categories,

Natural Superdisintegrants:
Examples: *Plantago ovata* seed mucilage, *Lepidium sativum* mucilage, Gum Karaya, Guar gum, Gellan gum, Xanthan gum, Cassia fistula gum, Fenugreek seed mucilage, Mango peel pectin, Agar and treated agar etc.

Synthetic Superdisintegrants:
Examples: croscarmellose sodium (Ac-Di-Sol) sodium starch glycolate (Primogel and Explotab) and crospovidone (Polyplasdone XL) etc.

Ideal properties of Superdisintegrants[10,29].

1. Poor solubility.
2. Poor gel formation.
3. Good flow properties and mould capabilities.
4. No propensity for the drugs to form complexes.
5. Possess a good mouth feel.
6. Compatible with other excipients and have desirable properties in tableting.

Mechanism of Superdisintegrants.

Superdisintegrants acts in four major ways they are as follows,

Swelling:

While not all effective disintegrating agents swell in interaction with water, swelling is known to be a process in which some disintegrating agents (such as starch) trigger disintegrating results. By swelling in contact with water, the adhesion to other materials in a tablet is resolved, allowing the tablet to break apart[30].

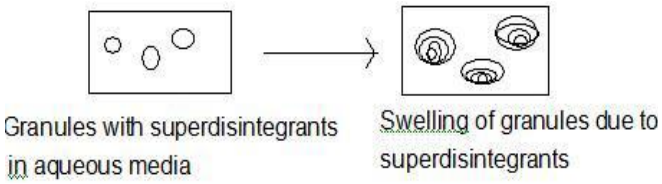


Figure 4: Mechanism of disintegration by swelling.

Porosity and capillary action (wicking):

The tablet in the aqueous media contributes to the penetration of the medium into the tablet and hence to the replacement of the adsorbed air resulting in the degradation of the intermolecular bond and the rupture of the tablet into fine particles[19].

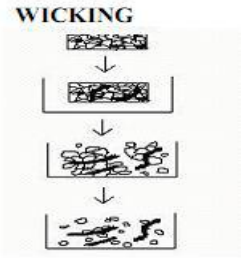


Figure 5: Mechanism of Superdisintegrants by porosity and capillary action (wicking).

Due to particle-particle repulsive forces:

Electrical repulsive forces between particles responsible for disintegrating [19].

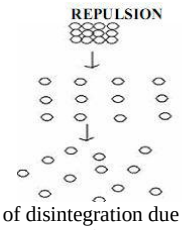


Figure 6: Mechanism of disintegration due to particle-particle repulsive forces.

Deformation:

On the tab. Compression, disintegrated particles are deformed when in contact with aq. Media is back to regular structure (Inc. in size)[19].

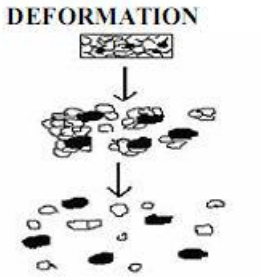


Figure 7: Mechanism of disintegration due to deformation.

By enzymatic reaction:

Enzymes found in the body function as disintegrants. These enzymes disrupt the binding action of the binder and help to disintegrate. In fact, due to swelling, pressure applied in the outer direction or radial direction, it allows the tablet to burst or rapid absorption of water contributing to an immense increase in the volume of granules to facilitate disintegration[19].

Table 2: A list of common Superdisintegrants[31].

Superdisintegrants	Example of	Mechanism of action	Comment
Crosscarmellose® **Ac-Di-Sol®**	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation
Crosspovidone **Crosspovidon M®** **Kollidon®** **Polyplasdone®**	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate **Explotab® Primogel®**	Crosslinked starch	-Swells 7-12 folds in <30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF **Satialgine®**	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides **Emcosoy®**	Natural super disintegrant	----------	-Does not contain any starch Or sugar. Used in nutritionalproducts.
Calcium silicate		-Wicking action	-Highly porous, -light weight -optimum concentration is between 20-40%

Conventional techniques for manufacturing of ODT's.

Many techniques have been employed for the formulation of fast dissolving tablets or orodispersible tablets,

Lyophilization or Freeze-Drying:[22]

Formation of porous substance in the freeze-drying process is used in the formulation of ODT's. Lyophilization is a process involving the elimination of solvents from a frozen suspension or a drug solution containing structure forming additives. Freeze-drying of therapeutic active agent along with additives imparts a glossy amorphous structure resulting in an extremely porous and lightweight product. The resulting tablet has accelerated disintegration and dissolution when placed on the tongue, and the freeze-dried tablet dissolves immediately to release the active agent.Several technologies are patented involving lyophilization process.

Moulding:

The moulding process involves moistening, dissolving or dispersing the drug with a solvent and then moulding the moist mixture into tablets (lower pressure compression moulding than standard tablet compression), evaporating the drug solvent from drug solution or suspension (no vacuum lyophilization) at ambient pressure, respectively.

The tablets formed by this technique are air dried. Moulded tablets results in a highly porous structure, which increases the product's disintegration and dissolution rate, since the compression force used is lower than traditional tablets. To further improve the dissolution, the powdered mixture should be sieved through a very fine screen or mesh [22].Tablets produced by the moulding technique are easier to scale up for industrial production in contrast to the lyophilisation technique [32].

Cotton candy process:

This method is so called because it utilizes a special spinning mechanism is used to create a floss-like crystalline structure that mimics cotton candy. This method of cotton candy process involves the formation of matrix of saccharides or polysaccharides the simultaneous action of flash melting and spinning. This matrix of candy floss is then milled and combined with active ingredients an excipients and compressed subsequently to ODT. High doses of drugs can be accommodated in this process and it also provides added mechanical strength [22]. The high processing temperature, however, restricts the use of this technology only to thermostable compounds [33].

Spray drying:[33]

Highly porous and fine powders are obtained when this process is employed. Hydrolyzed and unhydrolyzed gelatin as a medium supporting agent, mannitol as a bulking agent and sodium starch glycolate/croscarmellose as a disintegrant agent were limited in the preparation.This method is used to achieve immediate dissolution (<20 sec), but this technique requires both high manufacturing costs and time and produces tablets of very low mechanical strength.

Sublimation:[34]

The basis of this approach is to add solid ingredients which are readily volatilized, (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc) to other excipients in the tablet mixture and is then compressed into tablets. A porous structure is then generated when the volatile substance is removed via sublimation which increases the disintegration time.

Mass extrusion:

In this technique, the mixture of the therapeutic active drug and other excipients is softened using a solvent mixture of water-soluble polyethylene glycol, methanol is used, and then the softened mass is extruded through the extruder or syringe to obtain a cylinder of the product which is finally cut into even segments with the help of the heated blades. The dried cylinder can be used to coat the bitter granules to help mask in the taste masking of the ODT [30].

Direct compression:

It's the easiest way to make tablets. Conventional equipment, widely available excipients and a limited range of processing steps are used in direct compression. Even large doses can be accommodated and the final weight of the tablet can comfortably surpass that of most manufacturing processes. This technique can now be extended to fast-dissolving tablets thanks to the availability of improved tablets especially tablet disintegrants and sugar-based excipients [32].

Phase transition:

In this process, the mixing of low and high melting point sugar alcohols, as well as the transition step in the manufacturing method, is necessary for the production of ODTs without any difference in the apparatus[36].

Nanonization:

The ionization process has a reduction in the particle size of the drug to nano-size by the use of milling technique. This technique is suitable for drugs that are poorly water soluble. Drugs are stabilized against agglomeration of the surface absorption of selected stabilizers[35].

Sintering:

When thermal energy is applied to a compact powder, the compact is densified and the average grain size increases. The basic phenomena that occur during this process called sintering are densification and grain growth[32].

Table 3: Patented technologies for ODT's[22].

Patented technology	Technology based on	Examples (brand names)	Technology developed by company
Zydis[37]	Porous matrix	Olanzapine (ZyprexaZydis)	R.P.Scherer, Inc.
Quicksolv[38]	Lyophilization	Cisapride monohydrate (PropulsidQuicksolv)	Germany Janssen Pharmaceutical Inc
Flashtab[39]	Tableting with disintegrants and swelling agents	Ibuprofen (NurofenFlashTab)	Ethypharm France
Orasolv[32]	Tableting with effervescent disintegrants	Paracetamol (TempraQuicklets)	Cima Labs, Inc USA
Durasolv[40]	Direct compression	Zolmitriptan (Zolmig ZMT)	Cima Labs, Inc. USA
Wowtab[41]	Tableting with low and high moldability saccharides	Famotidine (Gaster D)	Yamanouchi Pharma Tech. Inc. USA
Ziplets[32]	Tableting with water in soluble ingredient and effective disintegrants	Ibuprofen (CibalginaDueFast)	Eurand International Italy
Advatab[22]	Microcaps and diffuscap CR Technology	Cetrizine hydrochloride AdvaTabcetrizine	Eurand International Italy
Flashdose[42]	Cotton Candy Process	Tramadol HCl (Relivia Flash dose)	Fuisz Technology, Ltd. USA
Oraquick[40]	Micromask taste Masking	Hyoscyamine Sulfate ODT	KV Pharm.Co., Inc. USA

Evaluation parameters of ODT's.

Evaluation parameters which are mentioned in the pharmacopoeias regarding tablets along with some special tests are supposed to be conducted,

Pre-compression parameters.

The powder blend was evaluated for flow properties such as angle of repose, bulk and tapped density, Carr's index and Hausner's ratio.

Angle of Repose:[43]

Fixed funnel method was used to determine the angle of repose for the powder blend. The accurately measured quantity of powder mixture was taken in a funnel. The height of the funnel was maintained in such a manner that the top of the funnel had just touched the apex of the powder heap. The powder was allowed to flow through the funnel without any resistance to the surface. Measurement of the diameter and height of the powder cone and the angle of repose was determined using the equation:

$$\tan \Theta = h/r$$

h= height and r= radius of the powder cone, respectively.

Bulk density and tapped density:[44]

Powder weighing 5g from each formula was introduced into a 25-ml measuring cylinder. It was initially gently shook to split any agglomerate that may have formed. The original volume was noted and the cylinder was allowed to fall under its own weight to a hard surface from 2.5cm in height at 2-second intervals. The tapping was continued until a constant volume was obtained.

LBD (loose bulk density) and TBD (tapped bulk density) were calculated using the formulas:

LBD = weight of the powder/ volume of packing.

TBD = weight of the powder/ tapped volume of the packing.

Compressibility index and Hausner's ratio:[44]

The following formulas was used to calculate the granule compressibility index and Hausner's ratio.

Carr's index = [(TBD – LBD) x 100] / TBD.

Hausner's ratio = Tapped density / Bulk density.

Post-compression parameters.

The formulated tablets were evaluated for the following parameters,

Tablet hardness:[45]

Hardness is a critical and vital parameter that avoids tablet breakage during shipping, handling and storage. The crushing intensity limit for ODT is typically held in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet was measured with the Monsanto hardness tester and expressed in terms of kg/cm^2.An average of three observations is reported.

Tablet thickness:[46]

From the formulated tablets a few were chosen at random and placed between the two arms of the Vernier calliper and thickness was determined. An average of five measurements were taken.

Weight variation:[46]

Twenty tablets were arbitrarily selected at random from each formulation and weighed individually using a digital balance. The individual weights were noted down and compared with the average weight of the tablets to determine the weight variation.

Friabilty:[47]

The formulated tablets should be well within the bound limits (0.1 – 0.9%) and it is a challenge to the formulator since all the factors involved in manufacturing of ODT's are responsible for rise in friability value. Twenty tablets were taken at random, weighed and then placed in a plastic chamber friabilator USP type Roche friabilator attached to a motor revolving at a speed of 25rpm for 4mins. The tablets re-weighed, and the %loss was calculated using,

Friability =[(initial weight – Final weight) /(initial weight)] x 100.

***In-vitro* disintegration time:**[48]

The time to disintegrate ODTs is usually <1 min and the actual time to disintegrate the patient's experiences varies from 5 to 30 secs. The disintegration time of all the formulations was determined using the tablet disintegration apparatus. Six tablets were placed individually in each of the tubes of disintegration test apparatus. The medium was maintained at a temperature of 37± 2º c and the time was noted for the disintegration of the entire tablet. The ODT disintegration test should imitate disintegration in the mouth with salivary contents.

Wetting time and absorption ratio(*R*):[46]

The ODT wetting time is another significant parameter that needs to be measured in order to gain insight into the tablet's disintegration properties. A petri dish (internal diameter of 5cm) containing 6ml water was taken and a tissue paper was taken and folded twice & placed in it. The ODT tablet was cautiously placed on top of it. The time taken for the water to reach the upper surface of the tablet and to completely wet it was noted as wetting time.

Water absorption ratio was then determined with the equation,

$R = 100 \times (Wa - Wb)/Wb$.

Where, Wa and Wb are weights of the tablet before and after water absorption.

Dissolution test:[49]

The development of dissolution methods for ODTs is similar to the methodology adopted for traditional tablets and is essentially equivalent. Dissolution apparatus USP 1 & 2 are used.USP 2 apparatus is used because although USP 1 have various applications, but often tablet pieces and disintegrated fragments gets stuck on the interior of the basket at the spindle resulting in no efficient stirring and unreproducible dissolution profiles.USP 2 is the most suitable and common choice for ODT's with a paddle and speed of 50rpm. Typically, the dissolution of ODT is very fast when using USP monograph conditions; thus, slower speeds of ODT can be used to obtain the profiles.

Stability studies:[50]

The stability analysis of the tablets was carried out by keeping the samples in the stability chamber at 40±20 C/75±5 per cent RH for 3 months, as per the ICH guidelines.

Drug content:[51]

UV method was used for the determination of uniformity in drug content. Calibration curve method was employed.

Moisture uptake studies:[22]

Moisture uptake tests for ODT should be performed to determine the stability of the formulation. Ten tablets in each formulation were deposited at 37°C for 24 hours in a desiccator over calcium chloride. The tablets were then weighed and exposed to 75% relative humidity at room temperature for 2 weeks. Required humidity was obtained by keeping the sodium chloride solution saturated at the bottom of the solution desiccator for three days. One tablet was kept under surveillance to test the absorption of moisture. Tablets were weighed and % increase in weight was calculated.

CONCLUSION.

A large portion of the world's population consists of paediatric and geriatric patients, the introduction of fast dissolving tablets has helped overcome the problems encountered during administration of drugs. This technology is mostly used for drugs to treat mental disorders, anti-allergic and analgesics. Dysphagia is also one of the major problems which was dealt with the invention of this novel drug delivery system. ODT's are the novel delivery system that have various advantages over conventional drug delivery in aspects of improved patient compliance, bioavailability and rapid onset of action. ODT's dissolve/disperse in saliva and can be administered without the need of water. The basic approach in the ODT technology is the maximize the porous structure of the tablet matrix to achieve rapid disintegration in the oral cavity & also provide excellent mouth feel,good taste masking properties of bitter drugs and good mechanical strength.

Intensive investigation is much needed in this promising area which can result in better result of newer cost effective technologies and improved excellent products.

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