Composition Ratio of Lactose and Corn Starch in Granule Capsule Formulation of 70% Ethanol Extract *Justicia Gendarussa* Leaves as Male Contraceptive

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Abstract: The objective of this study were to make a good physical properties of Justicia gendarussa granules with lactose and corn starch as filler. Optimizations were made into 3 formulas. The difference of each formula was in the ratio of corn starch and lactose. Formula 1 used ratio 3:7 for corn starch and lactose, Formula 2 used ratio 1:1 for lactose and corn starch, Formula 3 used ratio 7:3 for corn starch and lactose. Physical evaluation was held to evaluate and choose the best granule like flowability, fines content, angle of repose, moisture content, compressibility. The result for granules optimization, flowability formula 1 was 3,29 ± 1,08 g/s, formula 2 was 6,04 ± 1,80 g/s, formula 3 was 6,48 ± 1,32 g/s. Angle of repose for F1,2 and 3 were 30,54 ± 1,14o, 29,98 ± 0,34oand 26,98 ± 0,00o. Compressibilty index were 12,00% , 10,00% and 11,99%. Moisture content 1,82%, 2,08% and 2,75%. Fines content were above 20%. From the evaluation, F2 was selected as the best formula.

1 INTRODUCTION

Justicia gendarussa is a tropical plant which grow in tropic land including Indonesia. This plant have been used by society of Papua as male contraceptive[30] . Major components from genus *Justicia* are alkaloid, lignan, flavonoid and terpenoid. Gendarussa leaves also contain tannin, kalium, volatile oil.calcium oxalate and also alkaloid (justicina) which is toxic.[8]

Alkaloid have been isolated from *J.gendarussa* leaves are 2-amino benzyl alcohol; 2-amino-o-metyl benzyl alcohol; 2-(2'-amino-benzilamino) benzil alcohol; 2-(2'amino-benzil)-o-metil-benzil ackohol (Figure.1).[7]

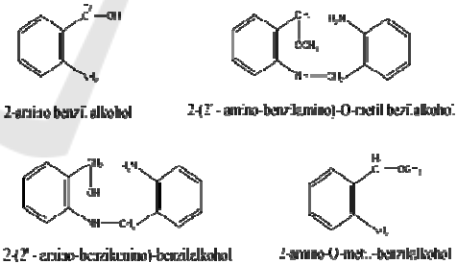

Figure.1 : Chemical structure aromatic amin substituted isolated from *J.gendarussa* leaves.[7]

Flavonoids from *Justicia gendarussa* Burm. f. are 6,8-di-C-α-L-arabinosil-4', 5,7 trihydroxy-flavon or 6,8-di-C-α-Larabinosilapigenin and this compound called gendarusin A, C-α-L-arabinopiranosil-4 ', 5,7 - trihydroxy-8-C-β-D-silopiranosilflavone or 6-C-α-L-arabinosil- 8-C-β-D-silosilapigenin and this compound called gandarusin B. Other flavonoids are gandarusin C, D and E. Gandarusin A is major component, steroid, volatile oil, alkaloids and other flavonoids

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(gandarusin B,C,D and E) are minor components in 70% ethanol extract *Justicia gendarussa* Burm.f. [31]

J.gendarussa extract have an antifertility effect that can inhibit spermatozoa penetration in-vitro with inhibit of hyaluronidase enzyme.[29] Therefore, *J.gendarussa* was developed into phytopharmaca drug. Phytopharmaca drug must be produced based on required standar to ensure the quality of product. The production process must conform the standards of GMP. GMP's requirement including raw material, equipment, sanitation and hygiene.

Further development of 70% ethanol extract *J.gendarussa* leaves into phytopharmaca drug, need formulation which have been conducted by several researchers. Granules formulation from water extract *J.gendarussa* leaves with avicel and lactose as filler made by wet granulation gave poor results because of the tablet hardness and slow disintegration time (almost 20 minutes). Based on that results, the filler change into lactose and corn starch and gave good results[39], the hardness of tablets and disintegration time were decreased. The addition of non-ionic surfactant,tween 80 is also made to improve the physical requirements and the dissolution rate of gendarusin A in the granules formula.[2] Then developed further by replacing Tween 80 with Poloxamer 188 as surfactant. In this study, the surfactant used is sodium lauryl sulfate. Replacement poloxamer 188 (non-ionic) with sodium lauryl sulphate which are anionic surfactants is based on research conducted by Alkhamis et al. (2003) who found that non-ionic surfactant demonstrated the ability solubilization smaller than the anionic and cationic surfactants on solubilization glikazid. Additionally, poloxamer 188 has a relatively expensive price so that less effective if will be developed later. This formula then regarded as the chosen formula by considering the parameters that can produce good product as an infertility drug.

Table 1 : Relationship between % compressibility and flowability[40]

% Compressibility	*Flowability*
5-12	Perfect
12-16	Good
18-21	Moderate
23-28	Poor
28-35	Poor
35-38	Very poor
> 40	Very-very poor (cohesive)

2 MATERIALS AND METHOD

2.1 Materials

Lactose (Lactose Monohydrate, Leprino USA), Corn starch (Amylum Maydis, Cargill Bio-Chemical China, Cab-o sil (Pluronic F-68, Sigma Life Scine USA), Sodium Lauryl Sulfate (SLS), Methanol p.a (Merck), Ethanol 70% *Nylon membrane* 0,2 µm (Whatman), *Filter holder* (Millipore), Aquadest.

2.1.1 Standarized Simplicia of *J.Gendarussa*

Nine months of *J.gendarussa* leaves have been harvested. Fresh leaves then made into simplicia by sortation (remove mechanical parts except leaf that are not needed like bark, stem, etc) and then washed and dried in drying cabinet at tempertaure below50°C. Dried simplicia then milled to a powder with a certain size[12]

2.1.2 Extraction

Gandarussa leaves powder extracted with macseration using ethanol 70% (1:10) for 24 hours. Re-extraction until three times. After extraction, the solvents were allowed to evaporate using rotary evaporator. Thus the highly concentrated ethanol extract were obtained. The extract then stored in refrigerator at 4^{o}C for further use for formulation process.

2.1.3 Formulation

Optimization were held with 3 formulas. *J.gendarussa* leaves granules were prepared by wet granulation method. Corn starch, lactose were used

as filler, sodium lauryl sulfate 1% was used as surfactant and cab o sil was used as glidant. The difference for each formula was on the ratio between lactose and corn starch. Formula 2 used ratio 1:1 for lactose and corn starch, Formula 1 used ratio 3:7 for lactose and corn starch, Formula 3 used ratio 7:3 for corn starch and lactose. Physical evaluation is held to evaluate and choose the best granule.

2.2 Evaluation of Granules

2.2.1 Flow Rate and Angle of Repose

The angle of repose was determined by allowing granules to flow through a funnel and fall freely onto a graph paper on a horizontal surface. The time taken for the weighed granules to flow out completely was recorded[5]. This was performed in triplicate.
Flow rate was obtained by the equation below:

Flow rate = weight of granules / time

The height and diameter of the resulting cone were measured and the angle of repose is calculated from this equation:

$$\tan Ø = h/r$$

Where :
h is the height of the powder cone and r is the radius of the powder cone

2.2.2 Bulk Density

The bulk density (ρ_b) of granules was determined by filling the material into a tarred graduated cylinder to the 100 ml mark. The graduated cylinder was weighted and the bulk density calculated as the ratio of the sample weight to sample volume

$$\rho bulk = W / V$$

Where :
ρbulk = Apparent bulk density,
W = Weight of the sample,
V = Apparent volume of powder

2.2.3 Tapped Density

A suitable amount of granules was placed in a 100 ml measuring cylinder. After absorbing its initial volume, the sample was tapped 500 times initially followed by an additional taps of 750 times until the difference between succeeding measurement is less than 2% and then tapped volume, was measured, to the nearest graduated unit. Tapped density was calculated using
equation

$$\rho tab = W / Vf$$

Where :
ρtab = Tapped Density,
W = Weight of the sample,
Vf = Tapped volume of powde

2.2.4 Moisture Content

Moisture content determination using Ohauss electronic Moisture balance 45 with place about 0,5-1g sample in sample pan. The sample pan must lie flat in the pan handler. Then, press the start button to start analyze. After ten minutes, % moisture content can read.

2.2.5 Fines Content

The determination of fines is done by inserting 100 grams of granules into a sieve with a hole diameter of 140 mesh (the equivalent of 100 micrometers). Then sieve vibrated for 20 minutes at a speed of 10 rpm. Weigh the amount of powder that escaped sieve (Wade and Weller, 1994). The amount of fines should not more than 20%. Particles that are larger than 250 μm is relatively free flowing, whereas particles have a size below 100 μm (fines) cause problems in the flow properties due to the occurrence of a large cohesive force.[3]

2.2.6 Statistical Analysis

Data analysis was performed on the physical parameters of the granules and then performed statistical analysis by one-way ANOVA (One-Way ANOVA). To determine whether there were significant differences between the formula, then followed by the Tukey-HSD test to determine any formula that provides a meaningful difference. Statistical analysis includes flow rate, angle of repose, moisture content and% compressibility with 95% confidence level ($\alpha = 0.05$). When Asymp. Sig. $\alpha < (0.05)$, then Ho is rejected and Ha accepted.

3 RESULTS AND DISCUSSION

J.gendarussa leaves extract have a viscous consistency therefore need filler composition like corn starch and lactose that can improve the physical properties of granules. With a viscous consistency and large water content, granulation process carried out by wet granulation to improve the flowability and compactibilty of granule mass.

Materials used as filler are lactose and corn starch. Lactose in the tablet formulation excipients serves as good as it can condense the mass of granules in the wet granulation or direct compression and can improve the flow properties because the lactose has a large specific gravity.[24] It is also the most widely used filler because it does not react with almost all of the ingredients. Generally, formulation with lactose showed a good rate of drug release, quick dry granules, disintegration time is not very sensitive to changes in the tablet hardness.[25] However, lactose may increase the hardness of the tablet therefore need a disintegrant to overcome. Corn starch has a lower specific gravity than the lactose that can help the bonds between the extract particles is not too strong so the combination of this two excipients lactose and corn starch can improve the physical quality of granules extract (*J. gendarussa*) as phytopharmaca drug.

The solubility of *J.gendarussa* extract that partially soluble caused a slow release of the active ingredients therefore the absorbtion and effect will be slow. Materials with low water solubility caused bad wetting because of their interfacial tension between the water phase, vapor phase and solid phase. As a result, drug will be difficult dissolved.[25] This requires the addition of a surfactant to improve the solubility.

In this study, the surfactant used was sodium lauryl sulphate (SLS). With the addition of this SLS, can reduce the surface tension between the particles, which occurs damping effect that makes the contact between the granules with media is large so the active substance is easier to get out of the granule and dissolve into the media. SLS as a wetting agent can also improve the dissolution rate of the drug due to its mechanism.[3]

The result of granules can be seen in figure.2, and evaluation of each formulas can be seen in table 2.

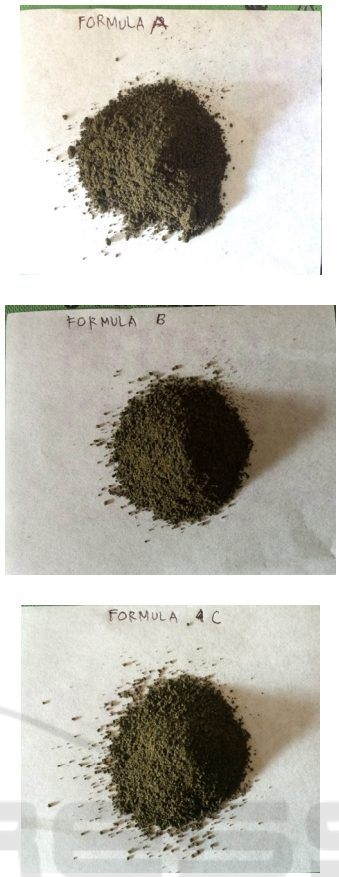

Figure.2: Granules formula 1,2,3 resulted from optimization

From the results in table 2.2, the flow rate of the granules, formula 1 was 3.28 ± 1.08 g / s, formula 2 was 6.04 ± 1.80 g / s, formula 3 was 6.48 ± 1.32 g / s. Based on the statistic results using ANOVA, there was no significant difference in flow rate between formula 1,2 and 3. formula granule flow velocity is considered good if it is in the range of 4-10 g/s. Formula 2 and 3 meet these requirements, while the formula 2 has a flow rate of <4 g/s so it can be considered to have difficult flow properties.[3]

The flowability can also be viewed from the angle of repose. Angle of repose resulting from formula 1 was 30.54 ± 1.14°, formula 2 was 29.98 ± 0.34° and formula 3 was 26.98 ± 0,00°. From the results of statistical tests on granules extract (J. gendarussa) , there was a significant difference between the angle of repose formula 1 and 3, Formula 2 and 3 on the confidence level of 0.95% ($\alpha = 0.05$). Angle of repose illustrate the magnitude of the frictional forces between the particles, so

Table 2 : Physical Evaluation of Granules

Evaluation	Formula 1	Formula 2	Formula 3	Requirement
Flowability (g/s)	*3.28±1.08	6.04±1,80	6.48±1,32	4-10g/s (Good flowability)
Angle of repose (º)	*30.54±1.14º	29.98±0,34º	26.98±0,00º	20-30º (Good flowability)
***fines* (%)**	24.15	25.97	21.09	< 20%
Compressibility (%)	12.00	10.00	11.99	5-12% (Perfect flowability)
***Moisture content* (%)**	1.82±0,02	2.08 ± 0,04	2.75 ± 0,02	2-4%
Yield (%)	61.63%	71.08%	78.40%	-

can demonstrate the flow properties of a granular indirectly.[6] Based on the angle of repose, all of

granules formula were meets the criteria of the granules with good flow properties, which have the angle of repose between 20-30º.[44] Good flow properties will make the die filling fulfilled evenly so the weight of the capsule is not distorted.[25]

Granule flow properties also have a relationship with compressibility. Granules have a perfect flow properties (granule flow freely) if it has a range of 5-12% compressibility.[40] In formula 1,2 and 3 the compressibility respectively were 12.07%, 9.68% and 13.11%. All formula meets the compressibility range with perfect flow properties. Formula 3 had the highest % compressibility. It can be related to the high moisture content 2.75%. Moisture content can affect the compressibility index and flowability because the moist powder mass will result in less free flowing powder.

High moisture content of the F3 can also be caused by the amount of corn starch higher than other formulas. Corn starch is hygroscopic so the granules will be more humid. The results of each formula met the requirements as good granules, the moisture content of the granules were in the range of 2% - 4%. These results can guarantee the granules are stable during storage. Humidity of a granule will affect the stability of the granules. The higher the humidity, the higher the potential for microbes to live so stability become shorter. When the moisture content too much can lead to sticky

and hard flowing granules, but small water content will produce a dry granule and easy fragile.

Fines content (particle size <100µm) from all formulas were more than 20%. From all that formula, the best formula chosen was determined based on the evaluation has been done. Formula 2 was chosen formula because the formula 3 had a high moisture content, it is feared the stability of the granules is getting shorter. While the formula 1 and 2 based on the results of the statistical analysis, flowability and angle of repose did not provide a significant difference but in terms of the yield obtained, compressibility and flowability, formula 2 was better than formula 1. Thus formula 2 with ratio 1:1 for lactose and corn starch was a best formula and chosen to do the next process.

CONCLUSION

Granules with filler ratio 1:1 for lactose and corn starch can result in good physical properties of granules.

REFERENCES

1. Ansel, H. C., Popovich, N. G., and Allen, L. V. 1995. **Pharmaceutical Dosage Form and Drug Delivery System, 6th ed**., Malvern: Williams and Wilkins, p. 60-65.
2. Arifani, G. 2012. Pengaruh Tween 80 Terhadap Laju Disolusi Gendarusin A dalam Granul Ekstrak Etanol 70% Daun *Justicia gendarussa* burm. f. Untuk Sediaan Kapsul. **Skripsi**. Fakultas Farmasi Universitas Airlangga.
3. Aulton, M. E. 2002. **Pharmaceutics : The Science of Dosage Forms Design**. London : Churchill Livingstone
4. Banker, G. S. and Anderson, N. R. 1989. Tablet, In: Lachman, L., Lieberman, H. A. And Kanig, J. L. (Eds). **Teori dan Praktek Farmasi Industri**, edisi ketiga, Vol II, Jakarta: Universitas Indonesia.
5. Bhagawan, W.S. 2015. Formulasi dan Uji Disolusi Granul Ekstrak Etanol 70% Terfraksinasi Daun Gendaarusa. **Thesis**. Fakultas Farmasi Universitas Airlangga.
6. Carstensen. 1977. **Pharmaceutics of Solid and Solid Dosage Forms**. New York: John Willey and Sons.
7. Carstensen, J.T. and Rhodes, C.T., 2000, **Drug Stability Principles and Practices, Third Edition, Revised and Expanded,** Marcel Dekker, Inc., New York : 238 – 381.
8. Chakravarty, A. K., Dastiar, P. P. G., and Pakrashi, S. C. 1982. Simple aromatic amines from *Justicia gendarussa* 13C NMR Spectra of the bases and their analogues. *Tetrahedron*. **Elsivier**, 18 (12):1797-1802.

9. Dalimartha, S. 2001. **Atlas Tumbuhan Obat Indonesia**, Jilid 1, Jakarta: Trubus Ariwidya.
10. Departement of Health. 2002. **British Pharmacopoeia**. London: The Stationary Office. p. 1003, A 241-242.
11. Departemen Kesehatan RI. 1995. **Farmakope Indonesia**. Edisi IV. Jakarta : Dirjen POM.
12. Departemen Kesehatan RI. 1995. **Materia Medika Indonesia**. Jilid VI. Jakarta: Departemen Kesehatan RI.
13. Departemen Kesehatan RI. 2000. **Parameter Standar Umum Ekstrak Tumbuhan Obat**. Jakarta: Departemen Kesehatan RI.
14. Dhirendra, K., Lewis, S., Udupa, N., and Atin, K. 2009. Solid Dispersion, India, **Manipal College of Pharmaceutical Science**. p. 234-246.
15. EMEA., 1999. Working Part on Herbal Medicinal Products (HMPWP), Stability testing of HD (Herbal Drug), HDP (Herbal Drug Preparation), and HMP (Herbal Medicinal Product), **Guidelines** *25* : 48.
16. Feher, M., and Schmidt, J. M. 2003, Property Distributions: Differences Between Drugs, Natural Products, And Molecules From Combinatorial Chemistry, **J. Chem. Inf. Comput. Sci.** 43, 1, 218-227
17. Gordon, R. E., Rosanske, T. W., Fonner, D. E., Anderson, N. R., and Banker, G. S. 1990. **Granulation Technology and Tablet Characterization.** In: Lachman, L., Lieberman, H. A., Schwartz, J. B. (Eds), Pharmaceutical Dosage Forms: Tablets, 2nd ed, Vol. 2, New York: Marcel Dekker, Inc.
18. Gunsel, W. C. and Kanig, J. L. 1976. Tablet, In: Lachman, Lieberma, H. A. and Kanig J. L., **The Teory and Practice of Industrial Pharmacy,** 2nd Ed., Lea and Febiger, Philadelphia.
19. Gupta, R. S., and Sharma, R. 2006. A Review on Medicinal Plants Exhibiting Antifertility Activity in Males. **Natural Product Radiance**. Vol. 5 (5), p. 389-410.
20. Handa, S. S., Khanuja, S. P. S., Longo, G., and Rakesh, D. D. 2008. **Extraction Technologies for Medicinal and Aromatic Plants**. Itali: International centre for science and high technology. pp.21-25.
21. Harborne, J. B., 1987. **Metode Fitokimia Penuntun Cara Modern Menganalisis Tumbuhan**, Edisi kedua. Bandung: Institut Teknologi Bandung Press.
22. Heyne. 1987. **Tumbuhan Berguna Indonesia**. Jilid III. Terjemahan Badan Litbang Kehutanan. Jakarta: Yayasan Sarana Wana. hal 1759.
23. Kiren, Y., Deguchi, J., Hirasawa, Y., Morita, H., and Prajogo, B. 2014. Justidrusamides A-D, new 2-aminobenzyl Alcohol Derivatives from *Justicia gendarussa*. **Journal of Natural Medicines**. Vol. 68, pp. 754-758.
24. Kusumahyuning, R., Soebagyo., Sulihtyowati, S. 2005. Pengaruh Laktosa dan Povidon dalam Formula Ekstrak *Kaempferia galanga* L. Secara Granulasi Basah. **Majalah Ilmu Kefarmasian**. Vol. II, No. 16, 110-115.
25. Lachman, L., Lieberman H.A., Kanig J.L. 1994. **Teori dan Praktek Farmasi Industri edisi III**. Jakarta : UI Press.
26. Lieberman, H.A., Lachman, L., Schwartz, J.B. 1990. **Pharmaceutical Dosage Forms.** New York : Marcel Dekker.
27. Ncube, N. S., Afolayan, A. J., and Okoh, A. I. 2008. Assessment Techniques of Antimicrobial Properties of Natural Compounds of Plant Origin: current methods and future trends. **African Journal of Biotechnology**. Vol 7, pp.1797-1806.
28. Prajogo, B. E. W., A. Khoiril, IGP Santa dan Soeharno. 1997. Efek Ekstrak Diklormetan dan Ekstrak Metanol Daun *Gendarussa vulgaris* Ness pada Spermatogenesis tikus, **Simposium PERHIPBA IX**, Universitas Gadjah Mada, Yogyakarta.
29. Prajogo, B. E. W., NS. Matty, IGP. Santa and PS. Onny. 1998. Efek Ekstrak Diklormetan dan Ekstrak Metanol Daun *Gendarussa vulgaris* Ness pada Aktivitas Enzim Spermatozoa Kelinci. **Symphosium** *POKJANAS TOI 8 VIII* Universitas Brawijaya, Malang.
30. Prajogo, B. E. W. 2002. Aktivitas Antifertilitas Flavonoid Daun Gendarusa Vulgaris Ness. Penelitian Eksperimental Pencegahan Penetrasi Spermatozoa Mencit dalam Proses Fertilisasi In Vitro. **Disertasi**. Program Pasca Sarjana Universitas Airlangga Surabaya.
31. Prajogo, B. E. W., Dudi, S., dan Mulya, H. S. 2007. Analisis Gendarusin A pada tanaman Budidaya *Justicia gendarussa* Burm f. **Jurnal Farmasi Indonesia**. 3: 176-180.
32. Prajogo, B. E. W., Pramesti, D., Musta'ina, S., Winarso, H., Radjaram, A., Suharjono., Zaini, N. C., Flourisa, J., Anggraeni, M. 2011. **Clinical Trial: The Use of Justicia gendarussa Burm. f. as Male Contraception.** APCRSHR 6. Yogyakarta: Indonesia.
33. Prajogo, B. E. W. 2014. **Autentik Tanaman Justicia gendarussa Burm. f. Sebagai Bahan Baku Obat Kontrasepsi Pria**. Surabaya: Airlangga University Press dengan LP3 UNAIR.
34. Pratama, B. O. 2012. Penentuan Standar Umum Ekstrak Etanol 70% Daun *Justicia gendarussa* Burm. f. **Skripsi**. Fakultas Farmasi Universitas Airlangga.
35. Radji, M., Oktavia, H., Suryadi, H. 2008. Pemeriksaan Bakteriologis Air Minum Isi Ulang Di Beberapa Depo Air Minum Isi Ulang

di Daerah Lenteng Agung dan Srengseng Sawah Jakarta Selatan. **Majalah Ilmu Kefarmasian**, Vol 5(2) : 101-109

36. Rajakumar, N., and Shivana, M. B. 2009. Ethno-medical Application of Plants in the Eastern Region of Shimoga Distric. **Journal Ethnopharmacology**. Vol 126, pp.64-73.
37. Rizqa, O, D., 2010. **Standardisasi Simplisia Daun *Justicia gendarusssa* Burm f. Dari Berbagai Tempat Tumbuh (Daerah Mojokerto lahan 1, Mojokerto Lahan II, dan Ponorogo)**. Skripsi, Fakultas Farmasi Universitas Airlangga, Surabaya.
38. Rowe, R. C., Paul, J. S., Sian, C. O. 2009. **The Handbook of Pharmaceutical Excipients**. 6th Ed, London: Pharmaceutical Press and American Pharmacist Association.
39. Sari, M.A. 2010. **Pengembangan Formula Granul Ekstrak Etanol 70% Daun *Justicia gendarussa* Burm.f. Sebagai Sediaan Fitofarmaka.** Skripsi, Fakultas Farmasi Universitas Airlangga, Surabaya.
40. Staniforth, J. N. 1988. **Powder Flow**. In: Aulton, M., Pharmaceutica: The Science Dosage Form Design, New York: Churchill Livingstche.
41. Sucker, H. 1982. **Test Methods for Granulates**, In Pharm Ind, 44th Ed, number 3, Switzerland.
42. United State Pharmacopoeia Convention. 2003. **The United State Pharmacopeia 26-National Formulary.**
43. United States Pharmacopeia Convention. 2002. **The United State Pharmacopeia 25-National Formulary.**
44. Wells, J. L. and Aulton, M. E. 1988. Preformulation, in Aulton, M. E., Editor, **Pharmaceuticals The Sciences Dosage Form Design**. London: Churcill Livingstone.
45. WHO. 1999. **WHO Monograph on Selected Medicinal Plants**. Vol.I, Geneva: WHO.
46. Zheng, Jack. 2009. **Formulation and Analytical Development for Low Dose Oral Drug Products**. New Jersey: John Wiley & Sons, Inc.