ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Domperidone Maleate Orodispersible Tablet Formulation Using Primojel® Superdisintegrant with the Wet Granulation Method

D. Gozali[1*], D. Priambodo[2], R. Mustarichie[3]

1. *Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Jatinanongor, Indonesia 45363.*
2. *Apothecary Program, Faculty of Pharmacy, Universitas Padjadjaran, Jatinanongor, Indonesia 45363.*
3. *Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Jatinanongor, Indonesia 45363.*

***Corresponding Author: D. Gozali**

Abstract

Orodispersible tablets are a solution for people who have problems swallowing drugs because they will break down instantly in the mouth without having to be swallowed. Objective: The aim of this research was to formulate orodispersible tablets using Primojel® as a superdisintegrant and domperidone male ate as an active compound to achieve the best disintegration time in the oral cavity by a wet granulation method had been carried out. Method: The tablet of 180 mg in weight was made with variation of concentration as followed 7, 2 mg (F1); 9 mg (F2); 10,8 mg (F3); 12,6 mg (F4); 14,4 mg (F5). F1, F3, F4, and F5 were qualified based on uniformity of weighing. Results: All of the formulas (F1, F2, F3, F4, and F5) were qualified based on the disintegrating time of orodispersible tablets (below three minutes). F2 has a quickest disintegration time and F1 has the longest disintegration time. Statistical analysis at α = 0, 05 showed that the concentration variation of Primojel® affected the disintegration time of the tablet. Hedonic test with five parameters included likeness, flavor, taste after taste showed that F5 was the most favorite formula. Conclusion: All formulas met the requirements of the Indonesian Pharmacopoeia IV crush time that was no more than 3 minutes. The results of the statistical analysis stated that F5 was the most preferred formula of domperidone maleate orodispersible tablets.

Keyword: *Orodispersible tablets, Primojel®, Wet granulation, Domperidone maleate, Tablet formulation.*

Introduction

Tablets are oral dosage forms that are preferred by many people because they are easy to use and practical to carry. However, many people have difficulty swallowing tablets for reasons of the bitter taste, a size that is too large and organ tremors that do not allow patients to swallow.

This usually occurs in children and the elderly and can cause a decrease in patient compliance in taking the drug [1, 2]. Orodispersible tablets are a solution for people who have problems swallowing drugs because they will break down instantly in the mouth without having to be swallowed. The disintegration time of the preparation of orodispersible tablets is no more than 3 minutes [3]. When a solid form of orodispersible tablets is placed in the mouth, the tablet will fuse and release the drug quickly. The drug will dissolve or be dispersed in saliva and will then be absorbed in the mouth and esophagus and along the pathway to the mouth thereby increasing the onset time and bioavailability [4].Orodispersible tablets that have been destroyed in the mouth can also be directly absorbed in the oral mucosa into the systemic circulation to avoid the metabolism of stage one in the liver [5, 6].

Domperidone maleate is a drug that is indicated for functional disorders of the stomach, such as nausea and vomiting, the effects of nausea and vomiting in cancer treatment and bromocriptine and levodopa therapy in Parkinson's patients.

Domperidone maleate works by blocking neurotransmission from the Chemoreceptor Trigger Zone to the vomiting center by blocking dopamine receptors. Domperidone maleate also facilitates gastric emptying and decreases the transit time of the stomach contents [7].This study reports the determination of the correct formulation of orodispersible tablets with the active ingredient domperidone maleate and super disintegrant Primojel® using the wet granulation method.

Materials and Methods

Tools

Flow velocity and rest angle testing tools, tablet hardness test equipment (ERWEKA Type TB-24), tablet crispness test (friability), tap density, dry shrinkage test equipment (OHAUS LTF-003), crush time test equipment, dissolution test equipment, spectrophotometer (Specord 200), calipers (Mitutoyo), tablet presses (single punch) (KORSCH), digital scales (Mettler Toledo-Dragon 204), stopwatches, thermometers, glassware that were common in the Non-Sterile Technology Laboratory.

Materials

Domperidone maleate (Aurobindo), Primojel® (Yung Zip), mannitol (Roquette), polyvinylpyrrolidone (PVP), polyethylene glycol 6000 (PEG 6000), magnesium stearate (FACI), talcum (Roquette), polyvinylpyrrolidone (PVP), polyethylene glycol 6000 (PEG 6000), magnesium stearate (FACI), talcum (Takehara), Aerosil® (Wacker Chemie), sucralose (Sugabung), tutti frutti (Firmenich). All ingredients unless otherwise stated were pharmaceutical grade.

Research Methods

Orodispersible tablets formulations were designed as shown in Table 1.

Sifting and weighing the ingredients used: The sifting process serves to eliminate the agglomerations of the ingredients so that the homogenization process could take place properly.

Manufacture of Inner Phases (Granule 1)

Mannitol and PVP were mixed until homogeneous. This mixture was then sprayed with water to form a mass that could be clenched. This mass was sifted using sifter number 14 to form granules and then dried again sifted using sifter number 20. This mass was sifted using sifter number 14 to form granules and then dried with an oven for 24 hours. The dried granules are then sifted again using sifter number 20.

Manufacture of Inner Phases (Granule 2)

The active ingredient of the domperidone maleate was very bitter so it needed to be done the process of closing the flavor using a flavor cover PEG 6000. At first, PEG 6000 was mashed then mixed with domperidone maleate. After being homogeneous, water was added to the mass to form a mass that can be clenched. This mass was sieved using sieve number 14 until granules were formed and then dried in the oven for 3 hours and again sifted using sieve number 20.

Print Mass Making

Granules 1, granules 2, outer phase (Primojel®, talc, magnesium stearate, Aerosil®, sucralose, and tutti frutti) were mixed until a homogeneous print mass was formed. Print mass was then tested its dry shrinkage, flow rate, resting angle, real density, incompressible density, and compressibility.

Printing of orodispersible tablets: Orodispersible tablets were printed using a single punch 8 tablet machine.

Tablet Evaluation

The tablet was evaluated its size uniformity, uniformity in weights, hardness, friability, disintegrating time, dissolution, concentration, hedonic test, and statistical analysis.

Results and Discussion

Domperidone Maleate Orodispersible Tablets Formulation

The orodispersible tablets domperidone maleate formula was shown in table 1. Formulations were made by referring to the existing textbook [8, 12]. As seen in the table, the uses of the active substance domperidone maleate with a concentration of 7.07% or 12.73 mg per tablet.

The use of a dose of 12.73 mg was intended as an antiemetic especially in the symptoms of nausea and vomiting caused by cancer treatment and bromocriptine and levodopa

therapy in Parkinson's patients. It is hoped that the preparation of the orodispersible tablets could make it easier for patients to take drugs, especially for children and elderly people, because they would quickly disintegrate in the mouth without swallowing [13]. Primojel® functions as a superdisintegrant to obtain the disintegration time that met the requirements for the disintegration time of available orodispersible tablets as stated on the pharmacopeia which was less than 3 minutes (180 seconds). Primojel® works as a super disintegrant based on its good hydration ability where Primojel® has a very large affinity for water so that it would expand when it was wetted and then disintegrated into small particles [14]. In the formulation of orodispersible tablets, the domperidone maleate was used mannitol as filler. Mannitol was chosen because it had a pleasant after taste and a cold sensation so that if the orodispersible tablets dissolve in the patient's mouth it would give a good taste. Also, mannitol had a low calorie because mannitol was sugar-free so it was safe for diabetic patients. Mannitol also did not cause tooth decay [15].

Table 1: Formula of Tablet Domperidone Maleate Orodispersible

Formula	F1	F2	F3	F4	F5
Composition	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
Domperidone Maleate	7.07	7.07	7.07	7.07	7.07
Primojel®	4	5	6	7	8
PVP	1	1	1	1	1
PEG 6000	4	4	4	4	4
Magnesium Stearate	1	1	1	1	1
Talcum	1	1	1	1	1
Aerosil®	0.5	0.5	0.5	0.5	0.5
Sucralose	0.15	0.15	0.15	0.15	0.15
Tutti Frutti	0.2	0.2	0,.	0.2	0.2
Mannitol	81.08	80.08	79.08	78.08	77.08
Total	100	100	100	100	100

The method used in the manufacture of orodispersible tablets this time was the wet granulation method [16]. The wet granulation method was chosen because the excipients used were in the form of powder so that the flow rate formed was very poor. This would be difficult when printing tablets. Therefore, a wet granulation method was used to form granules that were expected to increase the flow rate. The wet granulation method required a binder that could bind the particles into granules if a liquid was added. The wet binder used in this formulation of domperidone maleate orodispersible tablets was polyvinylpyrrolidone (PVP) [17].

With the addition of PVP, it was expected that orodispersible tablets domperidone maleate had good compactness. The active ingredient of the domperidone maleate was very bitter. This was very contrary to the goal of making orodispersible tablets which ought to be destroyed in the mouth. This bitter taste would cause discomfort in the mouth.

To overcome this, the domperidone maleate flavor closure process was carried out using PEG 6000 [18]. The PEG 6000 concentration used was 4%. Large PEG 6000 particles could bind and cover the surface of the domperidone maleate so that the bitter taste would be slightly covered. The use of Aerosil®, magnesium stearate, and talcum in the orodispersible tablets domperidone maleate formula functions as a lubricant. Each lubricant is used as much as 1% (magnesium stearate and talc) and 0.5% (Aerosil®) to help the print mass of the tablet so that it can flow properly during printing. Talcum and magnesium stearate also function to prevent the sticking mass of the print on the tablet machine [19].

Tutti frutti is used as a scent on domperidone maleate orodispersible tablets. Tutti frutti has a variety of fruit scents [20]. With a concentration of 0.2%, Tutti Frutti's aroma was found on Oodispersible tablets domperidone maleate.

Sucralose is used as a sweetener in domperidone maleate orodispersible tablets. The level of sweetness possessed by mannitol is very small, therefore additional sweeteners are needed. Sucralose has a degree of sweetness 600 times higher than sucrose [21].

The use of sucralose as much as 0.15% can give a sweet taste to orodispersible tablets domperidone maleate.

Manufacture of Inner Phases (Granule 1)

Mannitol and PVP were mixed until homogeneous. This mixture was then sprayed with water to form a mass that can be clenched. This mass was sifted using sifter number 14 to form granules and then dried again sifted using sifter number 20. This mass was sifted using sifter number 14 to form granules and then dried with an oven for 24 hours. The dried granules were then sifted again using sifter number 20.

Manufacture of Inner Phases (Granule 2)

The active ingredient of the domperidone maleate was very bitter so it needed to be done the process of closing the flavor using a flavor cover PEG 6000. At first, PEG 6000 was mashed then mixed with domperidone maleate. After being homogeneous, water was added to the mass to form a mass that could be clenched. This mass was sifted using sifter number 14 to form granules and then dried in the oven for 3 hours and again sifted using sifter number 20.

Print Mass Making

Granules 1, granules 2, outer phase (Primojel®, talc, magnesium stearate, Aerosil®, sucralose, and tutti frutti) were mixed until a homogeneous print mass was formed. Print Mass Testing was carried out on dry shrinkage, flow rate, resting angle, real density, incompressible density, and compressibility. Table2 showed the results of these tests. The flow rate check results showed that the print mass has a free flow type because it was valued at more than 10 g/s. The results of the break angle examination showed that the print mass had a very good type of powder flow because it was less than 25º [9].

Both of these indicate that the granulation process carried out successfully improved the print mass excipient flow rate. F1 and F3 had the highest flow rate and the lowest flow rate, respectively. F1 had the highest rest angle (19.72º) and F4 had the lowest rest angle (13.17º). Drying shrinkage test results were found at the ranged from 0.1653-0.4229% which indicated that the print mass of the tablet had met the requirements for good dry shrinkage of the print mass of the tablet which was not more than 2% [9]. On the compressibility of print mass also indicated that the print mass for all formulas had good compressibility (ranging from 11-15%) [9].

Table 2: Domperidone maleate orodispersible tablets print mass evaluation

Formula	F1	F2	F3	F4	F5
Drying shrinkage (%)	0.3678± 0.019	0.4265± 0.0089	0.2185± 0.0030	0.1651± 0.0123	0.3760± 0.0110
Real density (g/ml)	0.56± 0.008	0.54± 0.004	0.59± 0.005	0.58± 0.00	0.58± 0.005
Compressible density (g/ml)	0.66± 0.006	0.64± 0.006	0.67± 0.006	0.66± 0.006	0.68± 0.006
Compressibility (%)	15.01± 1.951	15.38± 0.729	11.38± 0.816	11.99± 0.705	14.2± 0.828
Flow rate (g/sec)	17.68± 0.875	16.24± 0.740	16.24± 0.741	17.18± 0.875	16.75± 1.340
Resting Angle	19.72± 1.003	17.83± 0.736	14.74± 1.076	13.17± 2.114	14.71± 0.768

Notes: All data obtained from 3 measurements

F_1: Formula with Primojel® 4% F_2: Formula with Primojel® 5%
F_3: Formula with Primojel® 6%, F_4: Formula with Primojel® 7%
F_5: Formula with Primojel® 8%

Tablet Evaluation

Orodispersible tablets were printed using a single punch 8 tablet machine. Tablet evaluation was carried out on size uniformity, uniformity in weights, hardness, friability, broken time, dissolution, concentration, and hedonic test; the results of which were shown in Table 3.

Table 3: Evaluation results of domperidone maleate orodispersible tablets

Formula	F1	F2	F3	F4	F5
Weight uniformity(mg)	175,105± 2,858	155,22± 2,595	173,525± 2,869	182,105± 3,217	181,845± 0,162
Diameter (mm)	7,971± 0,022	7,997± 0,015	7,993± 0,018	7,999± 0,022	8,0115± 0,019
Thickness (mm)	2,7575± 0,0275	2,6345± 0,032	2,806± 0,041	2,839± 0,0871	2,923± 0,040
Hardness (N)	33,875± 2,8232	23,675± 5,743	28,2± 3,160	31,8± 2,3306	30,475± 2,3306
Friability (%)	0,216	0,235	0,028	0,756	0,171
Disintegration time (sec)	160± 5,568	49,67± 4,163	145± 8,185	108,3± 1,155	62± 1,732

Notes: all data obtained from 3 measurements

Evaluation of size uniformity of the five domperidone maleate formulas orodispersible tablets, almost all tablets had a pretty good appearance, in terms of physical appearance and color. The average thickness of tablets of all formulas ranges from 2.6345 to 2.923 mm with an average diameter between 7.971-8.0115 mm. All formulas showed the size of tablets that met the requirements under the Pharmacopoeia of Indonesia III, the diameter of the tablet was not more than three times and not less than four-thirds the thickness of the tablet [22].

The data obtained from the evaluation of uniform weight showed that the uniformity of weights F1, F3, F4, and F5 meet the requirements as stated in Pharmacopoeia III which stated that the uniformity of the weight of tablets with a weight of 151-300 mg ought to meet the requirement that of the 20 tablets calculated for the average weight of each tablet if weighed one by one it should not be more than two tablets the weight deviates from the average weight greater than 7.5% and not a single tablet that weighs greater than 15%. The weight uniformity of F2 did not meet the requirements. This was due to a technical error in the machine because when printing the F2 the machine had jammed.

The hardness of the tablet was directly proportional to the time of disintegration. The higher the hardness, the more time would be destroyed. Therefore the hardness of orodispersible tablets domperidone maleate was made low to get a short disintegration time without increasing the friability of tablets. It was found F1 had the highest average hardness which was 33.875 N while F2 had the lowest average hardness which was 23.675 N. Friability testing needed to be done because at the time of packaging, packing, and distribution to consumers the tablet would experience shocks and pressure so that it was feared to be damaged.

According to USP 27, the maximum limit for tablet friability was 0.8% [23]. To get fast disintegration time, additional super disintegrant was needed. In this study, Primojel® was used as a superdisintegrant. It showed F2 with a Primojel® concentration of 5% had the fastest disintegration time (49.67 seconds). F1 with a Primojel® 4% concentration had the longest disintegration time (160 seconds). In theory, the higher the Primojel® concentration, the faster the disintegration time [24].

Therefore, F5 with a Primojel® 8% concentration should have the fastest disintegration time. This deviation was caused by F2 having the lowest average weight and hardness compared to all formulas. By using the standard curve and the maximum wavelength at 280 nm, the relationship between the time taken and the percentage of sample dissolution solubility obtained Domperidone Maleate Orodispersible Tablets Profile as shown in Fig. 1. The graph showed that domperidone maleate from orodispersible tablets gave good dissolution. At the fifth minute, the release of domperidone maleate reached 40% and at the thirtieth minute, there was almost 100%

release. From the graph, it appeared that there was a deviation in F1 where F1 dissolution reached 262.05% in the thirtieth minute. This error could be caused when technically taking samples where the volume of samples taken was not the same as the volume added again in the medium so that it changed the percentage of dissolved domperidone maleate. This deviation could also occur during sample preparation when measured on a spectrophotometer. Unclean cuvettes could cause the domperidone maleate active substance from the previous measurements. The graph also indicated that the higher the Primojel® concentration, the faster the release of domperidone maleate.

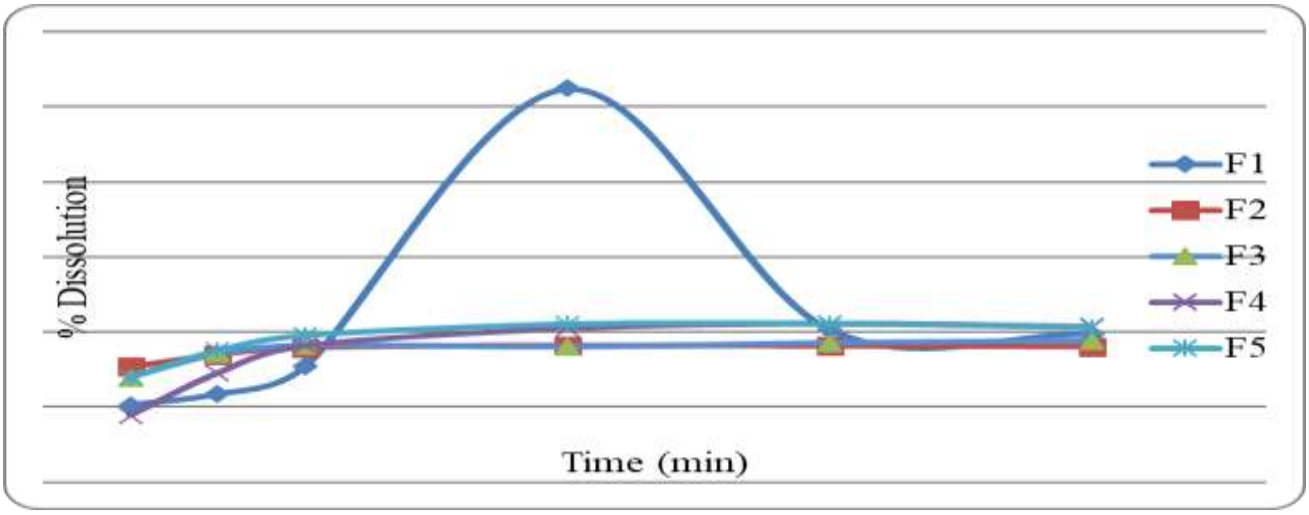

Fig. 1: Orodispersible tablets domperidone maleate dissolution profile

Notes: F1: Formula 1 with Primojel® 4%
F2: Formula 2 with Primojel® 5%
F3: Formula 3 with Primojel® 6%
F4: Formula 4 with Primojel® 7%
F5: Formula 5 with Primojel® 8%

From the evaluation of the determination of the content, concentration obtained measured levels of data in each formula ranged between 96.29-121.99%. For F2 the levels obtained met the requirements which were in the range of 95-105% [25]. For F1, F3, F4, and F5 the levels obtained do not meet the requirements (exceeding 105%). This very large level could be caused by the mixing process which was less homogeneous so that the active substances would collect in one part. This was because the dose was too small, which was 12.73 mg in 180 mg, making mixing difficult. Gathering active substances in one section would cause a lack of active substances in other parts. For the hedonic test, preferred test results for 30 panelists showed that F5 with a Primojel® 7% concentration was the most preferred formula

Statistical Analysis

To get accurate results, statistical tests were performed on tablet hardness, disintegration time, and hedonic tests. The results of this analysis test had been mentioned above. One example of how to carry out the statistical test that was a test of tablet hardness was given as follows.

Statistical model:

$$Y_{ij} = \mu + \tau_i + \varepsilon_{ij}$$

Where:

Y_{ij} = tablet hardness to j due to Primojel® concentration to i

μ = actual average

τ_i = the effects of Primojel® concentration to i

ε_{ij} = the effect of hardness of tablets to j due to the concentration of Primojel® to i

The model remains with the null hypothesis shaped

H_0: τi = 0; i = 1, 2,3,4,5 with Σ τi = 0

This meant there was no difference in the variation of Primojel® concentration on tablet hardness. Values required for ANOVA were as follows: Ry= $\frac{(2960, 5)^2}{100}$ = 87645.6

$$Py = \frac{(677, 5)^2}{100} + \frac{(473, 5)^2}{100} + \frac{(564)^2}{100} + \frac{(636)^2}{100} + \frac{(609, 5)^2}{100} - Ry = 88864, 54$$

Σ_{y2} = $(34)^2 + (38)^2 + \ldots (36)^2 = 90092,75$

Σ_y = 1228,213

Statistic F:

$F = \frac{KT (P)}{KT (E)}$

$= \frac{304,73}{12,929} = 23,570601$

From the calculation, following Table 4 was found:

Table 4: ANOVA Domperidone maleate orodispersible tablets

Source of variation	dk	JK	KT	F
Mean	1	87645,6	87645,603	
Superdisintegrant	4	1218,935	304,734	23,570601
Mistakes	95	1228,213	12,929	
Total	100	90092,75		

With a real level of 0.05, from the list of tables for distribution with v1 = 4 and v2 = 95 obtained F = 2.48. Because F arithmetic 23.57 was greater than F table 2.48, the hypothesis H0 was rejected. This meant that the five Primojel® concentration types had a significantly different effect on tablet hardness. To find out the difference, it could be seen from Newman-Keuls.

Mean	33,875	23,675	28,2	31,8	30,475
Treatment	1	2	3	4	5

From the ANOVA list, it was obtained KT (E) of 12,929 with dk = 95.

The average standard error for each treatment was the amount:

$$Syi = \sqrt{\frac{E}{n}}$$

$$= \sqrt{\frac{12,929}{20}} = 0,804$$

From the list E with v = 95 and α = 0.05 obtained:

P	2	3	4	5
Range	2,81	3,38	3,71	3,94

The resulting range was multiplied by 0.804. Then obtained RST for each P as follows:

P	2	3	4	5
RST	2,259	2,718	2,983	3,168

From the results of the average test after ANOVA with α = 0.05 using the Newman-Keuls range test it was found that the hardness of tablets with F1 (33.875 N) differed significantly from F2 (23.675 N), F3 (28.2 N), and F5 (30,475 N). F2 (23,675 N) was significantly different from F4 (31.8 N), F5 (30,475 N), and F3 (28.2 N). F3 was significantly different from F4 (31.8 N) and (30.475 N), while the comparison of F1 (33.875 N) to F4 (31.8 N), the comparison of F4 (31.8 N) with F5 (30.475 N) did not provide the significant difference.

Conclusion

Based on the results of the study, it was concluded that domperidone maleate tablets with super disintegrant Primojel® concentrated 4% (F1), 6% (F3), 7% (F4), and 8% (F5) had fulfilled the requirements of good orodispersible tablets. All formulas meet the requirements of the Pharmacopoeia IV crush time that is no more than 3 minutes (180 seconds). The higher the concentration of super disintegrant, the faster the time of destruction. The release of the domperidone maleate (dissolution) is directly proportional to the disintegration time. The greater the concentration of Primojel®, the faster and greater the release of domperidone maleate. The results of the statistical analysis state that F5 is the most preferred formula of domperidone maleate orodispersible tablets.

Acknowledgements

We thank D. Rostianty and Y.R. Pohan for technical support.

References

1. Jacques ER, Alexandridis P (2019) Tablet Scoring: Current Practice, Fundamentals, and Knowledge Gaps. Appl. Sci., 9: 30-66. doi:10.3390/app9153066
2. Ibrahim IR, Haddad SA, Ibrahim MIM (2012) The influence of consumers' preferences and perceptions of oral solid dosage forms on their treatment. Int. J. Clin. Pharm., 34(5):728-32. DOI: 10.1007/s11096-012-9667-6.
3. Council of Europe (2007) European Pharmacopoeia. Sixth Edition. Volume 2. Jerman: Druckerei C.H. Beck., 641 (780): 1745-1749.
4. Hirani JJ, Rathod DA, Vadalia KR (2009) Orally Disintegrating Tablets: A Review. Tropical Journal of Pharmaceutical., 8(2):161-72.
5. Zhang H, Zhang J, Streisand JB (2002) Oral Mucosal Drug Delivery. Clin Pharmacokine t 41(9):661-80. DOI: 10.2165/00003088-200241090-00003
6. Segale L, Maggi L, Machiste EO, Besse C (2007) Formulation design and development to produce orodispersible tablets by direct compression. Journal of Drug Delivery Science and Technology, 17(3):199-203. DOI: 10.1016/S1773-2247(07)50036-5
7. Lertxundi U, Domingo-Echaburu S, Soraluce A, García M, Ruiz-Osante B, Aguirre C (2013) Domperidone in Parkinson's disease: a perilous arrhythmogenic or the gold standard?. Curr Drug Saf., 8(1):63-8. DOI: 10.2174/1574886311308010009
8. Ansel HC (1989) Introduction to Pharmacy Dosage Forms (Indonesian: Pengantar Bentuk Sediaan Farmasi) 4th Ed. Jakarta: UI Press, 355.
9. Aulton ME (1998) Pharmaceutics: The Science of Dosage Form Design. New York: Churchill Livingstone, 248: 612-613.
10. Rowe RC (2006) Handbook of Pharmaceutical Excipients. London: Pharmaceutical Press, 188-190, 201-203,701-704, 430-432, 611-615, 767-769.
11. Mustarichie, Priambodo D (2018) Tablet formulation from meniran (Phyllanthus niruri L.) extract with Dirct Compression Method, Int. J. App. Pharm., 10(4): 98-102. DOI: http://dx.doi.org/10.22159/ijap.2018v10i4.26795
12. Mustarichie R, Priambodo D (2019) Formulation of orally disintegrating secang (Caesalpinia sappan l.) tablets as an antioxidant with hydroxypropyl cellulose as a masking agent, Int. J. App. Pharm., 11(4): 236-41. DOI: http://dx.doi.org/10.22159/ijap.2019v11i4.32663
13. Bandari S, Gannu R, Mittapalli R, Yamsani MR (2008) Orodispersible tablets: An overview. Asian Journal of

Pharmaceutics, 2(1):1-11. DOI: 10.4103/0973-8398.41557

14. Bhowmik D, Kumar KPS, Bhanot R (2018) Recent trends in the role of super disintegrants to the formulation of the solid oral dosage form. RJPDFT, 109040: 245-52. DOI: 10.5958/0975-4377.2018.00036.8
15. Caballero B, Finglas P, Toldra F (2003) Encyclopedia of Food Sciences and Nutrition, eBook ISBN: 9780080917917, Academic Press.
16. Pharma Tips (2015) Wet Granulation Process for Tablet Manufacturing. Available at: http://www.pharmatips.in/Articles/Production/Wet-Granulation-Process-For-Tablet-Manufacturing.aspx. (Downloaded on February 15, 2020)
17. Silva MF, de Oliveira LAS, Ciciliati MA, Lima MK, Ivashita FF, de Oliveira DMF, et.al (2017) The Effects and Role of Polyvinylpyrrolidone on the Size and Phase Composition of Iron Oxide Nanoparticles Prepared by a Modified Sol-Gel Method. Journal of Nanomaterials |Article ID 7939727 | 10 pages | https://doi.org/10.1155/2017/7939727
18. D'Souza AA, Shegokar R (2016) Polyethylene glycol (PEG): a versatile polymer for pharmaceutical applications. Journal Expert Opinion on Drug Delivery, 13(9):1257-75. https://doi.org/10.1080/17425247.2016.1182485
19. Li J, Wu Y (2014) Lubricants in Pharmaceutical Solid Dosage Forms, Lubricants, 2: 21-43. doi:10.3390/lubricants2010021
20. WebMD (2020) TUTTI FRUTTI Flavor Liquid Available at: https://www.webmd.com/drugs/2/drug-156663/tutti-frutti-flavor-bulk/details. (Downloaded on February 15, 2020)
21. Food Insight (2018) Everything You Need to Know About Sucralose. Available at: https://foodinsight.org/everything-you-need-to-know-about-sucralose/. Downloaded on February 15, 2020)
22. Departemen Kesehatan Republik Indonesia (1979) Farmakope Indonesia. Edisi III. Jakarta: Departemen Kesehatan Republik Indonesia, 6-7.
23. The Department of Health (2004) United States Pharmacopoeia. Twenty Seventh Edition. Kanada: Stationery Office, 2621-2.
24. Di Martino P, Martelli S, Wehrlé P (2005) Evaluation of different fast-melting disintegrants by means of a central composite design. Drug Dev. Ind. Pharm., 31(1):109-21. DOI: 10.1081/ddc-44233
25. Departemen Kesehatan Republik (1995) Farmakope Indonesia. Edisi IV. Jakarta: Departemen Kesehatan Republik Indonesia, 4-6 1083-1084, 1086-1088.

