Current developments in orally disintegrating tablet technology

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ABSTRACT

Over the decades, orally disintegrating tablet (ODTs) has expanded much attention as a preferred alternative to conventional oral dosage form such as tablet and capsules. Recently, ODTs 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, who have difficulty in swallowing conventional tablets and capsules. ODTs 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. Conventional preparation technologies like direct compression, lyophilization, spray drying, molding, phase transition process, melt granulation, sublimation, mass extrusion, etc., while various patented technologies like like Zydis, Lyoc, Quicksolv, Orasolv, Durasolv, Flashtab, Oraquick, Wowtab, Ziplet etc., have been developed for the production of ODTs. The present review addresses briefly about the current developments in ODT technologies and various leading technologies for their manufacturing. In addition, important aspects of ODT technology are discussed.

Keywords: Orally disintegrating tablets; direct compression; lyophilization; patented technologies.

INTRODUCTION

Despite noteworthy advancements in drug delivery technology, the oral route remains the trendy route for the administration of drugs because of accurate dosage, low cost of therapy, self-medication, non-invasive method, and ease of administration leading to high level of patient compliance[1]. Tablets and capsules constitute the foremost portion of oral dosage forms that are currently available in the market. However, traditional tablets and capsules administered with a glass of water may be inconvenient or unfeasible for some geriatric patients, because of changes in various physiological and neurological conditions associated with aging including dysphagia (difficulty in swallowing), hand tremors, hearing, memory, risk of choking in addition to change in taste and smell [2]. These solid dosage forms also present significant administration challenges in other patient groups, such as children, mentally retarded, bed ridden, uncooperative, nauseated, or on reduced water intake have suffered difficulties of swallowing these dosage forms[2-5]. Moreover, patients travelling with little or no access to water, limit utility of orally administered conventional tablets or capsules. To overcome these difficulties, pharmaceutical technologists have devoted considerable efforts for developing a novel type of dosage form for oral administration known as orally disintegrating tablets (ODTs).

Over the decade, the demand for the development of ODTs has enormously increased as it has notable impact on the patient compliance. ODTs are designed to disintegrate rapidly on contact with saliva and enable oral administration without water or chewing, these formulations offer increased convenience and ease of administration with the potential to improve patient compliance, particularly in certain populations, where swallowing of conventional solid oral dosage forms presents difficulties[6-8]. US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [9]. European Pharmacopoeia described ODTs as 'uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed' and as tablets which should disintegrate within 3 minutes[10]. ODTs are also called as orodisperse, mouth dissolving, rapidly disintegrating, fast melt, and quick dissolve system[11,12]. ODTs improve drug dissolution as

well as onset of clinical effect and the pregastric absorption of drugs, which avoids first pass hepatic metabolism to reduce the dose than those observed from conventional dosage forms and finally, increase the bioavailability of drugs[13,14]. ODTs release drugs in the mouth for absorption through local oromucosal tissues and through pregastric (e.g., oral cavity, pharynx, and oesophagus), gastric (i.e., stomach), and postgastric (e.g., small and large intestines) segments of the gastrointestinal tract (GIT). Again, ODTs allow the luxury of much more accurate dosing the primary alternate, oral liquids. ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population. From the perspective of the pharmaceutical industry, ODTs may provide new business opportunities in the form of product differentiation, line extension and life cycle management, exclusivity, uniqueness, and patent life extension. Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms[15], and most consumers would ask their doctors for ODTs (70 %) purchase ODTs (70 %), or prefer ODTs to regular tablets or liquids (> 80 %)[16]. The current review deals with significance of advancements in ODTs and various leading technologies for their manufacturing.

IDEAL PROPERTIES OF ODTS:

The performance of ODTs depends on the manufacturing technology and the most necessary property of such a dosage form is the ability of rapidly disintegrating and dispersing or dissolving in the saliva, thereby obviating the need for water intake. ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include[5, 13, 17]:

i. Convenient and easy to administer as does not require water for oral administration for swallowing purpose, but it should dissolve or disintegrate in the mouth usually within few seconds.

ii. Allow high drug loading.

iii. Provide pleasant feeling in the mouth.

iv. Be compatible with taste masking and other excipients.

v. Leave negligible or no residue in the mouth after oral administration.

vi. Have sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling.

vii. Insensitive to environmental conditions such as humidity and temperature.

viii. Adaptable and amenable to conventional processing and packaging equipments at nominal expense.

ADVANTAGES OF ODTS:

Advantages of ODTs include[13, 16-18]:

i. Ease of administration to geriatric, pediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.

ii. The ODTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance.

iii. Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

iv. Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus. Pregastric absorption can result in improved bioavailability and because of reduced dosage, improved clinical performance through a reduction of unwanted effects.

v. Rapid onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.

vi. Good mouth feels, especially for pediatric patients as taste-masking technique is used to avoid the bitter taste of drugs.

vii. Minimum risk of suffocation in airways due to physical obstruction, when ODTs are swallowed, thus they provide improved safety and compliance with their administrations.

viii. Rapid drug therapy intervention is possible.

ix. Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

x. No specific packaging is required. It can be packaged in push through blisters.

xi. Provide new business opportunities in the form of product differentiation, patent-life extension, uniqueness, line extension, and life-cycle management, and exclusivity of product promotion.

CHALLENGES IN FORMULATING ODTS:

i. ODT systems usually contain the drug in a taste-masked form, as most of the drugs are unpalatable. ODTs disintegrate or dissolve in patient's oral cavity, thus releasing the taste-masked drugs, and taste masking of drugs in ODT systems is critical for patient compliance[16, 19].

ii. For allowing disintegration of ODTs in the oral cavity, ODTs are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may increase the cost of the product[20,21]. Among various ODT technologies, only few technologies can produce tablets that are sufficient mechanical strength and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.

iii. The size of ODTs is also an important challenging factor in the ODT development, mainly due to the degree of ease, when swallowing a tablet depends on size. It has been reported that the easiest size of ODTs to swallow is 7-8 mm, while the easiest size to handle was one larger than 8 mm[5, 22]. Therefore, the ODTs size for both easy to swallow and easy to handle is difficult to achieve.

iv. Aqueous soluble drugs cause various formulation challenges, because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying due to loss of supporting structure during the sublimation process. Such collapse can be avoided by using various matrix-forming excipients such as mannitol, which can induce crystallinity and hence, impart rigidity to the amorphous composite [5].

v. Several ODTs are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity[5, 11]. Therefore, they need protection from humidity, which calls for specialized product packaging.

SELECTION OF DRUGS FOR THE ODT FORMULATIONS:

Generally, ODTs are formulated as bio-equivalent extensions of existing oral dosage forms. Under these circumstances, it is assumed that the absorption of drugs from ODTs occurs in the postgastric gastrointestinal tract segments, similar to the conventional oral dosage from. Nevertheless, this scenario may not always be the case. An ODT may have varying degrees of pregastric absorption of drugs and thus, the pharmacokinetic profiles of drugs will vary[5]. Therefore, the ODTs will not be bio-equivalent to the conventional dosage forms. For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profile compared with the name dose administered in a conventional dosage from[5, 23,24]. If significantly higher plasma levels have been observed, pregastric absorption leading to the avoidance of first–pass liver metabolism may play a significant role. This situation may have implications for drug delivery and efficacy, which may need to be addressed and assessed in a marketing application for an ODT[5]. The ideal characteristics of a drug for *in vivo* dissolution from an ODT include[5, 10, 25]:

i. No bitter taste.

ii. Small to moderate molecular weight.

iii. Good stability in water and saliva.

iv. Partially non-ionized at the oral cavities pH.

v. Ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferably > 2).

vi. Ability to permeate oral mucosal tissue.

vii. Dose should be low as possible.

Unsuitable drug characteristic for ODTs[13]:

i. Short half-life and frequent dosing.

ii. Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.

iii. Required controlled or sustained release.

TECHNOLOGIES USED IN ODT FORMULATIONS:

Conventional technologies:

The various conventional technologies were developed for the preparation of ODTs that are:

Direct compression: Direct compression is one of the popular techniques for preparation of these dosage forms of its easy implementation, use of conventional equipments along with commonly available excipients, limited number of processing steps and cost effectiveness. The introduction of superdisintegrants has augmented the popularity of this technology [26]. The basic principle involved in development of these dosage forms using this technique is the addition of superdisintegrants in optimum concentration (about 2-5 %) are mostly used so as to achieve rapid disintegration along with the good mouth feel[17]. The disintegrant efficacy of ODTs is strongly affected by tablet size and hardness. Cousin et al. have formulated ODTs using carboxymethyl cellulose as disintegrating agent and swelling agent consisting of modified starch or microcrystalline cellulose. The tablets disintegrate in the mouth in less than 60 seconds[27]. Bi et al. have evaluated the disintegrant property of the mixture of microcrystalline cellulose and low substituted hydroxy propyl cellulose (MCC: L-HPC) for ODT and found that shortest disintegration time was observed in the range of ratio of MCC: L-HPC, 8:2 to 9:1 [28]. The advantages and disadvantages of direct compression process for ODT formulation are given below:

· Advantages:

i. Requires fewer unit operations compared with wet granulation (shorter processing time and lower energy consumption).

ii. Fewer stability issues for drugs that are sensitive to heat or moisture.

iii. For certain drugs, faster dissolution rates may be generated from tablets prepared by direct compression compared with wet granulation; for example, norfloxacin.

· Disadvantages:

i. Issues with segregation– these can be reduced by matching the particle size and density of the active drug substance with excipients.

ii. In general, the drug content is limited to approximately 30 % or approximately 50 mg.

iii. May not be applicable for materials possessing a low bulk density because after compression the tablets produced may be too thin.

iv. Not suited for poorly flowing drugs.

v. Static charges may develop on the drug particles or excipients during mixing, which may lead to agglomeration of particles producing poor mixing.

Lyophilization or Freeze-drying: Freeze-drying or lyophilization is a process in which solvent is removed from a frozen drug solution or suspension containing structure-forming excipients. This technology consists of three phases[29]:

i. Freezing to bring the material below its eutectic zone

ii. Sublimation or primary drying to reduce moisture to around 4 % w/w of dry product.

iii. Desorption or secondary drying to reduce bound moisture to the required final value.

The tablets prepared by lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e. thermolabile substances[30,31]. This technology forms the basis of Zydis, Quicksolv and Lyoc technologies which are used to manufacture ODTs. Jaccard and Leyder used lyophilization to develop an oral formulation that not only dissolved rapidly but also exhibited improved bioavailability of several drugs such as spironolactone and trolendomycin[32]. Remon and Corveleyn studied various formulation and process parameters by using hydrochlorothiazide as a model drug and they have found maltodextrins very useful in preparing ODTs by lyophilization[33-34]. Ahmed et al. prepared lyophilized tablet using freeze-drying technique. The lyophilized tablet prepared by dispersing ketoprofen in aqueous solution of highly water-soluble carrier consisting of gelatin, glycine and sorbitol in blister packs and then subjected to lyophillization in blister packs. It was found that the increase in solubility of ketoprofen from lyophilized tablet matrix was nearly 3 times greater than solubility of the ketoprofen, which was due to supersaturation generated

by amorphous form of drug[35].

The ideal drug characteristics for this process are relative water insolubility with fine particle size and good aqueous stability in suspensions. Primary problems associated with water-soluble drugs are formation of eutectic mixture, because of freezing point depression (FPD) and formation of glassy solid on freezing which might collapse on sublimation. The addition of cryprotectants like mannitol, crystal-forming materials induces crystallinity and imparts rigidity to amorphous material and can prevent collapse of structure and mask the bitter taste. The advantage of using freeze-drying process is that pharmaceutical substances can be processed at nonelevated temperature, thereby eliminating adverse thermal effects. However, high cost of equipment and processing limits the use of this process. Other disadvantages include lack of resistance necessary for standard blister packs of the final dosage forms[18].

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. Spray drying can produce highly porous and fine powders that dissolve rapidly. 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 then mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and/or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray-dried powder disintegrated within 20 seconds when immersed in an aqueous medium. Allen et al. utilized this process for preparing ODTs. These formulations consisted of hydrolyzed/non hydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent, and sodium starch glycolate or croscarmellose sodium as disintegrating agent[36].

Molding: Molded tablets are designed to facilitate the absorption of active ingredients through mucosal linings of mouth. They are prepared by this method are solid dispersions. Molded tablets disintegrate more rapidly and offer improved taste because of the dispersion matrix, which is generally prepared from water-soluble sugars. Powdered blend (containing drug and excipients like binding agents e.g., sucrose, acacia, polyvinyl pyrrolidone etc.) is pushed through a very fine screen (to ensure rapid dissolution) and then moistened with a hydro-alcoholic solvent and molded into tablets under pressure lower than employed for conventional compressed tablets. The solvent is later removed by air-drying. A porous structure that enhances dissolution prepared by using water soluble ingredients meant to be absorbed through mucosal lining of mouth, thus increasing bioavailability and decreasing first-pass metabolism of certain drugs. As molding process is employed usually with soluble ingredients (mainly saccharides), which offer improved mouth feel and disintegration of tablets, have low mechanical strength, which results in erosion and breaking during handling[18, 37]. Different molding techniques can be used to prepare ODTs:

i. Compression molding: The manufacturing process involves moistening the powder blend with a hydro-alcoholic solvent followed by compressing into mold plates to form a wetted mass, which is, then air dried to remove the solvent. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution[38].

ii. Heat molding: A molten matrix in which drug is dissolved or dispersed can be directly molded into ODTs. The tablets prepared using heat molding process involves settling of molten mass that contain a dispersed or dissolved drug[39]. In this process, the suspension or solution of drug, agar, and sugar is prepared and then poured into the blister packaging. Then, it is solidified at room temperature to form a jelly and dried at 30°C under the vacuum.

iii. Molding by vacuum evaporation without lyophilization: This process involves evaporation of solvent from a drug solution or suspension at a standard pressure[40]. This method differs from the lyophilization technique, as in the former the evaporation of free unbound solvent occurs from a solid through the liquid phase to a gas, under controlled conditions, instead of the sublimation which takes place in the latter process. Unlike

lyophilization, vacuum drying helps to densify the matrix and thereby improves the mechanical strength of the ODT product[41].

- Advantages: As the dispersion matrix is made from water-soluble sugars, moulded ODTs disintegrate more rapidly and offer improved taste. These properties are enhanced when tablets with porous structures are produced or when components that are physically modified by the molding process are used. In comparison to lyophilization process, tablets produced by moulding technique are easier to adapt to the industrial scale.
- Disadvantage: As the molded tablets have poor mechanical strength, they may undergo erosion and breaking during handling. Though hardening can enhance the tablet strength; but, it would be at the cost of their disintegration time.

Phase transition process: In this technique, ODTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point. The combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, is important for making ODTs without any special apparatus. Here, tablet produced by compressing the powder containing two sugar alcohols of high and low melting point and subsequently heating at temperature between their two melting points. Orally disintegrating tablets 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 increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol[42]. Kuno et al. have studied the effect of preparation method on the properties of orally disintegrating tablets manufactured using phase transition of sugar alcohol. Before heating process, tablet did not have sufficient hardness because of low compatibility but after heating, increase in interparticular bonding or binding surface area occurs which then increased tablet hardness[43].

Melt granulation: Melt granulation is a process in which pharmaceutical powders are efficiently agglomerated by the use of binder that can be a molten liquid, a solid, or a solid that melts during the process. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. Abdelbary et al. prepared orally disintegrating tablet by incorporating a hydrophilic waxy binder PEG 6-stearate (Superpolystate®) in the formulation. It has melting point of 33-37°C and HLB value of nine. It acts as a binder and increases the physical resistance of tablet. It helps for fast disintegration of tablet when place in mouth and leaving no residue in oral cavity[44]. Perissutti et al. developed the orally disintegrating tablets of carbamazepine by melt granulation technique. The granules were prepared by using polyethylene glycol (PEG-4000) as a melting binder and lactose monohydrate as hydrophilic filler without using solvents or water. The dissolution profiles of granules containing crosspovidone as an intragranulating agent were found to be superimposable to those prepared without it. In addition, the extragranular addition of a small amount of crosspovidone gave rise to a further increase in disintegration rate and dissolution performances[45].

Sublimation: This technique is based on the use of volatile ingredients (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc.) to other tablet excipients and the mixture is then compressed into tablets. Entrapped volatile material is then removed via sublimation, which leads to formation of a porous structure. These compressed tablets which have high porosity (approximately 30 %) rapidly dissolved within 15 seconds in saliva. Several solvents like cyclohexane, benzene etc, can also be used as pore forming agents.

Orodispersible tablets with highly porous structure and good mechanical strength have been developed by this method. Makino et al. described a method of producing a fast dissolving tablet using water as a pore forming material. They used a mixture containing active ingredient and carbohydrates (glucose, mannitol, xylitol etc) which then moistened with water (1-3 % w/w) and compressed into tablets. Then water was removed, yielding highly porous tablet[46].

Mass Extrusion: This technology consists of softening the active blend using a solvent mixture of water-soluble polyethylene glycol with methanol and expulsion of softened mass through the extruder or syringe to obtain

cylinder of the product into even segments employing heated blade to form tablet. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masked their bitter taste[13].

Oral Disintegrating Thin Films: It is a newer developing front in ODT that provides a very suitable means of taking medications and supplements. In this technique, 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 are dissolved in non-aqueous solvent to prepare non-aqueous solution, which forms a film after evaporation of solvent[47]. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film[48]. After placing this film in mouth, it melts or dissolves rapidly and releases the drug in solution or suspension form. This system forms the thin films of size less than 2 X 2 inches which dissolves within 5 seconds with instant drug delivery and flavoured taste.

Taste Masking Technologies: Pharmaceutically active ingredients may leave an unpleasant taste after administration. A new generation of rapidly dissolving and safely swallowable tablets films etc. that are being developed should have sweet and pleasant taste. Various types of orally disintegrating formulation containing drugs in the taste masked form are available like chewing gums or tablets, multiparticulates or microparticulates, microspheres or comestible units, microcapsules, nanocrystals etc[1, 49].

Patented technologies:

The various technologies were developed for the formulation of ODTs and patented. These are:

Zydis® technology (Cardinal Health Inc.): Zydis® was first marketed technology and introduced by R. P. Scherer Corporation (Cardinal Health, Inc.) in 1986. It is a unique freeze-dried oral solid dosage form, that can be administered without water and it dissolves instantly on tongue in less than 3 seconds. The Zydis tablet is produced by lyophilizing the drug in a matrix. The matrix consists of water-soluble saccharides and polymer (gelatin, dextran, alginates) to provide rapid dissolution and to allow sufficient physical strength to withstand handling. The product is very lightweight and fragile and must be dispensed in a special blister pack.

A water-soluble drug can be incorporated only up to 60 mg. On the other hand, water insoluble drug can be incorporated only up to 400 mg per tablet or less. The preferred drugs are water insoluble, low dose, chemically stable, small particle size and tasteless. The two most commonly used structural additives are gelatin and mannitol. Some other structural additives (e.g., starches, gums etc.) may be used depending on the properties of the active ingredient. The best physical characteristics are achieved by using a mixture of a water-soluble polymer and a crystalline sugar alcohol or amino acid. The polymer gives the strength and resilience while the crystalline component gives the hardness and texture. Polymers such as gelatin, dextran or alginates are added to impart strength during handling. These form a glossy and amorphous structure. Mannitol or sorbitol is added to impart crystallinity, elegance, and hardness. Various gums may be added to prevent sedimentation of dispersed drug particles. Water is used as a medium to ensure the formation of a porous dosage form for rapid disintegration. Collapse protectants, like glycine is used to prevent the shrinkage of zydis unit during the process and long-term storage. If necessary, suspending agents and pH adjusting agents may be used[34]. As the Zydis dosage form is weak in physical strength, unit is contained in peelable blister pack, which allows removal of product without damaging it. Zydis formulation is also self-preserving, because the final water concentration in the freeze-dried product is too low to allow for microbial growth[50].

There are also several disadvantages of the Zydis® technology:

i. Formulation is very lightweight and fragile.

ii. Poor stability at higher temperatures and humidity and stress conditions.

iii. Relatively expensive and time-consuming manufacturing process.

Orasolv® technology (Cima Labs, Inc.): Orasolv® is Cima Lab's first orally disintegrating dosage form. This technology is based on the direct compression of effervescent agent and taste masked drug at low compression force in order to minimize oral disintegration and dissolution time. This technique is frequently used to

develop over the counter formulations. Orasolv® technology can accommodate a wide range of active ingredient from 1 mg to 500 mg. The effervescence occurs due to chemical reaction between organic acid such as citric acid, fumaric acid or maleic acid and a base such as sodium bicarbonate, potassium bicarbonate, magnesium bicarbonate, which result in generation of CO_2[51,52]. Effervescent disintegration agents evolve gas by means of chemical reaction called effervescent couple. Carbonates such as sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate, and acids like citric, tartaric, fumaric, adipic and succinic are used. Microparticles, effervescent agents, and other ingredient such as flavors, sweeteners, colorants, and lubricants are blended and compressed at a low degree of compaction[52]. The major disadvantage of Orasolv® technology is its low mechanical strength. The tablets produced are soft and friable and need to be packaged in specially designed pack.

Durasolv® technology (Cima Labs, Inc.): Durasolv® is Cima's second-generation fast- dissolving/ disintegrating tablet formulation. Durasolv® has much higher mechanical strength than Orasolv due to the use of higher compaction pressures during tableting. Durasolv® product is thus produced in a faster and more cost-effective manner. It is so durable that it can be packaged in either traditional blister packaging or vials. This technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike Orasolv®, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in Durasolv® may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, Durasolv® technology is best suited for formulations including relatively small doses of active compound. The tablets made by this technology consist of a drug, fillers, and lubricants, prepared by using conventional tableting equipment, and have good rigidity. Durasolv® product is so durable that it can be packed in either traditional blister pack or vials. Due to higher force of compaction used, tablets prepared are rigid[53]. It is one of the appropriate technologies for product requiring low amounts of active ingredients.

Lyoc Technology (Cephalon Corporation): Lyoc technique was owned by Cephalon Corporation. Lyoc utilizes a freeze-drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. The liquid solution or suspension preparation evolves fillers, thickening agents, surfactant, non- volatile flavoring agents, and sweeteners along with drug. This homogeneous liquid is placed in blister cavities and subjected to freeze-drying. To prevent inhomogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates are comparable to loosely compressed fast melt formulations[54].

Flashtab technology (Prographarm): Flashtab technology was developed by Prographarm. A disintegrating agent and a swelling agent are used in combination with coated taste-masked microgranules of drug. Flashtab involves coating a drug with a Eudragit polymer 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. This technology includes granulation of excipients by wet or dry granulation method followed by compression into tablets. Disintegrating agents include poly vinyl pyrrolidine (PVP) or carboxymethyl cellulose (CMC) and swelling agents include carboxymethyl cellulose (CMC), starch, modified starch, microcrystalline cellulose, carboxy methylated starch etc. These tablets have satisfactory physical resistance. Tablets containing hygroscopic materials can also be blister packed using high quality polyvinyl chloride or aluminum foils for providing the higher degree of moisture protection than normal polyvinyl chloride or polypropylene foils[53, 55].

Wowtab technology (Yamanouchi Pharma Technologies, Inc.): Wowtab technology was developed and patented by Yamanouchi Pharma Technologies. 'Wow' means 'without water'. The active ingredients may constitute up to 50 % w/w of the tablet. Here, saccharides of both low and high moldability are used to prepare the granules. Moldability is the capacity of a compound to be compressed. Highly moldable substance has high compressibility and thus slow dissolution. The combination of high and low moldability is used to produce tablets of adequate hardness & a rapidly melting strong tablet. Active ingredients are mixed with low moldability

saccharides, then granulated with high moldability saccharides, and then compressed into tablet. The Wowtab formulation is stable to environment due to its significant hardness than Zydis and Orasolv. Wowtab product dissolves quickly in 15 seconds or less. Wowtab product can be packed in both into conventional bottle and blister packs. This technology utilizes conventional granulation and tableting methods and used for both water soluble and insoluble drugs. The manufacturing process involves granulating low- moldable sugars (e.g. mannitol, lactose, glucose, sucrose, and erythritol) that show quick dissolution characteristics with high moldable sugars (e.g. maltose, maltitol, and sorbitol). The result is a mixture of excipients that have fast-dissolving and highly moldable characteristics[53, 55].

Frosta technology (Akina): Akina patents this technology. It utilizes the concept of formulating plastic granules and coprocessing 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 seconds depending on size of tablet[56].

AdvaTab technology (Eurand): In this technology, microencapsulation process is used for coating the drug particles with gastro soluble polymer to mask the taste along with restriction of drug dissolution in mouth cavity. AdvaTab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds. These tablets are especially suited to those patients that have trouble in swallowing capsules and tablets. AdvaTab is distinct from other orally disintegrating tablet 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)[56].

Flashdose technology (Fuisz Technologies, Ltd.): This technology is patented by Fuisz Technologies, Ltd. This technology utilized cotton candy process. This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. This technique involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have better flow properties and compressibility. This candyfloss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to orally disintegrating tablet. This process can accommodate larger drug doses and offers improved mechanical strength. However, high-process temperature limits the use of this process[57].

The method has certain drawbacks, like the dosage form can accommodate only up to 600 mg of drug, and tablets required specialized packing as highly friable, soft and moisture sensitive nature. Instead of a floss-like material, small spheres of saccharides can be produced to carry the drug. The process of making microspheres has been patented by Fuisz, and is known as Ceform and serves as an alternative method of taste masking. Ceform technology involves preparation of microspheres of the active drug. Drug material alone or in combination with other pharmaceutical substances, and excipients is placed into a rapidly spinning machine. The centrifugal force comes into action, which throws the dry drug blend at high speed through small heated openings. Due to the heat provided by carefully controlled temperature, drug blend liquefies to form a sphere, without affecting the drug stability. The formed microspheres are compressed into tablet. This technique effectively masked the taste of product[58-59].

Nanocrystal technology (Elan Corporation): This technology has patented by Elan, King of Prussia, and is based on concept that decreasing particle size increases the surface area, which leads to an increase in dissolution rate. Nanocrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by wet milling the drug. NanoCrystal™ fast dissolving technology provides for:

i. Pharmacokinetic benefits of orally administered nanoparticles (< 2 microns) in the form of a rapidly disintegrating tablet matrix.

ii. Product differentiation based upon a combination of proprietary and patent-protected technology elements.

iii. Exceptional durability, enabling use of conventional packaging equipment and formats (i.e., bottles and/or blisters).

iv. Wide range of doses (up to 200 mg of API per unit).

v. Utilization of non-moisture sensitive inactives.

vi. Cost-effective manufacturing processes that utilize conventional, scalable unit operations.

Nanocrystal 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. This approach avoids manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into orally disintegrating dosage forms because manufacturing losses are negligible[60].

OraQuick technology (KV Pharmaceutical Co. Inc.): OraQuick utilizes its own patented taste masking technology i.e. MicroMask®. In MicroMask® technology, taste-masking process is done by incorporating drug into matrix microsphere. In this technique, tablet is prepared by dissolving the sugar (sucrose, mannitol, sorbitol, xylose, dextrose, fructose, or mannose) and protein (albumin or gelatin) in a suitable solvent such as water, ethanol, isoproryl alcohol and ethanol-water mixture. The solution of matrix is then spray dried, yielding highly porous granules. In addition, utilization of lower heat of production is advantageous for heat-sensitive drugs. Granules formed then mixed with drug and other excipients and compressed at low compression force. KV pharmaceuticals claimed that matrix formed protects and surrounds the drug powder in microencapsulated particles is more reliable during this step[13].

Pharmaburst technology: SPI Pharma, New castle, patents this technology. It utilizes the coprocessed excipients to develop ODT, which dissolves within 30-40 seconds. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets. Tablets obtained have sufficient strength so they can be packed in blister packs and bottles[1].

Quick-Dis technology (Lavipharm): Lavipharm Laboratories Inc. has invented an ideal intraoral fast-dissolving drug delivery system called as Quick-Dis™. This is a thin, flexible, and quick- dissolving film. The film is placed on the top or the floor of the tongue. It retains at the site of application, and rapidly releases the drugs for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from unit-dose pouches to multiple-dose blister packages. Disintegration time 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[61].

EFVDAS technology (Elan Corporation): EFVDAS or Effervescent Drug Absorption System is a drug delivery technology that has been used in the development of a number of both OTC and prescription medications. This is particularly advantageous for conditions such as colds and flu, for which Elan has modified its EFVDAS technology to develop hot drink sachet products that combine medicines and vitamins for OTC use. The granular contents of the sachets can be added to boiling water to produce pleasant-flavored solutions. In these cases the effervescence of the granulate mixture is modified to accommodate the use of heated water. Examples of products that Elan has developed include effervescent ibuprofen, acetaminophen, cimetidine, naproxen, and acetaminophen and codeine combination product[62].

Multiflash technology (Prographarm): Multiflash is a multi-unit tablet composed of coated microgranules and fast-disintegrating excipients. This multiparticulate tablet quickly disintegrates in the esophagus after being swallowed with a minimum amount of water. This tablet avoids mucosal adhesion, and coated pellets can match various dissolution rates[63].

Table 1 represents the list of unique patented technologies and their scientific basis along with patent owners. There are several commercial ODT products available in the markets that are given in Table 2.

FUTURE PROSPECTS:

These dosage forms may be suitable for the oral

Table 1: Some ODT technological patents [1, 8, 64].

ODT Technologies	Technological basis	Patent owners
Zydis	Lyophilisation	R.P. Scherer Inc.
Quicksolv	Lyophilisation	Janseen Pharmaceutica
Flashtab	Multiparticulate compressed tablets	Prographarm
Lyoc	Lyophilisation	Cephalon Corporation.
Orasolv	Compressed tablets	Cima Labs Inc.
Durasolv	Compressed tablets	Cima Labs Inc.
Wowtab	Compressed molded tablets	Yamanouchi Pharma Technologies, Inc.
Flashdose	Cotton candy process	Fuisz Technologies, Ltd.
AdvaTab	microencapsulation	Eurand
Multiflash	Multi-unit tablet composed of coated microgranules	Prographarm
EFVDAS	Effervescent system	Elan Corporation

Table 2: ODT products available in the market [1, 15].

Brand names	Active ingredients
Benadryl Fastmelt	Diphendydramine
Cibalginadue FAST	Ibuprofen
Zomig ZMT	Zolmitriptan
Nulev	Hyocyamine sulphate
Feldene melt	Piroxicum
Pepeid ODT	Famotidine
Zyprexa	Olanzapine
Zofran ODT	Ondansetron
Klonopin Wafer	Clonaxepam
Kemstro	Baclofen
Imodium Instant melts	Loperamide HCl
Fabrectol	Paracetamol
Maxalt-MLT	Rizatriptan benzoate
Olanex Instab	Olanzapine
Romilast	Montelukast
Torrox MT	Rofecoxib
Rofadry MT	Rofecoxib
Dolib MD	Rofecoxib
Orthoref MD	Rofecoxib

delivery of drugs such as protein and peptide–based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Should next generation drugs predominantly protein or peptide based tablets may no longer be the dominant format for dosing such moieties injections generally are not to tutored for used by patients unless facilitated by sophisticated autoinjectors. Inhalator is one good alternative system to deliver these drugs, but the increased research into biopharmacuticles so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by ODTs, which may release these drugs in the oral cavity, are very promising for the delivery of high molecular weight protein and peptide.

CONCLUSION:

ODTs offer numerous significant advantages over conventional dosage forms because of improved efficacy, bioavailability, rapid onset of action, better patient compliance, and acceptance. Pediatric and geriatric patients are primary concerns, as both the groups find these dosage forms convenient to administer as compared to the conventional dosage forms. ODTs can be prepared in several ways and product performance depends upon the drug suitability and excipients selection in the delivery system. Due to the availability of various formulation techniques, good patient compliance and huge potential, several products have already been commercialized. Furthermore, market size and popularity of these dosage forms will surely expand in future. It is also emphasized that newer with continued development of new pharmaceutical scientific and technological innovations should be undertaken for the emergence of promising and versatile dosage form with novel performance and characteristics for ODTs in days to come.

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