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CRYSTALLO-CO-AGGLOMERATION OF SIMVASTATIN: IMPROVING DISSOLUTION AND MICROMERITIC PROPERTIES

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ABSTRACT

Simvastatin (SMV), a poorly soluble drug, faces challenges in pharmaceutical formulation due to its limited solubility and poor flow properties. This study aimed to enhance the physicochemical properties of SMV by preparing spherical crystals using a crystallo-co-agglomeration. Spherical crystals of SMV were prepared by dissolving the drug in methanol and adding it to an aqueous solution containing PVP K-30 and PEG 6000 under constant stirring. The resulting agglomerates were filtered, dried, and characterized using Fourier Transform Infrared (FTIR) spectroscopy, Powder X-Ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), and dissolution testing. Micromeritic properties, including bulk density, Hausner ratio, compressibility index, angle of repose, and flowability, were also evaluated. FTIR confirmed the chemical integrity of SMV with minor shifts indicating interactions with stabilizers. PXRD and DSC analyses revealed reduced crystallinity and partial amorphization in the spherical crystals. SEM showed spherical morphology. Dissolution testing demonstrated a significantly enhanced dissolution rate for the spherical crystals compared to pure SMV. Improved micromeritic properties were also observed, indicating better flowability and packing density. Spherical crystallization significantly improved the solubility, dissolution rate, and flowability of SMV. This technique offers a promising strategy for enhancing the bioavailability and pharmaceutical performance of poorly soluble drugs.

Keywords: Simvastatin, crystallo-co-agglomeration, dissolution rate, micromeritic properties

INTRODUCTION

Simvastatin (SMV), a widely prescribed statin, is renowned for its efficacy in lowering cholesterol levels and reducing the risk of cardiovascular events (Elkadi et al., 2017; Kim et al., 2011). However, its clinical performance is often hampered by its poor water solubility and suboptimal micromeritic properties, which affect its dissolution rate and bioavailability (Li et al., 2020). The modification of these physicochemical properties can significantly enhance the drugs therapeutic efficacy. One promising approach to address these issues is the crystallization technique known as

crystallo-co-agglomeration (CCA) (Maghsoodi et al., 2008; Raval et al., 2021).

Crystallo-co-agglomeration is an innovative technique designed to improve the dissolution rate and micromeritic properties of pharmaceutical compounds. This method involves the simultaneous crystallization and agglomeration of drug particles in the presence of suitable solvents and bridging agents, resulting in the formation of spherical agglomerates with enhanced flowability and compressibility (Garala et al., 2013; Makar et al., 2020). The technique is particularly advantageous for drugs like SMV, which suffer from poor aqueous solubility and irregular particle size distribution (Sanjeevani Shekhar Deshkar, Govind R. Borde, Rupali N. Kale, Balasaheb A. Waghmare, 2018).

Several studies have demonstrated the effectiveness of CCA in enhancing the solubility and dissolution rate of various poorly soluble drugs. For instance, Abba et al. (2023) showed that the CCA technique could improve the dissolution profile of Metronidazole by forming spherical agglomerates with superior micromeritic properties (Abdullahi et al., 2023). Similarly, Mahajan et al., 2018 reported significant improvements in the dissolution rate and bioavailability of Ritonavir using the CCA method. These findings suggest that CCA could be a valuable technique for enhancing the physicochemical properties of SMV. Additionally, the role of various polymers in stabilizing and enhancing the performance of agglomerates formed through CCA has been explored, with findings suggesting that polymers like PVP and PEG contribute substantially to the mechanical strength and dissolution behavior of the final product (Dalvadi et al., 2019; Patra et al., 2015; Ravouru et al., 2018).

In this study, we aim to modify the dissolution rate and micromeritic properties of SMV through the CCA technique. We hypothesize that applying CCA will result in SMV agglomerates with improved solubility, dissolution rate, and micromeritic characteristics, thereby enhancing its overall bioavailability. This study will involve the selection of appropriate solvents and bridging agents, optimization of process parameters, and comprehensive evaluation of the physicochemical properties of the resulting agglomerates.

METHODS

Materials

The materials used in this study include SMV (Ltd., Garcia), methanol (Merck), PVP K30 (Ltd. Bratachem), PEG 6000 (Ltd. Bratachem), chloroform (Ltd. Bratachem), distilled water (Ltd. Bratachem), sodium hydroxide (Ltd.,

Bratachem), and potassium dihydrogen phosphate (Ltd., Bratachem).

1. Preparation of Spherical Crystals of SMV

Spherical SMV crystals were prepared by dissolving 4 g of SMV in 20 ml of methanol. Simultaneously, 2% PVP K-30 and 0.5% PEG 6000 were dissolved in 200 ml of distilled water. The drug solution was rapidly added to the aqueous polymer mixture under constant stirring at 700 rpm. The resulting agglomerates were filtered and dried overnight at room temperature.

2. SEM Analysis

SEM analysis (Hitachi SU 3500, Japan) was conducted to observe the surface morphology of the samples. Powdered samples were mounted on aluminum stubs and coated with a thin layer of gold (approximately 10 nm). The samples were examined under various magnifications with the SEM operated at 20 kV and 12 mA.

3. FTIR Analysis

FTIR spectroscopy (Shimadzu, IRPrestige21, Japan) was used to identify the functional groups in the raw SMV and spherical crystals of SMV. Approximately 1-2 mg of each powdered sample was mixed with 10 mg of KBr and ground to a fine powder. The mixture was then compressed into a disc under vacuum at 800 kPa. Absorption spectra were recorded over the range of 4000-400 cm^{-1}.

4. PXRD Analysis

PXRD analysis (Rigaku, Japan) was performed to investigate the crystalline structure of the pure SMV and its spherical crystals. The samples were analyzed using a powder X-ray diffractometer set to 40 kV and 30 mA. Scanning was conducted from 5° to 50° 2θ at a rate of 0.06° per minute using Cu Kα1 radiation (λ = 1.5405 Å).

5. DSC Analysis

DSC analysis (Shimadzu, Japan) was carried out to determine the thermal properties of pure SMV and its spherical crystals. Samples weighing 4-5 mg were heated from 25°C to 250°C at 10°C per minute.

6. Dissolution Testing

The dissolution behavior of pure SMV and its spherical crystals was evaluated using a paddle-type dissolution apparatus. The dissolution medium was a phosphate buffer solution (pH 7.0, 900 ml). The test was conducted at 50 rpm and 37°C±0.5°C. Samples were withdrawn at 5, 10, 15, and 30-minute intervals. According to Varshosaz (2011), the samples were filtered through a 0.45 µm membrane filter and analyzed using a UV spectrophotometer at the maximum absorption wavelength.

7. Micromeritic Properties

Micromeritic properties, including bulk density, Hausner ratio, compressibility index, angle of repose, and flowability, were

measured for both pure SMV and its spherical crystals. These properties were assessed according to the methods described in the Farmakope Indonesia (Kementerian Kesehatan Republik Indonesia, 2020).

RESULTS AND DISCUSSION

Spherical agglomeration is a technique utilized in the pharmaceutical industry to convert crystals directly into compact spherical forms during the crystallization process. This method provides several advantages, such as enhancing the solubility, flow properties, and compression characteristics of active pharmaceutical ingredients (APIs) (Chatterjee et al., 2017). Through the use of emulsion-based crystallization, spherical crystalline agglomerates can be generated, enabling better control over crystal size during the downstream processing of APIs (Toldy et al., 2012). The process entails introducing a bridging liquid to agglomerate fine crystals into spherical particles, resulting in the creation of larger agglomerates with improved flow properties that can break down into smaller constituents during dissolution testing (Peña et al., 2019).

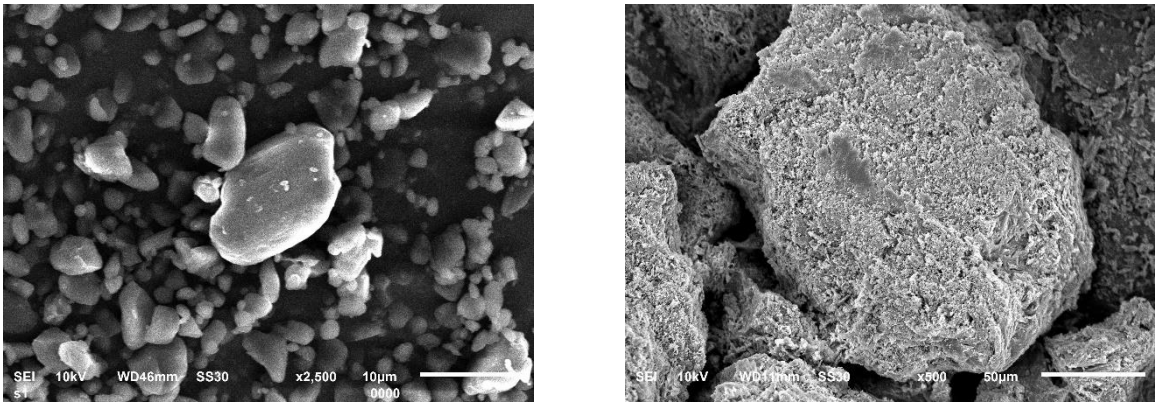
The transformation of SMV into spherical crystals through the crystallo-co-agglomeration method resulted in significant improvements in the drugs physical properties. The use of PVP K-30 and PEG 6000 as stabilizers facilitated the formation of uniform spherical agglomerates by reducing interfacial tension and ensuring a homogenous distribution of drug particles (Kovačič et al., 2012). This method effectively overcame the limitations of pure SMV, which typically exhibits irregular and poorly soluble particles. The spherical crystals (SMV-CCA) showed enhanced flow properties and compressibility, which are crucial for efficient pharmaceutical manufacturing and tablet formation (Manoj et al., 2019).

The SEM analysis (Figure 1) revealed distinct differences in the morphology of pure SMV and its spherical crystals. Pure SMV appeared as irregular, plate-like particles with rough surfaces and varied sizes. In contrast, the spherical crystals displayed spherical shapes, indicating successful agglomeration.

The improved morphology of the spherical crystals offers to enhance flow properties and packing density, which is beneficial for pharmaceutical manufacturing. These findings are consistent with previous studies, such as those by Hansen and Kleinebudde (2021), which reported that spherical crystals of other drugs showed better flow properties and compressibility (Hansen & Kleinebudde, 2021).

FTIR analysis was conducted to identify the functional groups in pure SMV, and SMV-CCA. The spectra in Figure 2a showed distinct peaks for SMV at 3540 cm^{-1} (O-H stretching), 2975 cm^{-1} (C-H stretching), 1725 cm^{-1} (C=O stretching), and 1605 cm^{-1} (C=C stretching). These peaks were also present in the spherical crystals, indicating that the chemical structure of SMV remained intact during the crystallization process. However, slight shifts in peak positions and changes in intensities were observed in the SMV-CCA, suggesting interactions between SMV and the stabilizing agents (PVP K-30 and PEG 6000).

The shifts in the O-H stretching peak to 3530 cm^{-1} and the C=O stretching peak to 1715 cm^{-1} in the SMV-CCA, along with the decreased intensity of the C-H stretching peak, indicate possible hydrogen bonding and van der Waals interactions between the drug and the stabilizing agents. These interactions can influence the stability and solubility of the drug, which is crucial for improving its dissolution properties. The observed modifications in the hydrogen bonding environment of SMV suggest that the crystallization process enhances its interaction with the dissolution medium, potentially leading to better bioavailability (Nitsure et al., 2020; Shah et al., 2023).



(a) **(b)**

Figure 1. SEM image of SMV crystal (a) and SMV-CCA (b)

Pure SMV exhibited a sharp endothermic peak at approximately 135°C, corresponding to its melting point, indicating its crystalline nature (Figure 2b). DSC thermogram of the SMV-CCA displayed a broad endothermic peak around 135°C, with a noticeable reduction in peak intensity, suggesting a decrease in crystallinity and partial amorphization of the drug. The endothermic peak observed

around 60 suggests a glass transition of PEG 6000 and PVP-K30, which generally shows a glass transition rather than a melting point.

The broadening of the endothermic peak and the reduced intensity in the SMV-CCA thermogram suggest that the crystallization process facilitated interactions between simvastatin and the stabilizing agents (PVP K-30 and PEG 6000). These interactions likely contribute to the formation of a less ordered structure, which is beneficial for improving the dissolution profile of the drug. This observation aligns with findings from previous studies, which demonstrate that partial amorphization can lead to better solubility and bioavailability (Knopp et al., 2018).

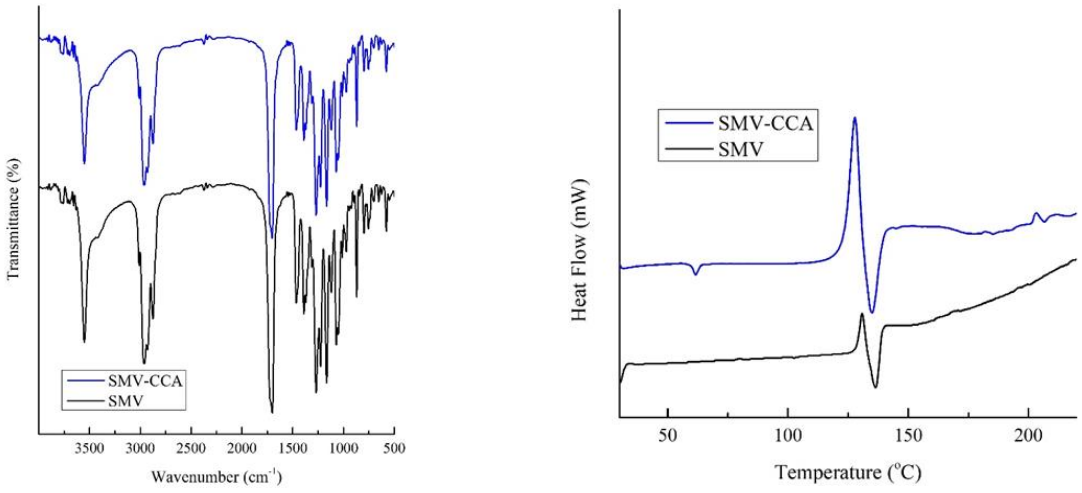
The PXRD patterns of pure SMV and SMV-CCA were recorded to determine their crystalline properties (Figure 3). The diffraction pattern of pure SMV exhibited sharp and intense peaks at specific 2θ values, indicating its crystalline nature. Notable peaks were observed at 9.2°, 10.8°, 16.9°, and 22.2° 2θ. In contrast, the PXRD pattern of the spherical crystals showed a reduction in peak intensity and an increase in baseline noise, suggesting a partial transformation to an amorphous form.

The amorphous form of a drug is often associated with enhanced solubility and dissolution rates compared to its crystalline counterpart. This is because the amorphous state has higher free energy and molecular mobility, facilitating faster dissolution (Flouda et al., 2014). The partial amorphization observed in the spherical crystals of SMV-CCA suggests that the crystallization process not only modified the morphology but also improved the solubility characteristics of the drug. This transformation is beneficial for drugs like SMV, which suffer from poor water solubility, as it can lead to improved bioavailability and therapeutic efficacy.

The dissolution test results showed that pure SMV exhibited a slow and incomplete dissolution, with only about 39% of the drug dissolved within 30 minutes. In contrast, the spherical crystals demonstrated a significantly enhanced dissolution profile, with over 85% of the drug dissolved within 30 minutes.

The most significant enhancement was observed with the spherical crystals, which dissolved much more rapidly and completely than raw SMV. This improved dissolution rate can be attributed to the reduced crystallinity and partial amorphization of the drug, as indicated by the DSC and PXRD analyses. The amorphous or partially amorphous state of SMV in the spherical crystals increases its molecular mobility and solubility, leading to a faster dissolution rate (Varshosaz, 2011).

The presence of stabilizing agents such as PVP K-30 and PEG 6000 also plays a crucial role in improving the wettability and dispersibility of the drug particles, facilitating a more efficient dissolution process (Octavia et al., 2015).



(a) **(b)**

Figure 2. analysis SMV and SMV-CCA with FTIR (a) and DSC (b)

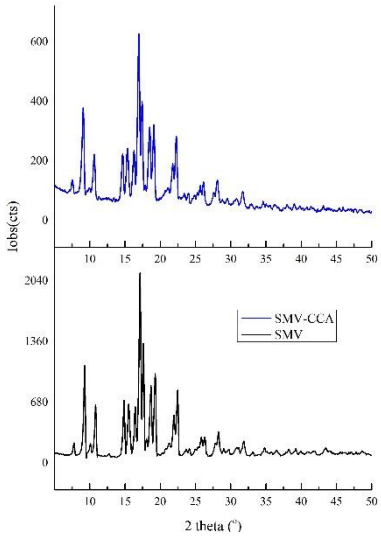


Figure 3. PXRD analysis for SMV crystal and SMV-CCA

The micromeritic properties of pure SMV and its CMV-CCA were evaluated, including bulk density, Hausner ratio, compressibility index, angle of repose, and flowability (Table 1). Pure SMV exhibited a bulk density of 0.45 g/cm³, a Hausner ratio

of 1.35, a compressibility index of 25.9%, and an angle of repose of 42°, indicating poor flow properties. In contrast, the SMV-CCA showed a bulk density of 0.55 g/cm³, a Hausner ratio of 1.15, a compressibility index of 13%, and an angle of repose of 28°, demonstrating significantly improved flow properties.

Pure SMV exhibited poor flowability, as indicated by a high Hausner ratio and compressibility index, along with a high angle of repose. These properties are typical of irregularly shaped, poorly flowing powders, which can lead to challenges in pharmaceutical processing and formulation, such as inconsistent dosing and poor content uniformity (Deshkar et al., 2016).

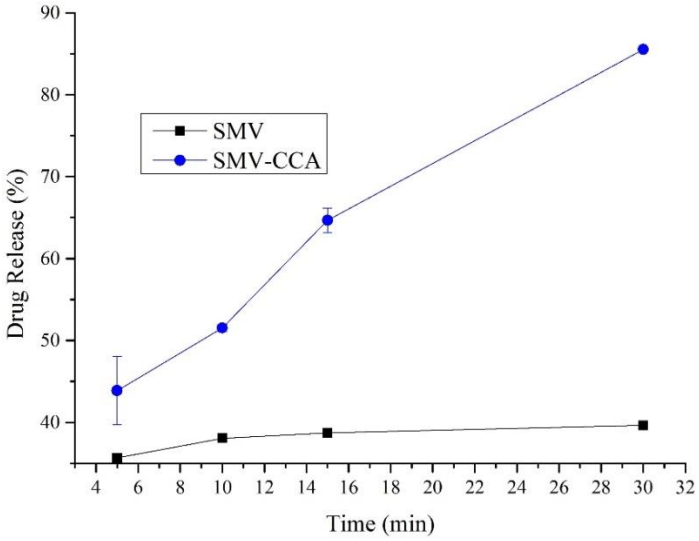


Figure 4. Dissolution profile of SMV and SMV-CCA

Tabel 1. Micromeritic properties of pure SMV and SMV-CCA

Parameter	SMV (n=3)	SMV-CCA (n=3)
Flowability	No. flowing	6 g/s
Angle of repose	38.69° ± 2.21	20.12° ± 4.30
Tap density	0.35 ± 0.007	0.28 ± 0.006
Houssner Ratio	1.45 ± 0.01	1.10 ± 0.02
Compressibility index	31.17 ± 0.54	8.89 ± 0.21

In contrast, the spherical crystals of SMV demonstrated significantly enhanced flow properties. The increased bulk density suggests better packing ability, which is beneficial for tablet compression. The lower Hausner ratio and compressibility index indicate reduced interparticle friction and better flowability. These improvements are attributed to the uniform spherical shape and smooth surface of the crystals, which facilitate easier movement and packing of the particles (Varshosaz, 2011).

The improved angle of repose further corroborates the enhanced flow characteristics of the spherical crystals. A lower angle of repose is indicative of better flowability, which is critical for ensuring uniform filling during tablet manufacturing and minimizing weight variation. These findings are consistent with previous studies that have shown spherical crystallization to significantly enhance the micromeritic properties of pharmaceutical powders (Octavia et al., 2015).

CONCLUSIONS

The study demonstrated that spherical crystallization significantly improved the physicochemical properties of SMV. FTIR confirmed structural integrity and beneficial interactions with stabilizers, while PXRD and DSC indicated reduced crystallinity and partial amorphization. Enhanced dissolution rates and improved micromeritic properties, including better flowability and packing density, were observed. This technique offers a promising approach to improving the bioavailability and pharmaceutical performance of poorly soluble drugs like SMV.

REFERENCES

Abdullahi, A. K., Olowosulu, A. K., & Allagh, T. S. (2023). Crystallo-co-Agglomeration Technique for Improving Physicochemical Properties, Compressibility and Solubility Characteristics of Metronidazole. *British Journal of Pharmacy*, *8*(1). https://doi.org/10.5920/bjpharm.1039

Chatterjee, A., Gupta, M. M., & Srivastava, B. (2017). Spherical Crystallization: A Technique Use to Reform Solubility and Flow Property of Active Pharmaceutical Ingredients. *International Journal of Pharmaceutical Investigation*, *7*(1), 4. https://doi.org/10.4103/jphi.jphi_36_16

Dalvadi, H., Parmar, K., & Yadav, S. (2019). Spherical agglomeration to improve dissolution and micromeritic properties of an anticancer drug, Bicalutamide. *Drug Development and*

Industrial Pharmacy, *45*(6), 968–980. https://doi.org/10.1080/03639045.2019.1585447

Elkadi, S., Elsamaligy, S., Al-Suwayeh, S., & Mahmoud, H. (2017). The Development of Self-nanoemulsifying Liquisolid Tablets to Improve the Dissolution of Simvastatin. *AAPS PharmSciTech*, *18*(7), 2586–2597. https://doi.org/10.1208/s12249-017-0743-z

Flouda, K., Qiu, D., & Tsolakou, T. (2014). *The Influence of Pressure on the Intrinsic Dissolution Rate of Amorphous Indomethacin*. 481–493. https://doi.org/10.3390/pharmaceutics6030481

Garala, K. C., Patel, J. M., Dhingani, A. P., & Dharamsi, A. T. (2013). Preparation and evaluation of agglomerated crystals by crystallo-co-agglomeration: An integrated approach of principal component analysis and Box-Behnken experimental design. *International Journal of Pharmaceutics*, *452*(1–2), 135–156. https://doi.org/10.1016/j.ijpharm.2013.04.073

Hansen, J., & Kleinebudde, P. (2021). Enabling the direct compression of metformin hydrochloride through QESD crystallization. *International Journal of Pharmaceutics*, *605*(March), 120796. https://doi.org/10.1016/j.ijpharm.2021.120796

Kementerian Kesehatan Republik Indonesia. (2020). Farmakope Indonesia edisi VI. In *Kementerian Kesehatan Republik Indonesia*.

Kim, K.-H., Park, J.-B., Choi, W.-J., Lee, H.-S., & Kang, C.-Y. (2011). Preparation and Characterization of Simvastatin Solid Dispersion using Aqueous Solvent. *Journal of Pharmaceutical Investigation*, *41*(4), 239–247. https://doi.org/10.4333/kps.2011.41.4.239

Knopp, M. M., Wendelboe, J., Holm, R., & Rades, T. (2018). Effect of amorphous phase separation and crystallization on the in vitro and in vivo performance of an amorphous solid dispersion. *European Journal of Pharmaceutics and Biopharmaceutics*, *130*(May), 290–295. https://doi.org/10.1016/j.ejpb.2018.07.005

Kovačič, B., Vrečer, F., & Planinšek, O. (2012). Spherical crystallization of drugs. *Acta Pharmaceutica*, *62*(1), 1–14. https://doi.org/10.2478/v10007-012-0010-5

Li, H., Zhang, M., Xiong, L., Feng, W., &

Williams, R. O. (2020). Bioavailability improvement of carbamazepine via oral administration of modified-release amorphous solid dispersions in rats. *Pharmaceutics*, *12*(11), 1–16. https://doi.org/10.3390/pharmaceutics12111023

Maghsoodi, M., Taghizadeh, O., Martin, G. P., & Nokhodchi, A. (2008). Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique. *International Journal of Pharmaceutics*, *351*(1–2), 45–54. https://doi.org/10.1016/j.ijpharm.2007.09.033

Mahajan, N. M., Malghade, A. D., Dumore, N. G., & Thenge, R. R. (2018). Design and development of crystallo-co-agglomerates of ritonavir for the improvement of physicochemical properties. *Turkish Journal of Pharmaceutical Sciences*, *15*(3), 248–255. https://doi.org/10.4274/tjps.44227

Makar, R. R., Latif, R., Hosni, E. A., & El Gazayerly, O. N. (2020). A new crystal engineering technique for dissolution enhancement of poorly soluble drugs combining quasi-emulsion and crystallo-co agglomeration methods. *Iranian Journal of Pharmaceutical Research*, *19*(2), 219–235. https://doi.org/10.22037/ijpr.2020.1101094

Manoj, K., Seenivasan, P., Arul, K., & Senthil Kumar, M. (2019). Study of the effect of pvp k30 in the enhancement of solubility of telmisartan by polymer assisted crystal agglomeration using polymer enriched bridging liquid technique. *International Journal of Research in Pharmaceutical Sciences*, *10*(3), 2290–2299. https://doi.org/10.26452/ijrps.v10i3.1466

Nitsure, A., Patel, D., & Wairkar, S. (2020). Improved processability of ethambutol hydrochloride by spherical agglomeration. *Pharmaceutical Development and Technology*, *25*(3), 376–384. https://doi.org/10.1080/10837450.2019.1705487

Patra, C. N., Swain, S., Mahanty, S., & Panigrahi, K. C. (2015). Design and characterization of aceclofenac and paracetamol spherical crystals and their tableting properties. *Powder Technology*, *274*, 446–454. https://doi.org/10.1016/j.powtec.2015.01.053

Peña, R., Jarmer, D. J., Burcham, C. L., &

Nagy, Z. K. (2019). Further Understanding of Agglomeration Mechanisms in Spherical Crystallization Systems: Benzoic Acid Case Study. *Crystal Growth and Design*, *19*(3), 1668–1679. https://doi.org/10.1021/acs.cgd.8b01519

Raval, M. K., Garala, K. C., Patel, J. M., Parikh, R. K., & Sheth, N. R. (2021). Functionality improvement of Chlorzoxazone by crystallo-co-agglomeration using multivariate analysis approach. *Particulate Science and Technology*, *39*(6), 689–711. https://doi.org/10.1080/02726351.2020.1799126

Ravouru, N., Penjuri, S. C. B., Damineni, S., Muni, R. L., & Poreddy, S. R. (2018). Preparation and in vitro evaluation of ibuprofen spherical agglomerates. *Turkish Journal of Pharmaceutical Sciences*, *15*(1), 7–15. https://doi.org/10.4274/tjps.09609

Sanjeevani Shekhar Deshkar, Govind R. Borde, Rupali N. Kale, Balasaheb A. Waghmare, A. B. T. (2018). Formulation of cilostazol spherical agglomerates by crystallo-co-agglomeration technique and optimization using design of experimentation Sanjeevani. *International Journal of Pharmaceutical Investigation*, *7*(3), 47–59. https://doi.org/10.4103/jphi.JPHI

Shah, D., Rawat, J., & Thakkar, H. (2023). Spherical Crystal Agglomeration Technique for Improved Flow Properties and Oral Bioavailability of Atazanavir Sulphate. *Therapeutic Delivery*, *14*(4), 269–280. https://doi.org/10.4155/tde-2022-0063

Toldy, A. I., Badruddoza, A. Z. M., Zheng, L., Hatton, T. A., Gunawan, R., Rajagopalan, R., & Khan, S. A. (2012). Spherical crystallization of glycine from monodisperse microfluidic emulsions. *Crystal Growth and Design*, *12*(8), 3977–3982. https://doi.org/10.1021/cg300413s