STUDI LITERATUR
PENGARUH PEMUATAN ZAT AKTIF FARMASI SUKAR LARUT AIR KE DALAM MESOPORI SILIKA TERHADAP KELARUTAN DAN DISOLUSINYA

SKRIPSI

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"Sebagai salah satu syarat untuk memperoleh gelar Sarjana Farmasi"

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Disetujui oleh :

Pembimbing	Pembimbing
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ABSTRAK

Berbagai pendekatan telah dilakukan untuk mengatasi tantangan formulasi dari obat yang memiliki kelarutan dan disolusi yang rendah. Oleh karena itu, untuk mengatasi masalah tersebut, berbagai pembawa dalam obat-obatan digunakan untuk membawa agen terapeutik ke situs target di tubuh, seperti mesopori. Mesopori yang dibuat dari bahan silika dikenal sebagai pembawa yang menjanjikan untuk mengatasi kelarutan dan disolusi obat serta sebagai penghantaran obat. Sifat-sifat mesopori silika meliputi ukuran pori, porositas, kapasitas pemuatan obat, serta morfologi permukaan, dapat diubah tergantung pada *template* yang digunakan. Adapun teknik pemuatan obat dalam mesopori di antaranya adalah metode peleburan, metode perendaman, metode adsorpsi pelarut dan metode evaporasi pelarut. Obat-obat yang telah berhasil dimuat dalam mesopori silika adalah *Aceclofenac, Albendazole, Apigenin, Carbamazepine, Clofazimine, Ezetimibe*, *Felodipine*, *Indometacin, Probucol Valsaltran,* dan *Vorinostat* dengan kapasitas pemuatan sebesar 12,8 - 47%. Adapun peningkatan kelarutan obat-obatan yang dimuat dalam mesopori silika sebesar 2,21 - 95 kali dan peningkatan disolusinya sebesar 1,73 – 12,14 kali. Peningkatan ini terjadi karena obat-obatan diubah menjadi amorf dan stabil dalam mesopori melalui proses adsorpsi ke permukaan partikel silika, yang terdiri dari matriks pori-pori dengan diameter antara 2 dan 50 nm. Berdasarkan kajian pustaka tersebut dapat disimpulkan bahwa bahwa pemuatan obat sukar larut air dalam mesopori memiliki potensi besar menjadi alternatif metode peningkatan kelarutan dan laju disolusi obat.

Kata kunci: Mesopori silika, kelarutan, disolusi

ABSTRACT

Various approaches have been taken to overcome the challenges of formulating drugs that have low solubility and dissolution. Therefore, to solve the problem, various carriers in medicines ware used to bring the therapeutic agent to target sites on the body, such as mesoporous. Mesoporous made from silica was known as a promising carrier for drug solubility and dissolution as well as drug delivery. The properties of mesoporous silica, including pore size, porosity, drug loading capacity, and surface morphology, could be changed depending on the template used. The techniques for loading drugs in mesopores include the melting method, the immersion method, the solvent adsorption method and the solvent evaporation method. The drugs that have been successfully loaded in mesoporous silica ware Aceclofenac, Albendazole, Apigenin, Carbamazepine, Clofazimine, Ezetimibe, Felodipine, Indometacin, Probucol Valsaltran, and Vorinostat with a loading capacity of 12.8 - 47%. The increase in the solubility of drugs contained in mesoporous silica was 2.21 - 95 times and the increase in solution was 1.73 - 12.14 folds. This enhancement occured because the drugs are converted to amorphous and stable in the mesoporous by the adsorption process onto the surface of the silica particles, which consist of a matrix of pores with a diameter between 2 and 50 nm. Based on the literature review, it can be concluded that the loading of water-insoluble drugs in mesoporous has great potential to be an alternative method of increasing the solubility and dissolution rate of drugs.

Keyword : *Mesoporous silica, solubility, dissolution*

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DAFTAR LAMPIRAN

DAFTAR PUSTAKA

Bai, A., Wu, C., Liu, X., Lv, H., Xu, X., Cao, Y., Shang, W., Hu, L., and Liu, Y. 2018. "Development of a tin oxide carrier with mesoporous structure for improving the dissolution rate and oral relative bioavailability of fenofibrate." *Drug Design, Development and Therapy* 12:2129-2138.

Bharti, C., Gulati, N., Nagaich, U., and Pal, A. 2015. "Mesoporous silica nanoparticles in target drug delivery system: A review." *International Journal of Pharmaceutical Investigation* 5(3):124-133.

Biswas, N. 2017. "Modified mesoporous silica nanoparticles for enhancing oral bioavailability and antihypertensive activity of poorly water soluble valsartan." *European Journal of Pharmaceutical Sciences* 99:152-160.

Bosselmann, S, Williams, R.O. 2012. "Route-Specific Challenges in the Delivery of Poorly Water-Soluble Drugs. In Formulating Poorly Soluble Drugs." Springer. New York. P. 1–26

Cavalcanti, N. C. T., Sousa, G. D., Tabosa, M. A. M., Sobrinho, J. L. S., Leal, L. B., and de Santana, D. P. 2012. "Assay and physicochemical characterization of the antiparasitic albendazole." *Brazilian Journal of Pharmaceutical Sciences* 48(2):281-290.

Chairunnisa, P.S., dan Wardhana, Y.W. 2016. "Karakterisasi Kristal Bahan Padat Aktif Farmasi : *Review*." Fakultas Farmasi Universitas Padjadjaran.

Chen, B., Quan, G., Wang, Z., Chen, J., Wu, L., Xu, Y., Li, G., and Wu, C. 2013. "Hollow mesoporous silicas as a drug solution delivery system for insoluble drugs." *Powder Technology* : 48-53.

Chen, B., Wang, Z., Quan, G., Peng, X., Pan, X., Wang, R., Xu, Y., Li, G., and Wu, C. 2012. "In vitro and in vivo evaluation of ordered mesoporous silica as a novel adsorbent in liquisolid formulation." *International Journal of Nanomedicine* 7:199-209.

Chen, W., Cheng, C. A., Lee, B. Y., Clemens, D. L., Huang, W. Y., Horwitz, M. A., and Zink, J. I. 2018. "Facile Strategy Enabling Both High Loading and High Release Amounts of the Water-Insoluble Drug Clofazimine Using Mesoporous Silica Nanoparticles." *ACS Applied Materials and Interfaces* 10(38):31870-31881.

Choudhari, Y., Hoefer, H., Libanati, C., Monsuur, F., and McCarthy, W. 2014. "*Mesoporous Silica Drug Delivery Systems. In Amorphous Solid Dispersions Theory and Practice*." Springer. New York. P 665–693.

Dening, T. J., and Taylor, L. S. 2018. "Supersaturation Potential of Ordered Mesoporous Silica Delivery Systems. Part 1: Dissolution Performance and Drug Membrane Transport Rates." *Molecular Pharmaceutics* 15(8):3489-3501.

Departemen Kesehatan RI. 2014. "*Farmakope Indonesia edisi V"*. Jakarta: Depkes RI.

Esperanza Adrover, M., Pedernera, M., Bonne, M., Lebeau, B., Bucalá, V., and Gallo, L. 2020. "Synthesis and characterization of mesoporous SBA-15 and SBA-16 as carriers to improve albendazole dissolution rate." *Saudi Pharmaceutical Journal* 28(1):15-24.

Han, C., Huang, H., Dong, Y., Sui, X., Jian, B., and Zhu, W. 2019. "A comparative study of the use of mesoporous carbon and mesoporous silica as drug carriers for oral delivery of the water-insoluble drug carvedilol." *Molecules* 24(9):1770.

Hartono, S. B., Hadisoewignyo, L., and Antaresti. 2017. "Pembuatan, Modifikasi Dan Pemanfaatan Material Nano-Pori." *Jurnal Ilmiah Widya Teknik* 16(2) : 1-9

Huang, Y., Zhao, X., Zu, Y., Wang, L., Deng, Y., Wu, M., and Wang, H. 2019. "Enhanced solubility and bioavailability of apigenin via preparation of solid dispersions of mesoporous silica nanoparticles." *Iranian Journal of Pharmaceutical Research* 18(1):168-182.

Jadach, B., Feliczak-Guzik, A., Nowak, I., Milanowski, B., Piotrowska-Kempisty, H., Murias, M., and Lulek, J. 2019. "Modifying release of poorly soluble active pharmaceutical ingredients with the amine functionalized SBA-16 type mesoporous materials." *Journal of Biomaterials Applications* 33(9):1214-1231.

Jambhrunkar, S., Qu, Z., Popat, A., Karmakar, S., Xu, C., and Yu, C. 2014. "Modulating in vitro release and solubility of griseofulvin using functionalized mesoporous silica nanoparticles." *Journal of Colloid and Interface Science* 434:218-225.

Kerns, E. H., and Di, L. 2008. "Drug-like Properties: Concepts, Structure Design and Methods." *In Drug-like Properties: Concepts, Structure Design and Methods* : 493-513.

Khadka, P., Ro, J., Kim, H., Kim, I., Kim, J. T., Kim, H., Cho, J. M., Yun, G., and Lee, J. 2014. "Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability." In *Asian Journal of Pharmaceutical Sciences* 9(6):1-13.

Kiekens, F., Eelen, S., Verheyden, L., Daems, T., Martens, J., and van den Mooter, G. 2012. "Use of ordered mesoporous silica to enhance the oral bioavailability of ezetimibe in dogs." *Journal of Pharmaceutical Sciences* 101(3):1136-1144.

Krishnaiah, Y. S. 2010. "Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs." *Journal of Bioequivalence & Bioavailability* 2(2): 028-036.

Kumar, A., Sahoo, S. K., Padhee, K., Pal, P., Kochar, S., Satapathy, A., and Pathak, N. 2011. "Reveiw on Solubility Enhancement Techniques for Hydrophobic Drugs." *International Journal of Comprehensive Pharmacy* 2(3):1-5.

Kumar, D., Sailaja Chirravuri, S. V., and Shastri, N. R. 2014. "Impact of surface area of silica particles on dissolution rate and oral bioavailability of poorly water soluble drugs: A case study with aceclofenac." *International Journal of Pharmaceutics* 30:459-468.

Lau, M., Giri, K., and Garcia-Bennett, A. E. 2019. "Antioxidant properties of probucol released from mesoporous silica." *European Journal of Pharmaceutical Sciences* 138:105038.

Letchmanan, K., Shen, S. C., Ng, W. K., and Tan, R. B. H. 2017. "Dissolution and physicochemical stability enhancement of artemisinin and mefloquine co-formulation via nano-confinement with mesoporous SBA-15." *Colloids and Surfaces B: Biointerfaces* 155:560-568.

Li, J., Guo, Y., Li, H., Shang, L., and Li, S. 2018. "Superiority of amino-modified chiral mesoporous silica nanoparticles in delivering indometacin." *Artificial Cells, Nanomedicine and Biotechnology* 46(5):1085-1094.

Liu, X., Wu, C., Bai, A., Lv, H., Xu, X., Cao, Y., Shang, W., Hu, L., and Liu, Y. 2018. "Preparation of a Mesoporous Structure of SnO2 for Increasing the Oral Bioavailability and Dissolution Rate of Nitrendipine." *AAPS PharmSciTech* 19(7):3228-3236.

Maleki, A., Kettiger, H., Schoubben, A., Rosenholm, J. M., Ambrogi, V., and Hamidi, M. 2017. "Mesoporous silica materials: From physico-chemical properties to enhanced dissolution of poorly water-soluble drugs. *In Journal of Controlled Release* 262:329-347.

Masturoh, I., Anggita, N. 2018. Metodelogi Penelitian Kesehatan. Jakarta : Mentri Kesehatan Indonesia.

Mccarthy, C. A., Ahern, R. J., Dontireddy, R., Ryan, K. B., and Crean, A. M. 2016. "Mesoporous silica formulation strategies for drug dissolution enhancement: A review." *Expert Opinion on Drug Delivery* 13(1):93-108.

Meka, A. K., Jenkins, L. J., Dàvalos-Salas, M., Pujara, N., Wong, K. Y., Kumeria, T., Mariadason, J. M., and Popat, A. 2018. "Enhanced solubility, permeability and anticancer activity of vorinostat using tailored mesoporous silica nanoparticles." *Pharmaceutics* 10(4):283.

Nair, A. K., Anand, O., Chun, N., Conner, D. P., Mehta, M. U., Nhu, D. T., Polli, J. E., Yu, L. X., and Davit, B. M. 2012. "Statistics on BCS classification of generic drug products approved between 2000 and 2011 in the USA." In *AAPS Journal* 14(4):664-666.

Niu, X., Wan, L., Hou, Z., Wang, T., Sun, C., Sun, J., Zhao, P., Jiang, T., and Wang, S. 2013. "Mesoporous carbon as a novel drug carrier of fenofibrate for enhancement of the dissolution and oral bioavailability." *International Journal of Pharmaceutics* 452(1-2):382-389.

Pankaj, S., and Prakash, J. 2013. "Solid Dispersion: An Overview.: International Journal of Pharmaceutical Research and BioScience 2(3):114-43.

Poelstra K., Prakash J., and Beljaars L. 2012. "Drug targeting to the diseased liver". *Journal of Controlled Release* 161:188-197.

Popat, A., Hartono, S. B., Stahr, F., Liu, J., Qiao, S. Z., and Lu, G. Q. 2011. "Mesoporous silica nanoparticles for bioadsorption, enzyme immobilisation, and delivery carriers." *Nanoscale* 3(7):2801-2818.

Price, D.J., Naira, A., Becker-Baldus, J., Glaubitz, C., Kuentz, M., Dressman, J., and Saal, C. 2020. "Incorporation of HPMCAS during loading of glibenclamide onto mesoporous silica improves dissolution and inhibits precipitation." *European Journal of Pharmaceutical Sciences* 14: 105113

Salonen, J., Laitinen, L., Kaukonen, A. M., Tuura, J., Björkqvist, M., Heikkilä, T., Vähä-Heikkilä, K., Hirvonen, J., and Lehto, V. P. 2005. "Mesoporous silicon microparticles for oral drug delivery: Loading and release of five model drugs." *Journal of Controlled Release* 108(3):362-374.

Savjani, K. T., Gajjar, A. K., & Savjani, J. K. 2012. "Drug Solubility: Importance and Enhancement Techniques." *ISRN Pharmaceutics* : 195727.

Sharma, D., Soni, M., Kumar, S., and Gupta, G. 2009. "Solubility enhancementeminent role in poorly soluble drugs." *Research Journal of Pharmacy and Technology* 2(2): 220–224.

Sree Lakshmi, C., and Badarinath, A. 2013. "An Updated Review of Dissolution Apparatus for Conventional and Novel Dosage Forms." *International Journal of Pharma Research & Review*2(7):42-53.

Ting, J. M., Porter, W. W., Mecca, J. M., Bates, F. S., and Reineke, T. M. 2018. "Advances in Polymer Design for Enhancing Oral Drug Solubility and Delivery." In *Bioconjugate Chemistry* 29(4):939-952.

Vemula, V. R., Lagishetty, V., and Lingala, S. 2010. "Solubility enhancement techniques." In *International Journal of Pharmaceutical Sciences Review and Research* 5(1):41-47.

Wagh, M. P., and Patel, J. S. 2010. "Biopharmaceutical classification system: Scientific basis for biowaiver extensions." In *International Journal of Pharmacy and Pharmaceutical Sciences* 2(1):12-19

Waters, L. J., Hussain, T., Parkes, G., Hanrahan, J. P., and Tobin, J. M. 2013. "Inclusion of fenofibrate in a series of mesoporous silicas using microwave irradiation." *European Journal of Pharmaceutics and Biopharmaceutics* 85(3):936-941.

Wu, C., Zhao, Z., Zhao, Y., Hao, Y., Liu, Y., and Liu, C. 2014. "Preparation of a push-pull osmotic pump of felodipine solubilized by mesoporous silica nanoparticles with a core-shell structure." *International Journal of Pharmaceutics* 475(2):298-305.

Wu, S. H., and Lin, H. P. 2013. "Synthesis of mesoporous silica nanoparticles." *Chemical Society Reviews* 42(9):3862-3875.

Zhang, W., Zheng, N., Chen, L., Xie, L., Cui, M., Li, S., and Xu, L. 2019. "Effect of shape on mesoporous silica nanoparticles for oral delivery of indomethacin." *Pharmaceutics* 11(1):4.

Zhang, Y., Zhi, Z., Li, X., Gao, J., and Song, Y. 2013. "Carboxylated mesoporous carbon microparticles as new approach to improve the oral bioavailability of poorly water-soluble carvedilol." *International Journal of Pharmaceutics* 454(1):403-411.

Zhao, Z., Wu, C., Zhao, Y., Hao, Y., Liu, Y., and Zhao, W. 2015. "Development of an oral push-pull osmotic pump of fenofibrate-loaded mesoporous silica nanoparticles." *International Journal of Nanomedicine* 10:1691-701.

Zhong, S., Huang, W., Tian, Y., & Wang, X. 2016. "Synthesis of mesoporous carbon spheres and release of albendazole." *Materials Letters* 179:86-89.