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PRESENT INVESTIGATIONS AND FUTURE PROSPECTS OF ORAL DISINTEGRATING TABLETS: A REVIEW

Basani Gavaskar*[1], Subash Vijaya Kumar[1], Guru Sharan[1], Nagaraju M[1] and Y Madhusudan Rao[2]

Department of Pharmaceutics, Vaagdevi College of Pharmacy[1], Warangal (AP), India
University College of Pharmaceutical Sciences, Kakatiya University[2], Warangal (AP), India

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Correspondence to Author:

Basani Gavaskar

Department of Pharmaceutics, Vaagdevi College of Pharmacy, Warangal (AP), India

E-mail: gavapharma@yahoo.com

ABSTRACT

Oral Disintegrating Drug Delivery Systems (ODDDS) have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. Methods to improve patient's compliance have always attracted scientists towards the development of fancy oral drug delivery systems. Among them, oral disintegrating drug delivery systems (ODDDS) have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patient life, which includes dysphagic, bed ridden, psychic, geriatric and pediatric patients. This review describes the various technologies developed for ODTs, different patented technologies and their products, disintegrated employed and their mechanism of action, taste masking methods and evaluation tests.

INTRODUCTION: The ODTs emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphagic patients[1].

This disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy[2]. One study showed that 26% out of 1576 patients experienced difficulty in swallowing tablets due to their large size, followed by their surface, shape and taste. Rapid-breakdown or fast disintegrating tablet of the type of those intended to undergo disaggregation in the mouth in contact with the saliva in less than 60 seconds, preferably in less than 40 seconds, forming a suspension which is easy to swallow[3]. It is better known by the phase "oral disintegrating tablets".

The Center for Drug Evaluation and Research defines ODTs as a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed under the tongue. The European Pharmacopeia however defines a similar term, Orodispersible tablets, or tablets intended to be placed in the mouth where it disperses rapidly before swallowing. ODTs are known by various names such as "fast-melting, fast-dissolving, mouth melts, mouth dissolving, quick disintegrating, porous tablets, rapimelts or orodispersible tablets." Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction[4]. It has been shown in Table 1.

TABLE 1: SOME OF PROMISING DRUG CANDIDATES FOR ORODISPERSABLE TABLETS

CATEGORY	EXAMPLES
Antibacterial agents	Ciprofloxacin, Tetracycline, Erythromycin, Rifampicin, Penicillin, Doxycyclin, Nalidixic Acid, Trimethoprim, Sulphacetamide, Sulphadiazine etc.
Anti Helmintics	Albendazole, Mebendazole, Thiabendazole, Livermectin, Praziquantel, Pyrantel Embonate, Dichlorophen etc.
Anti Depressants	Trimipramine maleate, Nortriptyline HCl, trazodone HCl, Amoxapine, Mianserin HCl, etc.
Anti Diabetics	Glibenclamide, Glipizide, Tolbutamide, Tolazamide, Gliclazide, Chlorpropamide etc.
Analgesics/Anti-Inflammatory agents	Diclofenac Sodium, Ibuprofen, Ketoprofen, Mefenamic Acid, Naproxen, Oxyphenbutazone, Indomethacin, Piroxicam, Phenylbutazone, etc.
Anti Hypertensives	Amlodipine, Carvedilol, Diltiazem, Felodipine, Minoxidil, Nifedipine, Prazosin HCl, Nimodipine, Terazosin HCl etc.
Anti Arrhythmics	Disopyramide, Quinidine Sulphate, Amiodarone HCl, etc.
Anti Histamines	Acrivastine, Cetrizine, Cinnarizine, Loratadine, Fexofenadine, Triprolidine, etc.
Anxiolytics, Sedatives Hypnotics and Neuroleptics	Alprazolam, Diazepam, Clozapine, Amylobarbitone, Lorazepam, Haloperidol, Nitrazepam , Midazolam Phenobarbitone, Thioridazine, Oxazepam, etc.
Diuretics	Acetazolamide, Clorthiazide, Amiloride, Furosemide, Spironolactone, Bumetanide, Ethacrynic Acid, etc.
Gastro-intestinal agents	Cimetidine, Ranitidine HCl, Famotidine, Domperidone, Omeprazole, Ondansetron HCl, etc.
Corticosteroids	Betamethasone, Beclomethasone, Hydrocortisone, Prednisolone, Methyl Prednisolone, etc.
Anti Protozoal agents	Metronidazole, Tinidazole, Omidazole, Benznidazole,

Advantages:

- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients[5].
- Pregastric absorption can result in improved bioavailability, reduced dose, avoids hepatic metabolism and improved clinical performance by reducing side effects[6].
- Cost effective[7].

Different Techniques for Formulation of ODTS:

- **Lyophillization or Freeze Drying**: A process, in which water is sublimated from the product after freezing, is called freeze drying. This process consists of three phases:
  - Freezing to bring the material below its eutectic zone
  - Sublimation or primary drying to reduce moisture to around 4% w/w of dry product.
  - Desorption or secondary drying to reduce bound moisture to the required final value.

The lyophilization process imparts glossy amorphous structure to the bulking agent and some times to the drug, thereby enhancing the dissolution characteristics of the formulation. Lyophilization can be used to prepare tablets that have light weight, with a very high specific surface area and very porous open matrix network into which saliva rapidly moves to disintegrate lyophilized mass after it is placed in mouth. In this method bioavailability also improved for water insoluble drugs. In this dosage form insoluble drugs are in suspension and it will be freeze dried in suitable molds (PVC blister) and results in content uniformity issues. The material to be dried is first frozen and then subjected under a high vacuum to heat (supplied by conduction or radiation or by both), so that the frozen liquid sublimed leaving only the solid, dried components of the original liquid. The four components of freeze driers are vacuum chamber for drying, vacuum source, heat source and vapor removal system[8]. Investigations reported the influence of various formulation and process parameters on the characteristics of rapidly disintegrating tablets in lyophilized form using hydrochlorothiazide as a model drug. They have concluded that maltodextrins are useful in the formulation of fast dissolving tablets made by freeze drying[9] employed lyophilization technique in making one oral pharmaceutical preparation and found increased absorption and bioavailability of spironolactone, nicergoline, and troleandomycin in comparison to their conventional formulation. Lyophilization is relatively expensive and time consuming manufacturing process.

- **Spray Drying**: Spray dryers are widely used in pharmaceuticals and biochemical processes. Spray drying provides a fast and economical way of removing solvents and producing highly porous fine powders. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This is then mixed with active ingredients and compressed into tablets used a spray drying technique to prepare fast dissolving tablets[10]. The tablets made from this technology are claimed to disintegrate within 20 seconds. The components included supporting agents composed of two polypeptide components of

the same net charge (non hydrolyzed and hydrolyzed gelatin), bulking agent (mannitol), and a volatilizing agent.

- **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 their by masking their bitter taste, formulated fast dissolving tablets of tizanidine hydrochloride by mass extrusion technique[11, 12]. Mass extrusion was the technique used for preparing taste masked granules. The tablet was prepared with three super disintegrate e.g. sodium starch glycolate, croscarmellose sodium and crosspovidone.

- **Sublimation**: The basic principle involved in preparing oral disintegrating tablets by sublimation technique is addition of a volatile salt to the tablet components, mixing the components to obtain a substantially homogenous mixture and volatilizing the volatile salt. The removal of volatile salt creates pores in the tablet, which help in achieving rapid disintegration, when the tablets come in contact with saliva[13]. Because of low porosity, compressed tablets composed of highly water soluble excipients as tablet matrix material often do not dissolve rapidly in the water. Porous tablets that exhibit good mechanical strength and dissolve quickly have been developed by the volatile materials include urea, ammonium carbonate, ammonium bi carbonate, hexa methylene tetramine, napthalene and camphor were added to other tablet excipients and the blend was compressed into tablet. Removal of volatile material by sublimation generated porous structure[14]. Vacuum is used to remove the volatile materials[15]. The full dissolution time was reduced from 10-15 mins for the tablets formed from trehalose alone to less than 1 minute. In some cases menthol, camphor, thymol, an organic acid such as adipic acid, and a lower fatty acid such as arachidic acid, caporic acid myristic acid, and palmitic acid were used as the volatile materials and sublimation temperature ranged from 40 to 60^{o}C.

  The disintegration time in the human mouth was claimed to be about 25 seconds[16]. Mannitol used as diluents and camphor as volatile material to prepare highly porous compressed tablets. The tablets were subjected to vaccum at 800c for 30 min to eliminate camphor and thus compressed into tablet[17] described a method for producing a fast dissolving tablet using water as a pore forming material. A mixture containing active ingredient and carbohydrates (glucose, mannitol, xylitol etc.) were moistened with water (1-3 %w/w) and compressed into tablets.

- **Cotton Candy Process**: The cotton candy process is also known as the candy floss process and forms crystalline structure on the basis of technologies such as flash dose. Cotton candy process involves formation of matrix of polysaccharides by simultaneous action flash melting and spinning. A mouth dissolving tablet is formed using a candy floss or shear form matrix[18]. This floss is commonly composed of saccharides such as sucrose, dextrose, lactose, and fructose. The saccharides are converted into floss by the simultaneous action of flash-melting and centrifugal force in a heat-processing

machine similar to that used to make cotton candy[19]. The matrix formed is partially recrystallized to have improved flow properties and compressibility. The candy floss can then be milled and blended with active ingredients and other excipients and subsequently compressed into mouth dissolving tablets. The technology also can be used to form microspheres instead of floss by modifying the design of the spinning heads. This process can accommodate high doses of drug and offers improved mechanical strength.

- **Molding**: Takeda[20] has developed compression- moulded mixtures containing a drug and a combination of starches and sugars with surfaces that have been wetted with a suitable amount of water. The wetted mass is compression molded and dried, porous tablets (with sufficient mechanical strength to resist destruction during further manufacturing) are obtained. The FMT rapid disintegration time in the mouth (30–50) according to examples reported in the patent application[21] improved the problem of mechanical strength by vaccum drying a frozen mixture containing a gum, carbohydrates and a solvent in a tablet shape mold had developed a particulate drug matrix by congealing a molten mixture of hydrogenated cotton seed oil, lecithin, poly ethylene glycol, sodium bicarbonate and drug and incorporated the same into a lactose based triturate form to produce taste masked mouth dissolving tablets[22].

- **Melt Granulation**: Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a melt able binder. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. It is a useful technique to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin [23]. This approach to prepare FDT with sufficient mechanical integrity, involves the use of a hydrophilic waxy binder (Superpolystate©, PEG-6-stearate). So it will not only act as a binder and increase the physical resistance of tablets but will also help the disintegration of the tablets as it melts in the mouth and solubilizes rapidly leaving no residues[24].

- **Phase Transition Process**: FDT were produced by compressing powder containing erythritol (melting point: 122 °C) and xylitol (melting point: 93 - 95 °C), and then heating at about 93 °C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol [25]. (Kuno et al., 2005.) Investigated effect of the type of lubricant on the characteristics of orally disintegrating tablets manufactured using the phase transition of sugar alcohol using lactose–xylitol granules, disintegrant, glidant and lubricant like (magnesium stearate (Mg-St), sodium stearyl fumarate (SSF), and talc.

- **Three-Dimensional Printing (3DP)**: The 3DP method provides zero order drug delivery, patterned diffusion radiant drug release by micro structure diffusion barrier technique, cyclic drug release and another drug release profiles. The technique is often referred to as solid free form fabrication or computer automated manufacturing or layered manufacturing[26]. Prototyping involves

constructing specific layers that uses powder processing and liquid binding materials. A novel fast dissolving drug delivery device (DDD) with loose powders in it was fabricated using the three dimensional printing (3DP) process. Based on computer-aided design models, the DDD containing the drug acetaminophen were prepared automatically by 3DP system[27]. It was found that rapidly disintegrating oral tablets with proper hardness can be prepared using TAG. The rapid disintegration of the TAG tablets seemed due to the rapid water penetration into the tablet resulting from the large pore size and large overall pore volume[28].

- **Direct Compression**: This method accommodates high dose and limited number of process steps. Sugar excipients like direct compressible mannitol, or spray dried mannitol can be used as bulking agents because of their high aqueous solubility and sweetness, pleasing mouth feel and good taste masking[29]. Tablet size and hardness strongly affect the disintegrant efficacy. Hard and large tablets have more disintegration time than normally required. Very soft and small tablets have low mechanical strength. So, an optimum kind and concentration of disintegrant should be chosen to achieve quick disintegration and high dissolution rates. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

- **Fast Dissolving Films:** In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.) drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film[30]. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2 x 2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste. It has been shown in Table 2.

TABLE 2: A COMPARISON OF CONVENTIONAL SOLID DOSAGE FORMS AND ODTs

CONVENTIONAL SOLID DOSAGE FORMS	ODTs
Swallowing problem interferes with patient compliance	Disintegrates in oral cavity, improving patient compliance
Reaches stomach in solid form, where it disintegrates and is absorbed	Reaches stomach in liquid form, which has several advantages: • Improved patient compliance • Faster onset of remedial action • Patient convenience

Patented Technologies:

- **Zydus Technology:** Using concept of[31] Scherer has patented the Zydus technology. Zydus, the best known of the fast-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The product is very light weight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydus product is made to dissolve on the tongue in 2 to 3 seconds[32].

- **Orasolv Technology:** OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The CIMA's (US-Pharmaceutical Company). OraSolv [33] is other manufacturing technology involves the direct compression of actives effervescent excipients and taste masking agents. Effervescent disintegration agents evolve gas by means of chemical reaction called effervescent couple. The tablet rapidly disintegrates and carbon dioxide is produced by contact with saliva or aqueous fluid. Carbonates such as sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate, acids such as citric, tartaric, malic, fumeric, adipic and succinics are used. This technology is frequently used to develop over-the-counter formulations. The major disadvantage of the OraSolv formulations is its mechanical strength. For that reason, Cima developed a special handling and packaging system for OraSolv. This initiated to develop Paksolv[34] a special packaging to protect tablets from breaking during storage and transport. It is a dome shape blister package, which prevents the vertical movement of tablet with in the depression. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. Their disintegration time is less than 30s. The OraSolv formulations are not very hygroscopic.

- **Durasolv Technology:** DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity. The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. Durasolv is an appropriate technology for products requiring low amounts of active ingredients[35].

- **Wow Tab Technology:** Wowtab technology is patented by Yamanouchi Pharmaceutical Co. The WOW in Wowtab signifies the tablet is to be given "Without Water". It has just recently been introduced into the U.S. This process uses a combination of low mouldability saccharides are lactose, mannitol, glucose, sucrose, erithytol, and xylitol (rapid dissolution) and high mouldability saccharides are maltose, manitol, sorbitol, and oligosaccharides.(good binding property). The result is a mixture of excipients that have fast-dissolving and highly moldable characteristics[36].

- **Flash Tab Technology:** Flash tab technology is yet another fast dissolving /disintegrating oral tablet formulation. It utilizes most of the same excipients as in conventional compressed tablets. Flash Tab is[37] a flash dispersal system which involves coating a drug with a Eudragit polymer (methacrylate copolymer) to provide rapid release of the drug in the stomach, and formulating this microencapsulated drug with an effervescent couple to produce a flash dispersal tablet. The process is thus a complicated and expensive one which also requires stringent environmental controls (<20°C/10&percent; relative humidity and tablet hardness about.1-2.5kP) and also specialized packaging. The microencapsulation system currently uses an undesirable solvent based manufacturing process, and the cost is higher.

- **Flash Dose Technology:** Flash dose technology utilizes a unique spinning mechanism to produce floss like crystalline structure much like cotton candy. The

crystalline sugar can then incorporate the active drug and be compressed into a tablet[3]. A sugar based matrix, called 'Floss' is used, which is made up of a combination of excipients (crystalline sugars) alone or in combination with drugs. Nurofen meltlet, a new form of Ibuprofen, as a mouth-dissolving tablet is the first commercial product prepared by this technology and launched by Biovail Corporation. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug.

- **Nano Technology:** NanoCrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling for the fast dissolving tablets.

  NanoCrystal™ Fast dissolving technology provides for:

  Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix. Product differentiation based upon a combination of proprietary and patent-protected technology elements. Cost-effective manufacturing processes that utilize conventional, scalable unit operations, exceptional durability, enabling use of conventional packaging equipment and formats (i. e. bottles and/or blisters), wide range of doses (up to 200mg of API per unit), use of conventional, compendial inactive components, employment of non-moisture sensitive inactive. Nano Crystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded As Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds.

- **Quick Solv Technology:** This technology is patented by Janssen Pharmaceuticals. This technology gives a porous solid form obtained by freezing an aqueous dispersion or solution of the active containing matrix then drying the matrix by removing the water using an excess of alcohol (solvent extraction) [39]. The final form disintegrates very rapidly but is limited to low drug content and can be used only with those activities that are insoluble in the extraction solvent. Thus the product had adequate strength for handling.

- **Ora Quick Technology:** Ora Quick appropriate for heat-sensitive drugs. KV Pharmaceutical also claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more applicable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. Ora Quick claims quick dissolution in a matter of seconds, with good taste-masking[40]. There are no products using the Ora Quick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives.

- **Quick Dis Technology:** The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages[41]. The typical disintegration time, is defined as the time at which the film begins to break. When brought into contact with water, is only 5 to 10 seconds for the Quick-Dis™ film with a thickness of 2 mm. The dissolving time, which is defined as the time at which not less than 80% of the tested film is dissolved in aqueous media, is around 30 seconds for Quick Dis™ film with a thickness of 2 mm. The typical release profile of an

active ingredient exhibited by a Quick-Dis™ drug delivery system is 50% released within 30 seconds and 95%within 1 minute.

- **Frosta Technology:** Akina patents this technology[42]. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.
- **Pharma Burst Technology:** Pharmaburst is a co-processed excipients system with specific excipients, which allows rapid disintegration and low adhesion to punch faces. This technology involves dry blending of drug, flavor, and lubricant that are compressed into tablets on a standard tablet press with stock tooling. These tablets are having sufficient strength so they can be packed in blister and bottles. These tablets disintegrate with in 30 - 40 seconds. It is shown Table 3.

TABLE 3: LIST OF PATENTED TECHNOLOGIES BASED BRANDED PRODUCTS

Patented Technology	Basic Technology	Technology Developed by Company	Active ingredient (Brand Names)
Zydus	Lyophilization	R.P.Scherer,Inc.	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)
Quicksolv	Lyophilization	Janssen pharmaceutics	Cisapride monohydrate (Propulsid Quicksolv), Risperidone (Risperdal M-Tab)
Lyoc	Lyophilization	Farmalyoc	Phloroglucinol Hydrate (Spasfon Lyoc)
Flashtab	Direct Compression	Ethypharm	Ibuprofen (Nurofen FlashTab)
Orasolv	Direct Compression	Cima Labs,Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Repimelt),
Durasolv	Direct Compression	Cima Labs, Inc.	Hyoscyamine Sulfate (NuLev) Zolmitriptan (Zolmig ZMT)
Wowtab	Direct Compression	Yamanouchi Pharma Tech. Inc.	Famotidine (Gaster D)
Ziplets	Direct Compression	Eurand International	Ibuprofen (Cibalgina DueFast)
Advatab	Microcaps and Diffuscap CR Technology	Eurand International	AdvaTab cetrizine, AdvaTab Paracetamol
Flashdose	Cotton Candy Process	Fuisz Technology, Ltd.	Tramadol HCl (Relivia Flash dose)
Oraquick	Micromask Taste Masking	KV Pharm.Co.,Inc.	Hyoscyamine SulfateODT
Fuisz	Sugar based matrix known as Floss	Fuisz Pharmaceutical Ltd.	Diphenydramine & Pseudoephedrine

- **Lyoc Technology:** Lyoc utilizes a freeze drying process but differ from Zydus in that the product is frozen[43] on the freeze dryer shelves. To prevent in homogeneity by sedimentation during this process, these formulations require a large proportion of un-dissolved inert filler (mannitol), to increase the viscosity of the In process suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are comparable with the loosely compressed fast melt formulations[44]. Lyocs unusual property is possesses poor mechanical resistance.

- **Ziplets/Advatab Technology:** AdvaTab is distinct from other ODT technologies as it can be combined with Eurand's complimentary particle technologies like its world leading Microcaps® taste-masking technology and its Diffucaps® , controlled release technology. The pairing of AdvaTab with Microcaps creates products that offer the dual advantage of a patient preferred dosage form, together with a superior taste and smooth mouth feel.

- **Dispersible Tablet Technologies:** This technology is patented by Lek, Yugoslavia. An improved dissolution rate of ODT by incorporating 0.8 to 10%, preferably about 4% by weight, of an organic acids and disintegrating agents. One of the essential excipients like disintegrating agents facilitates rapid swelling and good wetting capabilities to the tablets that results in quick disintegration. Disintegrants include starch, modified starches, microcrystalline cellulose, alginic acid, cross linked sodium carboxy methyl cellulose and cyclodextrins. A combination of two or more disintegrants produced better disintegration results. These tablets are disintegrated with in 1 min [45]. It has been shown Table 4.

TABLE 4: POPULAR DISINTEGRANTS USED IN TABLET

DISINTEGRANTS	MECHANISM	CONCENTRATION AND PERCENT'S 2/w
Starch	Disintegrate forms pathways throughout the tablet matrix that enable water to draw into the structure by capillary action, thus leading to disruption of tablet.	5-20
Pregelatinized starch	Responsible for increased dissolution rate from this tablet is rapid disintegration due to superior swelling capacity.	5-15
Sodium Starch Glycolate	Involves rapid absorption of water leading to an enormous increase in volume of granules result in rapid and uniform disintegration.	1-3
Cross-linked polyvinyl Pyrrolidone	The capillary activity of cross povidone for water is responsible for its tablet disintegration property.	0.5-5
Cellulose	They show their ability to swell on contact with water results in rapid tablet disintegration.	1-3
Microcrystalline Cellulose	Allowing water to enter the tablet matrix by means of capillary pores, which break the hydrogen bonding between adjacent bundles of cellulose microcrystals and exhibit very good disintegrant property	10-20
Alginates	High affinity for water absorption and high sorption capacity make it an excellent disintegrant.	1-5

Soy polysaccharides	Natural super disintegrant, Rapid swelling in aqueous medium or wicking action. Does not contain any starch or sugar. Used in nutritional products.	5-15
L-HPC	Both swelling and wicking	8-9
Gums	As disintegrants because of their tendency to swell in water	3-8
Chitin and Chitosan	Moisture sorption and water uptake was found the major mechanism of disintegration while dissolution related to swelling capacity	1-5
Smecta	Their layered leaves like structure consist of aluminium and octahydral layers sandwiched between two tetrahydral silica layers. It has a large specific area and high affinity for water makes it good disintegrant.	5-15
Isapghula Husk	Plantago ovata seeds husk has high swellability and gives uniform and rapid disintegration.	5-15
Polacrillin Potassium	It swells up at very fast rate upon contact with water or gastro intestinal fluid and act as an effective tablet disintegrant.	10-20
Ion Exchange Resins	Resins have ability to swell in the presence of water, showed disintegration of tablet.	0.5-5
Gas – Evolving disintegrants	These react in contact with water to liberate carbon dioxide that disrupts the tablet.	>10&percent;

- **Taste Masking Methods:** The drugs are mostly bitter in nature. Skillful taste masking is needed to hide the bitter taste in ODTs formulations. This can be achieved by using combination[46] of right flavor and right sweeteners. The taste masking in ODTs has more influences on dissolution method development, specifications, and testing. Following methods are used in taste masking is given as follows:

  - **Incorporation of Sweeteners and Flavors:** Mannitol and aspartame are most widely used excipients in formulating ODTs. (Chang et al., 2000.) Different flavors are also used in ODT formulations to mask the bitter taste and give pleasant mouth feel. Most commonly used flavors are mint, orange, strawberry, pineapple, peppermint flavors.

  - **Adjustment of pH values:** Many drugs are less soluble at pH different from the pH of the mouth, which are around 5.9. Drugs can be insufficiently solubilized to be available to taste if the equilibrium concentration is below the taste threshold[47].

  - **Effervescent Technique:** Effervescent tablet rapidly disintegrates and carbon dioxide is produced by contact with saliva or aqueous fluid. So the bitter taste of the drugs can be masked by this method[48].

  - **Spray Drying Technique:** Simple wet granulation method or roller compaction[49] of other excipients. Spray drying can also employed to shroud the drug.

  - **Coating of Drug Particles with Inert Agents:** Coating is an extremely useful technique for number of applications in the pharmaceutical field. By coordinating the right type of coating material it is possible to completely mask the taste of a bitter drug, while at the same time, not adversely affecting the intended drug release profile[50]. Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH would be an acceptable alternative for taste masking[51].

  - **Taste Masking by Formation of Inclusion Complexes:** The complexing agent is capable of masking the bitter taste of the drug by

decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Vander Waals forces are mainly involved in inclusion complexes[52]. Beta-cyclodextrin is most widely used complexing agent for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. Cyclodextrin help to solubilize many drugs.

- **Molecular Complexes of Drug with other Chemicals:** Molecular complex formation can decrease the intensity of bitterness of drug. Higuchi and Pitman reported that caffeine forms complexes with organic acids that are less soluble than xanthane and as such can be used to decrease the bitter taste of caffeine.

- **Solid Dispersion System:** Solid dispersion is also called as co precipitates for those preparations obtained by solvent method such as co precipitates of sulphathiazole and povidone. Solid dispersions using insoluble matrices or bland matrices may be used to mask the bitter taste of drugs. Also using them as absorbents on various carriers may increase the stability of certain drugs [53].

- **Microencapsulation:** Microencapsulation as a process has been defined by Bakan as a means of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion[54]. This process can be used for masking of bitter tasting drugs microencapsulating drug particles with various coating agents.

- **Mass Extrusion Method (Dispersion coating):** 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.

- **Ion Exchange Resin:** When the drug resinates comes into contact with the gastrointestinal fluids, such as the acid of the stomach. The drug is released from resinate directly into solution and then absorbed in the usual way. The resin passes through the GI tract without being absorbed. Examples of drugs where this technique has been successfully demonstrated include ranitidine, risperidone and paroxetine.

- **Evaluation of Fast Dissolving Tablet:** Tablets from all the formulation were subjected to following quality control test.

  - **General Appearance:** The general appearance of a tablet, its visual identity and over all “elegance” is essential for consumer acceptance. Include in are tablet’s size, shape, color, presence or absence of an odor, taste, surface texture, physical flow and consistency and legibility of any identifying marking.

  - **Tablet Thickness:** Ten tablets were taken and their thickness is recorded using micrometer. The size of the tablet can be dimensionally described, monitored and controlled.

  - **Uniformity of Weight:** USP procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance.

  - **Disintegration Time:** The test is carried out on the 6 tablets using the apparatus specified in USP distilled water at $37^{o}C\pm 2^{o}C$ was used as a disintegration media and the time in second taken for complete

disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

- **Wetting Time:** A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

- **Water Absorption Ratio:** For measuring water absorption ratio the weight of the tablet before keeping in the petridish is noted (wb). The wetted tablet from the petridish is taken and reweighed (wa). The water absorption ratio, R can be then determined according to the following equation;

$$R = 100 (wa-wb)/wb$$

- **Moisture Uptake Studies:** Moisture uptake studies for ODT should be conducted to have an insight into the stability of the formulation. Ten tablets from each formulation were kept in a desiccators over calcium chloride at 37^{o}C for 24 h. Tablets were weighed and the percentage increase in weight was recorded.

- ***In-vitro*** **Dispersion Time:** *In-vitro* dispersion time is measure by dropping a tablet in a beaker containing 50ml of Sorenson's buffer pH 6.8. Tablets from each batch are randomly selected and *In-vitro* dispersion time was performed.

- **Friability:** It is measured of mechanical strength of tablets. Roche friabilator.

% Friability = loss in weight / Initial weight X 100

- **Tablet Hardness:** Hardness of the tablet of each formulation is determined by using Pfizer/Monsanto Hardness tester.

- **Content Uniformity:** Ten randomly selected tablets are weighed and average weight is calculated, the tablets are powdered in a glass mortar. The weight equivalent to tablet is weighed. The weighed amount is dissolved in solvent system in a separate volumetric flask using magnetic stirrer, the volume is adjusted with Sorenson's buffer pH 6.8 and the solution was filtered. An aliquot of these solution are diluted with Sorenson's buffer pH 6.8 in a separate volumetric flasks in Lambert's- Berr's Range. The drug content in formulation is determined spectrophotometrically very easily.

- ***In-vitro*** **dissolution studies:** *In-vitro* dissolution studies for fabricated fast dissolving tablet is carried out by using USP 24 paddle method at 50rpm in 900ml of Sorenson's buffer pH 6.8 as dissolution media, maintained at 37±0.5^{o}C. Five ml aliquots was withdrawn at the specified time intervals, filtered and assayed spectrophotometrically. An equal volume of fresh medium, which was pre-warmed at 37^{o}C is replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Dissolution studies are performed in triplicate.

- **Clinical Studies:** Several clinical studies were conducted using therapeutic medications. For the medication, FDDTs was found to be superior to conventional tablets in terms of bioavailability of the

active ingredient. The most popular anti-ulcer drug, when delivered by FDDTs, had the same bioavailability and better patient compliance than the commercially available lyophilized wafer. The system also exhibited shorter t_{max} when compared with conventional marketed products for dysfunction.

- **Future Perspective:** With continued innovations in pharmaceutical excipients, one can expect the emergence of more novel technologies for ODTs in the days to come. These innovations may involve modifying formulation composition and processing to achieve new performance end-points or the merger of new technological advances with traditional pharmaceutical processing techniques for the production of novel oral disintegrating dosage forms. It is reasonable to expect that future trends in innovations of drug delivery systems will continue to bring together different technological disciplines to create novel technologies[54]. It has been shown Table 5.

TABLE 5: ODTS UNDER DEVELOPMENT

PRODUCT	MANUFACTURER	ACTIVE INGREDIENT	CATEGORY
Citalopram ODT	Biovail	Citalopram	SSRIs
Metoclopramide Zydus	Salix Pharmaceuticals	Metoclopramide	Dopamine receptor antagonists
Reglan ODT	Schwarz Pharma	Metoclopramide	Dopamine receptor antagonists
Tramadol/Acetaminophen ODT	Biovail	Tramadol/Acetaminophen	Opioid analgesic [Tramadol]
Zolpidem ODT	Biovail	Zolpidem	Non benzodiazepine Hypnotics

CONCLUSION: Our review article examine that, Oral disintegrating tablets had various advantage of dosage form, ideal for pediatric and geriatric patients and rapid onset of action. Due to such wide significance, this new generation drugs are very easily deliver by this system and may lead to better patient compliance and ultimate clinical output. Hence, in future patient demand and the availability of various technologies have increased the market share of fast dissolving tablets, which in turn prolongs the patient life and expect technology to be more popular.

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