Send Orders for Reprints to reprints@benthamscience.net

Recent Patents on Drug Delivery & Formulation 2020, *14*, 40-47

RESEARCH ARTICLE

Development of the Modified *Ocimum gratissimum* Seeds for Orally Disintegrating Tablets

Yen N.T. Dang[1,#], Phuong H.L. Tran[2,#] and Thao T.D. Tran[3,4,*]

[1]*International University, Ho Chi Minh City, Vietnam;* [2]*Deakin University, Geelong Australia, School of Medicine;* [3]*Department for Management of Science and Technology Development, Ton Duc Thang University, Ho Chi Minh City, Vietnam;* [4]*Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City, Vietnam*

ARTICLE HISTORY

Received: April 09, 2019
Revised: August 28, 2019
Accepted: October 08, 2019

DOI:
10.2174/1872211313666191029144038

Abstract: ***Background:*** Natural materials have been encouraged in controlled drug release and improved drug bioavailability.

Objective: This study aimed to develop a modification process for the use of a natural material, *Ocimum gratissimum* seeds (OGS), in Orally Disintegrating Tablets (ODTs).

Methods: The OGS was investigated with four different modification processes including only milling, swelling, swelling/milling, and swelling/milling/incubation. The ODTs containing the modified OGS as a disintegrant were prepared by the wet granulation method. Furthermore, an evaluation to assess parameters of tablets, such as weight variation, hardness, friability, wetting time, disintegration time, drug content, and dissolution studies, was performed.

Results: The modification of OGS using the swelling/ milling process resulted in a completion of OGS modification, leading to an ideal wetting time, disintegrating time, and dissolution rate. The OGS concentrations also affected the wetting and disintegrating time with the optimal range of ODTs from 15% to 20%. On the other hand, the modification with the incubation processes varied by temperature and time increased the wetting time and disintegrating time.

Conclusions: The modified OGS demonstrated that it is a potential material with the advantages of cost-effectiveness, non-toxicity and easy manufacture in the preparation of ODTs.

Keyword: Orally disintegrating tablets, *Ocimum gratissimum* seeds, disintegrant, modification, oral delivery, natural material.

1. INTRODUCTION

The development of natural products has been encouraged in recent pharmaceutical research of controlled drug release and improved drug bioavailability [1-8]. *Ocimum gratissimum* seeds (OGSs) were investigated in several studies as a suspending agent or a disintegrant [9, 10]. On the contact with water, a mucilaginous layer is formed surrounding the seeds due to its capability of excellent water uptake, demonstrating the swelling power of OGSs. A large amount of polysaccharide with a high capacity for hydration was attributed to the formation of the mucilaginous layer of the swollen seeds, showing the potential application in pharmaceutical formulations [11, 12].

Although tablets and capsules are extensively used as solid oral dosage forms in manufacturing operations, for some patients with persistent trouble in swallowing these kinds of dosage forms pose a real problem. Orally Disintegrating Tablets (ODTs) would be an appropriate choice for these patients [13]. ODTs are normally known as patient-friendly dosage forms, which are particularly suitable for pediatric and geriatric patients. ODTs rapidly disintegrate in the oral cavity by absorbing a small amount of water [14]. The absorption site of ODTs may improve the pharmacokinetics of therapeutic agents by reducing first-pass metabolism [15].

To develop an ODT formulation, a disintegrant should be noticed as a critical excipient in the formulation as it plays an important role in assuring the appropriate disintegration time and dissolution rate of the ODTs [16, 17]. ODTs hence provide a comfortable and safe drug delivery to therapeutic and patient compliance requirements [15]. Furthermore, ODTs also face the challenge of high production costs [15, 18]. Therefore, the present research aims to develop a modified OGS and investigate its role in formulating and manufacturing ODTs. This study may pave a way to use natural materials for the development of ODTs entailing great properties of safety and cost-effectiveness.

*Address correspondence to this author at the Ton Duc Thang University, Ho Chi Minh City, Vietnam; Email: trantruongdinhthao@tdt.edu.vn
[#]*These author contribution equal to this work.*

2212-4039/20 $65.00+.00 © 2020 Bentham Science Publishers

Recent Patents on Drug Delivery & Formulation

2. MATERIALS AND METHODS

2.1. Materials

Acetaminophen was purchased from Hebei Jiheng Pharmaceutical Co., Ltd. (China). Polyvinylpyrrolidone K30 (PVP K30) was purchased from BASF Group (Germany). *Ocimum gratissimum* seeds (OGS) were purchased at the local market and stored at room temperature (25°C) for the study. Aspartame was obtained from Anhui Wanhe Pharmaceutical Co., Ltd (China). Magnesium stearate (MgS) was purchased from Nitika Pharmaceutical Specialities Pvt. Ltd. (India). Mannitol (Pearlitol®) was obtained from Roquette Pharma Company (France).

2.2. Methods

2.2.1. Preparation of Modified OGSs for Tableting

Method 1 (M1): The pure seeds were simply milled and sieved with a 500 µm sieve.

Method 2 (M2): The powder of M1 was swelled in the distilled water for 1 h. The swelled OGS was dried at 60°C.

Method 3 (M3): The powder of M1 was also swelled in the distilled water for 1 h and immediately subjected to milling and sieving with a 500 µm sieve. The samples were then dried at 60°C.

Method 4 (M4): The powder of M1 was also swelled in the distilled water for 1 h and immediately subjected to milling and sieving with a 500 µm sieve. However, the samples were incubated at 50°C (and 90°C) for 3 h or 6 h before subjected to dry at 60°C.

In all methods mentioned above, the batch size equivalent to 10 g OGS seeds was milled by the blender machine (Sunari KT-BL 28, China) in 15 min to ensure all particles passed through a 500 µm sieve. Moreover, the samples after drying at 60°C were passed again through a 500 µm sieve to get the final powder for tablet preparations. All formulations are described in below Table **1**. The ODT tablets were prepared by wet granulation with a total weight of 200 mg (acetaminophen 40%, PVP K30 4%, aspartame 3%, magnesium stearate 1%, modified OGS from 5 to 20%, and the amount of mannitol was adjusted according to modified OGS). Briefly, after wet granulation, the dried granules containing acetaminophen, PVP K30, and aspartame were mixed with modified OGS, mannitol and magnesium stearate for tableting (batch size of 100 tablets). The hardness of the tablet was controlled in the range of 20-40 N.

2.2.2. Uniformity of Tablet

Thirty tablets were collected from each formulation and weighed individually using a digital balance, and then compared with the theoretical tablet weight (200 mg). According to the United States Pharmacopeia 29 – NF 24, the formulation passes:

Table 1. Modified OGS for tableting formulations of ODTs.

No.	OGS (%)	Method	Hardness (N)	OGS:water (w/v)	Incubation Temp (°C)	Modified Time (h)	Dried Temp (°C)
F1	5%	M1	40	1:50	-	-	60
F2	5%	M1	30	1:50	-	-	60
F3	5%	M1	20	1:50	-	-	60
F4	10%	M1	20	1:50	-	-	60
F5	5%	M2	40	1:50	-	-	60
F6	5%	M2	30	1:50	-	-	60
F7	5%	M2	20	1:50	-	-	60
F8	10%	M2	20	1:50	-	-	60
F9	15%	M2	20	1:50	-	-	60
F10	5%	M3	40	1:50	-	-	60
F11	5%	M3	30	1:50	-	-	60
F12	5%	M3	20	1:50	-	-	60
F13	10%	M3	20	1:50	-	-	60
F14	15%	M3	20	1:50	-	-	60
F15	20%	M3	20	1:50	-	-	60
F16	15%	M3	20	1:25	-	-	60
F17	15%	M3	20	1:100	-	-	60
F18	15%	M4	20	1:50	50	3	60
F19	15%	M4	20	1:50	50	6	60
F20	15%	M4	20	1:50	90	3	60
F21	15%	M4	20	1:50	90	6	60

- If no more than 2 tablets are outside the 7.5 % of tablet weight
- And if no more than 2 times the 7.5 % of tablet weight

2.2.3. Friability Test

Thirty tablets were weighed and then, they were placed in a friability tester (25 rpm for 4 min). The tablets were reweighed, and the friability was calculated using the following formula.

$$Friability = \frac{Initial\ weight - final\ weight}{Initial\ weight} \times 100\%$$

2.2.4. In vitro Wetting Study

A filter paper was put in a Petri-dish (diameter of 10 cm). Then, 10 mL of water and methylene blue was added to the Petri dish. A tablet was carefully dropped on the surface of the filter paper. The time when water reaches the upper surface of the tablets was noted as the wetting time [19].

2.2.5. In vitro Disintegration Test

The tablet was carefully put in the center of the Petri dish (10 cm in diameter) containing 10 mL of water. The disintegration was noted at the time for the tablet to disintegrate completely into fine particles [19].

2.2.6. Drug Content

Six tablets were weighed and crushed to a fine powder which was then dissolved in a 50 mL volumetric flask containing distilled water. The sample solutions were diluted with methanol for the HPLC test as described below.

2.2.7. High-Performance Liquid Chromatography (HPLC)

The quantification of acetaminophen in tablets was performed using Ultimate 3000 HPLC (USA) on a C18 (150 x 4.6 mm, 5 µm, Phenomenex, USA) column. The mobile phase containing buffer solution (pH 3.5, adjusted by phosphoric acid) and acetonitrile at the ratio 3:1 was controlled at a flow rate of 1 mL/ min. The UV/ VIS detector was set at a wavelength of 207 nm. The sample injection volume was 20 µL.

2.2.8. Dissolution Test

Dissolution tester (DT70 Pharmatest, Germany) was used for dissolution studies. The tests were conducted at 37 ± 0.5°C in a USP specification dissolution test type II apparatus (Paddle apparatus) according to the United States Pharmacopoeia 29 - NF 24. 900 mL of buffer pH 5.8 was added into each dissolution vessel. The apparatus was set up at 50 rpm of rotation speed. 1 mL of sample was collected from the media after 30 min and replaced by an equal volume of the fresh media. 100 µL sample solutions were diluted with 900 µL distilled water for the HPLC test.

3. RESULTS AND DISCUSSION

3.1. Effect of the Hardness and Modification Method on the Disintegrating Time and Wetting Time

Firstly, the ODTs were investigated upon the effect of the hardness on the disintegrating time and wetting time. The concentration of OGS in formulations was fixed at 5 % and screened with the three main hardness ranges 40 ± 2 N, 30 ± 2 N, and 20 ± 2 N. Fig. (**1**) shows the effect of hardness on

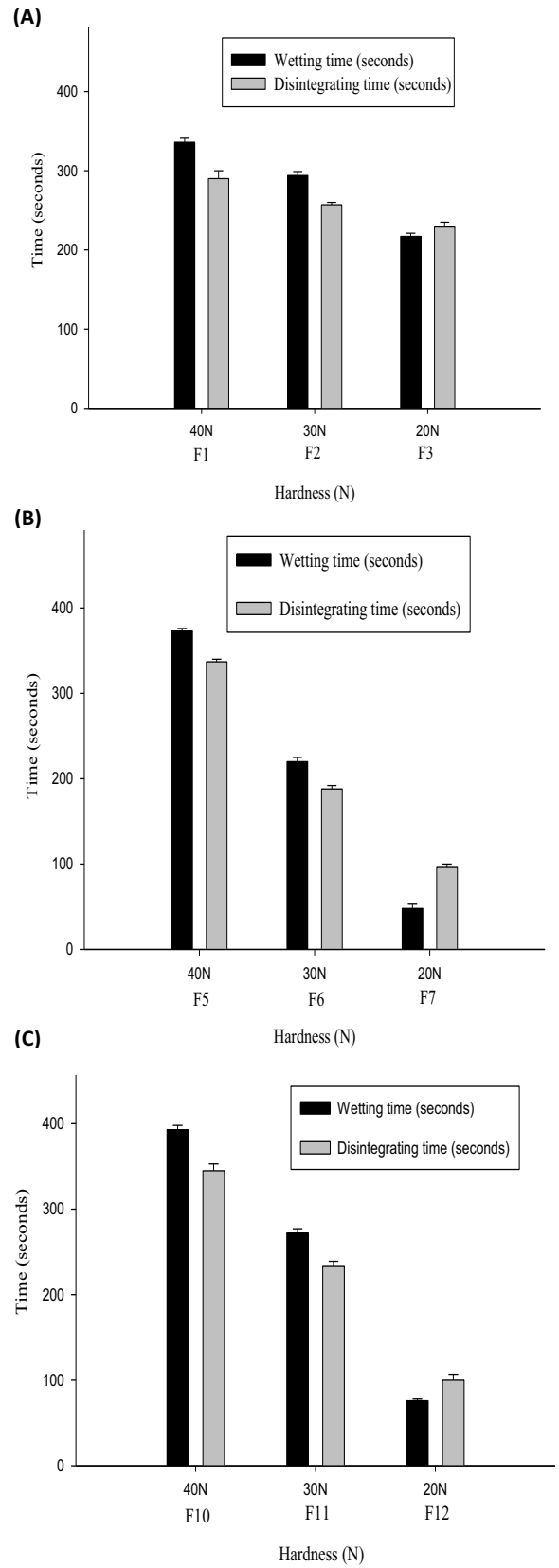

Fig. (1). Effects of hardness on the disintegrating time and wetting time of method 1 (**A**), method 2 (**B**), method 3 (**C**). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

the disintegrating time and wetting time of ODTs in three modified methods. Generally, the data indicated that the decrease in hardness improves the disintegrating time and wetting time of the tablets. Specifically, in Fig. (**1A**) which shows the 5 % OGS in formulations of method 1, the disintegrating times at 40 N, 30 N, and 20 N were 290 ± 10 s, 257 ± 3 s, 230 ± 5 s, respectively, and the corresponding wetting times were 336 ± 5 sec, 294 ± 5 sec, and 217 ± 4 s. Although the disintegrating and wetting times were proportional to the hardness of the tablets, they were 3 minutes longer than the acceptable range of the disintegrating and wetting times for common ODTs [20-22]. In contrast, Fig. (**1B** and **1C**) indicated that there was a significant change in the time of wetting and disintegration from more than 5 min at the hardness of 40 N to below 2 min when the hardness decreased to 20 N. Therefore, method 2 and method 3 demonstrated that the hardness had a direct effect on ODTs preparations using OGS as a disintegrant.

Moreover, Table **2** shows the average weight of all formulations. According to the United States Pharmacopeia, the percentage limit is ± 7.5 % due to the average weight of tablets less than 250 mg. There were no more than 2 tablets that were out of ±7.5 % and no more than ± 15 % percentage limit (date not shown). Hence, all formulations were acceptable in the uniformity range of tablets. In addition, Table **2** indicated that all formulations (except formulation F3 which was slightly out of the limitation) showed good mechanical strength because the friability values were less than 1.0 %.

In addition, formulation F3 in method 1 (containing5 % OGS) had a friability of 1.03 %, which was out of 1% of the limit acceptance for the friability test. Although the increase of OGS up to 10% could increase the mechanical strength in F4 formulation, the GGS without modification in method 1 was not suitable for the preparation of ODT tablet based on the friability, disintegration, and wetting test. In contrast, in method 2 and method 3, with the same concentration of OGS (5 %) the friability of these tablets was observed between 0.1 % and 0.76 %, which was less than 1 %, indicating that tablets had good mechanical resistance [23]. Therefore, the modification of OGS and the hardness were selected for further studies of ODT.

3.2. Investigation of OGS Concentration on the Disintegrating Time and Wetting Time

At the hardness of 20 N, method 3 (F12 – F15) had an ability to form tablets with OGS concentrations from 5 % to 20 % while method 2 only formed tablets at 15 %, the

Table 2. Uniformity and friability of ODTs

No.	OGS (%)	Method	Hardness (N ± SD, n=30)	Uniformity (mg ± SD, n=30)	Friability (%, n=30)
F1	5%	M1	40	205 ± 4	0.34
F2	5%	M1	30	196 ± 3.8	0.57
F3	5%	M1	20	198.7 ± 4.9	1.03
F4	10%	M1	20	191 ± 3.2	0.47
F5	5%	M2	40	198.2 ± 3.5	0.1
F6	5%	M2	30	193.8 ± 3.1	0.36
F7	5%	M2	20	198.2 ± 3.4	0.76
F8	10%	M2	20	202.9 ± 4.5	0.23
F9	15%	M2	20	190.6 ± 4.2	0.72
F10	5%	M3	40	205 ± 5.4	0.48
F11	5%	M3	30	190.5 ± 4.6	0.28
F12	5%	M3	20	197.3 ± 3.1	0.1
F13	10%	M3	20	197 ± 3.2	0.15
F14	15%	M3	20	208.6 ± 3.8	0.28
F15	20%	M3	20	191.5 ± 3.7	0.4
F16	15%	M3	20	193.4 ± 3.1	0.38
F17	15%	M3	20	197.2 ± 3.6	0.18
F18	15%	M4	20	198 ± 3.4	0.1
F19	15%	M4	20	199 ± 4	0.32
F20	15%	M4	20	203 ± 6.5	0.31
F21	15%	M4	20	195 ± 4.3	0.02

maximal concentration of OGS. As shown in Fig. (**2**) (top), only slightly changed disintegrating time was observed: 98s (5 % OGS), 95s (10 % OGS), and 92s (15 % OGS) with method 2. However, both wetting time and disintegrating time significantly changed with an increase of OGS concentration in method 3. Specifically, the disintegrating times were 100s (5 % OGS), 85s (10 % OGS), 73s (15 % OGS), and 50s (20 % OGS) in method 3 (Fig. **2**, bottom). This data demonstrated that the modification of method 3 was more effective than method 2. In method 2, only the shell of OGS was swelled in water, and the unswelled core still remained inside (Fig. **3**). In method 3, the powder OGS was swelled and then milled, leading to a complete swelling of all parts of seeds. Therefore, method 3 showed a higher swelling property by increasing water absorption with an increase of OGS concentration. The swelling property of OGS was due to the presence of polysaccharide, the main composition of the mucilage layer of OGS seeds [12]. The fast increased disintegration with increased polysaccharide content was attributed to the swelling of polysaccharide powder, which leads to penetration of water in the pores of tablets and hence, generate a hydrodynamic pressure for the quick and completed disintegration of tablets. In general, the modification of OGS with concentration from 5 % to 20 % using method 3 was ideal for ODTs. Moreover, 15 % and 20 % were the best two concentrations that facilitate the disintegrating and wetting time around 60s.

3.3. Effect of Amount of Water in the Modification Process on Wetting Time and Disintegrating Time

In this investigation, the amount of water for the swelling of OGS during the modification process was evaluated based on the effect on disintegrating time and wetting time. In fact, the formulations were fixed at 15 % OGS for the comparisons because of the ability of tablet formation for all formulations and the shortest disintegrating time and wetting time at this OGS level. Three ratios of OGS/water (w/v) 1:25 (F16), 1:50 (F14), and 1:100 (F17) were examined. In Fig. (**4**), the investigation clearly showed that the ratio suitable for OGS swelling completely was 1:50 w/v with the time for disintegrating and wetting were 73.4 ± 4 s and 49.7 ± 2 s, respectively. Meanwhile, the disintegrating time and wetting time were 125 ± 3 s and 54 ± 2 s at ratio 1:25 w/v; and 145 ± 2 s and 102 ± 2 s at ratio 1:100, respectively. Hence, less or more than 50 mL of water in the modified process also

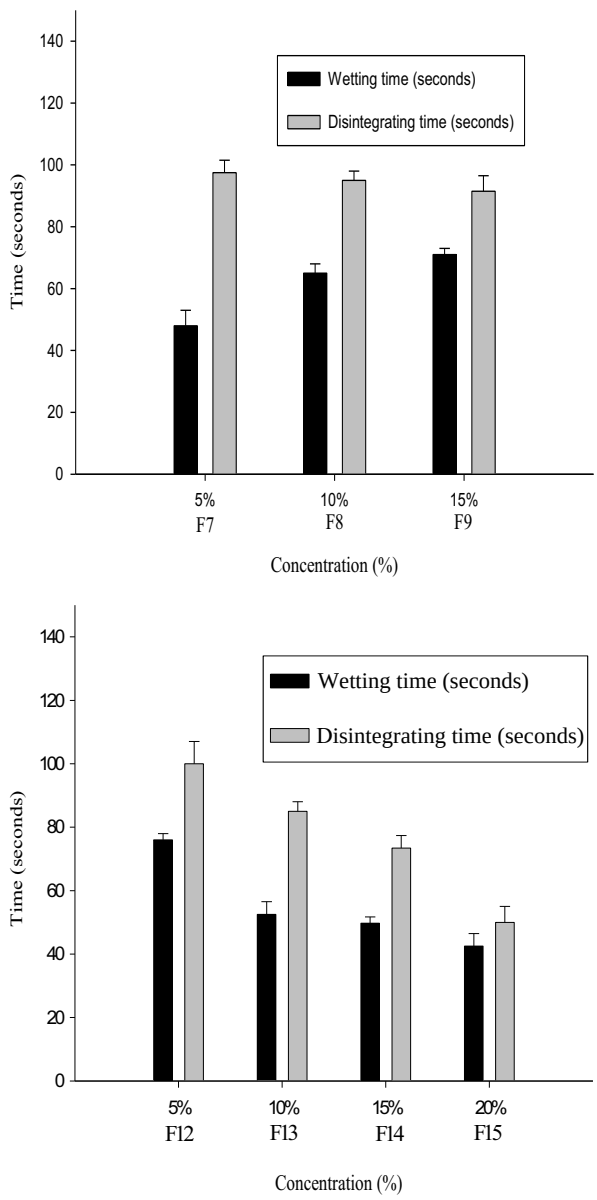

Fig. (2). Effect of OGS concentration on disintegrating time and wetting time in method 2 and method 3. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

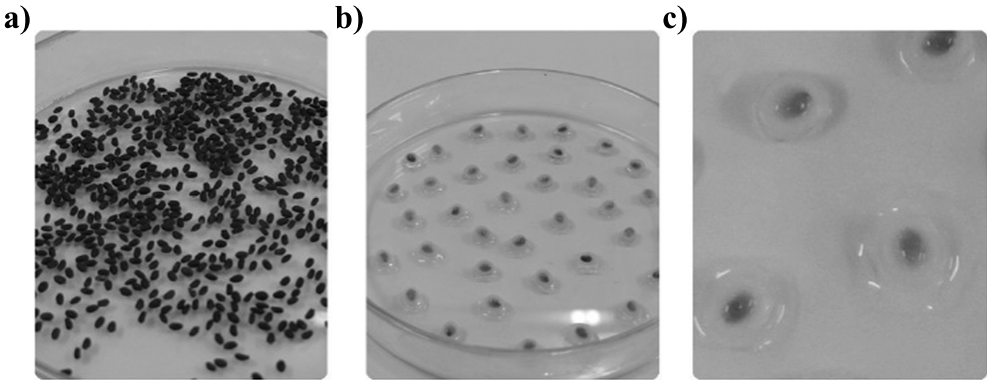

Fig. (3). *Ocimum grassium* seeds (**a**) dry, (**b**) swollen, (**c**) magnified. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

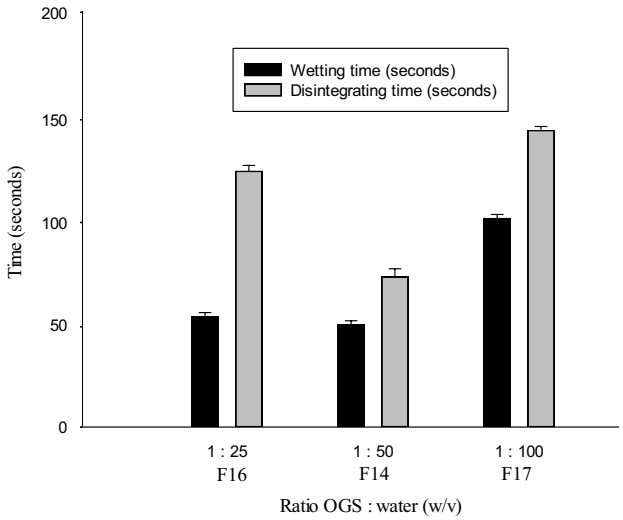

Fig. (4). Effect of the amount of water in the modification process on wetting time and disintegrating time. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

affected directly the disintegrating time and wetting time of the tablets, indicating that F14 was still the best formulation for ODTs.

3.4. Effect of the Incubation Processes on the Disintegrating Time and Wetting Time

In a further study on the modification process, temperature and time of the incubation were investigated. Fig. (**5**) demonstrates that the temperature and time of incubation process also directly affected the time of disintegrating and wetting. Firstly, the incubation temperatures of the swelling process at 50°C and 90°C were investigated and compared to the formulation prepared without incubation (F18, F20 *vs*. F14). All formulations in this test were fixed at the same concentration of 15 % OGS and the same range of 20 ± 2 N of the hardness. Fig. (**5**) indicated that the incubation process could lead to an increase in the wetting time and the disintegrating time. Specifically, the disintegrating time and wetting time of the incubation at 50°C were 132 ± 2.5 s and 73 ± 3.5 s, respectively. Similarly, the increase of the temperature to 90°C could also increase the disintegrating time to 148 ± 4.2 s and the wetting time to 92 ± 2.5 s. These values were out of the standard time for ODTs.

Secondly, at each temperature investigation above 50°C and 90°C, the incubation time was increased from 3h to 6h (F18 vs. F19 and F20 vs. F21). As a result, the increase of incubation time up to 6h resulted in 171 ± 3.2 s disintegrating time, 102 ± 3.6 s wetting time at 50 ºC (F19) and 183 ± 3.5 s disintegrating time, 109 ± 2.5 s wetting time at 90 ºC (F21). The data suggested that the modification of the incubation process might result in changing the ability swelling of OGS in ODT. Therefore, method 3 in the modification of OGS was optimized as an ideal fabrication for ODT.

3.5. Drug Content and Dissolution Studies

Four formulations of method 3 were tested with regards to the drug content and dissolution to ensure that the modification process is proper for the ODT quality. Table **3** shows the percentage drug content of the formulations in method 3 (F12 – F15) was 101.3 %, 103.5 %, 103.4 %, and 98.8 %, respectively. These values were found to be within an acceptable range and confirmed the use of OGS as a disintegrant. Furthermore, the percent of drug release in 30 min of formulations in method 3 (F12 – F15) was more than 80 %, which is acceptable according to the standard for ODTs by USP29/NF 24. Especially, the F15 formulation contained 20 % OGS in formulation had the drug release more than 90 %. Overall, the modified OGS concentration in ODT affected not only the disintegrating time but also the dissolution rate.

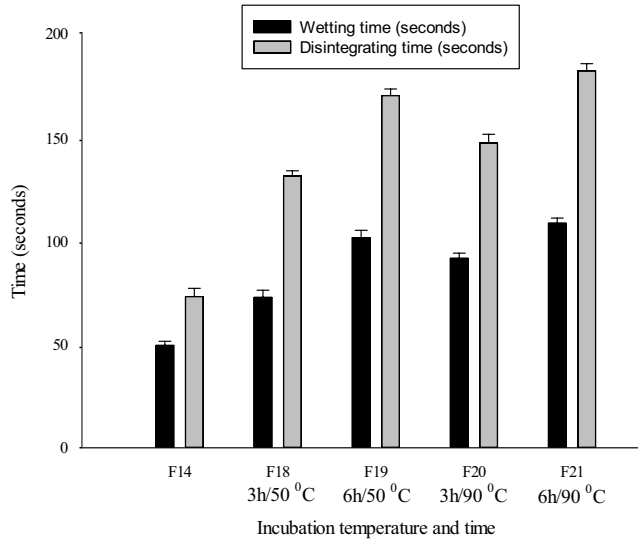

Fig. (5). Effect of the incubation processes including time and temperature on wetting time and disintegrating time. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 3. The percentage of drug content and drug release from ODT using modified OGS (F12–F15).

No.	Method	Concentration OBL	Drug Content (%)	Drug Release in 30 min (%)
F12	M3	5 %	101.3	83 ± 2.5
F13	M3	10 %	103.5	86 ± 2.3
F14	M3	15 %	103.4	88 ± 3
F15	M3	20 %	98.8	94 ± 1.4

CONCLUSION

This study successfully modified the OGS for ODTs. Method 3, in which OGS was swelled and milled during the modification process, demonstrated that OGS was an effective disintegrant in an ODT formulation. Of note, formulations containing 15 % OGS and 20 % OGS with the hardness 20 ± 2 N showed a rapid wetting time and disintegration time. The present work revealed that the modified OGS is a potential candidate for use as a disintegrant in the formulation of ODTs. Furthermore, taking the advantages of cost-effectiveness, non-toxicity, compatibility, and easy to manufacture, the modified OGS would be a promising material in ODT formulations as compared to synthetic disintegrants. Further *in vivo* studies of modified OGS will evaluate its application as a disintegrant in ODT tablets.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

We would like to thank the International University for supporting our studies. Dr. Phuong HL Tran is the recipient of the Australian Research Council's Discovery Early Career Researcher Award (project number DE160100900).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Luu T, Phan N, Tran T-D, Van Vo T, Tran P-L. Use of Microwave Method for Controlling Drug Release of Modified Sprouted Rice Starch. Toi VV, Lien Phuong TH, (Eds.). In: 5th International Conference on Biomedical Engineering in Vietnam. pp. 314-6, 2015. http://dx.doi.org/10.1007/978-3-319-11776-8_76

[2] Herman J, Remon J, De Vilder J. Modified starches as hydrophilic matrices for controlled oral delivery. I. Production and characterisation of thermally modified starches. Int J Pharm 1989; 56: 51-63. http://dx.doi.org/10.1016/0378-5173(89)90060-4

[3] Herman J, Remon J. Modified starches as hydrophilic matrices for controlled oral delivery. II. *In vitro* drug release evaluation of thermally modified starches. Int J Pharm 1989; 56: 65-70. http://dx.doi.org/10.1016/0378-5173(89)90061-6

[4] Herman J, Remon J. Modified starches as hydrophilic matrices for controlled oral delivery III. Evaluation of sustained-release theophylline formulations based on thermal modified starch matrices in dogs. Int J Pharm 1990; 63: 201-5. http://dx.doi.org/10.1016/0378-5173(90)90125-N

[5] Talukdar MM, Michoel A, Rombaut P, Kinget R. Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery I. Compaction and *in vitro* drug release behaviour. Int J Pharm 1996; 129: 233-41. http://dx.doi.org/10.1016/0378-5173(95)04355-1

[6] Peerapattana J, Phuvarit P, Srijesdaruk V, Preechagoon D, Tattawasart A. Pregelatinized glutinous rice starch as a sustained release agent for tablet preparations. Carbohydr Polym 2010; 80: 453-9. http://dx.doi.org/10.1016/j.carbpol.2009.12.006

[7] Balmayor ER, Tuzlakoglu K, Marques AP, Azevedo HS, Reis RL. A novel enzymatically-mediated drug delivery carrier for bone tissue engineering applications: Combining biodegradable starch-based microparticles and differentiation agents. J Mater Sci Mater Med 2008; 19(4): 1617-23. http://dx.doi.org/10.1007/s10856-008-3378-5 PMID: 18214645

[8] Reis AV, Guilherme MR, Moia TA, Mattoso LH, Muniz EC, Tambourgi EB. Synthesis and characterization of a starch−modified hydrogel as potential carrier for drug delivery system. J Polym Sci A Polym Chem 2008; 46: 2567-74. http://dx.doi.org/10.1002/pola.22588

[9] Nair A, Bhatnagar PS, Ghosh B, Parcha V. Studies on *Ocimum gratissimum* seed mucilage: Evaluation of suspending propertie 2005.

[10] Ravikumar, Shirwaikar AA, Shirwaikar A, Prabu DL, Mahalaxmi R, Rajendran K, Kumar CD. Studies of disintegrant properties of seed mucilage of Ocimum gratissimum. Indian J Pharm Sci, 2007; 69 (6): 753-758.

[11] Gupte A, Karjikar M, Nair J. Biosorption of copper using mucilaginous seeds of Ocimum basilicum. Acta Biologica Indica 2012; 1(1): 113-9.

[12] Zhou D, Jacob B, Welbaum GE. The Production and Function of Mucilage by Sweet Basil (*Ocimum basilicum L.*) Seeds Virginia Polytechnic Institute and State University, Blacksburg VA, USA.

[13] Parkash V, Maan S, Deepika, Yadav SK, Hemlata, Jogpal V. Fast disintegrating tablets: Opportunity in drug delivery system. J Adv Pharm Technol Res 2011; 2(4): 223-35. http://dx.doi.org/10.4103/2231-4040.90877 PMID: 22247889

[14] Kiniwa R, Miyake M, Kimura SI, Itai S, Kondo H, Iwao Y. Development of muco-adhesive orally disintegrating tablets containing tamarind gum-coated tea powders for oral care. Int J Pharm X 2019; 1100012. http://dx.doi.org/10.1016/j.ijpx.2019.100012 PMID: 31517277

[15] Wagner-Hattler L, Wyss K, Schoelkopf J, Huwyler J, Puchkov M. *In vitro* characterization and mouthfeel study of functionalized calcium carbonate in orally disintegrating tablets. Int J Pharm 2017; 534(1-2): 50-9. http://dx.doi.org/10.1016/j.ijpharm.2017.10.009 PMID: 28987455

[16] Olah I, Lasher J, Regdon G, Pintye-Hodi K, Baki G, Sovany T. Evaluating superdisintegrants for their performance in orally disintegrating tablets containing lysozyme enzyme. J Drug Deliv Sci Technol 2019; 49: 396-404. http://dx.doi.org/10.1016/j.jddst.2018.12.012

[17] Nishiyama T, Ogata T, Ozeki T. Preparation of bitter taste-masking granules of lafutidine for orally disintegrating tablets using water-insoluble/soluble polymer combinations. J Drug Deliv Sci Technol 2016; 32: 38-42. http://dx.doi.org/10.1016/j.jddst.2016.01.005

[18] Badgujar BP, Mundada AS. The technologies used for developing orally disintegrating tablets: A review. Acta Pharm 2011; 61(2): 117-39. http://dx.doi.org/10.2478/v10007-011-0020-8 PMID: 21684842

[19] Sammour OA, Hammad MA, Megrab NA, Zidan AS. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS PharmSciTech 2006; 2: 55.

[20] Fu Y, Yang S, Jeong SH, Kimura S, Park K. Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. Critical Reviews™ in Therapeutic Drug Carrier Systems 2004; 21(6): 433-475.

[21] European Pharmacopoeia. (EP 8.0) Strasbourg. Strasbourg 2014.

[22] Türkmen Ö, Ay Şenyiğit Z, Baloğlu E. Formulation and evaluation of fexofenadine hydrochloride orally disintegrating tablets for pediatric use. J Drug Deliv Sci Technol 2018; 43: 201-10. http://dx.doi.org/10.1016/j.jddst.2017.10.008

[23] Pawar H, Varkhade C, Jadhav P, Mehra K. Development and evaluation of orodispersible tablets using a natural polysaccharide isolated from *Cassia tora* seeds. Integr Med Res. 2014; 3(2): 91-98. http://dx.doi.org/10.1016/j.imr.2014.03.002