Pertanika J. Sci. & Technol. 28 (3): 1081 - 1090 (2020)

PERTANIKA JOURNALS

SCIENCE & TECHNOLOGY

Journal homepage: http://www.pertanika.upm.edu.my/

Evaluation of Ketoconazole Tablet Prepared using Dry Granulation Technique with Filler-Binder Excipients and Disintegration Agent

Dwi Setyawan*, Nisma Abdurahman Bawazier, Dini Retnowati and Diajeng Putri Paramita

Department of Pharmaceutics, Faculty of Pharmacy, Universitas Airlangga, 60115 Surabaya, Indonesia

ABSTRACT

Ketoconazole is one of high-dose treatment drugs with flowability issue so that it is commonly formulated using wet granulation technique. However, the technique impacts stability of ketoconazole which it changes in color upon solvent usage. This research was conducted to study tablet quality of ketoconazole as function of certain excipients in dry granulation technique. Combination of spray dried lactose (SDL) and Avicel® PH-102 as filler-binder excipients and sodium starch glycolate (SSG) as a disintegration agent were used for the purpose. Ketoconazole tablets were formulated based on 2^2 factorial design. Evaluation was performed on tablet properties, then statistically analyzed using Minitab® software. Tablet hardness and disintegration time increased in increasing level of filler combination and SSG concentration, but a decrease was observed for friability and % dissolved ketoconazole. Both filler combination and disintegration agent exhibited insignificant effect toward tablet properties evaluated. According to overlay contour plot, it is predicted that the optimum formulation of ketoconazole tablet can be set into SDL-Avicel® PH-102 ratio of at least 3:1 or higher and SSG concentration is higher than 3.5%.

Keywords: Avicel PH-102, dry granulation, ketoconazole, sodium starch glycolate, spray dried lactose

ARTICLE INFO

Article history:
Received: 04 November 2019
Accepted: 13 April 2020
Published: 16 July 2020

E-mail addresses:
dwisetyawan-90@ff.unair.ac.id (Dwi Setyawan)
nismazbd@gmail.com (Nisma Abdurahman Bawazier)
dini-r@ff.unair.ac.id (Dini Retnowati)
diajeng-putri-paramita@ff.unair.ac.id (Diajeng Putri Paramita)
* Corresponding author

INTRODUCTION

Ketoconazole is one of API that generally administered orally in tablet dosage form. Tablets are popular dosage form as for patient convenience, good stability, easy and low-cost manufacturing (Taneri et al., 2010; Gohel & Jogani, 2005). Tablet manufacturing involves compression of

ISSN: 0128-7680
e-ISSN: 2231-8526

powder mixture consisting of drug(s) and excipients. Tablet should possess certain properties in accordance with specifications required, i.e. tablet hardness, friability, disintegration time and dissolution (Edge et al., 2002).

Ketoconazole is a wide-spectrum antifungal drug derived from imidazole group. Based on the physicochemical properties, ketoconazole is classified in Biopharmaceutics Classification System (BCS) class II for drugs with low aqueous solubility yet high permeability (Viçosa et al., 2009). Ketoconazole is extremely hydrophobic with high molecular weight that leads to poor flowability and difficulty during compaction (Jacobs et al., 2016; Molaei et al., 2018). Suitable manufacturing process for this kind of drug is wet granulation technique so it can be compacted into a good tablet (Consiglieri et al., 2010; Javaheri et al., 2014). However, the resulting tablet shows a change in color, indicating instability issue due to photochemical reaction that becomes prominent after solvent exposure (Mhaske & Sahasrabudhe, 2011; Staub et al., 2010). Therefore, it is necessary to determine an appropriate technique in order to improve flowability without generating stability problem.

We suggested dry granulation technique as alternative solution to manufacture ketoconazole tablet, with spray dried lactose (SDL) and Avicel® PH-102 were used as filler-binder excipient in combination and sodium starch glycolate (SSG) was used as disintegration agent in the formulation of ketoconazole tablet. Dry granulation utilizes mechanical energy to promote powder agglomeration via compression (slugging) or compaction (roller compaction) and requires no solvent (Shanmugam, 2015). SDL is modified lactose from spray drying process and consisted of α-lactose monohydrate and amorphous lactose. SDL exhibits improved flowability and compaction behavior compared to conventional lactose attributable to smooth spherical particles of SDL, as well as the existence of amorphous lactose (Ruangchayajatuporn et al., 2011). Avicel® PH-102 is brand name of microcrystalline cellulose and the Arabic numerals represent grade of Avicel® PH itself. Avicel® PH-102 has larger mean particle size with coarser surface in comparison with Avicel® PH-101, another grade of microcrystalline cellulose commonly used in drug formulation. Tablet containing Avicel® PH-102 presented higher hardness and lower friability (Bastos et al., 2008). SSG is known as a so-called "super-disintegration agent" from cross-linked starch derivative. SSG acts as disintegration agent by swelling up to 12 folds in less than thirty min when in contact with water, inducing rapid disintegration of the tablet. Hence, for certain cases, SSG is also used to modify dissolution profile (Bhise et al., 2009; Kumar & Saharan, 2017).

In this research, ketoconazole tablet was prepared using dry granulation technique with filler-binder excipients and disintegration agent. Tablet formulation was optimized according to 2^2 factorial design. Evaluation of tablet properties included tablet hardness, friability, disintegration time, and dissolution rate. Effect of filler-binder excipients and

disintegration agent was analyzed using Minitab® software, as well as determination of the optimum formulation.

MATERIALS AND METHODS

Materials

Ketoconazole was obtained from dari Zhejiang East-Asia Pharmaceutical Co. Ltd., China. SDL (DMV International, Netherland), Avicel® PH-102 (Asahi Corp., Japan), SSG (Yung ZIP Chemical Co., China), and other excipients used in formulation were pharmaceutical grade.

Formulation Design

Ketoconazole tablets were formulated according to factorial design 2^2 with two factors, those are filler combination and disintegration agent, in two levels of concentration. Filler combination consisted of SDL and Avicel® PH-102 in weight ratio of 2:1 and 4:1 as the level difference. SSG was used as disintegration agent with two concentrations of 2 and 4%. API composition in each tablet was equal to 200 mg of ketoconazole. Four formulations of ketoconazole tablet can be seen in Table 1.

F1 contained both factors in low level; F2 contained low level of filler combination and high level of disintegration agent; F3 contained high level of filler combination and low level of disintegration agent; and F4 contained high level of both factors. Ketoconazole tablet was prepared using dry granulation technique. Ketoconazole was tumble-mixed first with SLS and a half part of SSG for 5 min, then with SDL and Avicel® PH-102 for 10 min, and with a half part of each talk and magnesium stearate for another 5 min. Slugging was performed on the mixture under compression force of 10 kN. Subsequently, the slugs were grinded into granule using an oscillating granulator Erweka AR-400 (Germany), and sieved through 1 mm mesh sieve. The remaining part of SSG, talk, and magnesium stearate was

Table 1
Formulations of ketoconazole tablet

Component(s)	Function	Composition (% b/b)			
		F1	F2	F3	F4
Ketoconazole	API	66.6	64.6	66.7	64.7
SDL	Filler	18.6	18.6	22.2	22.2
Avicel® PH-102	Filler	9.3	9.3	5.6	5.6
SSG	Disintegration agent	2	4	2	4
SLS	Surfactant	1	1	1	1
Magnesium stearate	Lubricant	1	1	1	1
Talk	Glidan	1.5	1.5	1.5	1.5
Total		100	100	100	100

added into the granule to be mixed homogenously for 5 min. Tablet form was obtained via compressing the granules on 14 mm diameter tablet die using a hydraulic press Natoli NP-RD10A (USA) with compression force of 10 kN.

Tablet Evaluation

Ketoconazole tablet was evaluated for its property of hardness, friability, and disintegration time in replication measurement. Tablet hardness was calculated from five tablets sample of each formula using Erweka TBH-220 hardness tester, Germany. Tablet friability was examined using Erweka TAP-31914 friability tester, Germany. Sample of 10 tablets from each formula was weighed first before rotated on friability tester at a speed of 25 rpm for 4 minutes. Tablet sample was dusted from fines, then re-weighed to calculate the weight loss presented as a percentage.

The disintegration test was carried out using Erweka ZT-501 disintegrator, Germany, with 900 mL of distilled water as disintegration medium at 37±2ºC. Six tablets were placed each in every wire-ended tube in a basket rack assembled on the disintegrator, then covered by transparent disk. The disintegrator was run until all tablets disintegrated completely.

Dissolution Test

Dissolution of ketoconazole tablet was measured using Erweka DT-700 dissolution instrumentation (Germany) with paddle apparatus in dissolution medium of 0.1 N HCl solution. Tablet sample from each formula was inserted into 900 mL dissolution medium and the instrument was run at stirring speed of 50 rpm and temperature of 37±0.5ºC. Sampling was conducted at time interval of 30 minutes and 5.0 mL solution was taken in every sampling that immediately replaced with fresh dissolution medium in the same amount. Then, the solution was filtered through 0.45 μm-pore cellulose nitrate membrane filter. The filtrate was read for the absorbance on Hitachi UH5300 UV-Vis spectrophotometer (Japan) at the maximum wavelength of ketoconazole at 222 nm. % dissolved ketoconazole was obtained through standard calibration curve and was reported as mean from triplicate measurements.

Statistical Analysis

Effect of filler combination and disintegration agent toward ketoconazole tablet properties was statistically analyzed using Minitab® 18 version (Minitab Inc., Australia). Using the software, the optimum formulation for ketoconazole tablet was also determined from the evaluated properties.

RESULTS AND DISCUSSIONS

Formulation of ketoconazole tablet prepared using dry granulation technique was optimized by factorial design approach. Factorial design employs mathematical equation construction to determine experimental procedure as a function of the factor levels, e.g. in two-level factors experiment, it is described as 2^f factorial design (f denotes the number of factors) (Chowdary & Shankar, 2016). Since factors evaluated in this research were filler combination and disintegration, the experiment was based on 2^2 factorial design resulting in four formulations. Table 2 shows the properties of ketoconazole tablet from four formulations. Tablet hardness of all formulations fell in value between 4.6 to 5.0 kP that within range of acceptable value (Fatmawati et al., 2017).

Table 2
The properties of ketoconazole tablet

Tablet Properties	F1	F2	F3	F4
Hardness (kP)	4.83±0.04	4.6±0.27	4.81±0.47	4.93±0.15
Friability (%)	1.00±0.09	0.55±0.20	0.67±0.22	0.74±0.14
Disintegration Time (min)	4.27±1.77	5.14±0.42	5.78±1.86	5.90±1.32
% Dissolved	72.69±1.24	63.79±4.22	80.27±9.54	73.92±4.74

The friability of ketoconazole tablets were mostly below 1% and met specification required (Winarti et al., 2017), except for F1. It is quite possibly caused by the low amount of SDL and SSG that the former possesses plastic deformation behavior of amorphous phase to form compacted tablet and the last belongs to starch derivative with binder property (Rassu et al., 2006; Rowe et al., 2009). During disintegration time test, ketoconazole tablets disintegrated completely under six minutes in all formulations. The result conforms the quality requirement that tablet disintegration should complete within fifteen minutes (Schmid & Löbenberg, 2010). Percentage of dissolution efficiency in 30 minutes (DE_{60}) was calculated as below: 60.07±2.12, 63.16±1.79, 65.02±3.73, and 62.39±1.97 for F1, F2, F3, and F4, respectively. According to the compendium, ketoconazole in tablet dosage form is required to dissolve not less than 80% in thirty minutes (Ministry of Health, 2014). However, only F3 complied with the requirement.

Analysis using Minitab® software obtains pareto charts, main effect plots, and contour plots that describe the effect of the factors on ketoconazole tablet properties statistically. Pareto charts explain the extent of which each factor impacts tablet hardness, friability, disintegration time, and dissolution. Meanwhile, main effect plots show the main effect generated by each factor in different level of concentration and contour plots show the relationship of the factors toward tablet properties evaluated. Figure 1 displays pareto charts of ketoconazole tablet properties. A factor is considered to have significant effect if the graphic bar crosses the red line and none does in our pareto charts. Therefore, both factors

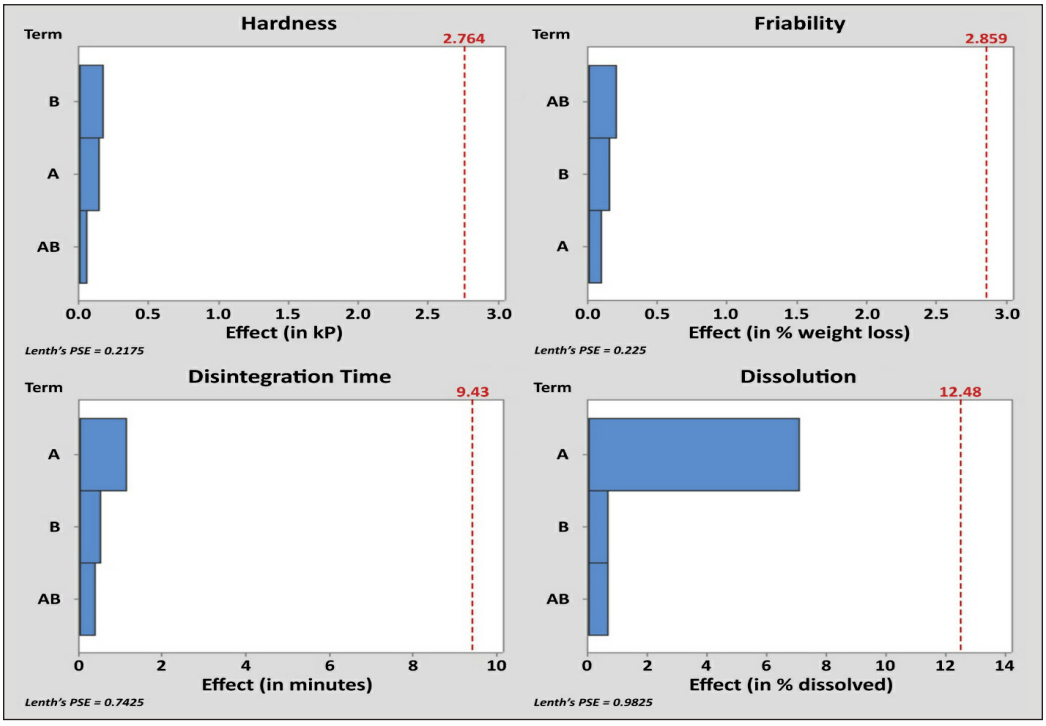

Figure 1. Pareto charts of ketoconazole tablet properties in a function of filler combination (A) and disintegration agent (B) as individual factor or in combination (AB)

used in this research, filler combination and disintegration agent, impact ketoconazole tablet properties in insignificant fashion, as an individual or in combination.

Main effect plots of ketoconazole tablet properties are given in Figure 2. An increment in SDL ratio in filler combination and SSG concentration increases tablet hardness and disintegration time, but decreases friability and % dissolved ketoconazole. Effect of SSG concentration on dissolution seems to be in much lower extent compared to ratio of filler combination. From contour plots shown in Figure 3, we can see combination effect of both factors on tablet properties. Low level of SDL ratio in filler combination and SSG concentration leads to tablet with low hardness and higher value can be obtained at higher level of both factors. Good friability is acquired from tablet with high level of SDL ratio, high level of SSG concentration, or high level of both factors (darker blue zone), as low level of both produces tablet with high friability. Disintegration time can be regulated faster with low level of SDL ratio and SSG concentration, meanwhile % dissolved ketoconazole can be obtained higher at high level of both factors.

Contour plots can be overlaid together to give a graphic seen in Figure 4, from which we can predict the optimum formulation for ketoconazole tablet. The feasible area is white-colored zone on the graphic. So, for manufacturing ketoconazole that readily

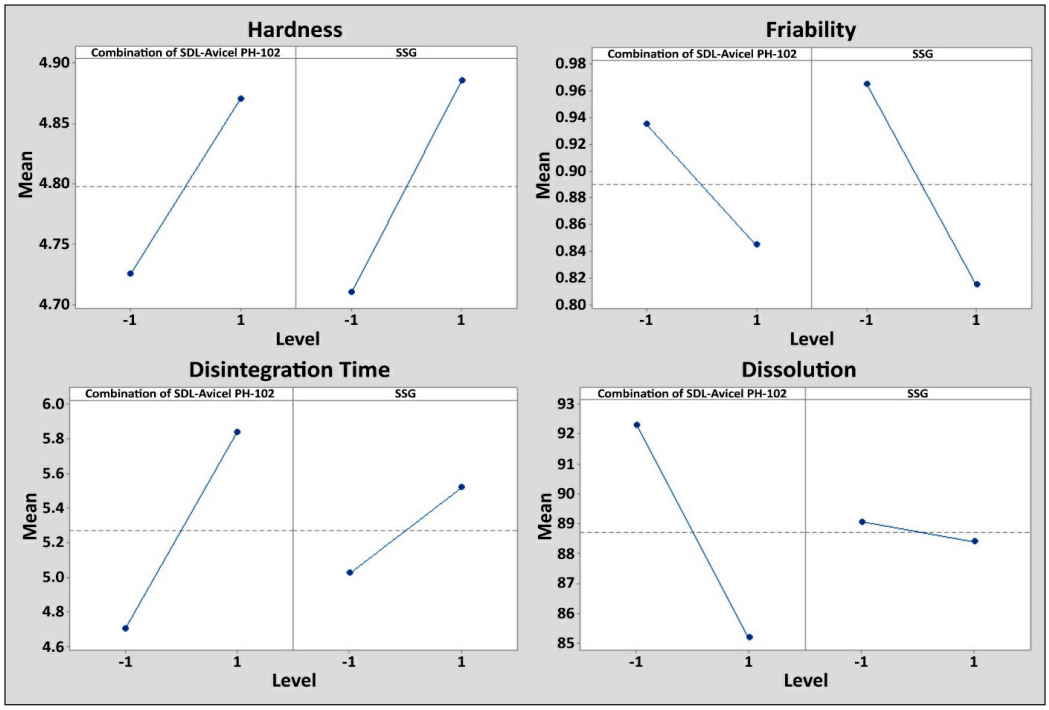

Figure 2. Main effect plots of ketoconazole tablet properties in a function of filler combination and disintegration agent in two levels (-1, low level; +1, high level)

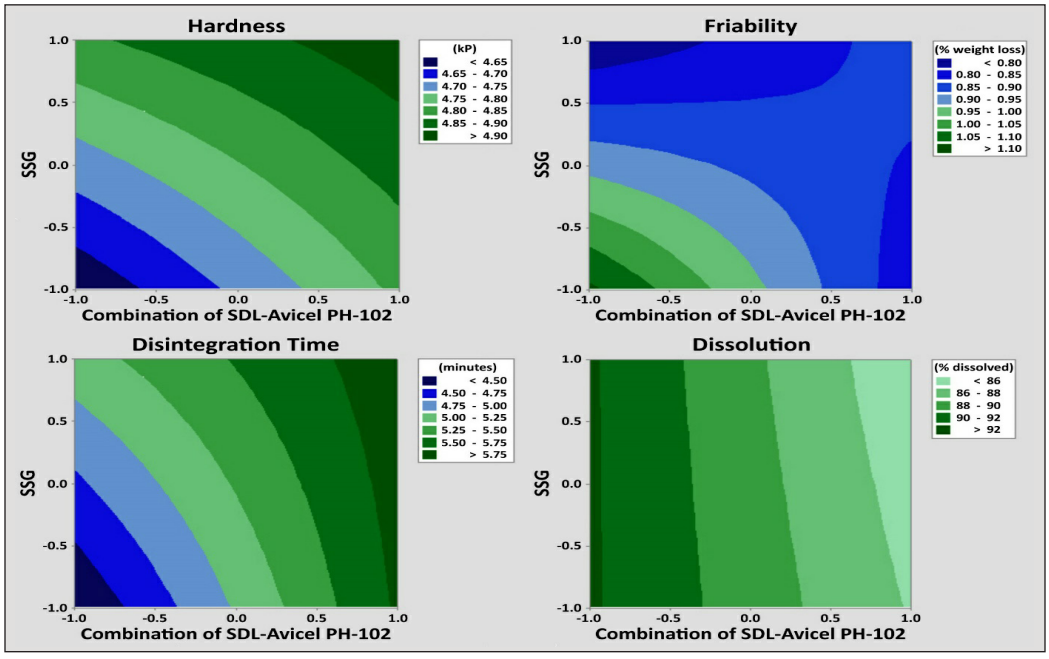

Figure 3. Contour plots of ketoconazole tablet properties in a function of filler combination and disintegration agent in two levels (-1, low level; +1, high level)

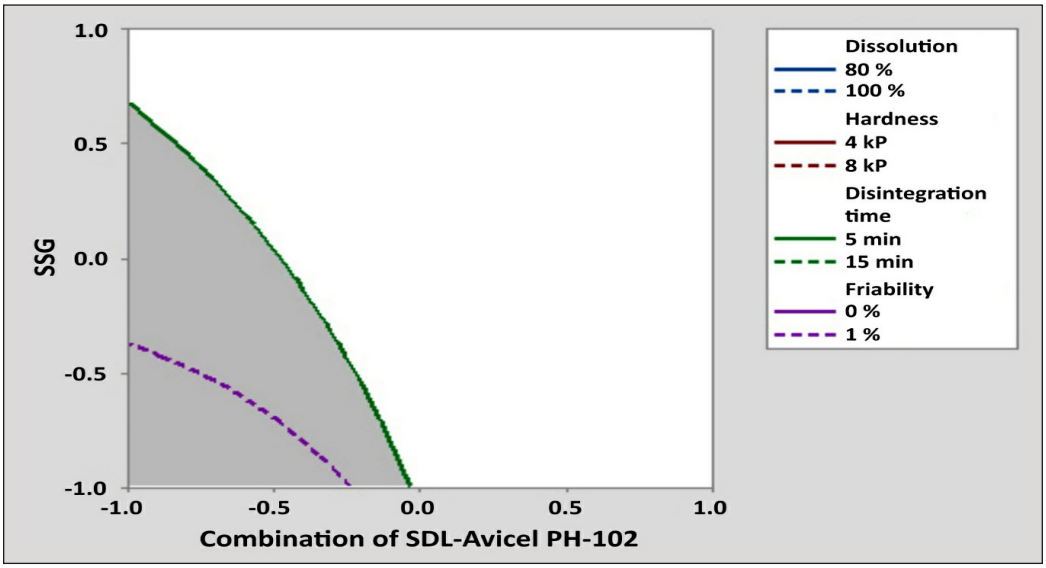

Figure 4. Overlaid contour plot of ketoconazole tablet derived from the evaluated properties (-1, low level; +1, high level)

complies with quality requirements using filler combination of SDL-Avicel® PH-102 and disintegration agent of SSG, SDL-Avicel® PH-102 ratio can be set at least 3:1 or higher and SSG concentration should be higher than 3.5%.

CONCLUSION

To manage stability issue generated from manufacturing ketoconazole tablet with wet granulation, dry granulation technique was explored to formulate ketoconazole tablet. Filler combination of SDL-Avicel® PH-102 and disintegration agent of SSG factors are known to impact tablet properties. Both factors increase tablet hardness and disintegration time, decrease friability and % dissolved ketoconazole, even though it is not significant statistically. Overlaid contour plot allows prediction of the optimum formulation for ketoconazole tablet using combination of SDL and Avicel® PH-102 and disintegration agent of SSG.

ACKNOWLEDGMENT

This research was fully funded by the Ministry of Research, Technology, and Higher Education through grant of Penelitian Dasar Unggulan Perguruan Tinggi (PDUPT) No. 623/UN3.14/LT/2019. This manuscript has been presented at the 2019 international joint symposium of the 8th Asia Pacific Pharmacy Education Network (APPEN) Conference and the 2nd Halal Pharmaceuticals and Cosmetics (HPC) Conference, 8-9 October 2019 at Universitas Airlangga, Surabaya, Indonesia.

REFERENCES

Bastos, M. O., Friedrich, R. B., & Beck, R. C. R. (2008). Effects of filler-binders and lubricants on physicochemical properties of tablets obtained by direct compression: A 2^2 factorial design. *Latin American Journal of Pharmacy, 27*(4), 578-583.

Bhise, S., Chaulang, G., Patel, P., Patel, B., Bhosale, A., & Hardikar, S. (2009). Superdisintegrants as solubilizing agent. *Research Journal of Pharmacy and Technology, 2*(2), 387-391.

Chowdary, K. P. R., & Shankar, K. R. (2016). Optimization of pharmaceutical product formulation by factorial designs: Case studies. *Journal of Pharmaceutical Research, 15*(4), 105-109.

Consiglieri, V. O., Mourão, S., Sampaio, M., Granizo, P., Garcia, P., Martinello, V., ... & Ferraz, H. G. (2010). Improvement of fluconazole flowability and its effect on dissolution from tablets and capsules. *Brazilian Journal of Pharmaceutical Sciences, 46*(1), 115-120.

Edge, S., Steele, D. F., Staniforth, J. N., Chen, A., & Woodcock, P. M. (2002). Powder compaction properties of sodium starch glycolate disintegrants. *Drug Development and Industrial Pharmacy, 28*(8), 989-999.

Fatmawati, D. A., Widjaja, B., & Setyawan, D. (2017). Optimasi tablet levofloksasin yang mengandung bahan pengikat PVP K-30 dan disintegran Vivasol [Optimization of levofloxacin tablet containing PVP K-30 and Vivasol]. *Jurnal Sains Farmasi dan Klinis, 4*(2), 9-15.

Gohel, M. C., & Jogani, P. D. (2005). A review of co-processed directly compressible excipients. *Journal of Pharmacy and Pharmaceutical Sciences, 8*(1), 76-93.

Jacobs, G. A., Gerber, M., Malan, M. M., du Preez, J. L., Fox, L. T., & du Plessis, J. (2016). Topical delivery of acyclovir and ketoconazole. *Drug Delivery, 23*(2), 631-641.

Javaheri, H., Carter, P., & Elkordy, A. A. (2014). Wet granulation to overcome liquisolid technique issues of poor flowability and compactibility: A study to enhance glibenclamide dissolution. *Journal of Pharmaceutics and Drug Development, 2*(3), 1-12.

Kumar, A., & Saharan, V. A. (2017). A comparative study of different proportions of superdisintegrants: Formulation and evaluation of orally disintegrating tablets of salbutamol sulphate. *Turkish Journal of Pharmaceutical Sciences, 14*(1), 40-48.

Mhaske, R. A., & Sahasrabudhe, S. (2011). Identification of major degradation products of ketoconazole. *Scientia Pharmaceutica, 79*, 817-836.

Ministry of Health. (2014). *Farmakope Indonesia* (5th Ed.). Jakarta, Indonesia: Ministry of Health Republic of Indonesia.

Molaei, M., Osouli-Bostanabad, K., Adibkia, K., Shokri, J., Asnaashari, S., & Javadzadeh, Y. (2018). Enhancement of ketoconazole dissolution rate by the liquisolid technique. *Acta Pharmaceutica, 68*(3), 325-336.

Rassu, G., Eissens, A. C., & Bolhuis, G. K. (2006). Tableting properties of an improved spray-dried lactose. *Journal of Drug Delivery Science and Technology, 16*(6), 455-459.

Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009). *Handbook of pharmaceutical excipients* (6th Ed.). London, United Kingdom: Pharmaceutical Press.

Ruangchayajatuporn, J., Amornsakchai, T., Sinchaipanid, N., & Mitrevej, A. (2011). Compaction behavior and optimization of spray-dried lactose with various amorphous content. *Journal of Drug Delivery Science and Technology, 21*(2), 175-181.

Schmid, K., & Löbenberg, R. (2010). Influence of the changed USP specifications on disintegration test performance. *Dissolution Technologies, 17*(1), 6-10.

Shanmugam, S. (2015). Granulation techniques and technologies: Recent progresses. *BioImpacts, 5*(1), 55-83.

Staub, I., Flores, L., Gosmann, G., Pohlmann, A., Fröehlich, P. E., Schapoval, E. S., & Bergold, A. M. (2010). Photostability studies of ketoconazole: Isolation and structural elucidation of the main photodegradation products. *Latin American Journal of Pharmacy, 29*(7), 1100-1106.

Taneri, F., Ozcan, I., & Guneri, T. (2010). *In vitro* and *in vivo* evaluation of oral tablet formulations prepared with ketoconazole and hydroxypropyl-beta-cyclodextrin. *Drug Delivery, 17*(3), 152-157.

Viçosa, A. L., Chatah, E. N., Santos, T. C., Jones, L. F. Jr., Dantas, C. B., Dornelas, C. B., ... & Cabral, L. M. (2009). Bioequivalence studies and sugar-based excipients effects on the properties of new generic ketoconazole tablets formulations and stability evaluation by using direct compression method. *Pharmaceutical Development and Technology, 14*(5), 530-539.

Winarti, L., Ameliana L., & Nurahmanto, D. (2017). Formula optimization of orally disintegrating tablet containing meloxicam nanoparticles. *Indonesian Journal of Pharmacy, 28*(1), 53-64.