STUDI LITERATUR
PENINGKATKAN KELARUTAN DAN DISOLUSI KOAMORF OBAT SUKAR LARUT AIR GOLONGAN ASAM KARBOKSILAT

SKRIPSI

JAN REZA PUTRA
A182015

SEKOLAH TINGGI FARMASI INDONESIA
YAYASAN HAZANAH
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SKRIPSI

Sebagai salah satu syarat untuk memperoleh gelar Sarjana Farmasi

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Disetujui oleh:

Pembimbing	Pembimbing
apt. Revika Rachmaniar, M.Farm.	apt. Lediansari, M.Farm.

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ABSTRAK

Beberapa obat termasuk dalam kelompok asam karboksilat yang sedikit larut dalam air. Obat yang sukar larut dalam air dapat menyebabkan disolusi dan bioavailabilitas yang buruk sehingga menghambat aktivitas obat. Salah satu solusi untuk mengatasi masalah tersebut adalah dengan pembentukan koamorf. Kajian literatur ini bertujuan untuk mengetahui pengaruh pembentukan koamorf terhadap peningkatan kelarutan dan disolusi obat golongan asam karboksilat. Kajian yang disusun berupa *systematic review journal* menggunakan protokol PICOC (*Population, Intervention, Comparison, Outcomes, and Context*). Tinjauan literatur menunjukkan koamorf *binary system* furosemid menggunakan verapamil HCl sebagai koformer dengan rasio molar 1:2 mengalami peningkatan kelarutan terendah yaitu 0,07 kali dan koamorf *binary system* indometasin menggunakan histidin sebagai koformer dengan rasio molar 1:1 mengalami peningkatan disolusi terendah, yaitu sebesar 1,25 kali. Koamorf *ternary system* valsartan menggunakan arginin dan histidin sebagai koformer dengan rasio molar 1:1:1 mengalami peningkatan kelarutan dan disolusi sebesar 222 kali dan 1260 kali secara berturut-turut. Ikatan hidrogen dan pembentukan garam bertanggung jawab atas peningkatan kelarutan dan disolusi valsartan. Berdasarkan kajian literatur ini disimpulkan bahwa strategi terbaik untuk mendapatkan koamorf yang memiliki kelarutan dan disolusi tinggi adalah koamorf sistem *ternary* pada rasio molar 1:1:1 menggunakan koformer golongan asam amino (arginin) dan metode *milling* yang mampu membentuk ikatan hidrogen dan garam.

Kata Kunci: Koamorf, kelarutan, disolusi, obat sukar larut air

ABSTRACT

Some drugs belong to the group of poorly water-soluble carboxylic acids. Drugs that are poorly soluble in water can cause poor dissolution and bioavailability, thereby inhibiting drug activity. One solution to overcome this problem is the formation of coamorphous. This literature review aims to determine the effect of coamorphous formation on increasing the solubility and dissolution of carboxylic acid drugs. The study was created in the form of a systematic review journal according to the PICOC protocol (Population, Intervention, Comparison, Outcomes, and Context). The literature review showed that the coamorphous of the binary system of furosemide using verapamil HCl as a coformer with a 1:2 molar ratio had the lowest increase in solubility of 0.07-fold and the binary coamorph of the indomethacin system using histidine as the Coformer with a 1:1 molar ratio experienced the lowest increase in resolution of 1.25 times. The valsartan ternary coamorphous system using arginine and histidine as coformers in a 1:1:1 molar ratio experienced a 222-fold and 1260-fold increase in solubility and resolution, respectively. Hydrogen bonding and salt formation are responsible for the increased solubility and dissolution of valsartan. Based on this literature review, it was concluded that the best strategy to obtain a coamorphous with high solubility and disolution was a ternary system coamorphous in a 1:1:1 molar ratio using amino acid group coformers (arginine) and milling methods that are capable of forming hydrogen bonds and salts.

***Keywords**: Coamorphous, solubility, dissolution, slightly solube drugs*

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DAFTAR ISI

DAFTAR TABEL

DAFTAR GAMBAR

DAFTAR LAMPIRAN

DAFTAR PUSTAKA

Ali, A.M.A., and Al-Remawi M.M.A. 2016. "Freeze Dried Quetiapine-Nicotinamide Binary Solid Dispersions: A New Strategy for Improving Physicochemical Properties and Ex Vivo Diffusion". *Journal of Pharmaceutics*, 2016:1–11.

Chavan, R. B., Thipparaboina, R., Kumar, D., and Shastri, N. R. 2016. "Co amorphous Systems: A Product Development Perspective." *International Journal of Pharmaceutics* 515(1–2): 403–415.

Delombaerde, D. 2018. "Co-amorphous Drug Formulations: Carbamazepine, Mefenamic Acid and Sulfamerazine." *Disertasi.* Faculty of Pharmaceutical Sciences. Kuopio: University of Eastern Finland. P. 1-52

Dengale, S. J., Grohganz, H., Rades, T., and Löbmann, K. 2016. "Recent Advances in Co-amorphous Drug Formulations." *Advanced Drug Delivery Reviews* 100(2016): 116–125.

Deruiter, J. 2005. "*Carboxylic Acid Structure and Chemistry : Part 1.. H The dipolar nature of acids"*. P. 1–11.

Dewi, F. A., Sopyan, I., dan Rusdiana, T. 2021. "Pemilihan Jenis Koformer dan Metode Preparasi dalam Sistem Penghantaran Sediaan Ko-amorf." *Jurnal Sains Farmasi dan Klinis* 8(3): 242.

Fael, H., and Demirel, A. L. 2020. "Tannic Acid as a Co-former in Co-amorphous Systems: Enhancing Their Physical Stability, Solubility and Dissolution Behavior." *International Journal of Pharmaceutics* 58(1): 119284.

Fael, H., and Demirel, A. L. 2021. "Indomethacin Co-amorphous Drug-Drug Systems with Improved Solubility, Supersaturation, Dissolution Rate and Physical Stability." *International Journal of Pharmaceutics,* 600(January): 120448.

Gao, Y., Liao, J., Qi, X., and Zhang, J. 2013. "Coamorphous Repaglinide-Saccharin with Enhanced Dissolution." *International Journal of Pharmaceutics* 450(1–2): 290–295.

Han, J., Wei, Y., Lu, Y., Wang, R., Zhang, J., Gao, Y., and Qian, S. 2020. "Co-amorphous Systems for The Delivery of Poorly Water-Soluble Drugs: Recent Advances and An Update." *Expert Opinion on Drug Delivery*. 17(10): 1411-1435.

Haneef, J., and Chadha, R. 2017. "Drug-Drug Multicomponent Solid Forms: Cocrystal, Coamorphous and Eutectic of Three Poorly Soluble

Antihypertensive Drugs Using Mechanochemical Approach." *AAPS PharmSciTech* 18(6): 2279–2290.

Huang, Y., Zhang, Q., Wang, J. R., Lin, K. L., and Mei, X. 2017. "Amino Acids as Co-amorphous Excipients for Tackling The Poor Aqueous Solubility of Valsartan". *Pharmaceutical Development and Technology* 22(1): 69–76.

Jensen, K. T., Löbmann, K., Rades, T., and Grohganz, H. 2014. "Improving Co-amorphous Drug Formulations by The Addition of The Highly Water Soluble Amino Acid, Proline." *Pharmaceutics* 6(3): 416–435.

Jensen, K. T., Blaabjerg, L. I., Lenz, E., Bohr, A., Grohganz, H., Kleinebudde, P., Rades, T., and Löbmann, K. 2016. "Preparation and Characterization of Spray-dried Co-amorphous Drug-amino Acid Salts". *Journal of Pharmacy and Pharmacology* 68(5): 615–624.

Karlsson, J., and Fowler, C. J. 2014. "Inhibition of Endocannabinoid Metabolism by The Metabolites of Ibuprofen and Flurbiprofen." *PLoS ONE* 9(7): 10–14.

Kasten, G., Nouri, K., Grohganz, H., Rades, T., and Löbmann, K. 2017. "Performance Comparison between Crystalline and Co-amorphous Salts of Indomethacin-lysine." International Journal of Pharmaceutics 533(1): 138–144.

Kasten, G., Lobo, L., Dengale, S., Grohganz, H., Rades, T., and Löbmann, K. 2018. "In Vitro and In Vivo Comparison between Crystalline and Co-amorphous Salts of Naproxen-arginine". *European Journal of Pharmaceutics and Biopharmaceutics*, 132(May): 192–199.

Kannan, K., Krishna, R., Manikandan, M., Selvamuthukumar, S., & Manavalan, R. 2012. "Development and Evaluation of Valsartan Film Coated Tablets". *Journal of Pharmaceutical Sciences and Research*, 4(6): 1866–1871.

Li, M., Wang, M., Liu, Y., Ouyang, R., Liu, M., Han, D., and Gong, J. 2021. "Co-amorphization Story of Furosemide-Amino Acid Systems: Protonation and Aromatic Stacking Insights for Promoting Compatibility and Stability." *Crystal Growth and Design* 21(6): 3280–3289.

Li, W., Song, J., Li, J., Li, M., Tian, B., He, Z., Liu, X., and Fu, Q. 2021. "Co-amorphization of Atorvastatin by Lisinopril as a Co-former for Solubility Improvement." *International Journal of Pharmaceutics* 607(103): 1-8

Löbmann, K., Laitinen, R., Grohganz, H., Gordon, K. C., Strachan, C., and Rades, T. 2011. "Coamorphous Drug Systems: Enhanced Physical Stability and Dissolution Rate of Indomethacin and Naproxen." *Molecular Pharmaceutics* 8(5): 1919–1928.

Löbmann, K., Grohganz, H., Laitinen, R., Strachan, C., and Rades, T. 2013. "Amino Acids as Co-amorphous Stabilizers for Poorly Water Soluble Drugs - Part 1: Preparation, Stability and Dissolution Enhancement." *European Journal of Pharmaceutics and Biopharmaceutics* 85(3 PART B): 873–881

Meng-Lund, H., Kasten, G., Jensen, K. T., Poso, A., Pantsar, T., Rades, T., Rantanen, J., and Grohganz, H. 2018. "The Use of Molecular Descriptors in The Development of Co-amorphous Formulations." *European Journal of Pharmaceutical Sciences* 119(2018): 31–38.

Mohapatra, T. K., Moharana, A. K., Swain, R. P., and Subudhi, B. B. 2021. "Coamorphisation of Acetyl Salicylic Acid and Curcumin for Enhancing Dissolution, Anti-Inflammatory Effect and Minimizing Gastro Toxicity." *Journal of Drug Delivery Science and Technology* 61(April): 102119.

Moinuddin, S. M., Shi, Q., Tao, J., Guo, M., Zhang, J., Xue, Q., Ruan, S., and Cai, T. 2020. "Enhanced Physical Stability and Synchronized Release of Febuxostat and Indomethacin in Coamorphous Solids." *AAPS PharmSciTech* 21(2): 41.

Nair, A., Varma, R., Gourishetti, K., Bhat, K., and Dengale, S. 2020. "Influence of Preparation Methods on Physicochemical and Pharmacokinetic Properties of Co-amorphous Formulations: The Case of Co-amorphous Atorvastatin: Naringin." *Journal of Pharmaceutical Innovation* 15(3): 365–379.

Petticrew, M., and Roberts, H. 2008. *Systematic Reviews in The Social Sciences: A Practical Guide*. Malden: Blackwell Publishing. P. 38-44.

Ruponen, M., Kettunen, K., Pires, M. S., and Laitinen, R. 2021. "Co-amorphous Formulations of Furosemide with Arginine and P-glycoprotein Inhibitor Drugs." *Pharmaceutics* 13(2): 1–18

Russo, M. G., Baldoni, H. A., Dávila, Y. A., Brusau, E. v., Ellena, J. A., and Narda, G. E. 2018. "Rational Design of a Famotidine-Ibuprofen Coamorphous System: An Experimental and Theoretical Study." *Journal of Physical Chemistry B* 122(37): 8772–8782.

Shayanfar, A., Ghavimi, H., Hamishehkar, H., and Jouyban, A. 2013. "Coamorphous Atorvastatin Calcium to Improve Its Physicochemical and Pharmacokinetic Properties." *Journal of Pharmacy and Pharmaceutical Sciences* 16(4): 577–587.

Shi, Q., Moinuddin, S. M., and Cai, T. 2019. Advances in Coamorphous Drug Delivery Systems." *Acta Pharmaceutica Sinica B* 9(1): 19–35.

Skotnicki, M., Jadach, B., Skotnicka, A., Milanowski, B., Tajber, L., Pyda, M., and Kujawski, J. 2021. "Physicochemical Characterization of a Co-amorphous Atorvastatin-Irbesartan System with a Potential Application in Fixed-dose

Combination Therapy". *Pharmaceutics* 13(1): 1–20.

Soyata, A., Sutoro, M., Devianti Sagita, N., Nadya Bestari, A., and Kusuma Dewi Muhammad Fauzi, M. 2022. "Impact of Preparation Method in Co-Amorphous System." *Sciences of Pharmacy* 1(1): 41–49.

Su, M., Xia, Y., Shen, Y., Heng, W., Wei, Y., Zhang, L., Gao, Y., Zhang, J., and Qian, S. 2019. "A Novel Drug-Drug Coamorphous System without Molecular Interactions: Improve The Physicochemical Properties of Tadalafil and Repaglinide." *RSC Advances* 10(1): 565–583.

Turek, M., Różycka-Sokołowska, E., Koprowski, M., Marciniak, B., and Bałczewski, P. 2021. "Role of Hydrogen Bonds in Formation of Co-amorphous Valsartan/Nicotinamide Compositions of High Solubility and Durability with Anti-hypertension and Anti-COVID-19 Potential." *Molecular Pharmaceutics* 18(5): 1970–1984.

Ukmar, T., Čendak, T., Mazaj, M., Kaučič, V., and Mali, G. 2012. "Structural and Dynamical Properties of Indomethacin Molecules Embedded within The Mesopores of SBA-15: A Solid-State NMR View." *Journal of Physical Chemistry C* 116(4): 2662–2671.

Wairkar, S., and Gaud, R. 2016. "Co-Amorphous Combination of Nateglinide-Metformin Hydrochloride for Dissolution Enhancement". *AAPS PharmSciTech* 17(3): 673–681.

Wairkar, S., and Gaud, R. 2019. "Development and Characterization of Microstructured, Spray-Dried Co-Amorphous Mixture of Antidiabetic Agents Stabilized by Silicate". *AAPS PharmSciTech* 20(3): 1–10.

Wang, M., Liu, S., Jia, L., Zhang, J., Du, S., and Gong, J. 2020. "Exploring The Physical Stability of Three Nimesulide–Indomethacin Co-amorphous Systems from The Perspective of Molecular Aggregates." *European Journal of Pharmaceutical Sciences* 14(7): 105294.

Wu, W., Löbmann, K., Schnitzkewitz, J., Knuhtsen, A., Pedersen, D. S., Grohganz, H., and Rades, T. 2018. "Aspartame as A Co-former in Co-amorphous Systems." *International Journal of Pharmaceutics* 549(1–2): 380–387.