

## PREPARATION AND EVALUATION OF ATENOLOL- $\beta$ -CYCLODEXTRIN ORALLY DISINTEGRATING TABLETS USING CO-PROCESS CROSPROVIDONE-SODIUM STARCH GLYCOLATE

NANI PARFATI, KARINA CITRA RANI\*, NATHANAEL CHARLES, VALENCIA GEOVANNY

Department of Pharmaceutics, Faculty of Pharmacy, University of Surabaya, Kalirungkut, Surabaya 60293, East Java, Indonesia  
Email: karinacitrarani@staff.ubaya.ac.id

Received: 15 Jun 2018, Revised and Accepted: 26 Jul 2018

### ABSTRACT

**Objective:** The aim of this current research was to formulate and analyze the characteristics of atenolol- $\beta$ -cyclodextrin which using co-process crospovidone-sodium starch glycolate as the disintegrants. Evaluation which has been conducted on orally disintegrating tablets consist of wetting time, water absorption ratio, *in vitro* dispersion time, and dissolution.

**Methods:** Inclusion complex of atenolol- $\beta$ -cyclodextrin which were prepared using solvent evaporation method, then formulated using co-processed crospovidone-sodium starch glycolate 1:1 (formula 1) and 1:2 (formula 2) into orally disintegrating tablets by direct compression technique. Orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin using a physical mixture of crospovidone-sodium starch glycolate 1:1 (formula 3), 1:2 (formula 4) was also prepared as a control. The prepared formulations (F1-F4) were evaluated by several parameters such as wetting time, water absorption ratio, *in vitro* dispersion time, and dissolution.

**Results:** Orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin using co-processed crospovidone-sodium starch glycolate 1:1 (formula 1) showed shorter wetting time (53.53 $\pm$ 2.26 seconds) and *in vitro* dispersion time (47.44 $\pm$ 2.49 seconds) compare to the other formulas. Formula 1 also exhibited the highest dissolution efficiency compare to the formula which was used in the physical mixture. The results of this study also revealed that there was a high correlation between *in vitro* dispersion time and dissolution efficiency of atenolol- $\beta$ -cyclodextrin orally disintegrating tablets.

**Conclusion:** Orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin showed enhanced dissolution efficiency due to the presence of inclusion complex and co-processed crospovidone-sodium starch glycolate. Formula 1 was found to be the best formula in this study. This formula effectively reduces *in vitro* dispersion time, hence the dissolution efficiency became higher.

**Keywords:** Atenolol, orally disintegrating tablets, Inclusion complex, Co-processed, crospovidone, sodium starch glycolate

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DOI: <http://dx.doi.org/10.22159/ijap.2018v10i5.27982>

### INTRODUCTION

Peroral drug delivery route was the most commonly used and convenient to deliver the drug because it is the most natural, not harmful, easy to use, and safe in terms of drug delivery [1]. To certain people, the use of conventional tablets has caused trouble, such as the elderly who are experiencing difficulties in using conventional dosage forms because of hand tremors and dysphagia [1, 2]. This condition produces non-compliance in a specified group of patients, especially geriatric. Statistics showed that approximately 50% of patients on long-term therapy did not comply with the prescribed treatment [3]. The outcomes from previous work revealed that the cost of treatment, discomfort with treatment, and long-term therapy were common reasons for non-compliance [4]. To overcome these problems, an effective drug delivery system is needed to provide a solution to the non-compliance issues. The orally disintegrating tablet is one of the peroral delivery systems which can exhibit improvement in compliance, especially in geriatric patients who take long-term therapy.

Orally disintegrating tablets are solid single-unit dosage forms that are designed to be placed in the mouth, allowed to disperse or dissolve in the saliva, and then swallowed without the aid of additional water. Orally disintegrating tablets must disperse or dissolve in the mouth quickly, within seconds [5]. US FDA stated that orally disintegrating tablet is a tablet which disintegrates in the oral cavity less than 30 seconds [6]. Orally disintegrating tablets also provide fast disintegration of the tablets results in a quick dissolution of the drug and fast absorption that provide rapid onset of action [7, 8]. The drug may get absorbed from the pharynx and esophagus or from other sections of GIT as the saliva travels down. In such cases, bioavailability is significantly greater than that observed from conventional tablet dosage form [9, 10].

The candidate drug categories for orally disintegrating tablets are diverse, such as cardiovascular drugs used for chronic conditions

with a large geriatric population as users [5]. Atenolol is classified as  $\beta$ 1-blocker and widely prescribed in diverse cardiovascular diseases such as hypertension, angina, arrhythmias, and myocardial infarction [11, 12]. Atenolol is slightly soluble in water. The solubility of atenolol in water (25 °C) is approximately 13.3 mg/ml [13, 14]. Consequently, in order to increase the solubility and dissolution rate of atenolol, inclusion complex formation with cyclodextrin becomes imperative [15].  $\beta$ -cyclodextrin as host molecules can interact with various drugs through the ability to entrap low solubility drugs in the hydrophobic cavity. Moreover, the exterior part of  $\beta$ -cyclodextrin which relatively hydrophilic can enhance the solubility of the drugs.

Formulation of orally disintegrating tablets also can enhance the dissolution of atenolol, because it can produce faster disintegration time compare to the conventional tablets. Superdisintegrants are the class of compounds which primarily aid the rapid disintegration of orally disintegrating tablets in the oral cavity [16]. Superdisintegrants are strongly hygroscopic materials that aid in wicking water from the saliva into the internal structure of the tablets. Nevertheless, the hygroscopicity of superdisintegrants is such that both their functionality and tablet stability can be compromised by excessive exposure to high humidity [5]. Hence, in the orally disintegrating tablets formulation, there is a need to have superdisintegrants with low or no moisture sensitivity and rapid disintegration ability. One approach for improving the characteristics of superdisintegrants is co-processing of two superdisintegrants [17]. Crospovidone and sodium starch glycolate were chosen for this study because of their valuable characteristics. Crospovidone had high capillary activity, pronounced hydration capacity and little tendency to produce gels. Sodium starch glycolate was chosen because of its high swelling capacity [5]. The aim of this study was to formulate and evaluate the characteristics of atenolol- $\beta$ -cyclodextrin using co-processed crospovidone-sodium starch glycolates to increase water uptake, shorten the wetting time,

and thereby decrease the disintegration time of the tablets by synergism effect of these two superdisintegrants and increased the dissolution efficiency.

## MATERIALS AND METHODS

### Materials

Materials that were used in this study consists of atenolol p. g (Reformed Chemicals, Lugono Switzerland),  $\beta$ -cyclodextrin (Roquette, France), crospovidone (Kollidon® CL) p. g (BASF South East Asia Pre-Ltd), sodium starch glycolate. g (Yung Zip Chemical IND. Co. LTD), magnesium stearate p. g (Faci Asia Pacific PTE LTD), aspartame f. g (Ajinomoto Co. Inc.), aqua demineralization (Laboratorium of qualitative chemistry, University of Surabaya), mannitol DC p. g (RoquetteFreses, Perancis), Aerosil® p. g (PT. Brataco), *mint flavor* f. g (KH Roberts), sodium dihydrogen phosphate. a ( $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ ) p. a (Merck), disodium hydrogen phosphate. a ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) p. a (Merck), sodium acetate trihydrate p. a. (Riedel), glacial acetic acid p. a (Merck), methanol pro-HPLC (Mallinckrodt Chemicals), Avicel PH 102® p. g (Mingtai Chemical Co. LTD), talk (PT. Brataco), and Whatman filter paper no 41.

### Methods

#### Preparation of inclusion complex of atenolol- $\beta$ -cyclodextrin

Inclusion complex of atenolol- $\beta$ -cyclodextrin was prepared by a solvent evaporation method. Atenolol and  $\beta$ -cyclodextrin were dissolved separately in ethanol; then the dispersion was mixed thoroughly by using magnetic stirrer for 2 h, then this mixture was placed in a water bath (90 °C) to evaporate the solvent. The

inclusion complexes were obtained as a crystalline powder pulverized. The inclusion complexes were sieved by using sieve no.60 and stored in airtight containers till further use.

#### Preparation of co-processed superdisintegrants (crospovidone-sodium starch glycolate)

The co-processed superdisintegrants were prepared by the solvent evaporation method. A blend of crospovidone and sodium starch glycolate (1:1 and 1:2) was added to 50 ml of ethanol in beaker glass. This mixture was mixed thoroughly and stirred on a magnetic stirrer while maintaining the temperature between 50-60 °C until ethanol has been evaporated [18]. Wet granule mass was sieved through #40 mesh; then wet granules were dried in a hot air oven at 60 °C for 20 min. The dried granules were sieved through #40 mesh and stored in airtight container and protected from light until further use.

#### Preparation of powder mixture

Inclusion complex of atenolol- $\beta$ -cyclodextrin which have been prepared then mixed with several excipients to produce orally disintegrating tablets. Preparation of powder mixture of compression was performed by mixing the component in table 1. Inclusion complex of atenolol- $\beta$ -cyclodextrin (equivalent to 25 mg of atenolol in each tablet) was premixed with a half portion of Aerosil 200® for 3 min. This mixture then mixed thoroughly with co-processed crospovidone-sodium starch glycolate, Avicel PH 102®, mannitol DC, aspartame, and mint flavor for 10 min in a tumbling mixer. In the final step, the powder mixture was mixed with talc, magnesium stearate, and Aerosil 200® for 3 min.

Table 1: Formula of atenolol orally disintegrating tablet using co-processed crospovidone-sodium starch glycolate

Contents	Co-processed		Physical mixture	
	Formula 1 (mg)	Formula 2 (mg)	Formula 3 (mg)	Formula 4 (mg)
Atenolol- $\beta$ -cyclodextrin	133.41	133.41	133.41	133.41
Co-processed crospovidone-sodium starch glycolate	30 (1:1)	30 (1:2)	-	-
Physical mixture crospovidone-sodium starch glycolate	-	-	30 (1:1)	30 (1:2)
Avicel PH 102®	94.87	94.87	94.87	94.87
Mannitol DC	23.72	23.72	23.72	23.72
Aspartam	9	9	9	9
Mint flavor	3	3	3	3
Magnesium stearate	1.5	1.5	1.5	1.5
Talk	3	3	3	3
Aerosil 200®	1.5	1.5	1.5	1.5

#### Preparation of atenolol- $\beta$ -cyclodextrin orally disintegrating tablets

Orally disintegrating tablets of atenolol were prepared by direct compression method. The powder mixture was mixed with external phase, then compressed into orally disintegrating tablets using Erweka® compression machine. The weight of the tablet was set at 300 mg and 11 mm in diameter.

#### Evaluation of atenolol- $\beta$ -cyclodextrin orally disintegrating tablets

Orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin were evaluated for various parameters such as wetting time, water absorption ratio, *in vitro* dispersion time, and dissolution. These parameters were evaluated to analyze the effect of the different components of superdisintegrants (co-processed crospovidone-sodium starch glycolate (1:1 and 1:2) and physical mixture of crospovidone-sodium starch glycolate (1:1 and 1:2)).

#### Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue. A linear relationship exists between wetting time and disintegration time or *in vitro* dispersion time. A circular filter paper of 8 cm diameter is placed in a Petri dish containing 10 ml of the blue dye solution. A tablet is carefully placed on the surface of the filter paper. The time requires for developing blue color on the upper surface of the tablet is noted as the wetting time [19].

#### Water absorption ratio

The weight of the tablet before keeping in the Petri dish was noted (Wb). Fully wetted tablet from the Petri dish was taken and reweighed (Wa). The water absorption ratio can be determined according to the following formula.

$$R = \frac{W_a - W_b}{W_b} \times 100$$

#### *In vitro* dispersion time

*In vitro* dispersion time was measured by dropping a tablet in a cylinder containing 6 ml of phosphate buffer pH 6.8 (simulated saliva fluid) with a temperature of 37±0.5 °C. The time required for complete dispersion was determined [17, 18].

#### Dissolution study

*In vitro* dissolution study was performed using USP Type II Apparatus (paddle type) at 50 rpm for 120 min. Acetate buffer pH 4.6 was used as a dissolution medium which was maintained at 37±0.5 °C. An aliquot (10 ml) was taken at specified time intervals (1, 2, 5, 15, 20, 45, and 60 min). An equal amount of fresh dissolution medium was replaced immediately following the withdrawal of the sample. The concentration of atenolol in the aliquot was determined using Ultra Performance Liquid Chromatography (UPLC). The data shown is the average of 6 determinations. A dissolution profile for each formula was plotted, and dissolution parameters such as %Q, TQ%, AUC, and dissolution efficiency was determined.

## RESULTS AND DISCUSSION

In this study, four formulas have been prepared to produce orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin. Two formulas (formula 1 and formula 2) were prepared using two different ratios of co-processed crospovidone-sodium starch glycolate. Formula 3 and formula 4 were prepared as a control, using a physical mixture of crospovidone-sodium starch glycolate in the same ratio compare to the co-processed superdisintegrants.

The powder mixture of each formula was compressed using direct compression technique. The compressed tablets were evaluated for physical properties such as organoleptic, dimension, uniformity of weight, wetting time, water absorption ratio, *in vitro* dispersion time, and disintegration time. These parameters were critical

parameters to evaluate the characteristics of orally disintegrating tablets which were produced using different preparation method (co-process and physical mixture) and the different ratio (1:1 and 1:2) of superdisintegrants.

The organoleptic characteristics of atenolol- $\beta$ -cyclodextrin orally disintegrating tablets which produced in this study were white, round shape, no odor, sweet and mint flavor. Dimension measurements of orally disintegrating tablets were done to ensure the dimension homogeneity of compressed tablets. The results showed that the diameter and thickness of the tablets from all formulas were uniform. Uniformity of the weight test showed that all the formulas were uniform and met the pharmacopeia specification. The results of physical and chemical evaluation of atenolol- $\beta$ -cyclodextrin orally disintegrating tablets are tabulated in table 2.

**Table 2: The results of physical and chemical evaluation of atenolol- $\beta$ -cyclodextrin orally disintegrating tablets (formula 1, formula 2, formula 3, and formula 4)**

Parameters		Specification	Results			
			Formula 1	Formula 2	Formula 3	Formula 4
Organoleptic	Shape	Round	Round	Round	Round	Round
	Colour	White	White	White	White	White
	Odor	Mint	Mint	Mint	Mint	Mint
	Tatste	Mint dan sweet	Mint dan sweet	Mint dan sweet	Mint dan sweet	Mint dan sweet
Tablet dimension (D/T)		$\leq 3.00$	2.94 $\pm$ 0.11	2.98 $\pm$ 0.09	2.99 $\pm$ 0.08	2.99 $\pm$ 0.08
<i>In vitro</i> dispersion (second)		<60 seconds	47.44 $\pm$ 2.49	49.67 $\pm$ 1.86	86.68 $\pm$ 2.43	88.83 $\pm$ 2.14
Wetting time (second)		-	53.53 $\pm$ 2.26	56.67 $\pm$ 2.50	86.49 $\pm$ 2.62	164.25 $\pm$ 1.92
Water absorption ratio (%)		-	89.61 $\pm$ 3.32 %	81.90 $\pm$ 1.41 %	120.84 $\pm$ 4.44 %	164.25 $\pm$ 1.93 %
AUC Dissolution		-	4343.34 $\pm$ 179.59	4121.82 $\pm$ 279.82	3970.94 $\pm$ 119.60	3609.61 $\pm$ 260.31
Dissolution Efficiency		-	72.39 $\pm$ 2.99 %	68.70 $\pm$ 4.66 %	66.18 $\pm$ 1.99 %	60.16 $\pm$ 4.34 %

\*(D/T): The ratio of the diameter and the thickness of orally disintegrating tablets. \*results were expressed in mean $\pm$ SD, n=6, SD-Standard Deviation

Wetting time evaluation was applied to predict how fast the medium penetrates into the structure of orally disintegrating tablets. The time for complete wetting was measured [20]. Six trials for each formula were conducted, and the standard deviation was also determined. The results of wetting time evaluation were shown in table 2. The wetting time of all the formulations was found to be in the range 53.53 $\pm$ 2.26 until 146.33 $\pm$ 3.72 seconds. The wetting times are the essential parameter for orally disintegrating, and those have to be ideally less than 1 min [21]. The wetting times of formula 1 and formula 2 which used co-process superdisintegrants satisfied the criteria of wetting times. The results of statistical analysis using One Way ANOVA revealed that there was a significant difference ( $p < 0.05$ ) of wetting time among all formulas. The wetting time of atenolol orally disintegrating tablets which used co-process crospovidone-sodium starch glycolate was shorter than atenolol orally disintegrating tablets which used the physical mixture of these superdisintegrants. Hence, there was no significant difference in wetting time between orally disintegrating tablets of atenolol which used co-processed crospovidone-sodium starch glycolate in 1:1 ratio and 1:2 ratios. One of the most desirable properties of the disintegrants is rapid swelling without gel formation since high viscosity on the surface of the tablet will prevent water penetration into the tablet matrix [5]. It was observed that co-processed superdisintegrants produce the inner structure of an orally disintegrating tablet more porous so that the wetting time became shorter.

Orally disintegrating tablets of atenolol which used co-process crospovidone-sodium starch glycolate exhibited shorter wetting time and needed less water to disintegrate. It was observed from the results of the water absorption ratio test. Water absorption ratio is an important criterion for understanding the capacity of disintegrants to swell in the presence of a little amount of water [21]. Orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin which used co-process crospovidone-sodium starch glycolate 1:1 showed the lowest water absorption ratio ( $p < 0.05$ ) compare to the other formulas. The difference in water absorption ratio among the four formulas in this study was due to the water uptake and the swelling behavior of superdisintegrants [22]. The difference of superdisintegrants preparation (co-processed and physical mixture) also

influence the water absorption ratios of atenolol- $\beta$ -cyclodextrin orally disintegrating tablets. Co-processed super-disintegrants reduce the water absorption ratio of orally disintegrating tablets, therefore the wetting time of the tablets became shorter. It can be concluded co-process superdisintegrants produce the higher ability of superdisintegrants to wick the water inside their structure and became more hydrated. This phenomenon can occur because co-process crospovidone-sodium starch glycolate combined the capillary characteristics of crospovidone and swelling effect of sodium starch glycolate in tablets disintegration mechanism. Co-processed superdisintegrants promote shorter wetting time of the tablets without high water absorption inside the structure of the tablets. The small amount of water or moisture which penetrated inside the structure of the tablets will produce enough pressure to disintegrate atenolol-beta-cyclodextrin orally disintegrating tablets. Based on this facts, co-processed superdisintegrants were promising to attempt the physical stability problems of orally disintegrating tablets which are formulated using a high amount of superdisintegrants. However, the increasing of sodium starch glycolate portion in co-processed crospovidone-sodium starch glycolate 1:2 showed a significant escalation in water absorption ratio. This was due to the characteristics of sodium starch glycolate which absorbed water until 200%-300% [5, 23].

*In vitro* dispersion time is a special parameter in which the time needed by the tablets to produce complete dispersion is measured [24]. *In vitro* dispersion time describe the behavior of orally disintegrating tablets when contact with a small amount of saliva in the mouth cavity [25]. The internal structure of the tablets, water absorption mechanism, and swelling characteristic of superdisintegrants are suggested to be the mechanisms of disintegration [26]. The results of *in vitro* dispersion time indicated that orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin which using co-process crospovidone-sodium starch glycolate dispersed rapidly in the mouth less than 60 seconds. Meanwhile, disintegrating tablets of atenolol- $\beta$ -cyclodextrin which using a physical mixture of crospovidone-sodium starch glycolate dispersed in the mouth longer. The results of statistical analysis using One Way ANOVA revealed that there was a significant difference ( $p < 0.05$ ) between

orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin which using co-process crospovidone-sodium starch glycolate and physical mixture of this superdisintegrants. Such a difference in disintegration time between both preparations of superdisintegrants indicates which there might be an improvement of capillary action on co-process superdisintegrants. This condition which might have led to improving water uptake [18]. It was also observed that formula 1 which using co-process crospovidone-sodium starch glycolate 1:1 took the shortest time to disperse in the small amount of buffer phosphate pH 6.8 ( $\pm 6$  ml). There was a correlation between wetting time and *in vitro* dispersion time. The

faster water can penetrate the structure of the tablets; the faster the tablets will be dispersed in the medium [25]. It was revealed that formula 1 which using co-process crospovidone-sodium starch glycolate 1:1 produce better wetting time, water absorption ratio, and *in vitro* dispersion time compare to the other formulas.

Dissolution study of atenolol orally disintegrating tablets was performed in pH 4.6 acetate buffer using USP Dissolution test apparatus with a paddle stirrer. Profile dissolutions of atenolol orally disintegrating tablet formula 1, formula 2, formula 3, and formula 4 are shown in fig. 1.

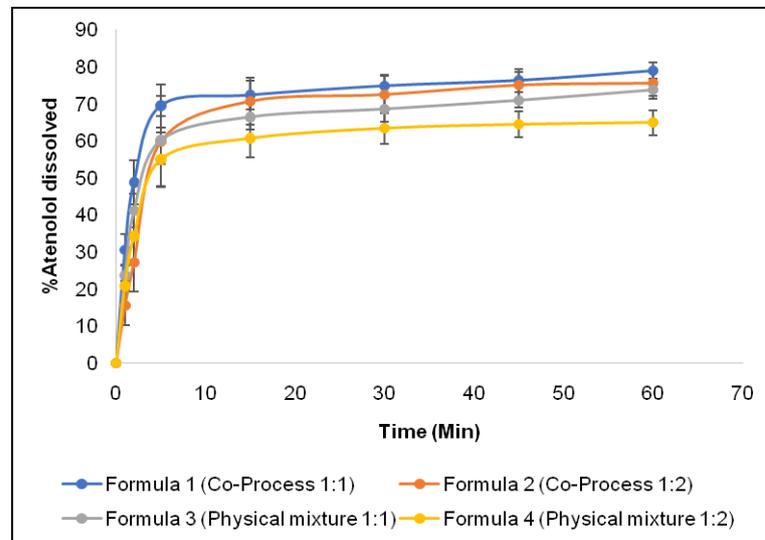


Fig. 1: Dissolution profile of orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin formula 1, formula 2, formula 3, and formula 4 [mean $\pm$ SD, n=6]

The result showed that formula 1 which using co-process crospovidone-sodium starch glycolate 1:1 release the highest amount of atenolol in 60 min among all formulas. Statistical analysis of area under the dissolution curve (AUC) using one-way ANOVA represented that there was a significant difference ( $p < 0,05$ ) between formulas which using co-process and physical mixture crospovidone-sodium starch glycolate. The results also revealed that formula 1 had shown the highest dissolution efficiency and the most rapid drug dissolution among all formulas. The rapid drug dissolution may be due to the presence of co-process superdisintegrants, which swells due to the rapid uptake of water from medium resulting in the breakdown of the tablet into smaller particles with the increased surface area, and hence increase the release of the drug into the dissolution medium [27, 28].

From this present work, it concludes that co-process crospovidone-sodium starch glycolate implied positive impact on wetting time, water absorption ratio, dispersion time, and dissolution efficiency of atenolol- $\beta$ -cyclodextrin orally disintegrating tablets. The results of evaluation parameters suggested that co-processed crospovidone-sodium starch glycolate in the 1:1 ratio was the best composition to produce efficacious orally disintegrating tablets of atenolol- $\beta$ -cyclodextrin as compared to the physical mixture.

## CONCLUSION

Based on the results of this study, it can be concluded that co-process superdisintegrants crospovidone-sodium starch glycolate could lead to the formation of rapid disintegrating and higher dissolution efficiency of atenolol- $\beta$ -cyclodextrin compared to the physical mixture. Among four formulas which have been analyzed in this study, formula 1 (co-process crospovidone-sodium starch glycolate 1:1) is the best formulation because this formula dispersed in the least time and released the highest percentage of atenolol in the same time. The results also revealed that the difference of superdisintegrants preparation (co-process and physical mixture)

and the amount of crospovidone and sodium starch glycolate which has been used in the formulas (1:1 and 1:2) significantly affect the dependent variables such as wetting time, water absorption ratio, *in vitro* dispersion time, and dissolution.

## ACKNOWLEDGMENT

The authors are thankful to KEMENRISTEK DIKTI, Indonesia for providing research grants in 2018 to execute this research.

## AUTHORS CONTRIBUTIONS

All the author have contributed equally

## CONFLICT OF INTERESTS

Declared none

## REFERENCES

1. Chang RK, Xiaodi, Guo, Burnside BA, Couch RA. Fast-dissolving tablet. *Pharm Technol* 2000;24:52-8.
2. Sandeep DJ, Rahul NK, Chetan MJ, Bharat WT, Vijay RP. Formulation and evaluation of fast dissolving oral film of levocetirizine dihydrochloride. *Int J Pharm Pharm Sci* 2012;4:337-441.
3. Morris LS, Schulz RM. Patient compliance-an overview. *J Clin Pharm Ther* 1992;17:283-95.
4. Taj R, Khan S. A study of reasons for non-compliance to psychiatric treatment. *J Ayub Med Coll Abbottabad* 2005;17:26-8.
5. Hahm HA, Augsburg LL. Orally disintegrating tablets and related tablet formulations. In: *Pharmaceutical Dosage Forms: Tablets*. New York: Informa Healthcare; 2008. p. 293-312.
6. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. *Guidance for industry: orally disintegrating tablets*. New Hampshire eve: Division of drug information food and drug administration; 2008.

7. Behnke K, Sogaard J, Martin S, Baumi J, Ravindran AV, Agren H. Mirtazapine orally disintegrating tablets versus sertraline: a prospective onset of action study. *J Clin Psychopharmacol* 2003;23:358-64.
8. Diaz JE, Montoya EG, Negre JM, Lozano PP, Minarro M, Tico JR. Predicting orally disintegrating tablets formulations of ibuprofen tablets: an application of the new sedem-odt expert system. *Eur J Pharm Biopharm* 2012;80:638-48.
9. Brown D. Orally disintegrating tablets: taste over speed. *Drug Delivery Technol* 2001;3:58-61.
10. Nagar P, Singh K, Chauhan I, Madhu V, Yasir M, Khan A, *et al.* Orally disintegrating tablets: formulation, preparation, techniques, and evaluation. *J Appl Pharm Sci* 2011;4:35-45.
11. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York: McGraw-Hill; 2008.
12. Ranch KM, Koli AR, Vyas BA, Parikh RK, Vyas RB, Maniyar NR, *et al.* Formulation, design, and optimization of orodispersible tablets of atenolol. *Int J Pharm Tech Res* 2009;1:1559-63.
13. Sweetman. *Martindale the complete drug reference*. 36<sup>th</sup> ed. London: Pharmaceutical Press; 2009.
14. Florey K. *Analytical profiles of the drug substance*. Vol. 13. Orlando: Academic Press; 1984.
15. Buha SM, Baxi GA, Shrivastav PS. Liquid chromatography study on atenolol- $\beta$ -cyclodextrin inclusion complex. *ISRN Anal Chem* 2012;1:1-8.
16. Mittapalli RK, Qhattal HS, Lockman PR, Yamsani MR. Varying efficacy of super disintegrants in orally disintegrating tablets among different manufacturers. *Pharmazie* 2010;65:805-10.
17. Nagendrakumar D, Raju SA, Shirsand SB, Para MS. Design of fast dissolving granisetron HCl tablets using novel co-processed super disintegrants. *Int J Pharm Sci Rev Res* 2010;12:58-62.
18. Kumare MM, Marathe RP, Kawade RM, Ghante MH, Shendarkar RR. Design of fast dissolving tablet of atenolol using novel co-processed superdisintegrants. *Asian J Pharm Clin Res* 2013;6 Suppl 3:81-5.
19. United States Pharmacopeial Convention. *United States Pharmacopeia 40 National Formulary 35*. Rockville: United States Pharmacopeial Committee; 2017. p. 2886-8.
20. Chandrasekhar P, Shahid MS, Niranjana BM. Formulation and evaluation of oral dispersible tablets of antihypertensive drug atenolol. *Int J Pharm* 2013;3 Suppl 2:79-84.
21. Venkateswarlu K, Naik SB, Chandrasekhar KB. Formulation and *in vitro* evaluation of orlistat orodispersible tablets for enhancement of dissolution rate. *Int J Pharm Pharm Sci* 2016;8:236-41.
22. Aulton M, Summers M. *In aulton's pharmaceuticals the design and manufacture of medicines*. Philadelphia: Churchill Livingstone; 2013. p. 187-99.
23. Avulapati S, Roy AP, Shashidhar KR, Reddy TU. Formulation and evaluation of taste masked and fast disintegrating losartan potassium tablets. *Int J Drug Dev Res* 2011;3:45-51.
24. Kulkarni SV, Kumar R, Basavaraj, Rao S, Ramesh B, Kumar A. Effect of superdisintegrants on the formulation of taste masked fast disintegrating lisinopril tablets. *Int J Curr Pharm Res* 2011;3:11-4.
25. Reddy BV, Navaneetha K, Reddy VR, Reddy PP, Reddy PU, Lavanya T. Formulation and evaluation of fast dissolving tablets of losartan potassium. *Indo Am J Pharm Res* 2014;4:2573-84.
26. Vijaya V, Niroosha C, Ravi M. Comparative formulation, evaluation, and optimization of imidapril mouth dissolving tablets using different synthetic superdisintegrating agents. *Int J Pharm Pharm Sci* 2016;8:150-6.
27. Mahendrakumar P, Liew CV, Heng PW. Review of disintegrants and disintegration phenomena. *J Pharm Sci* 2016;105:2545-55.
28. Preethi GB, Banerjee S, Shivakumar HN, Kumar RM. Formulation of fast dissolving tablets of doxazosin mesylate drug by direct compression method. *Int J Appl Pharm* 2017;9:22-8.