

DISSOLUTION PROFILE OF AMBROXOL HCl TABLET WITH ADDITIONAL VARIATIONS OF LUDIPRESS® AND LACTOSE USING THE DIRECT PRESS METHOD

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ABSTRACT

Objective: The drug will provide a therapeutic effect when dissolved so that it is easily absorbed. The process of dissolving drugs is called dissolution. Additional substances contained in pharmaceutical preparations, one of which serves to accelerate the solubility of active substances. The aim of this study was to obtain a comparative composition of Ludipress® and lactose additives suitable for producing ambroxol HCl tablets that met the ambroxol acceleration ambroxol in the body.

Methods: Ambroxol HCl tablets were made by direct pressing method. For research purposes, 4 formulas with variations of Ludipress® and Lactose were designed. The tablet was then evaluated, which includes uniformity in weight, diameter, thickness, hardness, friability, disintegration time, and dissolution. Data obtained in the analysis using the perfect random block design method (DBAS) with $\alpha = 0.05$ where blocks and groups were used.

Results: From the results of the Mass Printing Evaluation of Tablets, it was found that the four formulas that were designed met the resting angle, flow rate, real density, compressed density, and compressibility met existing requirements. The results of evaluation tablets, which included uniformity of weight, uniformity of size, hardness, friability, disintegration time, and dissolution test, were found that only F1 formula did not meet uniformity requirements. All four formulas meet the Indonesian pharmacopeia requirements for time of violence, fragility and disintegration. The dissolution test results showed that in the 45-minute test each percent dissolved concentration of the active substance for F1, F2, F3, and F4 was 58.77974, 66.91104, 80.09946, and 64.02293 suggesting only the F3 formula fulfilled the dissolution requirements according to European Pharmacopoeia which stated that the concentration of dissolved active tablets should not be less than 75% during the 45-minute test.

Conclusion: The formula that met the solubility requirements consisted of an additional 69% Ludipress® and 10% lactose with a solubility value of 80.09%.

Keywords: Dissolution profile, Ambroxol HCl tablets, Direct press, Ludipress®, Lactose

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INTRODUCTION

Dissolution test is one of the tests most often used to characterize drugs and control the quality of dosage forms. Investigation through dissolution carried out on powders enables optimization of formulation factors [1, 2]. Optimal dissolution can be obtained if the tablet can be crushed into particles quickly. It is generally known several years ago that before absorption occurs, a solid drug must undergo disintegration into small particles and release the active substance [3, 4].

Actually, there was some research regarding the ambroxol HCl tablet. Sharma *et al* [5], for example, wrote simultaneous estimation of ambroxol hydrochloride and cetirizine hydrochloride in pharmaceutical tablets using simultaneous equation spectrophotometric. Basak *et al* [6] mentioned formulation and release behavior of sustained-release ambroxol hydrochloride HPMC matrix tablet. A study on the effect of 20 mg ambroxol hydrochloride on acute cough was articulated by Hull University Teaching Hospitals NHS Trust [7]. *In vitro* characterization and release study of ambroxol hydrochloride matrix tablets prepared by direct compression was reported by Abd-Elbary *et al* [8, 9]. Rangnath *et al* [10] studied Development and validation for UV Spectrometric estimation of ambroxol hydrochloride in bulk and tablet dosage form using the area under curve method. Kinetic studies of ambroxol were studied by Akhter *et al* [11] and Hang *et al* [12]. Method for simultaneous estimation of levofloxacin hemihydrate and ambroxol hydrochloride in bulk and its pharmaceutical dosage form was reported by Sumithra *et al* [13]. Potawale *et al* [14], however, used Liquid chromatography tandem-Mass spectrometry to develop a method for simultaneous analysis of paracetamol, guaifenesin, phenylephrine hydrochloride, chlorpheniramine maleate, and ambroxol hydrochloride in bulk and tablet dosage form. Our current research is different from existing research studies.

Ludipress® is an additive or excipient consisting of 93% lactose, 3.5% Kollidon® 30, and Kollidon CL. Lactose functions as a carrier

and filler, Kollidon®30 as a binding agent, and Kollidon CL as a disintegrator. So that Ludipress® is a granule with a good flow rate, is not too hygroscopic, and has a strong tie. This makes the process of mixing with active substances become more homogeneous and can be pressed directly so as to produce high-quality tablets. Tablet formulations using Ludipress® only require active substances, Ludipress®, and lubricants, and then mixed and can be directly pressed [15, 16].

Ambroxol Hydrochloride is a compound used as a cough medicine that is as a mucolytic. Mucolytic is a drug that can thin the airway secretions by breaking the threads of mucoproteins and mucopolysaccharides from mucus. Mucus removal becomes easy, so it relieves breathing. Ambroxol is completely absorbed after oral administration. It breaks up phlegm, used in the treatment of respiratory diseases associated with viscid or excessive mucus. Recently, a hypothesis suggested that it may have a potential role in the treatment of Paget's disease of bone, Parkinsonism, and other common diseases of aging-associated diseases involving dysfunction of autophagy. The dose of Ambroxol Hydrochloride is between 30 mg to 120 mg per day for adults [17-19]. In this study, ambroxol, HCl tablets were made by direct pressing using a variation of Ludipress® and lactose additives in an effort to accelerate the solubility of active substances.

MATERIALS AND METHODS

Tools

Dissolution type 2 (Sotax), UV-VIS spectrophotometer (Analytic Jena), tapped density test equipment (Varian 50-1300), hardness tester (Erweka), tablet friability test equipment (Varian 453200), analytical balance (Mettler Toledo), single punch tablet machines (Korsch), crushed time test equipment (Erweka ZT3), sieves, thermometers, calipers, and glassware commonly used in laboratories.

Materials

The materials used in this study were ambroxol HCl (Dong Wha), Ludipress® (BASF), Lactose mesh 80 (DMV Fonterra).

Methods

Raw Material Preparation: Preparation of active substances based on Indonesian Pharmacopoeia literature [20, 21]. Preparation of

additional substances based on the Handbook of Pharmaceutical Excipient literature [22, 23].

Tablet formulation

In this study, four ambroxol, HCl tablet formulations were made with variations of additives Ludipress® and lactose. The ambroxol HCl tablet formulation can be seen in table 1.

Table 1: Designed formula tablet ambroxol HCl

Formula	F1	F2	F3	F4
Ambroxol HCl	30 mg	30 mg	30 mg	30 mg
Mg. Stearate	1 mg	1 mg	1 mg	1 mg
PVP K-30	15 mg	15 mg	15 mg	15 mg
Ludipress®	79%	74%	69%	64%
Lactose	-	5%	10%	15%

Tablet making

Tablets were made using the direct pressing method. The ingredients were sifted and weighed as needed. Ambroxol HCl was added with additional substances Ludipress®, lactose, and PVP K-30 according to the designed formula and mixed for about 10 min. After mixing, magnesium stearate was added and mixed again for about 30 sec.

The printed mass of tablets obtained was then evaluated against Flow Rate and Rest Angle, Real density, compressed density, and compressibility. The data obtained later would be referred to Relationships between flow rate and powder flow properties, resting angles and flow traits, and between the nature of powder flow with compressibility given by Aulthon [24]. Designed tablets were evaluated against Size of uniformity, Uniformity of weights, Tablet hardness, Toughness tablet, and Dissolution test.

Print mass evaluation

a. Flow Rate and Resting Angle: The mass of the press was placed in the flow rate test funnel whose bottom was closed. The mass of the press coming out of the tool was calculated its flow rate by calculating the time required by a number of powders to descend through the test tube funnel using a stopwatch. The calculation started when the bottom lid of the funnel was opened until all the mass of the press flows out of the tool.

Print mass deposits could be used to calculate the angle of rest. The average diameter of the pile and the height of the top of the pile were measured. The relationship between the angle of rest and the nature of the powder flow would be referred to Aulthon [24].

b. Real density, compressed density, and compressibility: Actual density was determined by placing a number of print masses into a

measuring cup and then measuring its volume and calculating its density by the following formula [24].

$$\text{Incompressible density} = \frac{(\text{powder weight})}{(\text{final powder volume})} \text{ (g/ml)}$$

Pressure could be seen from the value of Carr's compressibility index, which was very dependent on the real density and compressed density. The relationship between Carr's compressibility index with powder flow properties was given by Aulthon [24].

Tablet evaluation

a. **Size Uniformity:** Unless stated otherwise, the diameter of the tablet was not more than three times and not less than four-thirds of the thickness of the tablet [25]. The examination was carried out using twenty tablets. The examination was carried out on the diameter and thickness of each tablet. Then the average diameter and thickness of the tablet were calculated.

b. **Uniformity of Weights:** Non-coated tablets ought to meet the weight uniformity requirements set as follows: weigh 20 tablets, calculate the average weight of each tablet. If weighed one by one, it should not be more than 2 tablets, each weighting deviates from the average weight greater than the value set by column A, and not one tablet deviates from the average weight more than the value determined by the column. B. If there weren't enough 20 tablets, 10 tablets could be used; none of the tablets deviated more than the average weight set by column A and none of the tablets deviated more than the average weight set by column B [20]. Deviation of the average weight of tablets can be seen in table 2.

Table 2: Deviations in the average weight of tablets [11]

Average weight (mg)	Average weight deviation (%)	
	A	B
<25	15	30
26-150	10	20
151-300	7.5	15
>300	5	10

c. **Tablet hardness:** Twenty tablets were randomly taken and their hardness measured using a hardness tester, then the average was calculated [24].

d. **Tablet Friability:** The friability testing tool for the laboratory was known as the Roche friabilator. This tool treats a number of tablets to the combined effect of scratches and shocks by using a kind of plastic box that rotates at a speed of 25±1 rpm. Usually, weighed tablets were placed inside the device, then run 100 rounds. The tablets were then cleaned and re-weighed. Losing weight allowed 1.0% [25]. Tablets that were still intact were weighed and then calculated to lose weight and expressed in percentage using the following formula:

$$\text{Losing weight (\%)} = \frac{w1 - w2}{w1} \times 100\%$$

Where: w1 = initial tablet weight, w2 = tablet weight after fragility test

e. **Destructive time test:** Put one tablet in each tube from the basket then put a disc in each tube and run the tool, use water with a temperature of 37 ±2 °C as a medium unless stated using another liquid in each monograph. At the end of the time limit, as stated in the monograph, the basket was lifted, and all tablets were observed. All tablets ought to be completely destroyed. If 1 tablet or 2 tablets were not completely destroyed, repeated testing with 12 other

tablets: no less than 16 of the 18 tablets tested ought to be completely destroyed [21].

f. Dissolution tool

(i) The device consists of a closed container made of glass or other inert transparent material, a motor, a metal rod driven by a motor and a paddle consisting of leaves and stems as a stirrer. Oars meet the specifications of the distance of 25 mm±2 mm between the leaves and the inside of the container retained during the test. The preparation was allowed to sink to the bottom of the container before the paddle starts to spin [21].

(ii). Dissolution Media: Dissolution media used 0.1 N HCl solution [26].

(iii). Tablet dissolution: The dissolution medium was put into dissolution medium 900 ml and then heated to 37 °±0.5 ° C. Ambroxol HCl tablets were put into a dissolution vessel then rotated at 50 rpm. Samples were taken as much as 5 ml at intervals of 5, 10, 15, 20, 30, and 45 min. Every sample taken is then replaced with a dissolution medium as much as 5 ml. The sample taken was measured absorbance and determined its levels [26].

(iv). Determination of dissolved concentrations: Determination of the dissolved ambroxol HCl concentration using ultraviolet spectrophotometry at a maximum wavelength of around 244 nm. Within 45 min must dissolve not less than 75% of the active substance from the amount listed [26].

Data analysis

Dissolution test data analysis used the perfect randomized complete block design (RCBD) method with 95% confidence in which blocks

and groups were used [27, 28]. In this analysis time treatment acts as a block and variations were disintegrants as a group.

RESULTS AND DISCUSSION

Raw material preparation

Preparation of the active substance ambroxol HCl based on European Pharmacopoeia literature [26]. Examination of additional substances such as Ludipress®, lactose, PVP K-30, and magnesium stearate is based on the Handbook of Pharmaceutical Excipient literature [29].

Tablet formulation

In this study, four formula of ambroxol HCl tablets were made with Ludipress® and lactose additives. The test formula was presented in table 1. Mix ambroxol HCl with additives until it was homogeneous. The mass of the felt was then compressed. The weight of the resulting tablet was 220 mg and printed 200 pieces.

Print mass evaluation

The evaluation of the press mass was done before the tablet printing process. The print mass evaluation was useful to know how the state of the print mass before the tablet was pressed. When the print mass met the established standards, the tablet could be compressed. This test could be used as a supporting factor to determine the quality of the tablet. Evaluation of print mass includes resting angle, flow rate, real density, compressed density, and compressibility [30, 31]. From the results of the evaluation of the print mass, all formulas gave good results, so that the pressing process could be done by direct pressing method. The print mass evaluation results can be seen in table 3.

Table 3: Print mass evaluation results

Parameters	F1	F2	F3	F4
Break angle (°)	17.65±0.1907	17.21±0.2254	19.31±0.01	19.43±1.4104
Flow rate (g/sec)	20.23±0.111	23.08±0.1530	11.18±0.2426	23.78±0.3253
The real density	0.55±0.8717	1.51±0.0551	0.57±0.091	1.07±0.0737
Compressible density	0.672±0.1130	1.88±0.1205	0.711±0.2007	1.44±0.1159
Compressibility (%)	20.59±0.6209	18.92±0.1473	14.65±0.5719	23.17±0.2258

Notes: all data obtained from 3 measurements

Tablet evaluation

Tablet evaluation was carried out after the tablet printing process. Tablet evaluation was an evaluation conducted to find out that the tablets made have met the requirements. Tablet evaluation includes weight uniformity, size uniformity, hardness, friability, disintegration time, uniformity of dissolution and dissolution test. Flow and break angle tests were performed to determine the print mass flow capacity because if the print mass was easy to flow, the resulting tablet would have a good uniformity of weights. Literature, the nature of the flow was said to be good if it had a range of values of 4-10 g/s, said to be difficult to flow in the range of 1.6-4 g/s, and at values <1.6 g/s means it was very difficult to flow. A good resting angle value is in the range of 25 °-30 ° and a range of 30 °-40 ° was included in a fairly good group [24]. On the other hand, the compressibility test was done by

calculating the value of real tangibility and incompressible density through testing with a tap density device. The range of good compressibility was around 12-18 and in the range, 23-35 was poor [21]. The results obtained indicated that each formula had a poor compressibility value. Based on these results, it can be concluded that the print mass was quite good.

It was found that Formula 1 did not meet the requirements for uniformity of levels listed on the Indonesian Pharmacopoeia, with a value of 89.8735%. This could be due to the lack of homogeneity of ambroxol HCl during the mixing process. While the other three formulas met the requirements of Indonesian Pharmacopoeia uniformity levels because they fell within the range of requirements, namely 90%-110%. The results of the evaluation of ambroxol HCl tablets can be seen in table 4 and fig. 1.

Table 4: Tablet evaluation results

Parameters	F1	F2	F3	F4
Diameter (mm)	8.5245±0.3828	8.5235±0.3846	8.4786±0.4472	8.6349±0.13112+
Thickness (mm)	3.19±0.2100	3.22±0.2100	3.19±0.2150	3.22±0.2100
Weight (mg)	220.72±0.80133	221.43±2,4265	222.22±2.0800	221.39±3,4013
Hardness (N)	60.54±0,22270	58.35±1.5979	65.52±0.7343	48.25±0,1233
Friability (%)	0.065±0.002	0.040±0.002	0.007±0.010	0.255±0.117
Destruction time (min)	8.05±0.01	9.11±0.03	9.34±0.04	9.47±0.200
Content (%)	89.8723±0.0083%	94.2778±0.00911%	108.6666±0.1011%	94.6823±0.1944%

Notes: all data obtained from 3 measurements

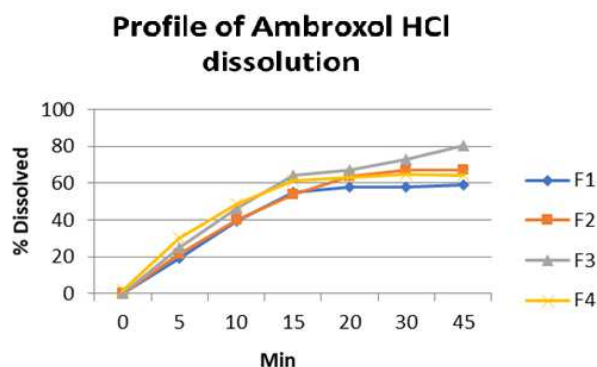


Fig. 1: Results of the dissolution profile of ambroxol HCl tablets

Hardness testing of tablets was done by using a hardness tester. The results of testing the hardness of tablets from each formula were 60.50 ± 9.2800 , 57.95 ± 12.7298 , 65.36 ± 9.43743 , and 48.175 ± 5.5042 this value was compromised to an official standard [32].

Friability Test: The friability test was carried out by weighing as many as 10 tablets. The results of the friability testing of the four formulas showed good value or qualify because it was less than one percent, that was, 0.065, 0.038, 0.007, and 0.310. Good Friability indicated the tablet could withstand minor scratches or damage during storage [27].

Dissolution profile results from four ambroxol tablet formulas, only formula 3 (F3) fulfilled dissolution requirements according to European Pharmacopoeia, namely within 45 min, Q value of 80.09946%. Formula three has high levels of ambroxol HCl based on assay uniformity test with a value of 108.6641%. This would have an impact on the active substances that would dissolve when dissolved.

For formula 1 (F1) which had a Q value of 58.77974%, it did not meet the existing requirements, because, at the time of uniformity testing, the concentration of the active substance ambroxol HCl was only 89.8735%, so it affected the dissolution test. For formula 2 and formula 4 also did not meet the dissolution test requirements, according to European Pharmacopoeia.

Data analysis

Dissolution test data analysis used the perfect randomized complete block design (RCBD) with $\alpha = 0.05$ where blocks and groups were used. In this analysis, time treatment acts as a block and variations in composition as a group. As a result, H_0 was rejected, which means there was a difference in the percentage of dissolved HCl ambroxol between formulas using 74% Ludipress® without lactose addition (F1), 69% Ludipress® with 5% lactose (F2), 64% Ludipress® with 10% lactose (F3), 59% Ludipress® with 15% lactose (F4) (see table 5).

Table 5: ANOVA of ambroxol HCl tablet dissolution

Variance source	dk	JK	KT	Fcount	Ftable
Average	1	59497.082	59497.082		
Time	6	15409.826	2568.034		
Concentration	3	354.162	118.054	8.189*	4.76
Errors	18	259.481	14.416		
Total	28	75520.550			

*Fcount > F table

CONCLUSION

In the dissolution profile of ambroxol HCl tablets with variations of Ludipress® and lactose additives that met the requirements of European Pharmacopoeia was a formula with 69% Ludipress® additives and 10% lactose with a Q value of 80.09946% within 45 min of testing. The other three formulas did not meet European Pharmacopoeia requirements with a Q value of less than 75% for 45 min of testing. It concluded that the formulation of ambroxol HCl tablets with 69% Ludipress® additives and 10% lactose using a direct pressing method meets the requirements listed in Pharmacopoeia Indonesia or in Pharmacopoeia Europe.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

There is no conflict of interest between authors

REFERENCES

1. Mark D, Zeitler JA. A review of disintegration mechanisms and measurement techniques. *Pharm Res* 2017;34:890-917.

2. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, *et al.* Pharmaceutical particle technologies: an approach to improve drug solubility, dissolution, and bioavailability. *Asian J Pharm Sci* 2014;9:304-16.
3. Jaysukh J, Hirani JJ, Rathod DA, Vadalia KR. Orally disintegrating tablets: a review. *Trop J Pharm Res* 2009;8:161-72.
4. Sharma D, Singh M, Kumar D, Singh G. Simultaneous estimation of ambroxol hydrochloride and cetirizine hydrochloride in pharmaceutical tablet dosage form by simultaneous equation spectrophotometric method: a quality control tool for dissolution studies. *ISRN Anal Chem* 2014:1-6. Doi:10.1155/2014/236570
5. Basak SC, Mani KPL, Reddy BMJ. Formulation and release behavior of sustained-release ambroxol hydrochloride HPMC matrix tablet. *Indian J Pharm Sci* 2006;68:594-8.
6. Hull University Teaching Hospitals NHS Trust. A Study of the Effect of 20 mg Ambroxol Hydrochloride on Acute Cough. Available from: <https://clinicaltrials.gov/ct2/show/NCT03415269>. [Last accessed on 05 Jan 2020]
7. Sandhya KM, Shanmugam S, Vetrichelvan T. Design and development of ambroxol hydrochloride sustained release matrix tablets. *Int J Pharm Pharm Sci* 2011;13 Suppl 3:200-3.
8. Abd Elbary A, Haider M, Sayed S. *In vitro* characterization and release study of ambroxol hydrochloride matrix tablets prepared by direct compression. *Pharm Dev Technol* 2012;17:562-73.

9. Rangnath RA, Kumar JH, Namdeorao GK. Development and validation for UV Spectrometric estimation of ambroxol hydrochloride in bulk and tablet dosage form using the area under the curve method. *Int Res J Pharm* 2014;5:580-3.
10. Akhter DT, Uddin R, Sutradhar KB, Rana S. *In vitro* release kinetic study of ambroxol hydrochloride sustained release matrix tablets using hydrophilic and hydrophobic polymers. *J Chem Pharm Res* 2012;4:1573-9.
11. Hang TJ, Zhang M, Song M, Shen JP, Zhang YD. Simultaneous determination and pharmacokinetic study of roxithromycin and ambroxol hydrochloride in human plasma by LC-MS/MS. *Clin Chim Acta* 2007;382:20-4.
12. Sumithra S, Shanmugasundaram P, Ravichandiran V. Quality by design-based optimization and validation of new reverse phase-high performance liquid chromatography method for simultaneous estimation of levofloxacin hemihydrate and ambroxol hydrochloride in bulk and its pharmaceutical dosage form. *Asian J Pharm Clin Res* 2016;9 Suppl 3:190-6.
13. Potawale RS, Gilhotra RM, Gabhe SY. Liquid chromatography-tandem mass spectrometry method development and validation for the simultaneous analysis of paracetamol, guaifenesin, phenylephrine hydrochloride, chlorpheniramine maleate, and ambroxol hydrochloride in the tablet dosage form. *Asian J Pharm Clin Res* 2018;11:375-82.
14. Brown CK, Friedel HD, Barker AR, Buhse LF, Keitel S, Cecil TL, *et al.* Meeting report: FIP/AAPS joint workshop report: dissolution/*in vitro* release testing of novel/special dosage forms. *AAPS PharmSciTech* 2011;12:782-94.
15. BASF. Technical Information. Germany: BASF Chemical Industry; 2003.
16. Heinz R, Karbstein HP, Wolf H, End L. Formulation and development of tablets based on ludipress and scale-up from laboratory to production scale. *Drug Dev Ind Pharm* 2000;26:513-21.
17. Malerba M, Ragnoli B. Ambroxol in the 21st century: a pharmacological and clinical update. *Expert Opin Drug Metab Toxicol* 2008;4:1119-29.
18. McNeill A, Magalhaes J, Shen C, Chau KY, Hughes D, Mehta A, *et al.* Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. *Brain* 2014;137:1481-95.
19. Ambroxol Hydrochloride. Available from: <https://www.drugs.com/ambroxol.html> [Last accessed on 05 Jan 2020]
20. Departemen Kesehatan Republik Indonesia. Farmakope Indonesia. Edisi III. Jakarta: Departemen Kesehatan Republik Indonesia; 1979
21. Departemen Kesehatan Republik Indonesia. Farmakope Indonesia. Edisi IV. Jakarta: Departemen Kesehatan Republik Indonesia; 1995.
22. Beringer P. Remington, the science and practice of pharmacy. 21st edition. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 889-91.
23. Gibson M. Editors. Pharmaceutical pre-formulation and formulation. Florida: CRC Press; 2004. p. 417-8.
24. Aulton ME. Pharmaceutics: the science of dosage form design. New York: Longman Group Churchill Livingstone; 2002. p. 02, 124, 246-48.
25. United States Pharmacopeial Convention. The United States Pharmacopeia 30. Twinbrook Parkway MD: United States Pharmacopeial Convention, Inc; 2007.
26. European Pharmacopoeia Commission. European Pharmacopoeia 6. Council of Europe; 2007.
27. Trochim WMK. Research Methods Knowledge Base. Available from: <https://socialresearchmethods.net/kb/randomized-block-designs/>. [Last accessed on 06 Jan 2020]
28. Grant T. The randomized complete block design (RCBD). Available from: <https://pbgworks.org/sites/pbgworks.org/files/RandomizedCompleteBlockDesignTutorial.pdf>. [Last accessed on 06 Jan 2020]
29. Rowe RC, Sheskey PJ, Cook WG, Quinn ME. Editors. Handbook of Pharmaceutical Excipients. 7th Edition. Pharmaceutical Development and Technology, UK: The Pharmaceutical Press; 2013;18:2,544.
30. Mustarichie R, Priambodo D. Tablet formulation from meniran (*Phyllanthus niruri* L.) extract with direct compression method. *Int J Appl Pharm* 2018;10:98-102.
31. Li Q, Guan X, Cui M, Zhu Z, Chen K, Wen H, *et al.* Preparation and investigation of novel gastro-floating tablets with 3D extrusion-based printing. *Int J Pharm* 2018;535:325-32.
32. The United States Pharmacopeia. The National Formulary 23. 29th Edition. Vol. I. Washington DC: United States Pharmacopeia Convention Inc; 2006.