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Orally Disintegrating Tablets: An Overview

Evren ALĞIN YAPAR*

Republic of Turkey, Ministry of Health, Turkish Medicines and Medical Devices Agency, Ankara, Turkey.

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ABSTRACT

Orally disintegrating tablets (ODTs) have greatly increased dosage forms which have remarkable impact on the patient compliance especially for the pediatric, geriatric and psychiatric patients with deglutition disorders. Several technologies either conventional or patented based on freeze drying/lyophilization, spray drying, moulding, phase transition process, melt granulation, sublimation, mass extrusion, cotton candy process, direct compression etc. have been developed for manufacturing of ODTs. In this review brief information about ODTs including definition, ideal and desired characteristics, advantages, limitations and disadvantages, drug canditates, challenges in formulation, excipients with recent developments in superdisintegrants, tast masking, manufacturing techniques, evaluation parameters and recent patents in ODTs are presentented.

INTRODUCTION

During the last decade, development of orally disintegrating tablets (ODTs) which offer benefits to the persons having difficulty in swallowing have intensely increased due to its remarkable effect on the patient compliance (Sastry *et al.*, 2000, Bandari *et al.*, 2008, Pahwa *et al.*, 2010, Bhasin *et al.*, 2011). It has been reported that deglutition disorders, dysphagia or difficulty in swallowing occurred as suffer in significant part of population (Sastry *et al.*, 2000).

In the treatment periods, solid dosage forms usually raised administration difficulties in pediatric, geriatric and psychiatric patients and also in some others like bed ridden, uncooperative or travelling patients (Sastry *et al.*, 2000, Pahwa *et al.*, 2010, Bhasin *et al.*, 2011). Most of the difficulties in treatment periods of swallowing tablets are indicated as size, surface, form, and their taste (Sastry *et al.*, 2000). Thus solid dosage forms that can be dissolved or suspended in the mouth to achieve easy swallowing are highly desirable for the above mentioned patient groups (Dobetti, 2000, Fu *et al.*, 2004). In this context, good taste and flavor, ease of administration and swallowing, need for quick action in some indications can be counted as main reasons for increasing indent for the ODTs (Bandari *et al.*, 2008, Bhasin *et al.*, 2011) in which also supported by market studies (Pfister and Ghosh, 2005). Clinically, in some cases ODTs may provide improved safety and efficacy. However there are limitations in some medications such as patients who have Sjögren's syndrome or dryness of the mouth due to decreased saliva production or take anticholinergic medications may not be convenient to use ODTs (Bharawaj *et al.*, 2010). Commercially enlarged product diversity, extended patent life, and marketing advantages can be counted as main reasons actuating ODT technology developments (Pfister and Ghosh, 2005).

DEFINITION AND IDEAL PROPERTIES FOR ODTs

In an extensive perspective ODTs are also called orally disintegrating, orodispersing, mouth-dissolving, melt-in-mouth tablets, rapid-dissolving, rapid-disintegrating tablets, repimelts, fast-dissolving multiparticulate, fast-melting, fast-dissolving, freeze-dried wafers, quick-dissolve and porous tablets in official documents and literature (US FDA, 2003, Pfister and Ghosh, 2005, Hirani *et al.*, 2009, Ratnaparkhi *et al.*, 2009, Thakur and Narwal, 2012). FDA definition for ODTs is a solid dosage form which disintegrates rapidly within a matter of seconds when placed under the tongue. The disintegrating time for

* *Corresponding Author*
Evren ALGIN YAPAR, The Ministry of Health of Turkey, Turkish Medicines and Medical Devices Agency, Sögütözü Mahallesi, 2176. Sokak, No:5, 06520 Çankaya, Ankara, Turkey. Telephone Number: +90. 532. 382 56 86. Fax Number: +90. 312. 218 35 85

ODTs can be differed seconds to minutes related to their size and formulation (US FDA, 2003, Hirani *et al.*, 2009, Thakur and Narwal, 2012).

In case of addressing ideal properties and desired characteristics which are necessary for the success of ODTs could be mainly counted as no water requirement for oral administration, dissolve/disperse/disintegrate in mouth in a matter of seconds, good bioavailability, rapid onset of therapeutic action, good compatibility with development technology including taste masking and other excipients, sufficient mechanical strength, thus harder enough and less friable and less sensitive to humidity and temperature to ensure stability and utilizing cost effective production method including packaging. Additionally, dissolution of drug in saliva, swallowability, allow high drug loading, avoid tablet size enlargement are desired characteristics for ODTs (Bandari *et al.*, 2008, Ratnaparkhi *et al.*, 2009, Bharawaj *et al.*, 2010, Wagh *et al.*, 2010, Saroha *et al*, 2010,Thakur and Narwal, 2012).

ADVANTAGES AND DISADVANTAGES OF ODTs

There are a lot of advantages of ODTs, make them preferable in most cases for whom cannot swallow conventional dosage forms such as pediatric, psychiatric, geriatric, bedridden, disabled, uncooperative patients and traveler, busy patients who do not always have access to water. Additionally enhance palatability, enhance bioavailability due to absorption beginning in mouth following pharynx and esophagus, allow rapid drug action to perform a medical intervention or urgency, allow high drug loading, no requirement of chewing, allow practicableness in administration and accurate dosing compared to liquids, avoiding the risk of physical obstructions, no need to special packaging and availability of push through blisters for them, being cost effective, offer good chemical stability because of being such a solid dosage form, allow commercial opportunities such as enlarging product diversity, extended patent life, marketing advantages and life cycle management (Pfister and Ghosh, 2005, Manivannan, 2009, Ratnaparkhi *et al.*, 2009, Bharawaj *et al.*, 2010, Wagh *et al.*, 2010, Thakur and Narwal, 2012, Kumar *et al.*, 2012, Beri and Sacher, 2013).

Although having many advantages, ODTs have also some disadvantages that can be counted as requirement of proper packaging for safety and stabilization of instable drugs, keeping in dry conditions due to their hygroscopic nature, presenting fragility, risk of unpleasant taste in mouth in case of formulation defects (Thakur and Narwal, 2012).

CHALLENGES IN FORMULATING ODTs

Challenges in formulating and manufacturing of ODTs mainly collocated as physico-mechanical properties, drug molecule and taste related properties, sensitivity to environmental conditions and cost. In order to disintegrate and swallow ODTs are made of porous or soft molded matrices make them fragile forms which requires peel-off blister packing, thus increases its cost. Drug properties have significant effect on formulation parameters like manufacturing method and thus characteristics of the final tablet. Chemical and physical properties of drugs that can exemplified as solubility, particle size, compressibility, hygroscopicity, etc. should take into consideration. Although no certain limit are defined for drug amount, generally it is advised to be around 50 w/w % or below of the entire tablet which is preferably 20 w/w % or below. The drug dose indicated that must be lower than 400mg for insoluble drugs and 60mg for soluble drugs where critical size to easy swallow and handle is around about 8mm. Generally it is hard to achieve stable ODTs for environment conditions such as humidity and temperature due to most of ingredients of ODTs dissolve in minimum quantity of water. Unless the technology used for a ODT does not utilizes cost effective production method which allow to use conventional processing and packaging equipments, the cost would be increase especially in case of using patented technologies (Bandari *et al.*, 2008, Ratnaparkhi *et al.*, 2009, Bharawaj *et al.*, 2010, Bhasin *et al.*, 2011, Thakur and Narwal, 2012).

Since most of drugs are unpalatable, proper taste masking technology is necessary to provide good taste for ODTs. Various techniques have been developed for masking the bitter taste of drugs; those include using ion-exchange resins, coating with hydrophilic vehicles, using lipophilic vehicles and using flavors and sweeteners. In case of mouth feel issue, it is undesirable to leave particles following disintegration which cause grittiness feeling and mouth feel can be improved by using flavors and cooling agents (Bandari *et al.*, 2008, Ratnaparkhi *et al.*, 2009, Bharawaj *et al.*, 2010, Saroha *et al.*, 2010, Wagh *et al.*, 2010, Bhasin *et al.*, 2011,Thakur and Narwal, 2012).

Generally all types of tablets are subjected to some control tests such as general appearance, size and shape, tablet thickness and finally clinical studies. However in case of ODTs especially weight variation, hardness, friability test, disintegration test, mechanical strength, uniformity of dispersion, wetting time and water absorption ratio, *in vitro* disintegration time, *in vitro* dissolution time, stability studies are need to be evaluated (Bhowmik *et al.*, 2009, Klancke, 2003, Ölmez and Vural, 2009, Manivannan, 2009, Pahwa *et al.*, 2010, Ölmez *et al.*, 2011, Thakur and Narwal, 2012, Beri and Sacher, 2013).

PROPERTIES FOR ODT DRUG CANDIDATES

In case of drug selection several factors must be considered including above mentioned in ideal properties and desired characteristics of ODTs. General propensity in formulating ODTs is considered as a bioequivalent type of an existing conventional oral dosage form in which the absorption of drug is presumed to be in the postgastric gastrointestinal track (GIT) segments (Fu *et al.*, 2004, Pfister and Ghosh, 2005). However, pregastric absorption may be occurred in different levels with ODTs which would be effective on the pharmacokinetic profile (Pfister and Ghosh, 2005). In this context some studies are

presented the comparison of ODTs and their conventional alternative concluded as they differ in the pharmacokinetic profile and bioavailability of the same dose of drug (Fu *et al.,* 2004, Pfister and Ghosh, 2005, Ghosh and Pfister 2005). Causal relationship for mentioned differences may be deemed to the drug physicochemical property, formulation structure, manufacturing process or all of them. Pharmacokinetic profile differences by means of higher drug plasma levels and systemic exposure could be deemed to the pregastric absorption which allows the avoidance of first-pass metabolism, thus effect the safety and efficacy of the drug (Pfister and Ghosh, 2005).

The ideal characteristics of a drug allow dissolution in the mouth and pregastric absorption from an ODT includes having no bitter taste, dose as low as possible (lower than 20 mg), small to moderate molecular weight, good solubility in water and saliva, partially non-ionized property at the oral pH, ability to diffuse and partition into the epithelium of the upper GIT (log P >1, or preferably >2) and ability to permeate oral mucosa (Pfister and Ghosh, 2005, Aurora and Pathak, 2005, Wagh *et al.*, 2010).

Conversely, having short half-life and need for frequent dosing, heavily bitter or unsuitable taste without possibly of masking, requirement of modified release may incapacitate a drug for ODTs (Pfister and Ghosh, 2005, Wagh *et al.*, 2010).

Drugs which are corporate in or candidates for ODTs are presented in Table 1.

TECHNIQUES FOR PREPARATION OF ODTs

The fast dissolving property of the ODTs requires quick ingress of water into tablet matrix thus requires some basic approaches such as maximizing the porous structure of the tablet, incorporation of suitable disintegrating agent and use of highly water-soluble excipients in the formulation. Excipients use in ODTs contain at least one superdisintegrant (having mecnanism of wicking, swelling or both), a diluent, a lubricant and optionally a swelling agent, a permeabilizing agent, sweeteners and flavorings (Kumar *et al.*, 2012, Beri and Sacher, 2013).

Important criteria for excipients would be used in the formulation of ODTs can be identified as ability of disintegrates quickly, not interfere in the efficacy and organoleptic properties of the ODTs due to individual properties, not interact with drug and other excipients, do not negatively affect the desired final integrity and stability of the product and having melting points of range between 30-35^{0}C (Bandari *et al.*, 2008, , Ratnaparkhi *et al.*, 2009, Bharawaj *et al.*, 2010, Bhasin *et al.*, 2011, Thakur and Narwal, 2012). Type, examples and amounts in general use of various excipients are presented in Table 2.

Between the excipients, as a critical component, superdisintegrants have extensively researched and reviewed in recent years (Deshmkh *et al.*, 2012, Dass and Mazumder, 2013, Kavitha *et al.*, 2013, Priyanka and Vandana, 2013, Khairnar *et al.*, 2014). Superdisintegrants can be classified as synthetic, natural and co-processed. In this context synthetic superdisintegrants can be exemplified with sodium starch glycolate, croscarmellose sodium, cross-linked polyvinylpyrrolidone, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, partially pregelatinized starch, cross-linked alginic acid and modified resin. Natural superdisintegrants of which are mainly processed mucilages and gums are obtained from plants can be exemplified with *Lepidium sativum* seed mucilage, *Plantago ovata* seed mucilage, *Trigonella foenum-graceum* seed mucilage, *Hibiscus rosa-sinesis* linn. mucilage, *Ocimum americanum* seed mucilage, *Aloe barbadensis* Miller mucilage, *Linum usitatissimum* seed mucilage, *Cucurbita maxima* pulp powder, Banana powder, Gellan gum, Locust bean gum, Xanthan gum, Guar Gums, Gum Karaya, Cassia fistula seed gum, Mangifera indica gum, Agar from *Gelidium amansii and other red algaes*, Soy polysaccharide and Chitosan (Deshmkh *et al.*, 2012, Gondaliya *et al.*, 2013, Gupta *et al.*, 2013, Kavitha *et al.*, 2013, Raulji *et al.*, 2013, Vani and Rasheed, 2014). Co-processing is the novel concept in which two or more excipients are incorporate to improve their individual properties and obtain a superdisintegrant. Ran Explo-S^{TM} (microcrystalline cellulose, silica and sodium starch glycolate), PanExcea MH300G^{TM} (microcrystalline cellulose, hydroxyl-propyl- methyl cellulose and crospovidone), etc are some commercial (Kavitha *et al.*, 2013) and complexation of chitosan and alginate (Kharade and Bhutkar, 2013), combination of croscarmellose sodium and crospovidone (Kumare *et al.*, 2013) and corporation of rice starch: PEG 1500: Aerosil (Chowdary and Aishwarya, 2014) are some latest research examples of co-processed superdisintegrants.

Various preparation techniques have been developed on the basis of different principles, thus present different properties of ODTs by means of mechanical strength, stability, mouth feel, taste, swallowability, dissolution profile and bioavailability (Parakh and Gothoskar, 2003, Shukla *et al.*, 2009, Wagh *et al.*, 2010). Some of those technologies are patented and while patented technology and its process principle presented in Table 3, basic pharmaceutical processes for manufacturing ODTs are following briefly explained (Prajapati and Ratnakar, 2009, Bharawaj *et al.*, 2010, Wagh *et al.*, 2010, Badgujar and Mundada, 2011, Beri and Sacher, 2013).

Freeze drying/ Lyophilization

This process is based on solvent removal from a frozen drug solution or suspension which contains structure forming excipients. The process generally resulted as very light and highly porous form in nature (Bandari *et al.*, 2008, Shukla *et al.*, 2009, Pahwa *et al.*, 2010, Bhasin *et al.*, 2011, Kumar *et al.*, 2012).

Spray drying

This process is based upon to use of a particulate support matrix prepared by spray drying. Support matrix and other components containing aqueous composition form a highly porous and fine powder, then disintegration and dissolution improve by adding effervescent components and finally spray dried to yield a porous powder (Bandari *et al.*, 2008, Shukla *et al.*, 2009, Pahwa *et al.*, 2010, Bhasin *et al.*, 2011, Kumar *et al.*, 2012).

Table. 1: Categories and names of some drugs/active molecules which are corporated in or candidates for ODTs (Zhou *et al.,* 1997, Green *et al.,* 2000, Ohkouchi and Koyama, 2002, Sharma *et al*., 2005, Sammour *et al.,* 2006, Jumaa *et al.,* 2006, Faiz Qadri *et al*, 2006, Ananda *et al.,* 2007, Li *et al.,* 2007, Malke *et al.,* 2007, Ratnaparkhi *et al.,* 2009, Manivannan, 2009, Ping and Jianping, 2009, Higuchi *et al.,* 2009, Shoukri *et al.,* 2009, Abed *et al.,* 2010, Kawano *et al.,* 2010, Lim *et al.,* 2010, Bhasin *et al.,* 2011, Badgujar and Mundada, 2011, Comoglu *et al.,* 2011, Patel *et al.,* 2011, Douroumis *et al.,* 2011, Ikeda and Ochiai, 2011, Mohammed *et al.,* 2011, Parkash *et al.,* 2011, Ram *et al.,* 2011, Arun *et al.,* 2012, Bharath Kumar and Vedavathi, 2012, Rani *et al.,* 2012, Thakur and Narwal, 2012, Errolla *et al.,* 2012, Jha and Chetia, 2012, Beri and Sacher, 2013, Olmez *et al*, 2013, Preethi *et al.,* 2013, Siden and Wolf, 2013, Leonardi *et al.,* 2013, Gupta *et al.,* 2013, Al-Shadeedi *et al.,* 2013).

Category	Active Molecule
Antiasthmatic	Montelukast Sodium.
Anticoagulants	Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.
Antidiabetics	Glipizide, Tolbutamide, Glibenclamide, Tolazamide, Gliclazide, Chlorpropamide.
Antigout Agents	Allopurinol, Probenecid, Sulphinpyrazone.
Antihypertensive	Amlodipine Beyslate, Carvedilol, Benidipine, Darodipine, Dilitazem, Diazoxide, Felodipine, Guanabenz Acetate, Indoramin, Isradipine, Minoxidil, Amlodipine, Nicardipine, Nifedipine, Nimodipine, Phenoxybenzamine, Prazosin HCl, Terazosin HCl, Reserpine.
Antihistamines	Loratadine, Cetrizine HCl, Cinnarizine, Triprolidine, Fexofenadine.
Antiepileptics	Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Phensuximide, Primidone, Sulthiame, Valproic Acid.
Antiarrhythmics	Flecainide Acetate, Quinidine Sulphate, Amiodarone HCl, Disopyramide.
Analgesics and Antiinflammatory Agents	Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Fenoprofen Calcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Naproxen, Oxaprozin, Oxyphenbutazone, Phenylbutazone, Sulindac, Diclofenac sodium, Piroxicam, Oxyphenbutazone, Indomethacin, Nimesulide, Rofecoxib, Paracetamol.
Antibacterial Agents	Benethamine Penicillin, Cinoxacin, Ciprofloxacin, Clarithromycin, Clofazimine, Cloxacillin Sodium, Demeclocycline, Doxycycline, Erythromycin, Ethionamide, Imipenem, Nalidixic Acid, Nitrofurantoin, Nalidixicacid, Rifampicin, Spiramycin, Sulphabenzamide, Sulphadoxine, Sulphamerazine, Sulphacetamide, Sulphadiazine, Sulphafurazole, Sulphamethoxazole, Sulphapyridine, Trimethoprim.
Antidepressants	Amoxapine, Ciclazindol, Maprotiline, Mianserin, Nortriptyline, Trazodone, Trimipramine Maleate, Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide, Glipizide, Tolazamide, Tolbutamide.
Anticonvulsant	Lamotrigine.
Antifungal Agents	Amphotericin, Clotrimazole, Econazole Nitrate, Fluconazole, Fiucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Sulconazole Nitrate, Terbinafine, Terconazole, Tioconazole, UndecenoicAcid.
Antihelmintics	Albendazole, Bephenium Hydroxynaphthoate, Cambendazole, Dichlorophen, Livermectin, Iverrnectin, Mebendazole, Oxarnniquine, Oxfendazole, Oxantel Embonate, Praziquantel, Pyrantel Embonate, Thiabendazole.
Antimalarials	Amodiaquine, Chloroquine, Chlorproguanil, Halofantrine, Mefloquine, Proguanil, Pyrimethamine, Quinine Sulphate.
Antimigraine Agents	Dihydroergotamine Mesylate, Ergotamine Tartrate, Methysergide Maleate, Pizotifen Maleate, Sumatriptan Succinate, Rizatriptan Benzoate, Diclofenac Potassium.
Antimuscarinic Agents	Atropine, Benzhexol, Biperiden, Ethopropazine HCl, Hyoscine Butyl Bromide, Hyoscyarnine, Mepenzolate Bromide, Orphenadrine, Oxyphencylcimine, Tropicamide.
Antineoplastic Agents And Immunosuppressants	Aminoglutethimide, Amsacrine, Azathioprine, Busulphan, Chlorambucil, Cyclosporin, Dacarbazine, Estramustine, Etoposide, Lomustine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitotane, Mitozantrone, Procarbazine, Tamoxifen Citrate, Testolactone.
Antiprotozoal Agents	Benznidazole, Clioquinol, Decoquinate, Diiodohydroxyquinoline, Diloxanide Furoate, Dinitolmide, Furzolidone, Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.
Antiparkinsonian Agents	Bromocriptine Mesylate, Lysuride Maleate, Selegiline.
Antithyroid Agents	Carbimazole, Propylthiouracil.
Anxiolytic, Sedatives, Hypnotics And Neuroleptics	Alprazolam, Amyiobarbitone, Barbitone, Bentazeparn, Bromazepam, Bromperidol, Brotizoiam, Butobarbitone, Carbromal, Chlordiazepoxide, Chlormethiazole, Chlorpromazine, Clobazam, Clotiazepam, Clozapine, Diazepam, Droperidol, Ethinamate, Flunanisone, Flunitrazepam, Fluopromazine, Flupenuiixol Decanoate, Fluphenazine Decanoate, Flurazepam, Haloperidol, Lorazepam, Lormetazepam, Medazepam, Meprobamate, Methaqualone, Midazolam, Nitrazepam, Oxazepam, Pentobarbitone, Perphenazine Pimozide, Prochlorperazine, Suipiride, Temazepam, Thioridazine, Triazolam, Zopiclone, Olanzapine.
Cardiac Inotropic Agents	Amrinone, Digitoxin, Digoxin, Enoximone, Lanatoside C, Medigoxin.
Corticosteroids	Beclomethasone, Betamethasone, Budesonide, Cortisone Acetate, Desoxymethasone, Dexamethasone, Fludrocortisone Acetate, Flunisolide, Flucortolone, Fluticasone Propionate, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone, Triamcinolone.
Diuretics	Acetazolarnide, Amiloride, Bendrofluazide, Bumetanide, Chlorothiazide, Chlorthalidone, Ethacrynic Acid, Furosemide, Metolazone, Spironolactone, Triamterene. Acetazolamide, Spironolactone, Furosemide, Amiloride, Ethacrynic Acid.
Enzymes	Co-Enzyme Q-10, All the Enzymes.
Gastrointestinal Agents	Bisacodyl, Cisapride, Diphenoxylate, Domperidone, Loperamide, Mesalazine, Sulphasaiazine, Nizatidine, Omeprazole, Ranitidine HCl, Famotidine, Cimitidine, Omeprazole, Ondansteron HCl, Domperidone, Mosapride Citrate.
Histamine H,-Receptor Antagonists	Acrivastine, Astemizole, Cinnarizine, Cyclizine, Cyproheptadine, Dimenhydrinate, Flunarizine, Loratadine, Meclozine, Oxatomide, Terfenadine, Triprolidine.
Lipid Regulating Agents	Bezafibrate, Clofibrate, Fenofibrate, Gemfibrozil, Probucol.
Local Anaesthetics	Lidocaine.
Neuromuscular Agents	Pyridostigmine.
Nitrates And Other Anti-Anginal Agents	Amyl Nitrate, Glyceryl Trinitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Pentaerythritol Tetranitrate.

Nutritional Agents	Betacarotene, Vitamin A, Vitamin B2 , Vitamin D, Vitamin E, Vitamin K, Vitamin C.
Opioid Analgesics	Codeine, Dextropropyoxyphene, Diamorphine, Dihydrocodeine, Meptazinol, Methadone, Morphine, Nalbuphine, Pentazocine.
Oral Vaccines	Vaccines for Influenza, Tuberculosis, Meningitis, Hepatitis, Whooping Cough, Polio, Tetanus, Diphtheria, Malaria, Cholera, Herpes, Typhoid, Hiv, Aids, Measles, Lyme Disease, Travellers Diarrhea, Hepatitis A, B And C, Otitis Media, Dengue Fever, Rabies, Parainfluenza, Rubella, Yellow Fever, Dysentery, Legionnaires Disease, Toxoplasmosis, Q-Fever, Haemorrhegic Fever, Argentina Haemorrhagic Fever, Caries, Chagas Disease, Pneumoccoccal Disease, Mumps.
Proteins, Peptides And Recombinant Drugs	Insulin, Glucagon, Somatotropin, Calcitonins, Enkephalins, Interferons.
Sex Hormones	Clomiphene Citrate, Danazol, Ethinyloestradiol, Medroxyprogesterone Acetate, Mestranol, Methyltestosterone, Norethisterone, Norgestrel, Oestradiol, Conjugated Oestrogens, Progesterone, Stanozolol, Stiboestrol, Testosterone, Tibolone.
Stimulants	Amphetamine, Dexamphetamine, Dexfenfluramine, Fenfluramine, Mazindol, Pemoline.
Tj-Blockers	Acebutolol, Alprenolol, Atenolol, Labetalol, Metoprolol, Nadolol, Oxprenolol, Pindolol, Propranolol.

Table 2. Type, examples and range in use (% in weight) of various excipients use in ODTs (Mohanachandran *et al*., 2011, Pahwa *et al*., 2010, Thakur and Narwal, 2012, Mrudula and Derle, 2012).

Type of the Excipients	Examples	% (w)
Superdisintegrants	Croscarmellose sodium, Crospovidone, Sodium starch glycolate, Microcrystalline cellulose, Carboxy methyl cellulose, Modified corn starch, Polacrilin potassium, etc.	1-15%
Binder	Polyvinylprolidone, Polyvinylalchol, Hydroxy propyl methylcellulose, etc.	5-10%
Antistatic agent	Sodiumlaurlysulfate,Sodiumdoecylsulfate, Polyoxyethylene sorbitan fatty acid esters, Polyoxyethylene steartes, etc.	0-10%
Diluents	Mannitol, Sorbitol, Xylitol, Calcium carbonate, Magnesium carbonate, Calcium sulfate, Magnesium trisilicate, etc.	0-85%

Table. 3: Name of patented technologies for preparation of ODTs and basic process for each patented technology.

Patented technologies for ODTs	Basic Process
Zydis®	Lyophilization
Quicksolv®	Lyophilization
Lyoc®	Lyophilization
Nanocrystal Technology®/ Nanomelt	Lyophilization
Flashtab®	Direct compression
Orasolv®	Direct compression
Durasolv®	Direct compression
Wowtab®	Direct compression
Ziplets®	Direct compression
Frosta ®	Direct compression
Pharmaburst technology®	Direct compression
Dispersible Tablet Technology®	Direct compression
Flashdose®	Cotton Candy Process
Sheaform Technology®	Cotton Candy Process
OraQuick®	Micromask taste masking
Ceform Technology®	Microspheres and compression
Advatab®	Microcaps® and Diffuscap® CR Technology

Table. 4: Various recents patents in ODTs field.

Title	Patent Number	Publication Year
Fast disintegrating tablets	EP 1 058 538 B2	2012
Disintegrating particle composition and orally rapidly disintegrating tablet	EP 2 465 539 A1	2012
Fast dissolving solid dosage form	EP 2 493 457 A1	2012
Rapidly disintegrating tablet	US 20120028949	2012
Quick dissolve compositions and tablets based thereon	US20120082729	2012
Orodispersible tablets	US20120077888	2012
Taste-masked orally disintegrating tablets of memantine hydrochloride	EP 2 583 669 A1	2013
Orally disintegrating tablet	EP 2 591 774 A1	2013
Mozavaptan formulations	EP 2 609 909 A1	2013
Coated effervescent tablet	EP 2595 609 A1	2013
Orally disintegrating composition comprising mirtazapine	T 0418/09	2013
Fast release solid oral compositions of entecavir	WO2013072937 A2	2013

Molding

This process is achieved by using water soluble ingredients mostly sugars. Drug and excipients powder blend is pushed through a very fine screen then moistened with a hydroalcoholic solvent and moulded into tablets under pressure, the process ended by evaporating of the solvent by air drying (Bandari *et al.,* 2008, Shukla *et al.,* 2009, Pahwa *et al.,* 2010, Bhasin *et al.,* 2011, Kumar *et al*., 2012).

Phase transition process

In this process, tablets which contain sugar alcohols having high and low melting points are prepared by compressing;

following heating to enhance bonding among particles resulted as sufficient hardness of tablets (Bandari *et al.,* 2008, Pahwa *et al.,* 2010, Kumar *et al.,* 2012).

Melt granulation

In this process powders are efficiently agglomerated by the use of binder which can be liquid or melting during the process by using high shear mixers, and temperature is raised above the melting point of the binder (Bandari *et al.,* 2008, Pahwa *et al.,* 2010).

Sublimation

For accomplishing this process some inert volatile substances like urea, camphor etc. is added to other tablet excipients and blend is compressed into tablet. Subsequently removal of volatile substances by sublimation generates a porous structure (Bandari *et al.,* 2008, Shukla *et al.,* 2009, Pahwa *et al.,* 2010, Bhasin *et al.,* 2011, Kumar *et al.,* 2012).

Mass extrusion

This process based on softening of the active blend by using a solvent mixture of water soluble polyethylene glycol and methanol. Following expulsion of softened mass through the extruder or syringe to get a cylindrical shaped, they cut into segments by using heated blade to form tablets (Bandari *et al.,* 2008, Shukla *et al.,* 2009, Pahwa *et al.,* 2010).

Cotton candy process

This process based on formation of matrix of polysaccharides or saccharides which are partially recrystallized and attain better flow properties and compressibility by concurrent action of flash melting and spinning. Then matrix is milled and blended with active ingredients and excipients, soon after compressed to form tablets (Bandari *et al.,* 2008, Shukla *et al.,* 2009, Pahwa *et al.,* 2010).

Direct compression

The basic principle of this technique is addition of superdisintegrants in optimum concentrations to tablet formulation in which powdered blend compress directly to form tablets (Shukla *et al.,* 2009, Pahwa *et al.,* 2010, Bhasin *et al.,* 2011, Kumar *et al.,* 2012).

In the light of developments in ODTs domain, new patent applications have been done and various recent patents in the field of ODTs are briefly listed in Table 4.

CONCLUSION

As a conclusion ODTs presenting many pharmaceutical and clinical advantages including availability of the oral delivery of protein and peptide-based active agents, improved efficacy, improved safety and commercial advantages including enlarged product diversity, extended patent life and marketing advantages have attract attention in the research and industrial fields.

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