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Review Article

INSIGHTS INTO FORMULATION TECHNOLOGIES AND NOVEL STRATEGIES FOR THE DESIGN OF ORALLY DISINTEGRATING DOSAGE FORMS: A COMPREHENSIVE INDUSTRIAL REVIEW

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ABSTRACT

Among the various routes of administration, the oral route remains the most convenient and commonly employed route for drug delivery. The oral conventional drug delivery systems have some drawbacks, such as possibility of gastrointestinal destruction of labile molecules, low absorption of macromolecules, slow onset of action, and unavoidable fluctuation in the concentration of drugs which can either lead to under-or over medication with concomitant adverse effects, especially for drugs with small therapeutic index. Therefore, it became essential to design novel oral drug delivery systems to achieve quick dissolution, absorption, rapid onset of action and reduction of drug dose. Among those novel drug delivery systems are oral disintegrating tablets (ODTs). The purpose of this review article is to report the recent advances in ODT systems with emphasis on their preparations, characterizations and applications. Also, it highlights future prospects and possible challenges in the development of an ideal ODT system.

Keywords: Oral disintegrating tablets, Preparations, Characterizations, Applications, Future prospects, Challenges

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INTRODUCTION

The oral mucosal cavity is a very attractive and feasible site for local and systemic drug delivery, since the mucosal membranes, upon which drug delivery systems are placed, are readily accessible by the patients [1]. The oral mucosal drug delivery exhibits many advantages over other routs of drug administration, which include increased accessibility by the patients as the dosage form can be accurately placed on the desired oral cavity membrane location and can be easily removed in order to terminate delivery if signs of adverse reactions are observed during treatment which increases patient acceptability [1-3]. Moreover, the oral mucosa is a well-vascularised tissue directly draining into the jugular vein [4], hence, allowing direct delivery into the systemic circulation and avoidance of first-pass hepatic degradation. Oral mucosal delivery also avoids the gastrointestinal tract (GIT) environment preventing possible drug hydrolysis in the GIT, in addition to avoiding enzymatic barriers; i.e. low gastric pH and protease enzymes. However, the oral mucosal drug delivery represents a challenging area because of the inherent functions of the oral cavity as swallowing, chewing, and speaking [5]. Furthermore, saliva is constantly secreted into the buccal cavity from both major and minor salivary glands, causing severe dilution of the drug or excessively fast erosion of dosage forms. Furthermore, salivation leads to swallowing which removes the drug from the targeted site of absorption. Moreover, the oral mucosa has a smaller absorptive surface area which is approximately 214 cm^2 [6] compared to the gastrointestinal mucosa (350.000 cm^2). Despite the aforementioned limitations, oral mucosal delivery remains a viable option for drug delivery [3].

There are two major routes of drug absorption via oral mucosa; the transcellular (where drugs permeate directly through the cells) and paracellular (where drugs permeate by passive diffusion through the spaces between the cells) routes. The drug absorption process by passive diffusion is best expressed by Fick's first law [7], which states that drug molecules diffuse from a region of higher to lower concentration until equilibrium is achieved.

$$P = \frac{D.Kp}{h} \quad \text{(Eq. 1)}$$

$$A = P.C.S.t = \frac{D.Kp}{h} x\, C.S.t \quad \text{(Eq. 2)}$$

where (P) is the permeability coefficient, (A) is the amount of drug absorbed via oral mucosa, (D) is the diffusion coefficient of the drug, (K_p) is the partition coefficient of the drug in between the oral mucosa and the specific medium used to deliver the drug, (h) is the thickness of the oral mucosa, (C) is the free drug concentration in the medium used to deliver the drug, (S) is the surface area of the oral mucosa, and (t) is the duration or time of drug interacting the oral mucosa.

There must be a balance between partition coefficient and drug's solubility for a suitable oral mucosal delivery. In general, the permeability coefficient of lipophilic drugs is higher than hydrophilic drugs, and vice versa for solubility (i.e. the aqueous solubility of lipophilic drugs are usually lower than the hydrophilic drugs). Thus, the amount of drug absorbed via oral mucosa may be low for high lipophilic drugs. As a result, permeation enhancers are subsequently used to enhance drug absorption and permeation [7].

Understanding the physicochemical and solid-state properties of a drug substance is essential to obtain a rational formulation process. The desirable physicochemical and solid-state properties for drug delivery through oral mucosa are shown in table 1 [3]. Two factors mainly affect the effectiveness of oral drug delivery systems; the retention time of the drug delivery system in contact with the oral mucosa and its permeation rate.

The need for development of oral disintegrating tablets

Conventional oral dosage forms like tablets and capsules pose a great swallowing problem for paediatrics and geriatrics. Approximately 35% of the general population suffers from dysphasia [8]. Oral disintegrating tablets (ODTs) are tablets which are placed in the mouth and then get dispersed in saliva without the need of water [9-11]. ODTs are considered the dosage form of choice for psychiatric patients, patients requiring fast intervention as well as patients suffering from nausea, vomiting and motion sickness [12], since the ODT system presents a patient friendly dosage form which ensures patient compliance and adherence to treatment.

ODTs combine the advantages of solid and liquid dosage forms. Like conventional tablets, ODTs present accurate drug dosing, ease of both manufacturing and packaging, good chemical stability, as well as ease of handling by patients [13]. They also exhibit the smooth mouth feel and avoidance of swallowing problems encountered with

liquid dosage forms. Additionally, ODTs provide rapid onset of action and improvement of the bioavailability of poorly absorbed drugs [14]. An ideal ODT exhibits the following characteristics [15]: (1) requires no water for oral administration, (2) dissolves, disperses or even disintegrates in the mouth in a matter of seconds, (3) has a pleasant mouth feel, (4) has good taste-masking potential, (5) has sufficient hardness and acceptable friability limit, (6) leaves minimal or no residue in mouth after oral administration, (7) exhibits low sensitivity to environmental conditions, (8) is manufactured using conventional manufacturing methods, and (9) utilizes cost effective production method. Table 2 shows the suitability of drug candidates for ODTs [15].

Table 1: The desirable physicochemical and solid-state properties of a drug delivery through oral mucosa [3]

Property	Normal range
Aqueous solubility	>1 mg/ml
Lipophilicity	10<oil: water partition coefficient<1000
Molecular weight	<500 Da
Melting point	<200 °C
pH of saturated aqueous solution	pH 5–9
Required dose deliverable	<10 mg/day
Irritation potential	No irritation to buccal tissue

Table 2: Choice of drug candidates for oral disintegrating tablets [15]

Suitable drug candidates for ODTs	Unsuitable drug candidates for ODTs
No bitter taste	Short half-life and frequent dosing
Good stability in water and saliva	Drug having very bitter taste
Taken in small doses	Required controlled or sustained release

The new generation of oral disintegrating tablets

The first generation ODTs suffered from many undesirable traits, mainly low density, poor mechanical strength, brittleness and difficulty in handling. This necessitated blister packaging, which is not patient friendly, and causes increase in production expenses [16]. Another disadvantage of first generation ODTs was the difficulty of masking the taste of bitter active ingredients loaded within these tablets [17], which led to the emergence of new generation ODTs that overcame the problems of taste masking, allowed for modified release of medications, solved solubility and bioavailability problems, resulted in ODT tablets with excellent physical and mechanical robustness, mouth feel sensation, disintegration and dissolution properties.

Challenges in formulating and developing oral disintegrating tablets

There are several challenges in formulating and developing ODTs, such as: (1) palatability and acceptability [18], (2) mechanical strength [19], (3) the amount of drug that can be incorporated into an ODT system [19], (4) size of tablet [20], (5) hygroscopicity [21], (6) aqueous solubility [22, 23], (7) physical and chemical stability.

Taste-masking of bitter and unpleasant taste of drugs is essential in order to achieve patient acceptability and compliance. Different techniques were developed and introduced for bitterness masking [24-32]. One of the most commonly used techniques for taste-masking of bitter and unpleasant APIs or drugs is the coacervation process [33]. Coacervation process has successfully taste-masked a wide variety of bitter drugs, including but not limited to, acetaminophen, cetirizine, ibuprofen, pseudoephedrine, ranitidine, sumatriptan, theophylline and zolpidem [33]. Coupling controlled release behaviour with specialized functional polymers and efficient coating processes creates ODT systems with modified and sustained release profiles.

Formulation processes for developing oral disintegrating tablets

Various pharmaceutical techniques are used in the manufacture of ODTs, including: (1) freeze-drying or lyophilization [34], (2) spray-drying [35, 36], (3) molding [37, 38], (4) phase transition process [39], (5) melt-granulation [40-42], (6) sublimation [43, 44] (7) mass extrusion [45], (8) cotton candy process [46, 47], (9) nanonization [48], and (10) direct compression [40, 49-53]. Admittedly, direct compression is the most commonly used technique in the manufacture of ODTs, owing to its easy-implementation and cost-effectiveness [40, 53]. These techniques are described below in detail.

Freeze-drying or lyophilization technique

Freeze-drying, also known as lyophilization or cryodesiccation, is a technique that yields amorphous highly porous structures with rapid disintegration and dissolution. Orodispersible tablets made by lyophilization are prepared by dissolving the drug substance in an aqueous mixture of carrier/polymer, the solution is then poured into the holes of blister packs which are subsequently frozen in order to continue the freeze-drying cycle, followed by blistering and finally packaging. Lyophilization technique is very suitable for heat-sensitive drugs (i.e. thermo-labile substances). Although ODTs prepared by freeze-drying process showed rapid disintegration and dissolution properties, but their industrial applications are limited since it is a high cost technique particularly in equipment and packing materials [34].

Spray-drying technique

Spray-drying is widely used in pharmaceutical industries nowadays. It provides a fast, efficient and economical way of removing solvents and producing free flowing, highly porous particles. In this process, gelatin is commonly used as a supporting agent, mannitol as a bulking agent, and sodium starch glycolate, crosscarmellose sodium and/or crospovidone as superdisintegrants. Orodispersible tablets made by spray-drying have been reported to disintegrate and dissolve in less than 20 seconds [35, 36].

Interestingly, Allen and Wang [54] fabricated a particulate support matrix for preparing ODTs by spray-drying, consisting of supporting agents of two polypeptide components from gelatin, a bulking agent (mannitol) and a volatilizing agent (ethyl alcohol). In order to maintain the net charges of both polypeptide components, a buffer system of an acidifying agent (citric acid) and an alkalinizing agent (sodium bicarbonate) is prepared and added to the tablet mixture. The mixture of the aforementioned components is then spray-dried to obtain porous granules. By incorporating a volatilizing agent as ethyl alcohol, the surface tension of the droplets is further reduced, and more porous structures are created. An effervescent agent could be optionally added to further enhance the dissolution.

Molding method

Molding is a solid dispersion method, involving the dispersion of APIs in an inert water-soluble carrier or matrix at solid-state form, prepared by solvent or heat method. Solvent method involves moistening the powder mixture with alcoholic or hydroalcoholic solvent, then molding into tablets under reduced pressure to form wet paste. This process is known as compression molding. The solvent is

then removed from the wet paste by air-drying. The resulting tablets possess fine powders and highly porous structures. Solid dispersions are prepared directly from a molten matrix in which the drug is dispersed in or by vaporizing the solvent at ambient pressure (no vacuum lyophilization). The drug molecule can be in the form of discrete-particles or microparticles, completely or partially dispersed in the molten matrix. Because of their composition, molded tablets offer rapid disintegration, dissolution and improved taste, but they suffer the disadvantage of poor mechanical strength. Compared to freeze-drying, molded tablets are simpler in production and easier for industrial scale-up, although disintegration times may not be comparable to those of lyophilized forms [37, 38].

Phase transition process

This process involves a combination of low-and high melting point sugar alcohols. Optimizing the phase transition in the manufacturing process is important for formulating tablets without the need of any equipment. Kuno *et al.* [39] prepared ODTs by phase transition process using compressible powder mixture of erythritol (a sugar alcohol with melting point: 122 °C) and xylitol (a sugar alcohol with melting point: 93-95 °C), followed by heating at 93 °C for a period of 15 min. As a result of heating, the median pore size of tablets increased, as well as tablet hardness.

Melt-granulation technique

The melt-granulation technique is based on incorporating a hydrophilic melting binder in the formulation, which increases the physical resistance of tablets and helps their disintegration and dissolution. In comparison with other granulation techniques as dry- and wet-granulation, melt-granulation is advantageous as no aqueous, alcoholic or even organic solvents are required. Melt-granulation is less time-consuming, cost-effective and easy to perform [40-42].

Interestingly, Abdelbary *et al.* [41] described a new approach for the preparation of ODTs of high mechanical strength involving the use of a hydrophilic waxy binder, PEG-6-stearate, commercially known as Superpolystate® by melt-granulation. Moreover, Agiba *et al.* [40] developed high-dose nutraceutical ODTs of glucosamine sulphate and chondroitin sulphate using a blend of hydrophilic melting binders as high molecular weight polyethylene glycols (PEG-4000 and PEG-6000). Although ODTs weighed around 1.30 gm with 60% drug load, they showed quick disintegration and dissolution properties, as well as a high mechanical strength.

Sublimation method

In this method, a sublimating agent like camphor is removed from the compressed tablets by sublimation. Highly porous structures are created as a result of removing camphor from the compressed tablets. The resulted tablets, characterized by high porous structures, could achieve fast disintegration in saliva. Examples of other volatile materials are adipic acid, ammonium carbonate, ammonium bicarbonate, arachidic acid, capric acid, camphor, menthol, myristic acid, and palmitic acid, thymol and urea. The sublimation temperature range is from 40 to 60 °C [43, 44].

Interestingly, Heinemann [55] prepared a highly porous tablet structure by using a mixture of volatile adjuvant, which was removed at the end by heating. On the other hand, Roser and Blair [56] removed the volatile materials by using vacuum, which reduced the dissolution-time from 15 min for the tablets containing trehalose (a disaccharide composed of 2 glucose units) alone to less than 1 minute. Moreover, Lo [57] developed an efficient method for the preparation of fast-dissolving tablets with highly porous structures.

Mass extrusion technique

In mass extrusion, the active and inactive ingredients are first softened using PEGs mixture and methanol as organic solvent, followed by extrusion and division into tablets using heated blades [45].

Cotton candy process

This technique involves the formation of a matrix of poly-or monosaccharides using flash melting and spinning to form floss like crystalline structure, which is then mixed with active/inactive ingredients and compressed into ODTs. This process can easily accommodate large doses of APIs with an improved mechanical strength. However, high-process temperature limits its use [46, 47].

Nanonization

Nanomelt is a recently developed nano-based drug delivery system, involving a reduction of drug particle size to be in nano-scale range by using a proprietary wet-milling technique. APIs usually present in the form of nanoparticles or nanocrystals are stabilized against possible agglomeration by surface adsorption onto preselected stabilizing agents incorporated into ODT systems. This technique is suitable for poorly water-soluble drugs, and the produced tablets exhibit rapid disintegration and dissolution [48].

Direct compression

Direct compression is the simplest, easiest and most widely used technique in ODT manufacturing, owing to its easy-implementation and cost-effectiveness. It involves using a blend of ingredients, which can provide rapid disintegration, as well as high physical integrity and stability. Sugar-based excipients as mannitol, sorbitol and lactose are commonly used as bulking agents, because of their high aqueous solubility and good taste-masking properties [40, 49-53].

In general, any tablet dosage form contains one or more of diluents/fillers, binders/adhesives, disintegrants, superdisintegrants, glidant/flowing agent and lubricant. Disintegrants and superdisintegrants are mainly incorporated into tablet formulations to promote their disintegration and dissolution. As the ability of the tablet to rapidly disintegrate is a prerequisite in ODT systems, ODTs usually contain high concentrations of disintegrants and superdisinetgrants. Examples of disintegrants and superdisintegrants are listed below.

Disintegrants and superdisintegrants

Various disintegrants and superdisintegrants are available in the pharmaceutical market and are readily used for the manufacture of ODTs.

Starch and modified starch

Starch is a versatile excipient with many applications in oral solid dosage forms as a diluent, binder, and disintegrant. Starch acts as a disintegrant at a concentration of 3-25% (w/w), with an optimum concentration of 15% (w/w) [58-61]. However, before using starch, a prior granulation step is required to avoid problems associated with low flowability and compressibility that can cause powder segregation. Examples of the most commonly used starches as disintegrants are maize, potato, rice, tapioca and wheat starch.

Directly compressible and modified starches have been introduced to overcome the problems associated with the conventional starches as pregelatinized starch (disintegrant) and sodium starch glycolate (superdisintegrant). Pregelatinized starch is a modified starch that has been mechanically and chemically modified through breaking all or part of the starch granules. Partially-pregelatinized starch, commercially known as Starch 1500® is a modified starch, mainly used in oral solid dosage forms as a diluent, binder [62, 63] and disintegrant [64]. Comparing conventional starches with partially-pregelatinized starch, partially-pregelatinized starch has better flowability and compressibility; therefore, it may be used as a binder and disintegrant in direct compression. It also has self-lubricating property. However, when it is used with other excipients, the addition of a lubricant as magnesium stearate (0.25%) (w/w) is necessary taking into consideration that concentrations greater than 0.25% (w/w) may have adverse effects on tablet disintegration and dissolution.

Sodium starch glycolate, commercially known as Explotab® or Primojel®, is also used in oral solid dosage forms as a superdisintegrant. It is commonly used at a concentration of 2 to 8% (w/w), with an optimum concentration of 4% (w/w) [58]. Disintegration occurs by rapid uptake of water followed by rapid swelling [65-67]. Increasing the tablet compression pressure did not seem to influence the disintegration time [68, 69].

Cellulose and modified cellulose

Microcrystalline cellulose, commercially known as Avicel PH®, is widely used in oral solid dosage forms as a binder or diluent in both direct-compression, dry-and wet-granulation methods, with some lubricant and disintegrant properties [58].

Croscarmellose sodium or cross-linked carboxymethylcellulose sodium, commercially known as Ac-Di-Sol®, Explocel® or Primellose® is widely used in oral solid dosage forms as a tablet superdisintegrant in both direct-compression, dry-and wet-granulations [58]. In wet-granulation, it can be added intra-and extragranularly, so that the wicking and swelling ability of the superdisintegrant is optimized [70, 71].

Low-substituted hydroxypropyl cellulose (L-HPC) is primarily used as a disintegrant in both dry-and wet-granulations, also used in the preparation of ODTs prepared by direct compression [58]. There are different grades of L-HPC that have different substitution levels and particle sizes. For example, LH-11 has the longest fibrous particles, and is typically used as a disintegrant for tablets prepared by direct compression method, while LH-21 is less fibrous and used in case of tablets prepared by wet-granulation method. LH-31 is a small particle size grade and mainly used in extrusion process to produce granules. LH-B1 is non-fibrous, high-density grade, typically produced for fluid-bed granulation. Low substitution grades LH-22 and LH-32 are usually used for enhancing the disintegration, and their concentrations are mainly depending on the characteristics of APIs [72]. The typical concentration of L-HPC in a solid formulation ranges from 5–50% (w/w) [58].

Crospovidone [58]

Crospovidone or cross-linked povidone (commercially known Kollidon CL-M®; Polyplasdone XL®) is a tablet superdisintegrant used at a concentration of 2–5% (w/w) in tablets prepared by direct compression, dry-or wet-granulations [73]. Crospovidone can also be used as a solubility enhancer for increasing the solubility and dissolution of poorly absorbed drugs by coevaporation technique.

Resin and its derivatives

Ion exchange resins have been introduced as tablet disintegrants. The most commonly used ion exchange resin is polacrilin potassium. Polacrilin potassium is a highly hydrophilic cation exchange resin having good swelling properties [74] as well as wicking and strain recovery characteristics [75, 76]. It is usually used in a concentration of 2-10% (w/w) in tablet formulations, although 2% (w/w) was reported to be sufficient.

Mechanisms of disintegrants

Swelling

The most common mechanism of tablet disintegration is swelling. Swelling is basically a dimensional-expansion process in which particles enlarge in every direction to push apart tablet components, thereby initiating the process of breaking-up of the tablet matrix [77, 78]. The swelling property of a disintegrant depends on many factors including chemical structure and degree of crosslinking [79]. Porosity of the tablet compact plays also a significant role in determining the performance rate of swelling disintegrants. A tablet matrix with low porosity and void spaces would reduce liquid penetration and thereby delay or prolong the disintegration time, and vice versa [77]. Therefore, tablets should be prepared at an optimal porosity to provide adequate mechanical integrity and good disintegrability [80]. There is a positive correlation between the disintegration force development rate and the disintegration time, while there is no correlation between the extent of swelling of a disintegrant and the maximum disintegration force. Thus, the disintegration force development rate is essential for rapid tablet matrix disintegration [80]

Wicking (capillary action)

Wicking is a process of liquid penetration by capillary action into the microstructured spaces in the tablet compact to displace the entrapped air (i.e. through porous structures within the tablet compact) [77, 81, 82]. As other water-soluble ingredients rather than disintegrants can contribute to improving disintegration by increasing tablet porosity as high-molecular weight polyethylene glycols, so wicking cannot be classified as a primary disintegration mechanism. However, water penetration into the tablet compact is essential for disintegrant activation [79]. Thus, the penetration rate will mainly depend on the balance between capillary and opposite viscous forces [83].

Strain recovery (process of deformation)

In tabletting process, tablet components are subjected to a high compaction pressure. During compaction, particles deform and interparticulate bonds are disturbed. Strain recovery is a reversible viscoelastic deformation process [84]. It elucidates the process of mechanical activation of disintegrant polymer chains when getting into contact with the aqueous media, causing a partial recovery into their original shapes [77]. Moreover, disintegration media contributes to the plasticization of disintegrant polymer chains and assists their accommodation into the most energetically stable positions. The resulting pressure could help in tablet disintegration [79]. Strain recovery process is unidirectional and exists in the opposite direction of exerted compaction force [78]. The recovery and relaxation of the stressed particles promotes rapid movement and volume expansion, causing the breakage of bonding bonds.

Interruption of particle-particle bonds

Interruption of particle-particle bonds is considered one of the most important mechanisms for tablet disintegration. Some previous studies suggested three different possible bonding mechanisms involved in tableting which are solid bridges, mechanical interlocking, and intermolecular forces [85]. Among those three bonding mechanisms, intermolecular forces are considered the most prevalent bonding mechanism in tablet disintegration [85, 86]. Various techniques have been introduced to identify the intermolecular bonds involved in the interruption of the tablet matrix. Luangtana-Anan *et al.* [87] showed a correlation between the intermolecular forces present in tablets and the disintegration time.

Heat of interaction

Two types of interactions result from the interaction of materials with aqueous media; endothermic (heat absorption) and exothermic (heat generation) [77]. Exothermic interactions are obtained from interacting disintegrants with the aqueous media, either water or buffer compartment [88], hence the heat generated causes localized stress within tablets which is usually associated with an expansion of air retained in the tablet compact, and subsequently increased disintegration time. Lowenthal [87] illustrated the importance of heat generation as an important mechanism in tablet disintegration. However, Luangtana-Anan *et al.* [88] explained the changes in enthalpy for different disintegrants and concluded that the amount of heat generated by wetting is rather small and insufficient to cause effective expansion of the entrapped air in the tablet compact. Furthermore, Caramella *et al.* [89] studied the relation between the temperature of the disintegration media and disintegration time and concluded that increasing the temperature of the aqueous media did not necessarily improve the disintegration process. Therefore, it is necessary to further study the mechanism of heat of interactions to identify its impact on tablet disintegration.

Coprocessed and multifunctional excipients

Developing a robust tablet formulation that can be easily scaled up to a drug product without any problematic issues is a big challenge. Today, there are many challenges in product manufacturing and scaling up; therefore, the need of new pharmaceutical techniques and novel excipients are necessary for manufacturing a high-quality product. Coprocessed and multifunctional excipients are designed to improve the formulation experience and performance. They are high-functionality excipients containing one or more diluents, binders, disintegrants, superdisintegrants and/or lubricants that could provide superior binding, high mechanical strength, quick disintegration and dissolution. The basic principle of coprocessing is based on particle engineering technologies. Any powdered substance is characterized by three different levels of solid-state;

molecular level (individual molecule level), particle level (individual solid particle level) and bulk level (as assembly of particulate species) [90]. These different levels are closely connected to each other in which changing in one level affects the other levels. The molecular level involves the arrangement of individual molecules in the crystal lattice and represented by polymorphism, pseudo-polymorphism, and the amorphous state. Particle level involves individual solid particle properties like arrangement, shape, size, surface area, and porosity. The bulk level involves large numbers of particles together and their properties like flowability and compressibility. All these levels are essential for evaluating the performance of excipients.

Methods of coprocessing include spray-drying, granulation, extrusion/spheronization, melt-extrusion, solvent-evaporation and crystallization. Examples of commonly used coprocessed and multifunctional excipients are listed in table 3. Coprocessed and multifunctional excipients represent the ultimate solution in developing orodispersible tablets with very few excipients and high functionalities and physicomechanical properties.

Table 3: The most common examples of high-functionality excipients

Excipient	Composition	Manufacturer
Prosolv® SMCC	Silicifed Microcrystalline Cellulose	JRS Pharma
Prosolv® EASYtab SP	Microcrystalline Cellulose Colloidal Silicon Dioxide Sodium Starch Glycolate Sodium Stearyl Fumarate	JRS Pharma
Prosolv® EASYtab Nutra CM	Microcrystalline Cellulose Silicon Dioxide Croscarmellose Sodium Magnesium Stearate	JRS Pharma
Prosolv® EASYtab Nutra GM	Microcrystalline Cellulose Silicon Dioxide Sodium Starch Glycolate Magnesium Stearate	JRS Pharma
Prosolv® EASYtab Nutra CP	Microcrystalline Cellulose Silicon Dioxide Croscarmellose Sodium Sodium Stearyl Fumarate	JRS Pharma
Prosolv® ODT G2	Microcrystalline Cellulose Silicon Dioxide Mannitol Fructose Crospovidone	JRS Pharma
Mannogem® EZ	Spray-dried Mannitol	SPI Pharma
Mannogem® XL	Spray-dried Mannitol	SPI Pharma
Compressol® SM	Mannitol, Sorbitol	SPI Pharma
Advantose® 100	Spray-dried Maltose	SPI Pharma
Advantose® FS95	Spray-dried Fructose	SPI Pharma
Lubripharm® SSF	Sodium Stearyl Fumarate	SPI Pharma
Pharmaburst® C1	Mannitol Sorbitol Crosspovidone Colloidal silicone dioxide	SPI Pharma
Tabulose®	Colloidal Microcrystalline Cellulose	Roquette Pharma
Pearlitol®	Spray-dried Mannitol	Roquette Pharma
Pearlitol® Flash	Mannitol, Starch	Roquette Pharma
Starlac®	Starch, Lactose	Roquette Pharma
Xylisorb®	Xylitol	Roquette Pharma
Ludipress®	Lactose Povidone Crospovidone	BASF Pharma
Ludiflash®	D-mannitol Crospovidone Polyvinyl acetate Povidone	BASF Pharma
Soluplus®	Polyethylene glycol polyvinyl acetate Polyvinylcaprolactame	BASF Pharma
Sepitrap™ 80	Magnesium Aluminometasilicate Polysorbate 80	SEPPIC
Sepitrab™ 4000	Magnesium Aluminometasilicate Polyoxyl 40 Hydrogenated Castor Oil	SEPPIC
HiCel™ HFE	Microcrystalline Cellulose, Mannitol	Sigachi Industries Pvt. Ltd
HiCel™ CE15	Microcrystalline Cellulose, Guar gum	Sigachi Industries Pvt. Ltd
HiCel™ SMCC	Microcrystalline Cellulose Colloidal Silicon dioxide	Sigachi Industries Pvt. Ltd
HiCellac™ 80 and 100	Microcrystalline Cellulose Lactose Monohydrate	Sigachi Industries Pvt. Ltd
HiCel™ DG	Microcrystalline Cellulose Dicalcium phosphate	Sigachi Industries Pvt. Ltd

Patented technologies

Several patented technologies are introduced for the manufacture of ODTs [14, 25, 53], including: (1) Zydis® technology [22], (2) Lyoc® technology [92], (3) WowTab® technology [93, 94], (4) FlashTab® technology and Multiflash® [49], (5) Durasolv® and Orasolv® technologies [95, 96], (6) Frosta® technology [14], (7) AdvaTab® technology [97], (8) FlashDose® technology [98], (9) OraQuick® technology [14], (10) Nanocrystal® and EFVDAS® and FastMelt® technologies [14, 99], (11) QuickDis® technology, and (12) Pharmabrust™ technology [14]. Table 4 summarizes the patented techniques used for the manufacture of ODTs and table 5 shows examples of globally marketed oral disintegrating tablets products.

Table 4: Patented technologies used to produce ODTs

Technology	Company	Description	Novelty aspect	Advantages	Disadvantages
Zydis® [22]	R. P. Scherer Corporation	- Lyophilizing the drug in a water-soluble matrix usually consisting of mannitol (a crystalline sugar) and gelatin (a water-soluble polymer). - Other excipients can be used depending on the properties of the drug.	First marketed new tablet technology	- Self-preservative - Rapid disintegration and dissolution - Improved bioavailability	- Expensive manufacturing process - Require special packaging materials - Unstable at higher temperature and humidity - Incompatible with high drug doses
Lyoc® [92]	Cephalon Corporation	- A freeze drying process but differ from Zydis where the drug product is frozen on freeze dryer shelves. - The homogeneous liquid or suspension is placed into blister cavities and subjected to freeze drying. - The homogenous liquid or suspension contains one or more of water-soluble fillers, thickening agents, surfactants and the drug substance.	A modified form of Zydis	- Self-preservative	- Expensive manufacturing process - Require high amounts of fillers to prevent possible sedimentation - The high amounts of fillers can reduce tablet porosity and prolong disintegration - Incompatible with high drug doses
WowTab® [93, 94]	Yamanouchi Pharma Technologies	- Wow means without water - This process involves granulating low-moldable sugars (e. g. mannitol, lactose, sucrose and glucose) that show rapid dissolution with high-moldable sugars (e. g. sorbitol, maltitol and maltose) with the drug substance.	Combination of low-and high-moldable sugars	- Rapid disintegration and dissolution	- No significant change in drug bioavailability
FlashTab® [49]	Prographarm	- This process involves coating a drug with a polymer as Eudragit to provide a rapid drug release in the stomach and formulating this microencapsulated drug with an effervescent base to produce a flash dispersible tablet. - This technology comprises the granulation of a drug and excipients by either dry-or wet-granulation then compressed into tablets.	A compressed tablet dosage form containing a drug as microcrystals or microgranules	- Conventional tabletting process - Easy to perform - Tablets dissolve within 1 minute.	---
DuraSolv® [95, 96]	Cima Labs, Inc.	- Conventional tabletting process (i.e. a direct compression method using higher compaction pressures during tabletting)	Second generation oral disintegrating tablets	- Higher mechanical - strength than Orasolv - Good tablet rigidity - Easy to perform - Low cost - Packaged in blisters, foil or bottles	- Incompatible with high drug doses because the formulations are subjected to high compaction pressures. Unlike OraSolv, the structural integrity of any taste-masking may be compromised with high drug doses. - No significant change in drug bioavailability
OraSolv® [95, 96]		- Conventional tabletting process (i.e. direct compression method using an effervescent base and taste masked drug.) - Effervescence agents cause the tablet to disintegrate rapidly in less than 1 min once contact with water or saliva, leaving coated drug powder. - Effervescent agents include carbonates such as sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate, and acids like citric, tartaric, fumaric, adipic and succinic.	Unique taste-masking process	- Taste-masking is two-fold - Rapid dissolution	- Low mechanical strength - Soft and fragile - Tablets; therefore, a special packing material system is required - No significant change in drug bioavailability
Frosta®[14]	Akina	- This technique comprises formulating plastic granules and compressing them at low compaction pressure to produce tablets with high porosity	Formation of highly porous, plastic granules	- High mechanical strength - Rapid	---

		- Plastic granules may contain porous and plastic materials, penetration enhancers and binders - The manufacturing process includes mixing the porous plastic materials with penetration enhancers, followed by granulating with the aid of binders		disintegration	
AdvaTab® [97]	Eurand	- A microencapsulation process for coating the drug particles with gastro soluble polymer to mask the bitter taste along and prevent the drug dissolution in mouth cavity. - It can be combined with Eurand's complimentary particle technologies as Microcaps® (taste-masking technology) and Diffucaps® (controlled release technology).	A microencapsulation process	- Rapid disintegration in mouth cavity, typically within 30 seconds	---
FlashDose® [98]	Fuisz Technologies, Ltd.	- This technique comprises a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy process. - This crystalline sugar-based matrix (floss) can incorporate the active drug and be compressed into tablets. - Instead of a floss-like crystalline sugar, small spheres of saccharides can be used as a carrier for the drug.	A unique spinning mechanism and an alternative method of taste masking	- Good taste-masking - High surface area for drug dissolution	- Require special packing materials as tablets are highly friable. - Require high temperature to melt the matrix; therefore, it cannot be used with heat and moisture sensitive drugs - It is suitable for doses up to 600 mg
OraQuick®[14]	KV Pharmaceutical Co., Inc.	- Taste masking process is done by incorporating drug into matrix microsphere. - In this technique, tablets are prepared by dissolving the sugar (e. g. mannitol, sorbitol or sucrose) and protein (gelatin or albumin) in a aqueous, alcoholic or hydroalcoholic solvent. The matrix is then spray dried, yielding highly porous granules. - The formed granules are mixed with the drug and other excipients then compressed at low compression force.	Unique taste-masking process (microencapsulated drug particles)	- appropriate for heat-sensitive drugs	---
NanoCrystal ® [14]	Elan Corporation	- The main concept of this technology is decreasing drug particle size and increasing surface area for drug absorption. - Nanocrystal particles are small particles of the drug substance, typically less than 1000 nm in diameter, which are - Manufactured by milling the drug substance using a suitable wet-milling method. - Nanocrystal colloidal dispersions of drug substances have been combined with water-soluble ingredients as mannitol and sorbitol, filled into blisters, and freeze-dried. The resultant blisters are remarkably robust yet dissolve in very small quantities of water in matter of seconds. This approach is suitable with highly potent or hazardous materials.	Wet-milling technique	- Easy to perform - Cost-effective manufacturing process - Use conventional packaging materials - suitable for doses up to 200 mg of API per unit	---
EFVDAS®[14]		- Known as Effervescent Drug Absorption System (EFVDAS) - Examples of EFVDAS products are acetaminophen, cimetidine, ibuprofen and naproxen.	Effervescent Drug Absorption System	- Used for OTC and prescription drugs - Also, for hot drink sachet products	
Fast Melt® [14]		- Combine the advantages of liquid formulations with those of solid dosage forms - Characterized by highly porous, micro-fine matrix tablet - Once placed onto the oral cavity, the matrix tablet rapidly absorbs water and disintegrates, and the drug is released into the oral cavity.	Highly porous, micro-fine matrix tablet	---	---
Pharmabrust™ [14]	SPI Pharm	- Tablets are manufactured by direct compression of drug substances, pharmabrust, flavours, colorants and a lubricant. - Tablets dissolve within 30-40 seconds. - Tablets have sufficient strength and can be packed in blister packs and bottles	Direct compression using Pharmabrust as a novel multifunctional excipient	---	---

Table 5: A list of marketed orally disintegrating tablet products

Commercial product	Active ingredient	Indication	Manufacturer	Technology
Abilify®	Aripiprazole	Anti-psychotic	Otsuka America Pharmaceutical, Inc.	Zydis®
Children's Dimetapp® ND	Loratadine	Anti-histaminic	Wyeth Consumer Healthcare	
Claritin® RediTabs®	Loratadine	Anti-histaminic	Bayern Schering Corporation	
Feldene Melt™	Piroxicam	Anti-inflammatory	Pfizer	
Grastek® Sublingual Tablets	Pollen allergen extract from Timothy grass *(Phleum pratense)*	Timothy grass or related grass-pollen allergies	Catalent Pharma Solutions for ALK-Abelló A/S	
Grazax 75,000 SQ-T Oral Lyophilisate	Pollen allergen extract from Timothy grass *(Phleum pratense)*	Timothy grass or related grass-pollen allergies	ALK-Abelló A/S	
Imodium® Instant Melts/Imodium® Lingual/ Imodium® Quick Dissolve	Loperamide HCl	Anti-diarrheal	Johnson and Johnson	
Klonopin® Wafers	Clonazepam	Anti-convulsive and Anxiolytic	Roche	
Maxalt-MLT®	Rizatritpan benzoate	Anti-migraine	Merck	
Motilium®	Domperidone	Anti-emetic	Johnson and Johnson	
Ondansetron-RL Zydis® Wafers	Ondansetron HCl	Anti-emetic	GlaxoSmithKline	
Ondaz Zydis® Wafers	Ondansetron HCl	Anti-emetic	Sandoz	
Pepcid®	Famotidine	Anti-ulcer	Merck	
Ragwitek® Sublingual Tablets	Pollen allergen extract from Short Ragweed *(Ambrosia artemisiifolia)*	Ragweed pollen allergies	ALK-Abelló A/S	
Risperdal® M-Tab™	Risperidone	Anti-psychotic	Johnson and Johnson	
Zelapar™	Selegiline HCl	Parkinson's disease	Elan/Amarin Corporation	
Zofran® ODT	Ondansetron HCl	Anti-emetic	GlaxoSmithKline	
Zubrin®	Tepoxalin	Anti-inflammatory	Schering Corporation	
Zyprexa®	Olanzapine	Anti-psychotic	Eli Lilly	
Loperamide® Lyoc®	Loperamide chlorhydrate	Anti-diarrheal	Teva	Lyco®
Paralyoc®	Paracetamol	Analgesic, anti-pyretic	Teva	
Proxalyoc®	Piroxicam	Anti-inflammatory	Teva	
Seglor® Lyoc®	Dihydroergotamine mesylate	Migraine	UCB Pharma	
Sermion® Lyco®	Nicergoline	Potent vasodilator	Pfizer	
Spasponlyoc®	Phloroglucinol dihydrate	Anti-spasmodic	Teva	
Vogalene® Lyoc®	Metopimazine	Anti-emetic	Teva	
Reminly® OD Tablets	Galantamine	Alzheimer's disease	Janssen/Takeda	Quicksolv®
Risperdal® M-Tab	Risperidone	Anti-psychotic	Janssen Pharma	
Allegra®	Fexofenadine	Anti-histaminic	Aventis Pharmaceuticals	OraSolv®
Clarinex RediTab®	Desloratadine	Anti-histaminic	Schering-Plough	
Fluxid™	Famotidine	Anti-ulcer	Azur Pharma	
Orapred® ODT	Prednisolone sodium phosphate	Asthma	Concordia Pharmaceuticals	
Remeron® SolTab	Mirtazapine	Anti-depressant	Organon Inc.	
Tempra® Quicklets/ Tempra® FirsTabs	Acetaminophen	Analgesic	Bristol-Myers Squibb	
Triaminic® Cold Cough Softchews	Chlorpheniramine maleate, Dextromethorphan HBr, Pseudoephedrine HCl	Cold cough	Novartis Consumer Health	
Zomig® Rapimelt	Zolmitriptan	Migraine	AstraZeneca	
Alavert®	Loratadine	Anti-histaminic	Wyeth Consumer Healthcare	DuraSolv®
Dimetapp® ND	Loratadine	Anti-histaminic	Wyeth Consumer Healthcare	
FazaClo® LD (low dose) and FazaClo® HD (high dose)	Clozapine	Schizophrenia	Alamo Pharmaceuticals	
Kemstro™	Baclofen	Anti-spastic analgesic	Schwarz Pharma	
Niravam™	Alprazolam	Anxiety	Schwarz Pharma	
NuLev®	Hyoscyamine sulfate	Antispasmodic	Schwarz Pharma	
Benadryl® Fastmelt	Diphenhydramine Citrate	Anti-histaminic	Pfizer	WowTab®
Gaster® D	Famotidine	Anti-ulcer	Yamanouchi	
Harnal® D	Tamsulosin HCl	Benign prostatic hyperplasia	Astellas Pharma Inc.	
Irribow® OD	Ramosetron HCl	Irritable bowel syndrome	Astellas Pharma Inc.	
Nasea® OD	Ramosetoron HCl	Anti-emetic	Yamanouchi	
Vesicare® OD	Solifenacin succinate	Overactive bladder	Astellas Pharma Inc.	
Calpol® Six Plus Fastmelts	Paracetamol	Analgesic, anti-pyretic	McNeil Products Ltd	Flashtab®
Dolflash®	Acetaminophen	Analgesic, anti-pyretic	Sanofi-Aventis	
Excedrin Quicktabs	Acetaminophen, Caffeine	Analgesic, anti-pyretic	Bristol-Myers Squibb	
Nurofen® Flashtab	Ibuprofen	Analgesic, anti-pyretic	Boots Healthcare	
Ondansetron Flashtab®	Ondansetron	Anti-emetic	Teva	
OxynormOro®	Oxycodone chlorhydrate	Cancer related pain	Mundipharma	
Paracetamol Flashtab®	Paracetamol	Analgesic, anti-pyretic	Ranbaxy	

Prevacid® SoluTab (Delayed release ODT)	Lansoprazole	Gastroesophageal reflux disease	Takeda	
Solupred Orodispersible Tablet	Prednisolone	Asthma	Sanofi-Aventis	
Tachipirina Flashtab®	Paracetamol	Analgesic, anti-pyretic	Angelini	
Tramalene® Flashtab®	Tramadol HCl	Potent analgesic	Ethypharm	
Trambax® MD	Tramadol HCl	Potent analgesic	Ranbaxy	
Zamadol® Melt	Tramadol HCl	Potent analgesic	MEDA Pharma	
Citalopram® ODT	Citalopram hydrobromide	Anti-depressant	Biovail	FlashDose®
Fluoxetine® ODT	Fluoxetine	Anti-depressant	Biovail	
Ralivia FlashDose®	Tramadol HCl	Potent analgesic	Biovail	
Tovalt™ ODT	Zolpidem tartrate	Insomnia	Biovail	
Lamictal® ODT	Lamotrigine	Bipolar disorders	GlaxoSmithKline	AdvaTab®
Unisom® SleepMelt	Diphenhydramine HCl	Anti-histaminic	Chattem, Inc.	
Caffe Magia®	Vitamin B and Caffeine	Stimulant	Akina	Frosta®
Ceto-Q®	Mannitol, Calcium carbonate, Xylitol, Yucca extract	Toothpaste tablet	Akina	
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	Anti-ulcer	Perrigo	OraQuick®

Characterizations of oral disintegrating tablets

Evaluation of powders or granules (pre-compression parameters evaluation)

Bulk and tapped density

Ten gm of a dry powder or granular sample is placed in a 100 ml graduated cylinder. The volume occupied by the powder or granules is measured and the bulk density is calculated using equation 3. Tapped density is determined by a tapped density tester. The volume occupied by the powder or granules after tapping is used to calculate the tapped density using equation 4 [40, 100].

$$Bulk\ density = \frac{weight\ of\ the\ powder}{bulk\ volume\ of\ the\ powder} \quad \textbf{(Eq.3)}$$

$$Tapped\ density - \frac{Weight\ of\ the\ bulk\ sample}{bulk\ volume\ of\ the\ bulk\ sample\ on\ tapping} \quad \textbf{(Eq. 4)}$$

Hausner ratio and carr's compressibility index

Hausner ratio and carr's compressibility index are calculated based on bulk and tapped density results using equations 5 and 6, respectively.

$$Hausner\ ratio = \frac{tapped\ density}{buk\ density} \quad \textbf{(Eq. 5)}$$

$$Carr's\ compressibility\ index\ (\%) = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100 \quad \textbf{(Eq. 6)}$$

Flowability is determined based on the results of hausner ratio and carr's compressibility index as shown in table 6.

Table 6: Specification for hausner ratio and carr's compressibility index

Hausner ratio	Carr's compressibility index (%)	Flowability
1.00-1.11	0-10	Excellent
1.12-1.18	11-15	Good
1.19-1.25	16-20	Fair
1.26-1.34	21-25	Passable
1.35-1.45	26-31	Poor
1.46-1.59	32-37	Very poor
>1.60	>38	Very, very poor

Table 7: Specification of angle of repose (Θ)

Angle of repose (degree)	Flowability
25–30	Excellent
31-35	Good
36-40	Fair
40-45	Passable
46-55	Poor
56-65	Very poor
>66	Excellent

Angle of repose (Θ)

Angle of repose (Θ) is determined by the fixed funnel and free-standing cone method. The method employed a funnel that is fixed at a certain height (h) on a graph paper placed on a flat horizontal surface. The powder or granules sample is carefully passed through the funnel till the apex at the conical pile touched the tip of the funnel. Thus, with (r) being the radius of the base of the conical pile as shown in equation 7 [101].

$$Tan\ \Theta = \frac{h}{r} \quad \textbf{(Eq. 7)}$$

Where, (h) and (r) are the height and radius of the base of the conical pile

Flowability is determined based on the results of angle of repose as shown in table 7.

Porosity (ε)

Porosity (ε) is calculated from apparent density (ρapp) and true density (ρtrue) as in equation 8 [40].

$$\varepsilon = \left[1 - \left(\frac{\rho app}{\rho true}\right)\right] x\ 100 \quad \textbf{(Eq. 8)}$$

The true density (ρtrue), which is the density of the particles that make up a powder or particulate solid, is measured by gas displacement using a pycnometer [102].

Evaluation of tablets (post-compression parameters evaluation)

(1) Weight uniformity or % of weight variation

Twenty tablets were randomly selected from the production batch and weighted individually to check their weight uniformity. The percentage of weight variation is calculated using equation 9 [40, 103].

$$\%\ of\ weight\ variation = \frac{(individual\ weight - average\ weight)}{individual\ weight} \times 100 \quad \text{(Eq. 9)}$$

The percentage of tablet weight deviation is shown in table 8.

Table 8: Uniformity of weight of tablets

Average tablet weight (mg)	% Deviation
Less than 80 mg	±10
More than 80 mg but less than 250 mg	±7.5
250 mg and more	±5

Tablet hardness

Tablet hardness is measured by the hardness tester in newton (N) or kilopond (kP) per unit tablet. Each tablet is placed individually in the hardness tester and the crushing load is measured. In general, the hardness of ODTs is set to be lower than conventional tablets because of increasing hardness results in decreasing tablet disintegration rate [40, 103].

Tablet friability

Twenty tablets are accurately weighted and placed in the friabilator chamber, then allowed to rotate at 25 rpm for 4 min. Tablets are collected and reweighted. The percentage of weight loss in tablet is calculated using equation 10 and taken as a measure of friability. Tablets pass the friability test if not more than 1% of the tablets weight was lost [40, 103].

$$\%\ \text{Friability} = \frac{(W_0 - W_f)}{W_0} \times 100 \quad \text{(Eq. 10)}$$

W_0: initial weight of tablets

W_f: final weight of tablets

Tablet thickness and diameter

Tablet thickness and diameter are measured by using a micrometer caliper in millimeter (mm) per unit tablet [40].

Uniformity of dispersion

Twenty tablets are placed in a beaker containing 100 ml of purified water and stirred gently for 2 min. The dispersion is allowed to pass through 22 mesh screen. Tablets would pass the test if no residue remained on the screen [104].

Water absorption ratio

A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of purified water. A tablet is placed onto the tissue paper and the time required for completely wetted is measured. The wetted tablet is then re-weighed. Water absorption ratio (R) is calculated by using equation 11 [104].

$$R = \frac{(W_a - W_b)}{W_b} \times 100 \quad \text{(Eq. 11)}$$

W_b: is the weight of tablet before water absorption

W_a: is the weight of tablet after water absorption

Wetting time

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time [50, 101].

***In-vitro* disintegration time**

Disintegration time is evaluated using the disintegration tester without disk. The disintegration medium is usually 900 ml of purified water kept at 37±0.5 °C. The time required for complete disintegration is in seconds [40, 103].

***In-vitro* and comparative dissolution**

Four dissolution medias are commonly used for evaluating *in vitro* and comparative dissolution, namely 0.1N HCl (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.8) and artificial saliva solution (pH 7.0). Dissolution tester is used for experimental evaluation following the USP paddle (most common). All dissolution tests are usually conducted in 900 ml of each dissolution media maintained at a constant temperature of 37 °C±0.5 °C with paddle rotation speed of 25, 50, 75 or 100 rpm. Comparative dissolution studies is mainly conducted against the reference marketed product. Dissolution profiles are compared with the reference marketed product using the similarity factor (f2) defined by the following equation 12 [40, 103].

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad \text{(Eq. 12)}$$

Where (n) is the number of sampling time points, (R_t) and (T_t) are the mean percent dissolved of the reference product and the prepared ODTs respectively, up to each time point (t), (f_2) represents a logarithmic transformation of the sum-squared error of difference between the reference and the test products over all time points. In order to consider similar dissolution profiles, (f_2) values should be higher than 50.

Novel formulations of oral disintegrating tablets

Many reported applications of ODTs have been described in the literature. Agiba *et al.* [40] incorporated a high dose of nutraceuticals glucosamine sulphate (GluS) and chondroitin sulphate (CS) into ODTs in order to improve their disintegration, dissolution and subsequent their bioavailability. GluS/CS ODTs were prepared by direct compression and melt-granulation techniques, using a blend of conventional and coprocessed multifunctional excipients as Pharmaburst™ C1. Pharmaburst™ C1 turned out to be the key excipient in improving the tablet characteristics, disintegration and dissolution profile. Kumar and Saharan [101] developed ODTs of salbutamol sulphate, using a combination of three different superdisinetgrants in different ratios. They concluded that the binary combination of superdisintegrants was more effective in disintegration and dissolution than the individual use of one superdisintegrant. Dave *et al.* [105] developed ODTs of chlorpheniramine maleate based on lyophilization technique, using superdisinetgrants as croscarmellose sodium and crospovidone for faster disintegration and dissolution. Türkmen *et al.* [106] developed fexofenadine hydrochloride ODTs by direct compression using high functionality excipients as F-Melt®, Pearlitol® Flash, Pharmaburst® 500, Prosolv® Easytab SP, Ludiflash® and Parteck® ODT. ODTs formulated with Pharmaburst® 500 were the most promising formulation with respect to physical characteristics and dissolution rate. Shoormeij *et al.* [107] developed meloxicam ODTs using solid dispersions followed by direct compression. Meloxicam solid dispersions were prepared by the melting method, using poloxamer 188 as a hydrophilic carrier and crospovidone as a superdisintegrant. Moqbel *et al.* [108] developed ODTs of

chlorzoxazone using two different approaches; co-processed excipients or liquisolid technique. F-melt®, Pearlitol® flash, Pharmaburst® 500, Prosolv® ODT and Starlac® were used as co-processed multifunctional excipients, whereas in liquisolid method, Avicel® PH101, Cellactose® 80 and Microcelac® 100 were used as carriers, while Aerosil® 200 was a coating material. Both approaches were capable of producing ODTs with ease and low cost of manufacture. ODTs formulated with Pharmaburst® 500 showed the best results in terms of palatability, mechanical strength, disintegration and dissolution. Ibrahim and El Sayeh [109] formulated orally disintegrating tablets containing furosemide; a potent diuretic used mainly in the management of hypertension. ODTs were prepared by direct compression method for taste-masking purposes. Nishiyama *et al.* [110] prepared taste-masking granules of lafutidine for ODTs using water-insoluble/water-soluble polymers combinations. Lafutidine taste-masking granules were prepared by coating lafutidine granules with a taste-masking layer prepared by combining ethylcellulose (water-insoluble polymer) and hypromellose (water-soluble polymer), and ODTs were prepared by direct compression method using mannitol as a diluent, low-substituted hydroxypropyl cellulose as a disintegrant and sodium stearyl fumarate as a water-soluble lubricant. Desai *et al.* [111] developed β-cyclodextrin (β-CD) solid dispersion-based ODTs of eslicarbazepine acetate (ESL), for improving the dissolution and providing rapid anti-epileptic action. ESL-β-CD solid dispersion was prepared by solvent evaporation method and then compressed into ODTs by direct compression, using superdisintegrants as crosspovidone, sodium starch glycolate, pregelatinzed starch and croscarmellose. Microcrystalline cellulose was further added to aid in tabletting. Yıldız *et al.* [112] developed new ODTs containing mirtazapine; an antidepressant drug molecule having bitter taste by coacervation followed by direct compression using different fillers (Ludiflash®, Phamaburst™ C1, Galen® IQ, F-Melt® and Mannitol Parteck® M100), disintegrants (Kollidon® CL, Ac-Di-Sol®, Explotab® and Kollidon® CL/Amberlit® IRP-88 mixture), glidant (Aerosil® 200), citric acid and sodium carbonate (effervescent mixture). Chen *et al.* [113] prepared montelukast sodium ODTs with a similar dissolution profile as the marketed product, Romilast® ODTs (Ranbaxy). Montelukast sodium ODTs were prepared by direct compression and wet-granulation methods, using a variety of excipients such as microcrystalline cellulose (M105 and M301), mannitol (SD200 and 160C), croscarmellose soldium, hydroxypropyl cellulose, and magnesium stearate. The prepared ODTs showed equivalent dissolution profiles to the marketed product in four different media. El-Maghraby and El-Sergany [114] enhanced the intra-oral administration of nisoldipine used in the treatment of angina pectoris and hypertension by its formulation in ODTs with subsequent fast dissolution. Nisoldipine ODTs were formulated by solid dispersion technique by using solvent evaporation method. Cantor *et al.* [115] described a novel formulation approach for taste-masking drugs with poor organoleptic properties such as clindamycin hydrochloride. Taste-masked ODTs of clindamycin hydrochloride were prepared by its coating with microcrystalline cellulose beads followed by the addition of a taste-masking layer of amino methacrylate copolymer coating suspension.

Future prospects and possible challenges in the development of oral disintegrating tablets

Despite the advances in ODT technologies, formulation of hydrophobic drugs with poor bioavailability is still a big challenge, particularly at high doses. The need of a new technology to incorporate higher doses of hydrophobic drugs without affecting the mechanical and disintegrating properties is crucial. The disintegration times of most marketed ODTs are acceptable (within 3 min as stated by European Pharmacopeia), but certainly further improvement would be an advantage. Generally, the disintegration time is affected by many formulation variables, therefore, a balance between the disintegration time and other tablet properties as mechanical strength, friability, thickness and diameter should be well-considered. Development of cheap and effective direct taste-masking methods would also be advantageous. On the other hand, the development of ODTs usually requires large amounts of excipients and having large drug doses will make the final dosage form very large. Therefore, the formulation of ODTs containing high doses drugs is still a problematic issue and need further new and advanced technologies.

CONCLUSION

The popularity of ODTs has increased dramatically over the last few decades. There are many globally marketed products that have been formulated into ODT dosage forms. The most important parameters in ODT formulations are rapid onset of action, very fast drug release, quick disintegration and dissolution, and these could be achieved by formulating tablets with high porous structures or by adding a blend of disintegrants, superdisintegrants, effervescent systems, and/or coprocessed multifunctional excipients. ODTs prepared by direct compression technique usually have good mechanical properties but could be further improved by using high functionality excipients. Considering many advantages and benefits of ODT systems, it is only a matter of time till the majority of oral solid dosage forms become ODT formulations.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors report no conflicts of interest

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