

Daftar Pustaka

- Aakeroy, C.B and Salmon, D.J, 2005, *Building Co-crystals with Molecular Sense and Supramolecular Sensibility*, CrystEngComm, 2005,7(72): 439-448.
- Amelinchx, S, Van Dyck, D, Van Landuyt, J, Van Tendeloo, G, 1997, *Electron Microscopy: Principles and Fundamentals*, A Wiley Company.
- Ansel, H.C, 1985, *Introduction to Pharmaceutical Dosage Form* : Tejemahan oleh Farida Ibrahim, UI-Press, Jakarta.
- AHFS, 2008, *Drug Information*, American Hospital Formulary
- Ain, Shabnam, Ain, Qurratul and Parveen, Shama, 2009, *An Overview on Various Approaches Used for Solubilization of Poorly Soluble Drugs*, The Pharma Research: 84-104
- Alpha Pharmaceutical, 1999, *Alpha-aciclovir*, (online) [http:// www.Medsafe.govt.nz/profs/datasheet/alphacicilovirtab.htm](http://www.Medsafe.govt.nz/profs/datasheet/alphacicilovirtab.htm). diakses tanggal 5 April 2010
- Anonim, *Ascorbic Acid*, (online) [www. Inchem .org/documents/pims/pharm/ ascorbic.htm](http://www.Inchem.org/documents/pims/pharm/ascorbic.htm). diakses tanggal 07 April 2011
- , *Differential Scanning Calorimetry*, 2005 (online) [http://pslc.ws/macrogess/ dsc.html](http://pslc.ws/macrogess/dsc.html). Department of Polymer Science, University of Southern Missisipi, diakses tanggal 27 Juni 2010
- Arnal, J, Gonzales-Alvares, I, Bermejo, M, Amidon, G.L, Junginger, H.E, Kopp, S, Midha, K.K, Shah, V.P, Stavchansky, S, Dressman, J.B, Barends, D.M. 2008, *Biowaiver Monographs for Immediate Release Solid Oral Dosage Form: Aciclovir*, Journal of Pharmaceutical Sciences, Vol.97 : 5061 – 5073
- Basavoju, S, Bostrom, D, Velaga, S.P. 2007, *Indomethacin-Saccharin Cocystal: Design, Synthesis and Preliminary Pharmaceutical Characterization*, Pharmaceutical Research, Vol.25: 537 – 541
- Bhatt, P.M, Ravindra, N.V, Banerjee, R and Desiraju, G.R, 2005, *Saccharin as a salt former. Enhanced Solubilities of Saccharinates of Active Pharmaceutical Ingridients*, Chem.Commun: 1073-1075

- Blagden, N, Berry, D.J, Parkin, A, Javed, H, Ibrahim, A, Gavan, P.T, De Matosa, L.L, Seaton, C.C, 2008, *Current Direction in Co-crystal Growth*, New Journal of Chemistry, Vol.32 : 1659-1672
- Braga, D, Grepioni, F, Maini, L, and Polito, M. 2009, *Crystal Polymorphism and Multiple Crystal Form*, Struct Bond 132: 25 – 30
- Bethune, S.J, 2009, *Thermodynamic and Kinetic Parameters that Explain Crystallization and Solubility of Pharmaceutical Cocystal*, Disertasi: University of Michigan.
- Carstensen, J.T, 1998, *Pharmaceutical Preformulation*, Technomic Publishing Company, Lancaster, Pennsylvania
- Cao Wey-Yun, 2007, *Combined Used of Acyclovir Vitamin C with Interferon in Treating Herpes Simple Keratitis*, Journal of Shandong Medical College
- Childs, S. 2007, *Cocrystallization Methods*, US Patent Application
- Crowley, PJ and Martini L.G., 2004, *Formulation Design: New Drugs from Old*, Drugdiscoverytoday.com. 537 – 542
- Drug Bank, 2009, *Drug Card for Aciclovir (DB00787)*, (online) <http://www.drugbank.ca/drugs/DB00787>. diakses tanggal 5 April 2010
- Dressmann and Kramer, 2005, *Pharmaceutical Dissolution Testing*, Taylor and Francis. London, New York, Singapore
- Direktorat Jenderal Pengawasan Obat dan Makanan, 1995, *Farmakope Indonesia*, Edisi IV, Departemen Kesehatan RI, Jakarta
- Doherty, M.F, 2008, *From Form to Function: Crystallization of Active Pharmaceutical Ingredients*, AIChE Journal, Vol.54.7 : 1682-1688
- Ganiswarna, S.G.,2002, *Farmakologi dan Terapi*: Edisi 4, Bagian Farmakologi Fakultas Kedokteran Universitas Indonesia, Jakarta
- Hammod, C, 2009, *The Basic of Crystallography and Diffraction*, Oxford University Press. New York
- Hetal, T. Bindesh, P. and Sneha, T.,2010, *A Review on Technique for Oral Bioavailability Enhancement of Drugs*, International Journal of Pharmaceutical Sciences Review and Research, Vol.4: 203-223.

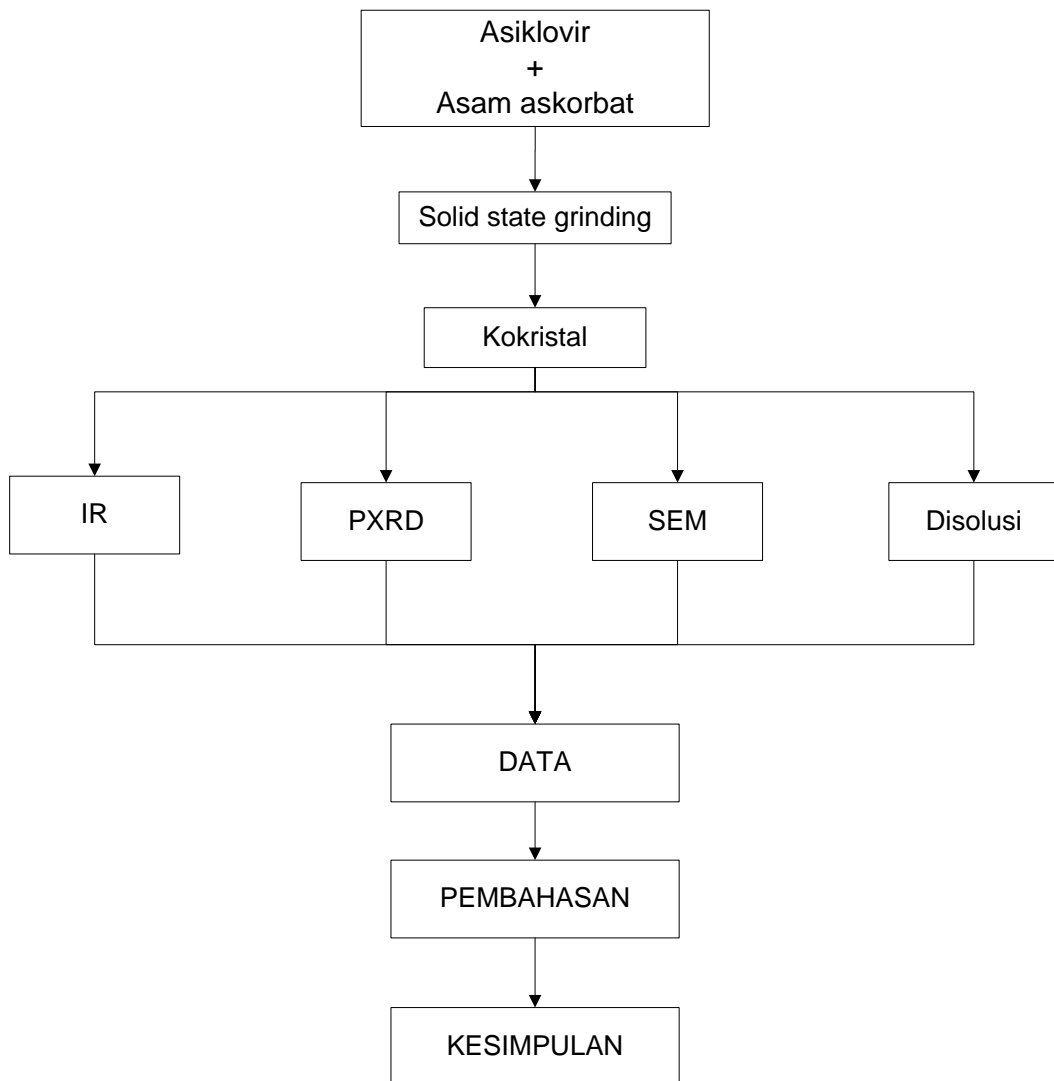
- Hilfiker, R, 2006, *Polimorphism: in Pharmaceutical Industry*, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim
- Jayasankar, A, Somwangthanaroj, A, Shao, Z.J, and Hornedo, N.R, 2006, *Cocrystal Formation During Cogrinding and Storage is Mediated by Amorphous Phase*, *Pharmaceutical Research*, Vol.23: 2381-2392
- Jones, W, Motherwell, W.D.S, and Trask, A.V. 2006, *Pharmaceutical Cocrystal: An Emerging Approach to Physical Property Enhancement*, *MRS Bulletin*, 31: 875-879
- Karki, S, Friscic, T, Jones, W, and Motherwell, S.W.D. 2007, *Screening for Pharmaceutical Cocrystal Hydrates via Neat and Liquid-Assisted Grinding*, *Molecular Pharmaceutics*, Vol.4: 347 – 354.
- Kumar, S, Parkash, C, Kumar, P, and Singh, S.K, 2009, *Applicatin of Some Novel Technique for Solubility Enhancement of Mefenamic Acid, A Poorly Water Soluble Drug*. *International Journal of Pharmaceutical Science and Drug Research*, Vol.1 : 164-171
- McMahon, J, Peterson, M, Zaworotko, M.J., Shattock, T, Hickey, M.B., 2010. *Pharmaceutical Co-crystal, Composition and Related Methods of Use*, United States Patent: US 7,803,786,B2.
- Morisette, S.L, Almarsoon, O, Peterson, M.L, Remenar, J.F, Read, M.J, Lemmo, A.V, Ellis, S, Cima, M.J, and Gardner, C.R, 2003, *High-throughput Crystallization: Polimorphs, Salt, Co-crystals and Solvate of Pharmaceutical Solids*, *Advanced Drug Delivery Reviews* 56: 275-300
- McNamara, D.P, 2006, *Use of Glutaric Acid Cocrystal to Improve Oral Bioavailability of a Low Solubility API*, *Pharmaceutical Research*, Vol. 23: 1888-1897.
- Mirza, S, Miroshnyk, I, Heinamaki, J, Yliruusi, J. 2008, *Co-Crystals: An Emerging Approach or Enhancing Properties of Pharmaceutical Solids*, *Dosis*, Vol.24 : 90-96.
- Nai-Ning, Shao-Yu, and Chang-Xiao, 2004, *Overview of Factors Affecting Oral Drug Absorption*, *Asian Journal of Drugs Metabolism and Pharmacokinetics*, Vol. 4(3). 167-176
- Peterson, M.L, Hickey, M.B, Zaworotko, M.J, and Almarsson, O. 2006, *Expanding the Scope of Crystal Form Evaluation in Pharmaceutical Science*, *J Pharm Pharmaceut Sci*, Vol 9 (3): 317-326

- Rodriguez.N, Nehm, S.J, and Jayasankar, A. 2007, *Cocrystal: Design, Properties and Formation Mechanisms*, Encyclopedia of Pharmaceutical Technology, Informa Healthcare: 615 – 633
- Rowe, Raymond C, Sheskey, Paul J, and Owen, Sian C, 2006, *Handbook of Pharmaceutical Excipient*, 5th edition, Pharmaceutical Press, London.
- Seefeldt, K, Miller, J, Alvarez, F, and Rodriguez,N . 2006, *Crystallization Pathway and Kinetics of Carbamazepine-Nicotinamide Cocrystal From the Amorphous State by In Situ Thermomicroscopy, Spectroscopy, and Calorimetry Studies*, Journal of Pharmaceutical Science, Vol.96, 2007: 1147-1158
- Settle, F, 1997, *Handbook of Instrumental Techniques for Analytical Chemistry*, Prentice Hall PTR, Upper Saddle River
- Schultheiss, N and Newman, A, 2009, *Pharmaceutical Cocrystal and Their Physicochemical Properties*, Crystal Growth and Design, Vol.9 : 2950 – 2967
- Shan, N and Zaworotko, M.J.,2008, *The Role of Cocrystal in Pharmaceutical Science*, Drug Discovery Today, Vol.13: 440 – 446
- Sekhon, BS., 2009, *Pharmaceutical Co-crystal- a Review*, Ars Pharm, Vol.50 : 99 – 117
- Shiraki, K, Takata, N, Takano, R, Hayashi, Y, and Terada, K. 2008, *Dissolution Improvement and The Mechanism of The Improvement from Cocrystallization of Poorly Water Soluble Compounds*, Pharmaceutical Research, Vol.25: 2581-2592.
- Shinde, A.J, 2007, *Solubilization of Poorly Soluble Drugs: A Review*. (Online) <http://www.pharmainfo.net/review/solubilization-poorly-soluble-drugs-review>, diakses 15 Januari 2010.
- Swarbrick, J, 2007, *Encyclopedia of Pharmaceutical Technology*, Third Ed. Informa Healthcare, New York, London.
- Trask, A.V, Motherwell, W.D.S, and Jones, W. 2004, *Solvent-drop Grinding: Green Polymorph Control of Cocrystallisation*, Chem.Comm., 2004: 890-891
- Trask, A.V, Shan, N, Motherwell, W.D.S, Jones, W, Feng, S, Tan, R.B.H, Carpenter, K.J. 2005, *Selective Polymorph Transformation via Solvent-drop Grinding*, Chem.Comm., 2005: 880 – 882

- Trask, A.V, Motherwell, W.D.S, and Jones, W. 2006, *Physical Stability Enhancement of Theophylline via Cocrystallization*, International Journal of Pharmaceutics, 320: 114 – 123
- Trask, A.V, Streek, J.V, Motherwell, W.D.S, and Jones, W 2005, *Achieving Polymorphic and Stoichiometric Diversity in Crystal Formation: Importance of Solid-State Grinding, Powder X-Ray Structure Determination and Seeding*, Crystal Growth and Design, Vol. 5(6): 2233 – 2241.
- Trask, A.V and Jones, W, 2005, *Crystal Engineering of Organic Cocrystal by the Solid-State Grinding Approach*, Tur Curr Chem, 251: 41-70.
- Trask, A.V, Motherwell, W.D, and Jones, W. 2004, *Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration*, Crystal Growth & Design, 5: 1013 – 1021
- Thomson Healthcare. Online *Micromedex Healthcare Series*, <http://www.micromedex.com/products/hcs/>. Diakses tanggal 5 Maret 2010
- USP 29 – NF 24, *Acyclovir*, (online) http://www.pharmacopeia.cn/v29240/usp29nf24s0_m890.html. diakses. diakses 5 April 2010
- Vishweshar, P, McMahon, J.A, Peterson, M.L, Hickey, M.B, Shattock, T.R, and Zaworotko, M.J. 2005, *Crystal Engineering of Pharmaceutical Co-crystal From Polymorphic Active Pharmaceutical Ingredients*, Chem.Comm, 4601 – 4603
- Yadav, A.V, 2009, *Co-crystal: A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical ingredients*, Review Article. Vol.71: 359 – 370.

Lampiran 1 : Skema Kerja

SKEMA KERJA



Gambar 18 : Skema kerja karakterisasi struktur dan uji disolusi kokristal Asiklovir-Asam Askorbat.

Lampiran 4 : Hasil analisis puncak difraksi sinar X

a. Hasil analisis puncak sampel Asiklovir

No	2-THETA	INT.	WIDTH	d	I/Io
1	43,640	98	0,450	2,027	86
2	44,600	113	0,360	2,030	100
3	50,700	40	0,300	1,799	35
4	64,620	11		1,441	9
5	74,720	46	0,480	1,269	40

b. Hasil analisis puncak sampel asam askorbat

No	2-THETA	INT.	WIDTH	d	I/Io
1	43,600	110	0,510	2,074	74
2	44,520	149	0,330	2,033	100
3	50,820	36	0,300	1,795	24
4	64,620	13		1,441	9
5	74,780	35	0,540	1,269	23

Lampiran 8 : Tabel Data Disolusi Asiklovir

Waktu (menit)	Per-Lakuan	Serapan	Kadar (mg/1000 ml)	Kadar (mg/900 ml)	Faktor koreksi	Setelah koreksi	% disolusi
5	1	0,849	51,6250	46,4625			
	2	0,971	59,2500	53,3250			
Rata-rata		0,91	55,4375	49,8937	0	49,8937	49,89
10	1	1,031	63,0000	56,7000			
	2	1,130	69,1875	62,2687			
Rata-rata		1,080	66,0937	59,4843	0,3304	59,8147	59,81
15	1	1,092	66,8125	60,1312			
	2	1,148	70,3125	63,2812			
Rata-rata		1,12	68,5625	61,7062	0,6732	62,3784	62,38
20	1	1,117	68,3750	61,5375			
	2	1,155	70,7500	63,6750			
Rata-rata		1,136	69,5625	62,6062	1,021	63,6272	63,63
25	1	1,135	69,500	62,5500			
	2	1,166	71,4375	64,2937			
Rata-rata		1,150	70,4687	63,4218	1,3733	64,7951	64,80
30	1	1,171	72,0000	64,8000			
	2	1,164	71,3125	64,1812			
Rata-rata		1,167	71,6562	64,4906	1,7316	66,2222	66,22
45	1	1,174	71,9375	64,7437			
	2	1,169	71,6250	64,4625			
Rata-rata		1,171	71,7812	64,6031	2,0905	66,6936	66,69
60	1	1,174	71,9375	64,7437			
	2	1,169	71,6250	64,4625			
Rata-rata		1,172	71,7812	64,6031	2,4494	67,0525	67,05

Lampiran 9 : Tabel Data Disolusi Kokristal Asiklovir-Asam Askorbat (1:1)

Waktu (menit)	Per-lakuan	Serapan	Kadar (mg/1000 ml)	Kadar (mg/900 ml)	Faktor koreksi	Setelah koreksi	% disolusi
5	1	1,141	69,8750	62,8875			
	2	1,100	67,3125	60,5812			
Rata-rata		1,120	68,5937	61,7343	0	61,7343	61,73
10	1	1,172	71,8125	64,6312			
	2	1,141	69,8750	62,8875			
Rata-rata		1,156	70,8437	63,7593	0,3542	64,1135	64,11
15	1	1,181	72,3750	65,1375			
	2	1,146	70,1875	63,1688			
Rata-rata		1,164	71,2812	64,1531	0,7106	64,8637	64,86
20	1	1,184	72,5625	65,3062			
	2	1,158	70,9375	63,8437			
Rata-rata		1,171	71,7500	64,5749	1,0693	65,6442	65,64
25	1	1,185	72,6250	65,3625			
	2	1,169	71,6250	64,4625			
Rata-rata		1,177	72,1250	64,9125	1,4299	66,3424	66,34
30	1	1,187	72,7500	65,4750			
	2	1,174	71,9375	64,7437			
Rata-rata		1,180	72,3437	65,1093	1,7916	66,9009	66,90
45	1	1,189	72,8750	65,5875			
	2	1,180	72,3125	65,0812			
Rata-rata		1,185	72,5937	65,3343	2,1546	67,4889	67,49
60	1	1,189	72,8750	65,5875			
	2	1,187	72,7500	65,4750			
Rata-rata		1,188	72,8125	65,5312	2,5186	68,0498	68,49

Lampiran 10: Contoh Perhitungan Uji Disolusi

- a. Perhitungan konsentrasi dalam 1000 ml

Contoh untuk asiklovir pada 5 menit.

Persamaan garis kurva baku : $y = 0,016 x + 0,023$

$$X = \frac{y - a}{b}$$

$$\begin{aligned} X &= \frac{0,849 - 0,023}{0,016} \\ &= 51,6250 \text{ mg} / 1000 \text{ ml} \end{aligned}$$

- b. Konsentrasi dalam 900 ml

$$\begin{aligned} &51,6250/1000 \text{ ml} \times 900 \text{ ml} \\ &= 46,4625 \text{ mg} \end{aligned}$$

- c. Perhitungan faktor koreksi

Faktor koreksi = $5 \text{ ml} / 900 \text{ ml} \times \text{konsentrasi per } 900 \text{ ml} + \text{faktor koreksi}$
sebelumnya

Contoh untuk 10 menit,

$$5/900 \times 59,4843 + 0 = 0,3304$$

- d. Perhitungan konsentrasi setelah koreksi;

Kadar sebelum koreksi + faktor koreksi

Contoh: untuk 10 menit

$$59,4843 + 0,3304 = 59,8147$$

3. Persen terdissolusi ;

Kadar setelah koreksi / bobot sampel x 100 %

Contoh: $59,8147 / 100 \text{ mg} \times 100 \%$

$= 59,81 \%$