

REVIEW ARTICLE

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Evaluation of preparation methods for orally disintegrating tablets**Yagmur Akdag¹, Tugba Gulsun¹, Nihan Izat¹, Meltem Cetin², Levent Oner¹, Selma Sahin¹**¹*Hacettepe University Faculty of Pharmacy Department of Pharmaceutical Technology, Ankara Turkey*²*Ataturk University Faculty of Pharmacy, Department of Pharmaceutical Technology, Erzurum, Turkey*

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Abstract

Oral disintegrating tablets (ODT) are orally administered solid dosage forms commonly used in pediatric and geriatric patients with difficulty in swallowing. The lack of need for water during the use of ODTs is another advantage that increases patient compliance. Many methods are used for the production of ODTs such as direct compression (DC), freeze-drying (FD), spray drying, 3-D printing, melt granulation, phase transition process, molding, sublimation, mass extrusion, cotton candy process. Since the ODTs produced are aimed to disintegrate and dissolve rapidly, and consequently act quickly, the production method parameters need to be optimized in line with the critical product parameters. In this study, the most widely used manufacturing methods (especially DC and FD) for ODT and in vitro quality control tests of ODT are evaluated.

Keywords: Orally disintegrating tablets, direct compression, freeze drying, spray drying, disintegration, dissolution

Introduction

Oral route is the commonly preferred drug administration route, because it is easy to administer, comfortable, safe to apply, and provides high patient compliance [1]. ODTs are solid dosage forms with fast disintegration and dissolution characteristics, and can be used without any need for water [2]. ODTs are mainly preferred by patients with swallowing difficulties [3]. ODT formulations usually contain superdisintegrants, flavoring agents, sweetener, surface active agents, binder, coloring agents, lubricant and filler as excipients. There are various ODT preparation methods including DC, FD, spray drying, 3-D printing, melt granulation, phase transition process, molding, sublimation, mass extrusion, cotton candy process [4].

In this study, the most widely used manufacturing methods (especially DC and FD) for ODT and in vitro quality control tests of ODT are evaluated.

Direct Compression Method

DC method is a convenient method if the flowability and

compressibility of the bulk powder is suitable. The formulation can be developed by using conventional excipients and improving the powder characteristics by granulation techniques and adding glidants. ODT formulations are designed to disintegrate in the mouth quickly. Therefore, a disintegrant/superdisintegrant or their combination (e.g. sodium starch glycolate, croscopovidone, Ac-Di-Sol®) is the main excipient in the formulation. Currently, in the market there are ready-to-use ODT excipients (Ludiflash®, Parateck ODT®, Disintequick™ ODT, PROSOLV® ODT G2) mostly contain the filler, binder and disintegrant/superdisintegrant together, and show great flow performance to be directly compressed. The compression force must be optimized to obtain tablets in suitable hardness and friability that do not adversely affect the disintegration rate in the mouth. Considering the oral disintegration, hydrophobic excipients (e.g. stearic acid and its salts) are generally avoided. It is possible to produce ODTs with high mechanical strength and stability by DC method with low cost and short processing time. However, compared to the FD methods, directly compressed ODTs are tend to disintegrate slowly and show decreased dissolution rate [4-7].

Gulsun et al. [1] developed furosemide ODT formulations using microcrystalline cellulose, hydroxypropylcellulose, aspartame, sodium stearyl fumarate for direct compression method. It was reported that furosemide ODTs disintegrated within 15 seconds and had a friability of less than 1%.

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Spray Dried Excipient Based Method

DC method may also be performed by spray drying of the active substances and excipients. Spray dried excipients have porous structure, and show better flow properties as they have a spherical shape [8]. This method can also be used for taste masking by encapsulating the active substance into the microsphere. The spray-dried excipient based method is a valuable and important technique to improve the characteristics such as disintegration time, dissolution of ODT prepared by DC method.

Tanimura et al. [9] produced the spray-dried composite particles of erythritol and porous silica, and used DC method to prepare ODTs with sufficient tensile strength and acceptable disintegration time (<30 s).

Freeze Drying Method

In FD method, active substances and suitable excipients are suspended or dissolved to form a stable suspension/solution. The obtained mixture is equally distributed into blisters and frozen at -20°C. Afterwards, the lyophilization procedure is applied under the recommended pressure and temperature conditions (0.44 mbar and -55°C) to obtain freeze dried ODTs. In this method, the critical materials are antifoaming such as simethicone, and matrix forming agents such as gelatin and sodium alginate. According to the properties of the matrix forming excipients, the disintegration, and thus dissolution properties of the ODTs might vary. This method is appropriate for heat sensitive drugs, and low dose drug since it is dissolved/dispersed in the mixture. Although, the hardness and friability of ODTs prepared by FD method are less than that of the ODTs prepared by DC method, they are produced in the final package and enough tablet strength can be achieved. Moreover, ODTs prepared by FD method show faster disintegration and increased dissolution rate than the ODTs prepared by DC method [5, 6].

Gulsun et al. [5] developed terbutaline sulfate-containing ODTs using DC and FD methods, and obtained that the disintegration times of ODTs prepared by DC and FD methods were approximately 3 min and 11s, as respectively.

Molding

Molding is categorized in two methods (compression molding and heating molding), and includes wetting, dispersing or dissolving, tablet compression and evaporation of the remaining solvents [10]. Hydrophilic excipients are used to achieve maximum solubility. Tablets prepared by compression molding have very porous structure due to removing the solvents by drying [11], and have low mechanical strength due to the tablet compression is performed with low pressure [12].

In heating molding method, a suspension of the drug with water-soluble sugar such as xylitol, agar, mannitol, lactose, sucrose is prepared. Agar solution is used as a binder. This mixture is then added to the blisters. Agar solution is solidified at room temperature to obtain a gel form, and finally dried under vacuum at about 30 °C [13]. There are several patents describing the molding method [14,15].

Sublimation

Sublimation is a process in which water passes directly from its solid state to vapor without becoming liquid [13]. Volatile

components such as urea, camphor, ammonium carbonate, ammonium bicarbonate and hexamethylene-tetramine are widely used to form a porous matrix are used in the sublimation method. Then, it is mixed with other excipients and compressed with low pressure.

Koizumi et al. [16] manufactured porous tablets using a subliming material (camphor) and mannitol. As a result, the ODTs with approximately 30% porosity were obtained, and the ODTs rapidly dissolved (15 s) in saliva.

Phase Transition Method

Orally disintegrating tablets can be prepared by combining low and high melting point sugar alcohols (such as mannitol, erythritol, and sorbitol), and providing phase transition during production. The ODTs are obtained by heating to a temperature between the melting points of these sugar alcohols and then cooling. The content of low melting point sugar alcohol and the heating process may affect the properties of ODTs such as hardness and disintegration time. The hardness of the tablets increases by the heating process [17].

Kuno et al. [18] formulated the ODTs by phase transition method using lactose as a high melting point saccharide and xylitol as the low melting point sugar alcohol. They also evaluated the effect of the type of lubricants (talc, sodium stearyl fumarate, and magnesium stearate) on the characteristics of ODTs. As a result, talc was shown to be the most suitable lubricant for preparing ODTs by this method.

Mass Extrusion Method

This technology involves softening of a blend of active substance(s) and the other ingredients with a mixture of polyethylene glycol and ethanol, and then the expulsion of this soft mass through a syringe or extruder to form a cylindrical shape, which are used to prepare tablets [11].

Patil et al. [19] developed tramadol hydrochloride containing ODT using mass extrusion method to mask the bitter taste of drug. The blend of tramadol hydrochloride and Eudragit E100, which was used a taste masking agent, was softened by ethanol, and then extruded using a syringe. Afterwards, ODTs were prepared using the obtained taste-masked granules, various superdisintegrants (croscarmellose sodium, crospovidone, sodium starch glycolate) and other excipients (diluents and lubricant) by DC method. The fastest disintegration was observed for the ODTs containing crospovidone.

Cotton Candy Method

With fast melting and spinning, polysaccharides or saccharides form a matrix called a floss. The resulting matrix is partially recrystallized to improve flow properties and sustainability. After milling the floss matrix, it is mixed with the active substance and excipients, and then compressed [20]. There are many patents describing the cotton candy process [21,22].

Nanocrystal Technology

Nanocrystal technology is based on reducing the particle size to nanoscale. The nanocrystals obtained by milling are stabilized to prevent agglomeration by physical adhesion on the surface of the inert material. The tablets prepared by this method disintegrate very quickly. In addition, the solubility, absorption rate and

bioavailability of ODTs are also increased [4].

Lai et al. [23] prepared piroxicam-containing nanocrystal formulations using high pressure homogenization technique and poloxamer 188 as stabilizer. Then, they used the prepared formulation and the other ingredients (xanthan gum, maltodextrins, and PEG 4000) to obtain ODTs by FD method. The ODTs containing nano-sized piroxicam had a higher piroxicam dissolution rate compared to untreated piroxicam-containing ODTs.

Oral films/wafers

In this method, water soluble film forming polymer (e.g. hydroxyl propylcellulose, sodium alginate, pullulan, hydroxypropyl methylcellulose, carboxy methylcellulose, polyvinyl alcohol), drug and taste masking agents are dissolved in a nonaqueous solvent. After evaporation of the solvent, a film is formed [24].

Liew et al. [25] were developed taste-masked oral disintegrating film formulation containing donepezil (as active ingredient) and polymeric bases such as polyethylene glycol, crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, and corn starch. They found that the mean in vitro disintegration time of the oral disintegrating film was 44 s, and the oral disintegrating film was stable for at least 6 months at 40°C and 75% relative humidity.

Lai et al. [26] developed quercetin nanocrystal-containing ODT, using glycerin (plasticizer) and maltodextrins (film forming material) to enhance oral bioavailability of quercetin.

The aim of this study was to evaluate different methods in terms of ODT production and quality control parameters.

Quality Control Tests of Manufactured ODTs

In this context, the thickness, diameter, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution rate of ODTs are often determined.

Thickness, Diameter and Hardness of ODTs

Thickness (n=20), hardness (n=10) and diameter (n=20) are determined to evaluate batch-to-batch uniformity of produced ODTs. The hardness of ODTs is an important characteristic which has to be obtained over 5 kg (49.04 N) for uncoated tablets to maintain their mechanical stability. However, it should be adjusted optimally to avoid reduced disintegration and dissolution rates which are also key parameters for ODT preparations and aimed to be improved [27].

Friability of ODTs

Friability indicates the weight loss of ODTs due to abrasion and loss of fine particles from tablet surface because of poor cohesion among the tablet ingredients [27,28].

If the percentage weight loss of uncoated tablets is less than 1%, the tablets pass the friability test [28]. To evaluate friability, 20 tablets are rotated at 25 rpm for 4 minutes. Friability (%) is calculated using the following equation:

$$\% \text{ Friability} = [(W1 - W2) / W1] \times 100$$

where, W1= Weight of tablet before test, W2 = Weight of tablet after test

Wetting Time and Water Absorption Capacity

Water absorption is an important parameter for ODTs, since these tablets generally disintegrate by swelling. According to the widely used simple method [1, 29-32], a glass petri dish containing 6 mL water (with/without a dye) and a filter paper are required to perform the test. Pre-weighed tablet is placed on the filter paper, and the time required for complete wetting of the tablet is recorded. Water absorption capacity is calculated using the following equation [33]:

$$\text{Water absorption capacity} = [(Ww - Wd) / Wd] \times 100$$

Ww: weight of wet ODT; Wd: weight of dry ODT.

Disintegration Study

In disintegration test, ODTs (n=6) are placed in tubes of the basket-rack assembly and the assembly is moved up and down in 1000 mL of distilled water at $37 \pm 2^\circ\text{C}$. Disintegration time is determined according to European Pharmacopoeia 8.2, ODTs should disintegrate within 3 min [28].

Dissolution Study

Dissolution test conditions (apparatus, rate, dissolution media and volume, time intervals for sampling) for the compound of interest are generally obtained from mainly the pharmacopeia. The dissolution test is performed using a dissolution testing device. Since ODTs are expected to disintegrate rapidly, frequent samples should be taken at the first time points of the dissolution study.

Results and Discussion

Thickness, Diameter and Hardness

The standard deviations of thickness, diameter and hardness values are required to be low as an indicator of uniform ODTs. On the other hand, freeze drying method has no compression procedure and therefore, ODTs tend to have weaker strength, and achievement of uniform thickness values is challenging as compared to directly compressed tablets. In our previous study, it was reported that the hardness values of terbutaline sulfate-containing ODTs prepared by DC method using Ludiflash® and Parateck ODT® as ready-to-use tableting excipients were 173.03 N and 212.58 N, respectively. However, the hardness of terbutaline sulfate-containing ODTs prepared by FD method was less than 20 N [5]. In another study, it was aimed to optimize a freeze dried ODT matrix for multiparticulate delivery by means of matrix content with a central composite face centered design. It was demonstrated that increasing the gelatin and alanine concentrations was the most effective approach. Considering the other parameters, the formulation was optimized and the hardness of the formulation was recorded as $17.22 \pm 0.74 \text{ N}$ [34].

Friability

Friability is used as an indicator of physical strength of ODTs. Friability of uncoated tablets is required to be less than 1% [33]. The freeze-dried ODTs are more fragile than the directly compressed ODTs, and thus, it is more difficult to maintain in tablet form [4]. However, since the freeze-dried tablets fill the blister chamber precisely, they do not move during transport, which reduces the possibility of breaking tablets from production to consumption.

Water Absorption, Disintegration and Dissolution

ODTs are usually expected to rapidly absorb water, swell and disintegrate. Therefore, water absorption capabilities of ODTs are considered as an indicator of their disintegration ability. However, it was observed that lyophilized tablets do not swell but disintegrate very rapidly [5]. Freeze dried ODTs have very low disintegration time, therefore, their dissolution rate tends to be higher than the other ODTs such as direct compressed, spray dried [7,35]. According to European Pharmacopoeia 8.2, ODTs should disintegrate within 3 min [33].

Dissolution studies of ODTs are performed in accordance with dissolution databases in Pharmacopoeia or FDA. The selected manufacturing method and excipients may affect the dissolution rate. For example, freeze dried ODTs have very low disintegration time, hence their dissolution rate is very fast [7,35].

Elkhodairy et al. [31] were prepared flutamide containing ODTs by superdisintegration, effervescence and sublimation approaches. Two-fold increase in the superdisintegrant content decreased the disintegration times from 46 to 38 s. The combination of effervescence approach and superdisintegrant addition resulted faster disintegration (22 s), however, dissolution rate was not altered. The major increase in the dissolution rate (73.12 to 96.99% after 15 min) was achieved by the preparation of solid dispersion of the active compound with PEG6000.

Conclusion

In conclusion, ODTs can be prepared by several techniques and the use of variety of excipients. The suitable preparation method should be selected according to the specifications of the active pharmaceutical ingredient, the properties of excipients, target patient population and intended disintegration time enabling the effective treatment.

Competing interests

The authors declare that they have no competing interest.

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Ethical approval

No Ethical approval is needed for this research

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