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Side by Side Layers Freeze Dried Orally Disintegrating Tablets

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Abstract

This study aimed to develop methodologies for the fabrication and testing of side by side layers freeze dried (lyophilized) orally disintegrating tablets (ODT) for same or different phase formulation. These side by side layers tablets will provide opportunities for combination therapies for patients who experience swallowing difficulty (e.g. geriatrics and paediatrics) and might enhance the bioavailability and incompatibility of some drugs. Two different solutions (A and B) were prepared separately and each solution was to create a different formulated layer to obtain different release profiles. The first layer was fabricated by injecting the solution A to an empty tablet blister to the half and freezing at -80°C for one hour in an external freezer. After the first layer was completely frozen, the solution B was injected into the rest half of the tablet blister and frozen at -80°C for one hour in an external freezer to create the second layer. Then, frozen side by side layers tablet was freeze dried and the resulting multilayer tablets were investigated. The study has shown that side by side layers freeze dried orally disintegrating tablets can be fabricated and formulated for same or different phase and with different disintegrating time for each layer to provide different release profiles. The optimization of adhesion between layers is required. The study has also shown that concentrations of gelatin and mannitol can affect the formulation characteristics.

Keywords: ***Orally disintegrating tablet (ODT); Multilayers ODT; Freeze drying; Lyophilization***

Introduction

Most of patients prefer oral drug delivery route for administration their medications due to the compliance and convenience [1]. Indeed, the preference of oral route by most patients is due to several advantages of the oral route (e.g. self-administered, pain free compared to parenteral, easy to take and no need to training, cheap compared to most other routes, and absorbed in wide surface area through gastrointestinal tract (GIT) compared to other routes) [2].

Conventional bilayer tablets, which are produced by the compaction of granules and/or powders, provide opportunities for combination therapy while increasing patient compliance. Examples of the main advantages of bilayer tablets are (i) the

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formulation of two chemical incompatible drugs in one tablet, (ii) control release (e.g. tablets with an extended release and an immediate release profiles), (iii) synergistic effect, and (iv) improving patient compliance by decreasing the dosing unit load thereby [3]. However, the difficulties that some patient groups have in swallowing a conventional tablet (i.e. elderly, children and unconscious patients) is one of the major disadvantages of these delivery systems.

However, swallowing difficulty or dysphagia is one of the limitations of the oral drug delivery route. Moreover, difficulty in swallowing tablets or dysphagia is in a high percentage of residents as Patients Association has reported up to 75% of residents are experienced by swallowing difficulty to administer their medications in a recent report [4]. Therefore, the demand of ODTs has been increased due to the providing convenient solutions in most cases of difficulty in swallowing (e.g. paediatric and geriatric), enhancement the bioavailability of some drugs by the pregastric absorption, and meet patients' needs [5-7].

Orally disintegrating tablets (ODTs) or orodispersible tablets or fast disintegrating tablets are solid dosage forms which disintegrate in the mouth rapidly once placed on the tongue without the requirement for water. According to the British Pharmacopeia, orodispersible or ODTs are tablets disperse rapidly before being swallowed and disintegrate within 3 minutes [8]. As per the US Pharmacopoeia (USP), ODTs disintegrate in less than 30 seconds, and tablet weight should not exceed 500 mg. In addition, the drug dose in freeze dried ODTs must be less than 400 mg for insoluble drug and less than 60 mg for the soluble drug [9].

ODTs have a lot of advantages (e.g. enhanced palatability, enhanced bioavailability, fast onset, exact dosing compared to liquids, no physical obstructions because there is no need to swallow the tablet, and good chemical stability) [6,10-12]. The bioavailability of ODTs is better than conventional tablets due to the avoiding of the first pass metabolism, which is shown in the lyophilized orally disintegrating selegiline hydrochloride tablets which is dosed at 1.25 mg selegiline hydrochloride per single dose instead of 10 mg conventional tablets viewing similar pharmacokinetic profiles [13].

Aside from the direct compression method, there are other technologies for preparing ODTs; for example, freeze drying (lyophilization), spray drying, and molding. Disintegration times vary between all these technologies, from 3 seconds to 3 minutes, with the freeze-drying technology providing the fastest. The commercial ODTs that prepared by freeze drying disintegrate rapidly in few seconds due to high porosity that allows the penetration of saliva through pores when placed on the tongue. Freeze drying or lyophilization is a solvent removal process from a frozen drug solution or suspension to form a highly porous structure [14]. Claritin (loratadine) formed by Zydis was the first ODT which got approval from the US Food and Drug Administration (FDA) in 1996 [15].

However, to date, the idea that side by side layer tablets might be designed to function as an orally disintegrating tablet has largely been overlooked. There are patents to create the orally disintegrating tablet in conventional multilayers (layers are vertically on the top of each other), one of these patents by direct compression while others by freeze drying [16]. One of these patents is to create a lyophilized fast dissolving in a multi-phasic dosage form which means one phase formulation is containing a non-gelling matrix while the other formulation is containing a gelling gelatin [16].

Therefore, the main aim of this investigation was to develop methodologies for the creation and testing of side by side layers freeze dried orally disintegrating tablet for same or different phase formulation (solution, jelly, and suspension). These side by side layers tablets will provide opportunities for combination therapies for patients who experience swallowing difficulty (e.g. geriatrics and paediatrics) and might enhance the bioavailability and incompatibility of some drugs. In addition, different disintegrating time can be achieved by preparing different concentrations of excipients of the formulation of each layer to obtain different releasing profiles (immediate and extended release). Side by side layers freeze dried orally disintegrating tablets have an advantage of ensuring the dryness of all layers during the freeze-drying cycle over the conventional multilayers freeze dried orally disintegrating tablets which the drying of the bottom layer can be blocked by the top layer, and possibility of creation all layers from the same phases or different phases (multi-phasic).

Side by side layer tablet can be combined of two layers or more than two layers. These layers combination can be (i) two different layers joined by an adhesive interface layer (ii) three layers, two are different layers and the third one is an adhesive layer (iii) three different layers joined together by an adhesive interface layer FIG. 1. There are some challenges that restrict the optimization and formulation of the ODTs e.g. mechanical strength, tablet size, disintegration time, water solubility, taste masking, and mouth feel [17]. The opportunity to optimize one or more of these challenges can help to improve the orally disintegrating tablets as one layer or multilayers which provide chances for combination therapies for patients who involved in swallowing difficulty case.

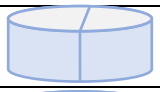
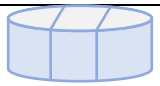
Two different layers	
Two different layers + adhesive layer	
Three different layers	

FIG. 1. **Layers combination options of the side by side layers freeze dried orally disintegrating tablet.**

Materials and Methods

Materials

Gelatin and mannitol powder were found in lab HB3.16. Green S 0.01%w/v aqueous solution and Carmoisine 0.01%w/v aqueous solution were obtained from lab HB3.08. All materials were used without any modifications in the matter as they were supplied by the respective companies.

Methods

Formulation of tablets: Two different solutions (A and B) were prepared separately to create a different formulated layer to obtain different release profiles. Solution A was prepared by dissolving 5 g of gelatin in a double distilled water at 50°C using a water bath and then 5 g of mannitol was added to the solution to obtain a concentration of 5%w/v of gelatin and 5%w/v of mannitol. Solution B was prepared by dissolving 4 g of gelatin in double distilled water at 50°C using a water bath and then 6 g of mannitol was added to the solution to obtain a concentration of 4%w/v of gelatin and 6%w/v of mannitol. Solution B was dyed by a green S 0.01%w/v aqueous solution to distinguish between layers by colours after the completion of the freeze-drying cycle. Solutions were left to be cooled at room temperature.

Injecting layers: The first layer was created by filling 1 ml of the solution A by syringe into an empty tablet blister volume 2 ml to be half filled. The tablet blister was vertically held by a created mould holder and sealed with a foil tape to prevent the seepage of the solution while vertical holding (FIG. 2).

The injected first layer was frozen at -80°C in an external freezer for one hour. Then, the second layer (1 ml) was injected inside the external freezer, to minimize the effects of temperature changes on the frozen first layer, and was frozen in the external freezer at -80°C for one hour.

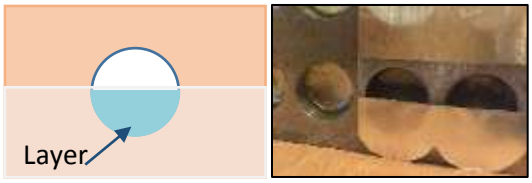


FIG. 2. **A tablet blister sealed with foil tape and filled with layer A, ready to be frozen in an external freezer at the vertical position.**

Freeze drying: Side by side layers frozen tablets were moved from the external freezer to the freeze dryer and the foil tape was removed immediately to be prepared for the freeze drying. Side by side frozen tablets were frozen at -40°C for 240 minutes and freeze-dried (VirTis advantage Plus Freeze-dryer) according to an optimised regime (primary drying for 48 hours at a shelf temperature of -40°C, followed by secondary drying for 10 hours at a shelf temperature of 20°C, vacuum of 50 mTorr).

Mechanical properties

Side by side layers freeze dried orally disintegrating tablets were investigated by direct eye watching and handling by hands directly.

Determination of the diameter and thickness of the tablet

The diameter and the height (thickness) of the side by side layer freeze dried orally disintegrating tablet were measured using a ruler. In addition, the dimension of each layer was measured separately. Values were reported for measurements of five side by side layer freeze dried orally disintegrating tablets and the mean was obtained ± standard deviation.

Tablet disintegrating test

The *in vitro* disintegrating time of the side by side layer freeze dried ODTs was determined using the Pharma Test DIST3 type disintegration testing instrument. Distilled water (800 ml) was used as a dipping fluid, and was heated to and maintained at a temperature of 37˚C, which similar to the human body temperature. The temperature of the water inside the bath was continually checked with a thermometer. The disintegrating time was defined as the time needed for each layer of each tablet of ODTs to completely disintegrate without any solid residue remains (3 minutes according to the official European Pharmacopoeia monograph). A total of five side by side layer freeze dried orally disintegrating tablets were tested and the results reported are mean ± standard deviation.

Friability test

A total of five tablets were cleaned and pre-weighed (Wa). Then, tablets were tested in ERWEKA ‘ROCHE’ FRIABILATOR tester at a speed of 25 rpm for 4 minutes. Then, tablets were removed, cleaned and reweighed (Wb). The

percentage of weight reduction was calculated according to the Equation 1 below. The accepted boundary of friability test for ODTs is not more than 1% [18].

$$F=((Wa-Wb))/Wa \times 100$$

Equation 1: Friability test calculation formula (F=Friability).

Texture analysis test (hardness)

The TA.XTPlus texture analyser instrument attached to a computer was used to evaluate the hardness of each layer of the tablet. The hardness was tested using a compression probe (6 mm diameter) at a speed of 2 mm/sec and a depth of 3 mm. The force in Newton (N) was measured at a depth of 1 mm after compression. The hardness of the side by side layer freeze dried orally disintegrating tablet was measured for each layer of each one tablet by compression the probe in the surface middle of each layer in every tablet. Once the measurement was completed, the data were exported and analysed using the Microsoft Excel software. A total of five side by side layer freeze dried orally disintegrating tablets were tested and the results reported are the mean.

Scanning electron microscopy

Scanning electron microscopy (SEM) was performed on cross-section samples for each layer of the tablet to investigate the inner structural morphology of each layer of the tablet. Slices samples of each layer were prepared by cutting a thin slice of the top and the side section of each layer of the tablet using a scalpel. The top samples were taken in horizontal section while the side samples were in vertical section. Samples were coated by gold sputter using Quorum apparatus (15 nm) and measured by SEM (ZEISS EVO instrument) at 500, and 1 K magnifications.

Wetting time test and water absorption ratio

The wetting time test was calculated by placing five circular tissue papers of 10 cm diameter in a 10-cm diameter Petri dish. Then, ten milliliters of a dyed distilled water solution was added to the Petri dish. Tablets were placed on the tissue paper surface individually. The required time for water to spread on the upper surface of the tablet was measured as the wetting time of each tablet. The water absorption ratio (R) was calculated according to the Equation 2 below. A total of five side by side layer freeze dried orally disintegrating tablets were pre-weighed before placing in the Petri dish (Wb) and reweighed after water absorption (Wb) [19].

$$R=((Wa-Wb))/Wb \times 100$$

Results and Discussion

Mechanical properties

Tables appeared in a uniform shape and acceptable size with a height (thickness) mean of ± 7.9 mm, and diameter mean of ± 18.8 mm. The means of dimensions of layers were ± 10.25 mm and ± 8.6 mm for layer A and layer B respectively (TABLE 1). Tablets were in a spongy nature and a smooth surface feeling. Layers adhered together perfectly through an interface thin layer. A slight gap between layers of some tablets (~10% of tablets) was observed. The seepage of the layer B after injecting was not presented around the frozen layer A.

TABLE 1. **Diameter, thickness, and weight of side by side layers freeze dried orally disintegrating tablets. The represented values are mean ± standard deviation (n=5).**

Diameter (mm)			**Thickness (mm)**	**Weight (gram)**
Whole tablet	Layer A	Layer B		
18.8 ± 0.3	10.25 ± 0.21	8.6 ± 0.38	7.9 ± 0.25	0.22 ± 0.01

Disintegration time

TABLE 2 presents the mean disintegration time of the layers of side by side layers tablet was 36.2 seconds (Layer A) and 26 seconds (Layer B). As each layer of the tablet was created by different formulation, tablets provided two different disintegrating times and that different release profile was because of the concentration of gelatin which layer B with low gelatin concentration (4%) disintegrated faster than layer A 5% gelatin concentration [20]. The different release form of one tablet can be used to achieve improved solubility of drugs, allow adequate absorption as the surface area of mouth is slightly small, and enhance chemical incompatibility of drugs.

Although, the disintegration time of each layer was within the limit of the orally disintegrating tablet according to the European Pharmacopeia, tablets required to be improved to match the disintegration time of the other freeze-dried products which disintegrate in seconds.

TABLE 2. **Disintegrating time in seconds for each layer of the side by side layers tablet.**

Tablets	Layer A (Disintegrating time in seconds)	Layer B (Disintegrating time in seconds)
1	33	25
2	35	22
3	40	29
4	36	26
5	37	28
Mean	36.2	26

Fracturability

The measurement of fracturability was shown on the limit of accepted friability. According to the Equation 1, friability (F) was calculated as 1%, as reviewed the fracturability increases with an increase in mannitol concentration [20]. Although the friability within the limited range, the adhesion between layers in one tablet needs to be improved as was noticed weak (50% of tablets' layers were broken during the factorability test).

Hardness

As shown in FIG. 3, means of hardness measurements were 25 N and 16 N for layer A and layer B respectively at the distance of 1 mm of penetration. The adequate hardness might due to the high concentration of gelatin which caused increases in overall hardness of ODT because the 3D network formed by gelatin fibre allowed the trapped frozen water to sublimate [21]. In addition, mannitol provides a synergistic effect to enhance the hardness of ODTs that already obtained from gelatin, and as shown in the adequate hardness of layer B in FIG. 3 which the concentration of gelatin in layer B was less than layer A [20].

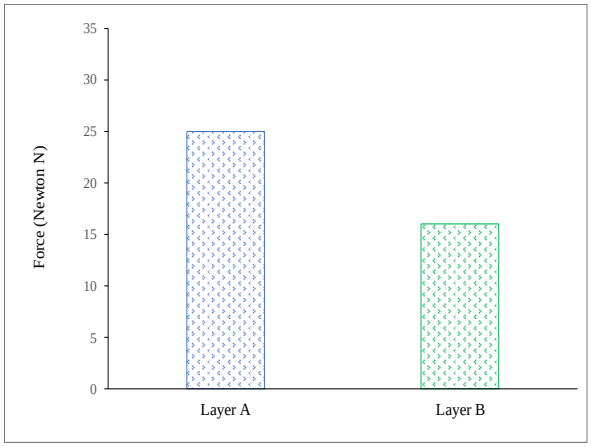


FIG. 3. **The mean of the hardness of forces comparison (Newton) between layers**.

Scanning electron microscopy

FIG. 4 shows the structure of the tablet in the top and side section. SEM micrographs reveal that samples present a highly porous and formed structure. The structure of pores, large size, and high formed number were noticed increase with increasing the gelatin concentration in addition of mannitol as the formation of 3D mesh which provides a chance of big portion of trapped water to sublimate during freeze drying cycle which result in optimized disintegrating [20]. Pores images of layer A present a bigger size than layer B because of the different in gelatin concentration between layers.

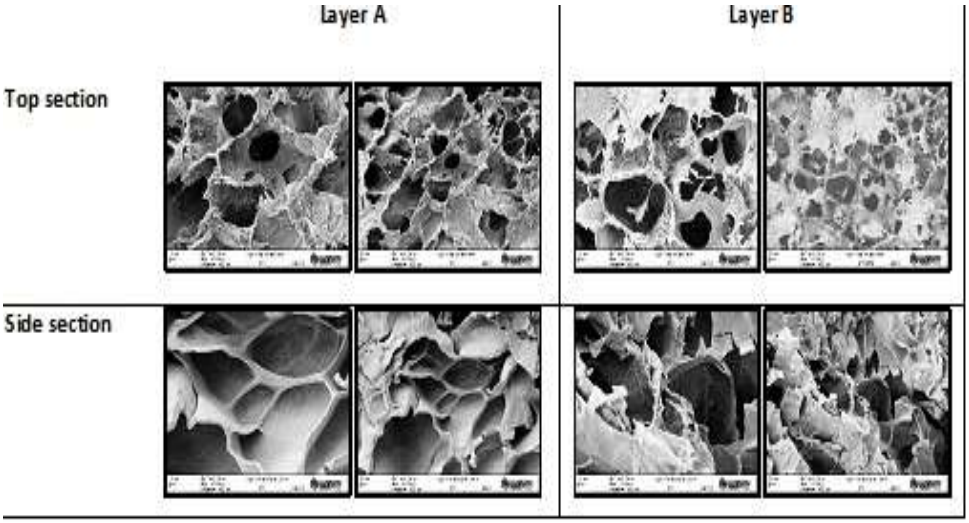


FIG. 4. **SEM images of the top and side sections of layers of the tablet at 1 K and 500 magnifications.**

Wetting time and water absorption ratio

The measurements of wetting time of both layers of tablets were in a range of 115-170 seconds with a mean of 130 seconds and 155 seconds of layer A and layer B respectively. The difference in the wetting time between layers might be due to the concentration of gelatin as more pores formed [22]. The water absorption ratio according to the mean of calculating a total of five tablets was 86% of the whole tablet. Wetting time aids in the investigation of the effects of several excipients on the disintegrating time of the tablet, as a lower wetting time reveals faster disintegrating time [23,24] .

Conclusion

The study aimed to find a methodology to fabricate a multilayer freeze dried orally disintegrating tablets with accepted mechanical and chemical properties and with different release profiles to provide opportunities for combination therapies for patients who experience swallowing difficulty. The study has shown that side by side layers freeze dried orally disintegrating tablets can be fabricated and formulated for same or different phase and with different disintegrating time for each layer to provide different release profiles. The adhesion between layers of each single tablet requires more investigation and optimization. The study has also shown that concentrations of gelatin and mannitol influence formulation characteristics, such as structure porosity, fracturability, and disintegrating time.

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