JURNAL ILMIAH MEDICAMENTO

Vol.12 No.1 (March 2026)
page 90-101
https://doi.org/10.36733/medicamento.v12i1.12523
e-ISSN: 2356-4814

Original Article

Meloxicam Nanocrystals with HPMC and Decyl Glucoside for Enhanced Solubility

Nur Achsan Al-Hakim[1], Titta Hartyana Sutarna[1*], Hestiary Ratih[1], Karina Putriani Azzara[1]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Jenderal Achmad Yani, Cimahi 40531, West Java, Indonesia

Submitted : 02-09-2025
Revised : 14-02-2026
Accepted : 05-03-2026

Keywords: meloxicam, nanocrystals, solubility, stabilizers.

Correspondence:
Titta Hartyana Sutarna
titta.hartyana@lecture.unjani.ac.id

Abstract

Background: Low solubility in water is a major obstacle for Meloxicam (MLX) and has implications for its limited bioavailability. Nanocrystallization techniques show potential for improving drug solubility, but nanoparticles tend to aggregate, suggesting the use of a combination of Hydroxypropyl Methylcellulose (HPMC) and Decyl Glucoside (DG) as stabilizers to overcome this problem.
Objective: This study aims to develop and characterize meloxicam nanocrystals (MLX-NC) with a combination of HPMC and DG in an effort to improve solubility. MLX-NC was synthesized using ultrasonication and dried by lyophilization.
Methods: The resulting formulation exhibited excellent physical stability over 28 days, as evidenced by consistent particle size (~11 nm) and polydispersity index (<0.3). Physical evaluation and characterization were performed, including particle size analysis (DLS), zeta potential, particle morphology (SEM), thermal analysis (DSC), X-ray diffraction (XRD), and saturated solubility testing.
Results: The MLX-NC formulation showed a more than 200-fold increase in solubility compared to pure MLX, from 0.005 mg/mL to 1.064 mg/mL. XRD and DSC analyses confirmed that the nanocrystallization process converted the crystalline phase of MLX into an amorphous phase. These results indicate that induced amorphization can significantly improve solubility.
Conclusion: The solubility of MLX can be significantly improved using ultrasonication combined with HPMC and DG. This approach has the potential to overcome the solubility limitations of BCS Class II drugs.

How to Cite: (*citation style* AMA 11th Ed.)
Al-Hakim NA, Sutarna TH, Ratih H, Azzara KP. Meloxicam Nanocrystals with HPMC and Decyl Glucoside for Enhanced Solubility. *J. Ilm. Medicam.*, 2026;12(1): 90-101. https://doi.org/10.36733/medicamento.v12i1.12523

INTRODUCTION

Meloxicam (MLX) is a non-steroidal anti-inflammatory drug (NSAID) that is widely used to treat pain and inflammation associated with conditions such as osteoarthritis and rheumatoid arthritis. It works by selectively inhibiting the cyclooxygenase-2 (COX-2) enzyme, which reduces the production of prostaglandins that mediate inflammation and pain.[1,2] However, the therapeutic potential of MLX is hampered by its very low water solubility, which causes unpredictable drug absorption and limited bioavailability. It is known that the solubility of MLX in water is around 2.2 to 7.15 µg/mL, depending on pH and temperature conditions. Based on the Biopharmaceutical Classification System (BCS), MLX belongs to class II, which is characterized by high permeability but low solubility.[3,4] Solubility is a critical aspect of the physicochemical properties of drugs in pharmaceutical product development because it tends to affect bioavailability, especially when the drug is administered orally.[5]

Various formulation strategies have been developed to overcome the solubility challenges of MLX, including salt formation, solid dispersion, complexation, lipid-based delivery, and particle size reduction techniques.[6–10] Among these methods, nanocrystallization has shown significant potential in improving drug solubility.[11–13] This technique involves the formation of solid crystals ranging in size from 1 to 1000 nm, which exhibit a significantly increased surface area to volume ratio. This increase in surface area facilitates the release of drug molecules into the dissolution medium, which ultimately increases solubility and dissolution rate.[14,15] Nanocrystals can enhance particle adhesion to the intestinal mucosal surface, prolonging residence time at the absorption site, thereby potentially increasing bioavailability. In addition, nanocrystal systems stabilized with polymers and surfactants can reduce pharmacokinetic variability and improve physical stability during storage.[16,17]

However, nano-sized particles have high surface free energy and tend to aggregate, so the challenge of stabilization is a major concern.[18,19] Stabilizers play an important role in preventing aggregation, which can reduce the effective surface area and inhibit the benefits of nanonization, as well as maintaining the desired particle size characteristics during formulation and storage.[20]

A stabilizer commonly used in aggregation prevention efforts is Hydroxypropyl Methylcellulose (HPMC). HPMC is a polymer that is widely used in pharmaceutical formulations. It is hydrophilic and functions as a stabilizer by forming a good film layer on the surface of particles, thereby preventing aggregation.[21] It has been reported that HPMC has been used to stabilize nano particle size, including in solid dispersion systems, nanocrystals, and nanosuspensions.[22–24] In addition, in an effort to improve the function of the stabilization system, the surfactant decyl glucoside (DG) was added. DG, also known as alkyl polyglycoside, is a non-ionic surfactant with amphiphilic properties, biodegradability, and the ability to provide electrostatic stabilization and improve wettability.[25–27] The development of nanocrystal systems using alkyl polyglycoside surfactants has been reported to provide stabilizing ability.[28] Research on the specific combination of HPMC with the nonionic surfactant DG to stabilize meloxicam nanocrystals is still limited. The synergy between the steric stabilization of the polymer and the reduction of surface tension of the surfactant in a single formulation system for MLX has also not been widely explored. Therefore, the combination of HPMC and DG is expected to provide a synergistic effect in stabilizing meloxicam nanocrystals (MLX-NC) and provide a more optimal effect in maintaining the physicochemical stability of MLX-NC and significantly increasing its solubility.[29]

This study aims to develop and characterize MLX-NC using HPMC and DG as stabilizers in an effort to improve solubility. This study is expected to make a valuable contribution to the development of efficient nanocrystal-based drug delivery systems, as well as similar pharmaceutical active ingredients in overcoming solubility limitations.

METHODS

Tools. The equipment used in this study included an Ultrasonic Probe Sonicator (Biostellar BSD-250W, Beijing), Lyophilizer freeze dryer (Biobase BK-FD10P, Beijing), Nanoparticle analyzer (Horiba SZ-100V2, Japan), X-Ray Diffractometer (Rigaku MiniFlex 600, Japan), Differential Scanning Calorimeter (Shimadzu DSC-60 Plus, Japan), Scanning Electron Microscopy (Hitachi S4700, Japan), and UV-Vis Spectrophotometry (Shimadzu 1800, Japan).

Materials. The raw materials used include meloxicam (obtained from PT. Kimia Farma Tbk., Indonesia), hydroxypropyl methylcellulose (HPMC) K100M, decyl glucoside (DG), mannitol, and distilled water (obtained from industrial chemical supplier PT. Indo Sukses Pratama, Indonesia), all of which are pharmaceutical grade and analytical grade.

Research Procedure

Material Preparation and Initial Characterization of Raw Materials

Preparation of the required raw materials and initial characterization of MLX, HPMC, and DG included organoleptic examination and XRD and DSC analysis to ensure the identity, purity, and quality of the raw materials. A calibration curve for MLX in water was also prepared.

Preparation of Meloxicam Nanocrystals (MLX-NC)

Preparation of MLX-NC using a modified ultrasonication method. Weigh 20 mg of MLX (~ MLX solubility 0.0057 mg/mL), then add 3% HPMC and DG as stabilizers dispersed in 100 mL of water in a beaker. Particle size reduction and suspension homogenization were performed using an Ultrasonic Probe Sonicator (Biostellar BSD-250W, Beijing), with an amplitude of 75% at a temperature of 80°C for 40 minutes.[30]

Lyophilization of Meloxicam Nanocrystals (MLX-NC)

The nanosuspension was dried using the lyophilization method, with slight modifications. The aim was to convert the liquid phase into a solid phase to obtain dry nanocrystals. Freeze-drying was performed using a freeze dryer lyophilizer (Biobase BK-FD10P, Beijing), freezing the sample at -40°C for 24 hours, followed by drying for 72 hours at a pressure of 0.01 mbar, with the addition of 3% mannitol as a cryoprotectant.[10]

Characterization of Meloxicam Nanocrystals (MLX-NC)

a) Measurement of Particle Size, Polydispersity Index, and Zeta Potential

Particle size and polydispersity index analysis were performed using the Photon Correlation Spectroscopy (PCS) or Dynamic Light Scattering (DLS) methods, while zeta potential was measured using the Electrophoretic Light Scattering (ELS) principle, using the same instrument, a Nanoparticle analyzer (Horiba SZ-100V2, Japan). This analysis reports the

average particle size and polydispersity index values that indicate the particle size distribution parameters and zeta potential values. The measurements were determined by measuring the change in light intensity scattered from the sample. Approximately 5 mL of nanosuspension sample liquid was placed in a cuvette cell. Measurements were performed at a temperature of 25°C and a scattering angle of 90°. Measurements of particle size, PDI, and zeta potential were performed on days 0, 7, 14, 21, and 28 to assess physical stability during storage at room temperature.[31] All measurements were performed in triplicate (n=3). Data are reported as mean ± standard deviation (SD). Physical stability was evaluated based on the direction of change in particle size and PDI during a 28-day storage period.

b) X-Ray Diffraction (XRD)

X-ray diffraction analysis is used to characterize the crystal form of samples using an X-ray Diffractometer (Rigaku MiniFlex 600, Japan). The diffraction pattern was scanned with Cu Kα radiation generated at 40 mA and 40 kV with a scanning speed of 10°/minute in the angle range of 5–45° (2θ).[32]

c) Differential Scanning Calorimetry (DSC)

Thermal analysis by measuring the heat flow absorbed or released from the sample using a Differential Scanning Calorimeter (Shimadzu DSC-60 Plus, Japan). Samples weighing 2–5 mg were placed in an aluminum pan, then heated at a linear heating rate of 10°C/minute in a temperature range of 30–350°C in a nitrogen atmosphere.[33]

Scanning Electron Microscopy (SEM)

SEM analysis was used to determine the particle morphology of MLX-NC using Scanning Electron Microscopy (Hitachi S4700, Japan). Observations were made using an acceleration voltage of 15 kV at a current of 10 mA for 10 minutes with air pressure ranging from 1.3 to 13.0 mPa.[34]

Saturated Solubility Test

The solubility test aims to determine the saturated solubility by comparing pure MLX and MLX-NC. This is done by weighing 100 mg of the sample and placing it in a vial containing 10 mL of water. The liquid is then shaken using an orbital shaker at a temperature of 25°C for 24 hours, then filtered, and the filtrate solution is measured for absorption using UV-Vis Spectrophotometry (Shimadzu 1800, Japan) at a maximum wavelength of 362.20 nm.[35]

RESULT AND DISCUSSION

Material Preparation and Initial Characterization of Raw Materials

The preparation of the required raw materials was the first step in this study, followed by an examination of the identification of each material used in MLX, HPMC, and DG, including organoleptic testing and initial characterization using XRD and DSC analysis, which aimed to provide a clearer description of the properties of the materials and ensure that the raw materials used met the requirements of the compendium or supporting literature. The results of the organoleptic examination of MLX, HPMC, and DG, compared with the literature review, showed that all raw materials used were in accordance with the compendium and supporting literature.[36,37] Next, an MLX calibration curve was created, and the solubility of pure MLX was determined as the initial state before modification into nanocrystals. The results of the MLX calibration curve determination can be seen in **Figure 1**, with a linear regression equation of y = 0.0447x + 0.0855. Where y is the absorption value obtained from the instrument response, and x is the sample concentration (µg/mL), and the R^2 value = 0.998. The maximum wavelength (λmax) of MLX in water was obtained to be 362.20 nm, as previously reported.[38]

Preparation of Nanosuspension and Lyophilization of MLX-NC

The synthesis of MLX-NC was carried out by initially forming a nanosuspension using a top-down method based on ultrasonication.[39] The MLX-NC formulation is prepared with a composition of 20 mg meloxicam, 3% HPMC b/v, and 0.5% DG b/v in 100 mL of water. This method works by utilizing high-frequency ultrasonic waves that create acoustic cavitation generated by an ultrasonic probe, thereby producing high energy that can break down solid particles into nano-sized particles.[40] The addition of HPMC and DG as stabilizers serves to coat the particle surface by creating an exclusion zone around it and providing steric and ionic barriers that prevent agglomeration and maintain the particle size within the targeted range.[41] After obtaining the desired particle size (<500 nm), which is the optimal size for pharmaceutical active ingredient nanocrystals, they exhibit good solubility and stability.[16] The nanosuspension liquid is then dried through freeze drying or lyophilization, a process of removing water from a sample involving freezing, sublimation, and desorption, to obtain a dry solid.[42,43]

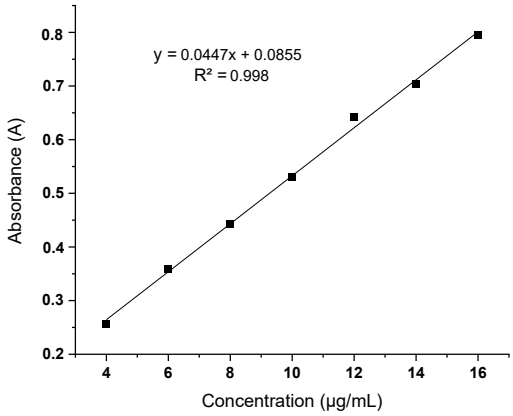

Figure 1. MLX reference calibration curve in water.

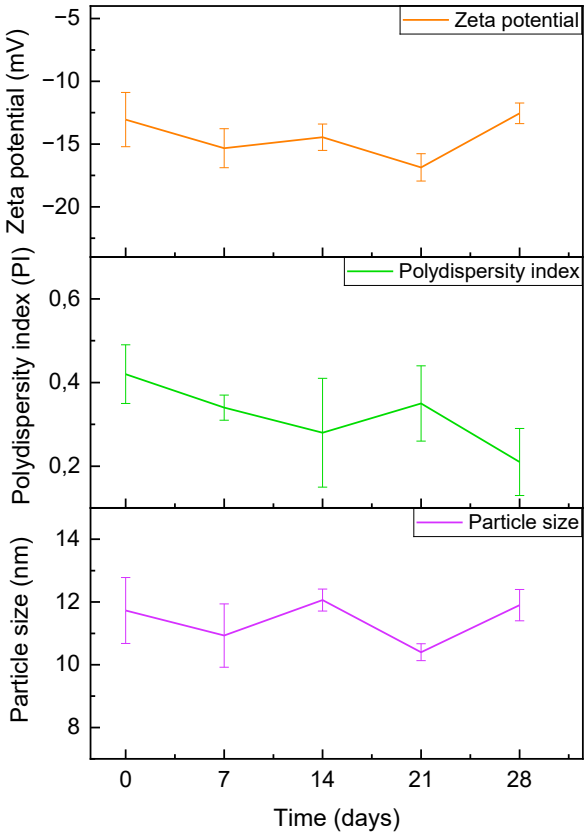

Figure 2. Physical characterization profile of MLX-NC includes particle size, polydispersity index, and zeta potential during a 28-day storage period.

Analysis of Particle Size, Polydispersity Index, and Zeta Potential

Analysis of particle size and polydispersity index using the principle of Photon Correlation Spectroscopy (PCS) with a Nanoparticle analyzer aims to characterize the particle size distribution and evaluate the stability and homogeneity of the formulated nanosuspension system. Small and stable particle size is very important because it directly affects bioavailability and therapeutic efficacy, with smaller particles increasing solubility and dissolution rate.[44] The MLX-NC formulation showed good physical stability during a 28-day storage period at room temperature, characterized by stable particle size and polydispersity index, as shown in **Figure 2**. Particle size analysis showed minimal fluctuations, with an average size ranging from 10.40 nm to 12.06 nm. This small particle size is important for improving the solubility of hydrophobic drugs such as MLX.[45] In addition, the homogeneous particle size distribution, as indicated by a low PDI value (< 0.5), ensures consistent product quality and minimizes drug release variation.[46]

This analysis supports the physical stability data of the MLX-NC formulation in the dispersion system. The data shows a consistently negative zeta potential, ranging from -12.55 mV to -16.86 mV.[47] This negative zeta potential indicates the presence of electrostatic repulsion between particles, which prevents agglomeration.[48] Although the zeta potential values are in the moderate range, the combination of small particle size and low polydispersity index indicates that this system has adequate stability, possibly also supported by other stabilizing mechanisms such as steric and electrostatic effects generated by the polymers and surfactants used in the formulation.[49,50] Steric stabilization is provided by HPMC through the formation of a hydration layer around the particles, preventing agglomeration through steric repulsion.[51] Meanwhile, DG provides electrostatic stabilization through negative charges at the particle-water interface, increasing the zeta potential and preventing particle aggregation.[52]

X-Ray Diffraction (XRD) Analysis

X-ray diffraction (XRD) pattern analysis was used to characterize the solid phase of pure MLX, HPMC, and MLX-NC. The XRD diffractograms are presented in **Figure 3**, showing significantly different patterns among the three samples. The diffraction pattern of pure MLX is specific and characterized by a series of sharp and intense diffraction peaks at 2 theta angles of 6.46°, 12.9°, 14.9°, 18.64°, 20.9°, and 25.76°, reflecting the crystalline nature of the sample and confirming its ordered crystal structure.[53] In contrast, the HPMC diffractogram showed a broad and blunt "halo" pattern, with peaks identified at angles of approximately 2θ 20.32°, which is characteristic of amorphous materials with irregular molecular arrangements.[54] The diffraction pattern of MLX-NC showed a drastic change compared to pure MLX. The sharp crystalline peaks of pure MLX disappear and are replaced by very broad peaks at an angle of 2θ 20.22°. This change indicates that the nanocrystal synthesis process has converted the crystalline phase of MLX into an amorphous phase. This phenomenon is known as "amorphization," most likely caused during the nanocrystallization process, high mechanical energy and shear stress generated during the probe ultrasonication process, which can damage the regularity of the crystal lattice, thereby inducing amorphization.[55] In addition, it may be caused by the use of a less-than-optimal concentration of stabilizing agent, as reported by previous researchers.[56] Instead of the initial expectation of maintaining the crystalline phase in the form of nanocrystals, these results indicate the formation of an amorphous solid dispersion. Amorphous solid dispersion is a system in which drugs are converted into an amorphous form in a polymer matrix, thereby increasing solubility through increased free energy and supersaturation. Meanwhile, nanocrystals are a system in which drug particles remain in crystalline form but are reduced in size to the nanoscale, resulting in increased solubility mainly due to increased particle surface area and higher stability.[57,58] However, this phase transformation may be in line with the expected research objective, which is to increase the solubility of MLX, as explained in the saturated solubility study results.

Differential Scanning Calorimetry (DSC) Analysis

Thermal analysis using Differential Scanning Calorimetry (DSC) was performed to evaluate the thermal phase of pure MLX, HPMC, and MLX-NC. The DSC thermogram can be seen in **Figure 4**, showing a sharp endothermic peak at 257.94 °C, which represents the crystal melting point for the pure MLX sample and is consistent with the crystalline characterization shown by the X-ray diffractogram. Meanwhile, the HPMC thermogram pattern displays a broad peak at 54.7 °C, indicating a glass transition temperature (Tg) change, or the loss of water molecules attached to the characteristic features of amorphous materials.[59] Meanwhile, the MLX-NC thermogram shows significant changes compared to pure MLX. The MLX crystal melting peak at 257.94 °C disappears completely and is replaced by a broad endothermic peak at a lower temperature (117.42 °C). This data is consistent with the results of XRD analysis, in which the sharp peak pattern of pure MLX changed to a broad peak pattern in MLX-NC, indicating that the crystalline phase of MLX underwent a transformation into an amorphous phase, as reported in previous studies.[60] The transformation of the crystalline phase into an amorphous phase is thought to be caused by the high mechanical energy of ultrasonication, which disrupts the crystal structure, as well as molecular interactions between MLX and the HPMC polymer matrix that prevent recrystallization.[61]

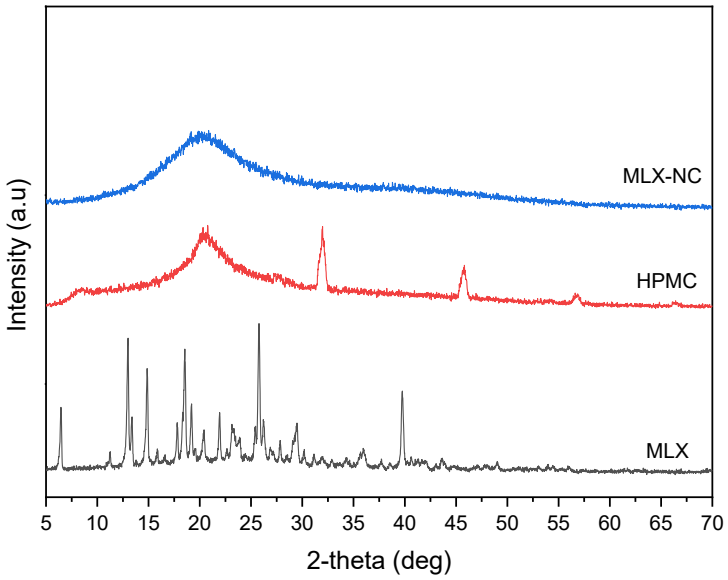

Figure 3. XRD diffractogram patterns of MLX, HPMC, and MLX-NC showing a decrease in crystallinity in MLX-NC.

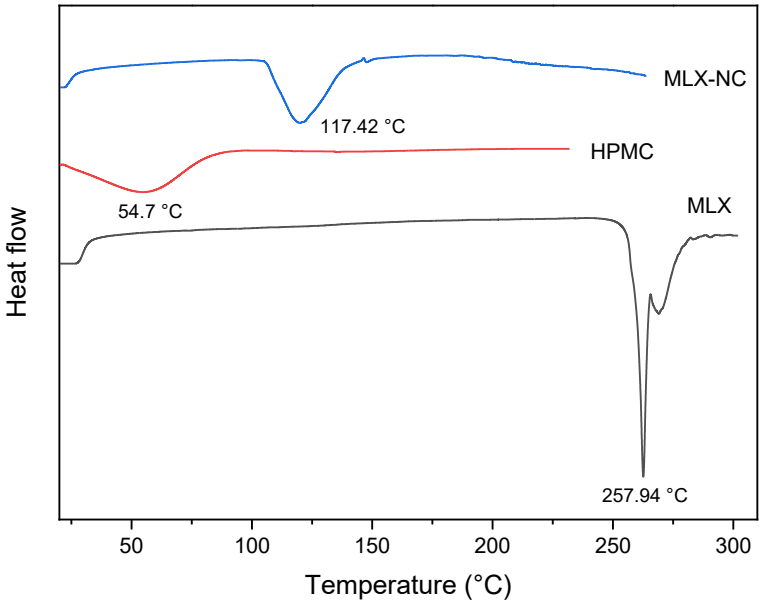

Figure 4. DSC thermogram comparing MLX, HPMC, and MLX-NC.

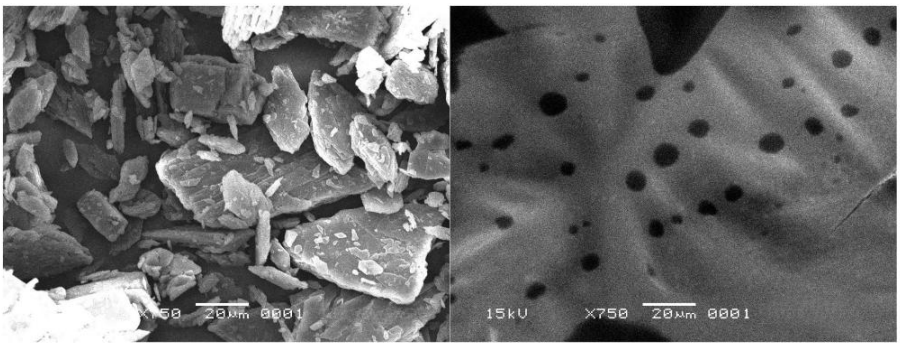

Figure 5. Topographical representation of particle surfaces showing (a) pure MLX and (b) MLX-NC, based on SEM analysis.

Scanning Electron Microscopy (SEM) Analysis

Based on Scanning Electron Microscopy (SEM) analysis with 750x magnification at a scale of 20 µm and an acceleration voltage of 15 kV. The morphology of pure MLX and MLX-NC particles shows very significant differences. **Figure 5a** shows the morphology of pure MLX, with large and varied particles with a crystalline morphology such as sheets or irregular plates, similar to the morphology of medicinal materials in powder form.[62] In contrast, **Figure 5b** shows the morphology of MLX-NC, particles that have undergone a nanonization process, appear more homogeneous and smaller crystal particles are scattered among the polymer matrix.[63] The presence of pores or dark spots on the surface of MLX-NC particles indicates the presence of HPMC polymer matrix covering the particles.[22] The pore structure and film-like morphology of MLX-NC are likely caused by the sublimation of water during lyophilization, which leaves voids in the polymer matrix, as well as the formation of an HPMC layer that coats the MLX particles. The change in morphology from large particles to smaller particles confirms the particle size analysis data. This reduction in particle size can increase the surface area, which ultimately can improve the solubility of MLX, which is difficult to dissolve in water.[53]

MLX-NC Saturation Solubility Test

The saturated solubility study showed a very significant increase in solubility in MLX-NC compared to pure MLX. As shown in **Table 1**, the solubility of pure MLX in water was only 0.005 ± 0.001 mg/mL, confirming its highly insoluble nature. In contrast, the solubility of MLX-NC increased dramatically to 1.064 ± 0.006 mg/mL. This substantial increase in solubility is a direct consequence of the nanonization process, which produces particles with a very small size (approximately 10-12 nm) and a much larger surface area, in accordance with the thermodynamic principle described by the Ostwald-Freundlich equation,[64] These small particles have high surface energy, making it easier for molecules on the surface to escape into the solvent, thereby increasing solubility.[15]

In addition, the alleged increase in solubility may also be caused by the use of functional additives, in this case as stabilizers for HPMC and DG. HPMC functions as a steric stabilizer polymer by absorbing onto the surface of nanoparticles, forming a protective layer that prevents aggregation and crystal growth.[65] Meanwhile, DG acts as an effective surfactant in reducing the surface tension between hydrophobic particles and the aqueous medium. This reduction in surface tension increases the wettability of the particles, facilitating better contact with the solvent and accelerating the dissolution rate.[66] The combination of steric stabilization and surface tension reduction effects allows MLX nanoparticles to maintain their properties. DG has an HLB (Hydrophilic-Lipophilic Balance) value of around 13–15, falling into the category of hydrophilic surfactants that are effective in reducing surface tension and improving the wetting of hydrophobic particles such as MLX, thereby accelerating the dissolution rate.[67] Therefore, the MLX-NC formulation shows a significant increase in solubility as a result of the synergy between particle size reduction and the use of polymer stabilizers and surfactants.

Table 1. Comparison of the solubility of pure MLX and MLX-NC in water.

Sample	Solubility (mg/mL)
MLX	0.005 ± 0.001
MLX-NC	1.064 ± 0.006

Note: Representation of mean values ± SD (n=3), MLX (pure meloxicam) and MLX-NC (meloxicam nanocrystals).

The correlation between the results of XRD and DSC analysis and the data on saturated solubility and particle size characterization shows that the nanocrystallization process has caused a phase transformation in MLX. This is evidenced by the disappearance of sharp crystalline diffraction peaks in pure MLX, which are replaced by broad diffraction patterns in MLX-NC, as well as the disappearance of the melting endotherm in the DSC thermogram, which consistently indicates amorphization. Given that the nanocrystallization system uses HPMC as a stabilizing polymer, this condition is thought to allow MLX to disperse molecularly in the polymer matrix, so that the resulting system is consistent with the characteristics of amorphous solid dispersion.[68] Although the nanocrystallization process was initially intended to produce nano-sized particles with crystalline properties, the characterization results show that MLX-NC undergoes amorphization. Interestingly, this phenomenon actually provides formulation advantages, because the amorphous phase has a higher Gibbs free energy than the crystalline phase, thereby significantly increasing solubility and dissolution rate. This is in line with the results of the saturated solubility test, which showed an increase in the solubility of MLX-NC by more than 200 times compared to pure MLX.[69,70]

Critical Implications and Study Limitations

The observed amorphization of MLX, while advantageous for solubility, raises considerations regarding long-term physical stability. Amorphous systems are inherently higher in energy and may be prone to recrystallization during storage, which could revert the solubility benefits. Future studies should include long-term stability testing under various temperature and humidity conditions. Furthermore, while saturated solubility tests show remarkable improvement, in vitro dissolution studies and in vivo pharmacokinetic evaluations are necessary to confirm the enhanced biopharmaceutical performance of this formulation.

CONCLUSION

The ultrasonic-based nanocrystallization process using HPMC and DG as stabilizers produces MLX with nanometer-sized particles that exhibit a decrease in crystallinity and a tendency toward an amorphous state, as indicated by XRD and DSC analysis. This change correlates with an increase in the saturated solubility of MLX-NC by more than 200 times compared to pure MLX, so that nanocrystallization with a polymer-surfactant combination can be seen as a pharmaceutical approach to overcome solubility limitations and increase the biopharmaceutical potential of class II BCS compounds with poor solubility.

FUNDING

This research was supported by an internal grant from LPPM Universitas Jenderal Achmad Yani (Grant No. Skep/188/Unjani/VI/2025).

ACKNOWLEDGMENTS

The authors acknowledge the support of LPPM Universitas Jenderal Achmad Yani for facilitating the publication of this research. The authors also thank the Laboratory of the Faculty of Pharmacy, Universitas Jenderal Achmad Yani, for providing the research facilities.

GENERATIVE AI DISCLOSURE STATEMENT

During the preparation of this manuscript, generative artificial intelligence tools (i.e., Gemini Pro) were used solely to assist with language editing and to improve the clarity of the text. All research design, data analysis, interpretation of results, and conclusions were conducted entirely by the authors, who assumed full responsibility for the content of this manuscript.

AUTHOR CONTRIBUTION STATEMENT

Nur Achsan Al-Hakim: Software, Data curation, Writing—original draft preparation, Visualization; **Titta Hartyana Sutarna:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Project administration; **Hestiary Ratih:** Formal analysis, Writing—review and editing, Supervision; **Karina Putriani Azzara:** Investigation, Formal analysis.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest among the authors in the research and publication of this manuscript.

REFERENCES

1. Lakshmi D, Geetha V, Murali V. From prescription to pollution: The ecological consequences of NSAIDs in aquatic ecosystems. *Toxicol Reports*. 2024;13:101775. doi:10.1016/j.toxrep.2024.101775
2. Zhong Y, Zhou Y, Ding R, Zou L, Zhang H, Wei X, He D. Intra-articular treatment of temporomandibular joint osteoarthritis by injecting actively-loaded meloxicam liposomes with dual-functions of anti-inflammation and lubrication. *Mater Today Bio*. 2023;19:100573. doi:10.1016/j.mtbio.2023.100573
3. Tinjacá DA, Martínez F, Almanza O, Jouyban A, Acree WE. Solubility of Meloxicam in Aqueous Binary Mixtures of Formamide, N-Methylformamide and N,n-Dimethylformamide: Determination, Correlation, Thermodynamics and Preferential Solvation. *J Chem Thermodyn*. 2021;154:106332. doi:10.1016/j.jct.2020.106332

4. Hanna PA, Al-Abbadi H, Hashem MA, Mostafa AE, Mahmoud YK, Ahmed MF. Development of a novel intramuscular liposomal injection for advanced meloxicam delivery: Preparation, characterization, in vivo pharmacokinetics, pharmacodynamics, and pain assessment in an orthopedic pain model. *Int J Pharm X*. 2024;8. doi:10.1016/j.ijpx.2024.100284
5. Alatas F, Stiawan D, Al-Hakim NA. Solubility and Scale-Up Potency of Norfloxacin-Urea Co-Crystal Prepared by Ultrasound-Assisted Slurry Co-Crystallization Method. *Borneo J Pharm*. 2023;6(2):158-167. doi:10.33084/bjop.v6i2.4173
6. Li S, Kou L, Qin Y, Wang Y, Sun Y, Liu X. A ternary system of meloxicam with matching hydrophilic polymer and cyclodextrin for improved stability in liquid preprations. *RSC Adv*. 2024;14(30):21260-21268. doi:10.1039/d4ra02811b
7. Annisa R, Hendradi E, Melani D. Pengembangan Sistem Nanostructured Lipid Carriers (NLC) Meloxicam dengan Lipid Monostearin dan Miglyol 808 Menggunakan Metode Emulsifikasi. *J Trop Pharm Chem*. 2016;3(3):156-169. doi:10.25026/jtpc.v3i3.102
8. Ratan R. Improving Oral Bioavailability of Meloxicam: Development and Characterization of Solid Dispersions. *J Biomed Pharm Res*. 2024;13(1):84-99. doi:10.32553/jbpr.v13i1.1081
9. Bartos C, Motzwickler-Németh A, Kovács D, Burián K, Ambrus R. Study on the Scale-Up Possibility of a Combined Wet Grinding Technique Intended for Oral Administration of Meloxicam Nanosuspension. *Pharmaceutics*. 2024;16(12):1512. doi:10.3390/pharmaceutics16121512
10. Ambrus R, Alshweiat A, Szabó-Révész P, Bartos C, Csóka I. Smartcrystals for Efficient Dissolution of Poorly Water-Soluble Meloxicam. *Pharmaceutics*. 2022;14(2). doi:10.3390/pharmaceutics14020245
11. Tabatabaei MS, Tabatabaei FAS, Moghimi HR. Drug self-delivery systems: A comprehensive review on small molecule nanodrugs. *Bioimpacts*. 2024;15. doi:10.34172/bi.30161
12. Sutarna TH, Alatas F, Purnamasari N, Alifah M. Utilization rhizome of jahe merah (Zingiber officinale Roscoe) as a bioreductant in the manufacture of gold nanoparticles with addition of polyvinylpyrrolidone 90 (PVP K90) as a stabilizer. 2023;8(3):1367-1378. doi:10.30604/jika.v8i3.1964
13. Mohammad IS, Hu H, Yin L, He W. Drug nanocrystals: Fabrication methods and promising therapeutic applications. *Int J Pharm*. 2019;562:187-202. doi:10.1016/j.ijpharm.2019.02.045
14. Joshi K, Chandra A, Jain K, Talegaonkar S. Nanocrystalization: An Emerging Technology to Enhance the Bioavailability of Poorly Soluble Drugs. *Pharm Nanotechnol*. 2019;7(4):259-278. doi:10.2174/2211738507666190405182524
15. Vadher B, Shah S, Dudhat K, Dhaval M, Sing S, Prajapati BG. Ketoconazole Nanocrystals Fortified Gel for Improved Transdermal Applications. *Nanofabrication*. 2024;9:1-15. doi:10.37819/nanofab.009.1885
16. Liu Y fen, Li Y, Xu P, Shen Y, Tang B, Wang Q. Development of Abiraterone Acetate Nanocrystal Tablets to Enhance Oral Bioavailability: Formulation Optimization, Characterization, In Vitro Dissolution and Pharmacokinetic Evaluation. *Pharmaceutics*. 2022;14(6):11-34. doi:10.3390/pharmaceutics14061134
17. Macedo LOD, Masiero JF, Bou-Chacra N. Drug Nanocrystals in Oral Absorption: Factors That Influence Pharmacokinetics. *Pharmaceutics*. 2024;16. doi:10.3390/pharmaceutics16091141
18. Mohd NK, Khalik W, Azmi AA. Synthesis and Characterization of Silica-Silver Core-Shell Nanoparticles. *Malaysian J Anal Sci*. 2019;23(2):290-299. doi:https://doi.org/10.17576/mjas-2019-2302-13
19. Nurmayansih A, Hariani P, Said M. Synthesis NiFe2O4 Nanoparticles by co-Precipitation Method for Degradation of Congo Red Dye. *Indones J Fundam Appl Chem*. 2020;6(3):115-121. doi:10.24845/ijfac.v6.i3.115
20. Yang DX, Wang L, Zhang L, Wang M, Li D. Construction, characterization and bioactivity evaluation of curcumin nanocrystals with extremely high solubility and dispersion prepared by ultrasound-assisted method. *Ultrason Sonochem*. 2024;104. doi:https://doi.org/10.1016/j.ultsonch.2024.106835
21. Shi S, Mandal P, Chen T. Mechanical Properties and Tribological Behavior of MoS2-Enhanced Cellulose-Based Biocomposites for Food Packaging. *Polymers (Basel)*. 2021;13(11):18-38. doi:10.3390/polym13111838
22. Kumar M, Shanthi N, Mahato AK, Soni S, Rajnikanth P. Preparation of luliconazole nanocrystals loaded hydrogel for improvement of dissolution and antifungal activity. *Heliyon*. 2019;5(5). doi:10.1016/j.heliyon.2019.e01688
23. Bhakay A, Rahman M, Davé R, Bilgili E. Bioavailability Enhancement of Poorly Water-Soluble Drugs via Nanocomposites: Formulation–Processing Aspects and Challenges. *Pharmaceutics*. 2018;10(86). doi:10.3390/pharmaceutics10030086
24. Ahire ED, Thakkar S, Darshanwad M, Misra M. Parenteral nanosuspensions: a brief review from solubility enhancement to more novel and specific applications. *Acta Pharm Sin B*. 2018;8(5):733-755. doi:10.1016/j.apsb.2018.07.011

25. Chung KH, Park H, Jeon K, Park Y, Jung S. Microporous Zeolites as Catalysts for the Preparation of Decyl Glucoside from Glucose with 1-Decanol by Direct Glucosidation. *Catalysts*. 2016;6(12):216. doi:10.3390/catal6120216
26. Cortés H, Hernández-Parra H, Bernal-Chávez SA, Prado-Audelo MLD, Magaña J, Leyva-Gómez G. Non-Ionic Surfactants for Stabilization of Polymeric Nanoparticles for Biomedical Uses. *Materials (Basel)*. 2021;14:3197. doi:10.3390/ma14123197
27. Lu L, Xu Q, Wang J, Wu S, Luo Z, Lu W. Drug Nanocrystals for Active Tumor-Targeted Drug Delivery. *Pharmaceutics*. 2022;14. doi:10.3390/pharmaceutics14040797
28. Köpke D, Pyo S. Symurban Nanocrystals for Advanced Anti-Pollution Skincare. *Cosmetics*. 2020;7(1). doi:10.3390/COSMETICS7010017
29. Yu Q, Wu X, Zhu Q, Chen Z, Li Y, Lu Y. Enhanced transdermal delivery of meloxicam by nanocrystals: Preparation, in vitro and in vivo evaluation. *Asian J Pharm Sci*. 2017;13(6):518-526. doi:10.1016/j.ajps.2017.10.004
30. Iurian S, Tomuță I, Rus L, Achim M, Leucuta S. Optimization of the sonication process for meloxicam nanocrystals preparation. *Clujul Med*. 2015;88:366-372. doi:10.15386/cjmed-445
31. Ubgade S, Bapat A, Kilor V. Effect of various stabilizers on the stability of lansoprazole nanosuspension prepared using high shear homogenization: Preliminary investigation. *J Appl Pharm Sci*. 2021;11(9):085-092. doi:10.7324/JAPS.2021.110910
32. Tang S, Chen Z, Chen F, Wei Q, Chen X, Jiang C. Extraction and Surface Functionalization of Cellulose Nanocrystals from Sugarcane Bagasse. *Molecules*. 2023;28(14). doi:10.3390/molecules28145444
33. Wang Y, Wang S, Xu Y, Wang P, Liu M, Jin X. Etoposide amorphous nanopowder for improved oral bioavailability: Formulation development, optimization, in vitro and in vivo evaluation. *Int J Nanomedicine*. 2020;15:7601-7613. doi:10.2147/IJN.S265817
34. Party P, Bartos C, Farkas Á, Szabó-Révész P, Ambrus R. Formulation and In Vitro and In Silico Characterization of "Nano-in-Micro" Dry Powder Inhalers Containing Meloxicam. *Pharmaceutics*. 2021;13. doi:10.3390/pharmaceutics13020211
35. Alatas F, Ratih H, Sutarna TH, Fauzi ML. The Binary and Ternary Amorphous Systems of Candesartan Cilexetil Preparation To Improve Its Solubility. *Int J Appl Pharm*. 2024;16(5):367-372. doi:10.22159/IJAP.2024V16I5.51141
36. Kemenkes RI. *Farmakope Indonesia-Edisi VI*. Dirjen Kefarmasian dan Alat Kesehatan, Kementerian Kesehatan RI.; 2020.
37. Sheskey PJ, Cook WG, Cable CG. *Handbook of Pharmaceutical Excipients, 8th Edition*. London : Pharmaceutical Press ; Washington, DC : APhA; 2017. doi:10.1016/B978-0-12-820007-0.00032-5
38. Nikolaychuk PA. UV-Spectrophotometric Determination of the Active Pharmaceutical Ingredients Meloxicam and Nimesulide in Cleaning Validation Samples with Sodium Carbonate. *J*. 2023;6(2):248-266. doi:10.3390/j6020019
39. Jiao H, Mao Q, Razzaq N, Ankri R, Cui J. Ultrasound technology assisted colloidal nanocrystal synthesis and biomedical applications. *Ultrason Sonochem*. 2024;103:106798. doi:10.1016/j.ultsonch.2024.106798
40. Ghasemian E, Rezaeian B, Alaei S, Vatanara A, Ramezani V. Optimization of Cefixime Nanosuspension to Improve Drug Dissolution. *Pharm Sci*. 2015;21:136-144. doi:10.15171/PS.2015.28
41. Touqeer SI, Jahan N, Abbas N, Ali A. Formulation and Process Optimization of Rauvolfia serpentina Nanosuspension by HPMC and In Vitro Evaluation of ACE Inhibitory Potential. *J Funct Biomater*. 2022;13. doi:10.3390/jfb13040268
42. Pinar SG, Oktay AN, Karakucuk A, Çelebi N. Formulation Strategies of Nanosuspensions for Various Administration Routes. *Pharmaceutics*. 2023;15(5):1520. doi:10.3390/pharmaceutics15051520
43. Jacob S, Nair AB, Shah J. Emerging Role of Nanosuspensions in Drug Delivery Systems. *Biomater Res*. 2020;24(1). doi:10.1186/s40824-020-0184-8
44. Elshafeey A, El-Dahmy RM. Formulation and Development of Oral Fast-Dissolving Films Loaded with Nanosuspension to Augment Paroxetine Bioavailability: In Vitro Characterization, Ex Vivo Permeation, and Pharmacokinetic Evaluation in Healthy Human Volunteers. *Pharmaceutics*. 2021;13. doi:10.3390/pharmaceutics13111869
45. Awan AM, Farid A, Shah S, Khan D, ur Rehman F, Dar MJ, Iftikhar T, Ghazanfar S, Galanakis CM, Alamri A, Asdaq SM, Shah K. Nanocrytals-Mediated Oral Drug Delivery: Enhanced Bioavailability of Amiodarone. *Pharmaceutics*. 2022;14. doi:10.3390/pharmaceutics14061300
46. Moreira FF, Ziebarth J, Babinski TP, Mainardes R. Development and Characterization of Zein/Eudragit Composite Nanoparticles for Insulin Intranasal Delivery. *ACS Omega*. 2025;10:21236-21249.

doi:10.1021/acsomega.4c10474

47. Jeyaraj M, Gurunathan S, Qasim M, Kang M, Kim JH. A Comprehensive Review on the Synthesis, Characterization, and Biomedical Application of Platinum Nanoparticles. *Nanomaterials*. 2019;9. doi:10.3390/nano9121719
48. Qureshi S, Nizamuddin S, Xu J, Vancov T, Chen C. Cellulose nanocrystals from agriculture and forestry biomass: synthesis methods, characterization and industrial applications. *Environ Sci Pollut Res Int*. 2024;31:58745-58778. doi:10.1007/s11356-024-35127-3
49. Elmowafy M, Shalaby K, Al-Sanea MM, Hendawy O, Salama A, Ibrahim MF. Influence of Stabilizer on the Development of Luteolin Nanosuspension for Cutaneous Delivery: An In Vitro and In Vivo Evaluation. *Pharmaceutics*. 2021;13(11). doi:10.3390/pharmaceutics13111812
50. Chantaburanan T, Teeranachaideekul V, Jintapattanakit A, Chantasart D, Junyaprasert V. Enhanced stability and skin permeation of ibuprofen-loaded solid lipid nanoparticles based binary solid lipid matrix: Effect of surfactant and lipid compositions. *Int J Pharm X*. 2023;6. doi:10.1016/j.ijpx.2023.100205
51. Miocić S, Torić J, Juretić M, Đoković JB, Randjelović D V, Filipović-Grcić J. Characterisation and Stabilisation Mechanisms of Azelaic Acid Nanosuspensions: Insights from a Dual Stabiliser System. *Pharmaceutics*. 2025;17(4). doi:10.3390/pharmaceutics17040439
52. Nooshkam M, Varidi M, Zareie Z, Alkobeisi F. Behavior of protein-polysaccharide conjugate-stabilized food emulsions under various destabilization conditions. *Food Chem X*. 2023;18. doi:10.1016/j.fochx.2023.100725
53. Yu Y, Tian Y, Zhang H, Du Y, Song S, Zheng A. The Evaluation of Meloxicam Nanocrystals by Oral Administration With Different Particle Sizes. *Molecules*. 2022;27(2):421. doi:10.3390/molecules27020421
54. Dinte E, Muntean D, Andrei V, Boşca B, Dudescu C, Barbu-Tudoran L. In Vitro and In Vivo Characterisation of a Mucoadhesive Buccal Film Loaded with Doxycycline Hyclate for Topical Application in Periodontitis. *Pharmaceutics*. 2023;15(2). doi:10.3390/pharmaceutics15020580
55. Han S, Zhao L, Jiang Q, Lian J. Deformation-induced localized solid-state amorphization in nanocrystalline nickel. *Sci Rep*. 2012;2. doi:10.1038/srep00493
56. Willmann AC, Berkenfeld K, Faber T, Wachtel H, Boeck G, Wagner K. Itraconazole Nanosuspensions via Dual Centrifugation Media Milling: Impact of Formulation and Process Parameters on Particle Size and Solid-State Conversion as Well as Storage Stability. *Pharmaceutics*. 2022;14. doi:10.3390/pharmaceutics14081528
57. Budiman A, Ivana H, Huang KA, Huang SA, Nadhira MS, Rusdin A. Biocompatible Natural Polymer-Based Amorphous Solid Dispersion System Improving Drug Physicochemical Properties, Stability, and Efficacy. *Polymers (Basel)*. 2025;17(15). doi:10.3390/polym17152059
58. Shen B de, Shen C ying, Zhu W, Yuan H. The contribution of absorption of integral nanocrystals to enhancement of oral bioavailability of quercetin. *Acta Pharm Sin B*. 2021;11(4):978-988. doi:10.1016/j.apsb.2021.02.015
59. Kumar S, Raghu S, Demappa T, Sannappa J. Effect of NaBr on the Structural, Thermal and Mechanical Properties of HPMC:NaBr Composite Films. *Asian J Chem*. 2022;34(2):305-310. doi:10.14233/ajchem.2022.23507
60. Ashfaq R, Tóth N, Kovács A, Berkó S, Katona G, Ambrus R, Polgár T, Szécsényi M, Burián K, Budai-Szűcs M. Hydrogel–Nanolipid Formulations for the Complex Anti-Inflammatory and Antimicrobial Therapy of Periodontitis. *Pharmaceutics*. 2025;17(5):620. doi:https://doi.org/10.3390/pharmaceutics17050620
61. Nugroho RWN, Tardy B, Eldin SM, Ilyas RA, Mahardika M, Masruchin N. Controlling the critical parameters of ultrasonication to affect the dispersion state, isolation, and chiral nematic assembly of cellulose nanocrystals. *Ultrason Sonochem*. 2023;99. doi:10.1016/j.ultsonch.2023.106581
62. Maggi L, Friuli V, Cerea B, Bruni G, Berbenni V, Bini M. Physicochemical Characterization of Hydroxyapatite Hybrids with Meloxicam for Dissolution Rate Improvement. *Molecules*. 2024;29(11). doi:10.3390/molecules29112419
63. Bartos C, Jójárt-Laczkovich O, Katona G, Budai-Szűcs M, Ambrus R, Szabó-Révész P. Optimization of a combined wet milling process in order to produce poly(vinyl alcohol) stabilized nanosuspension. *Drug Des Devel Ther*. 2018;12:1567-1580. doi:10.2147/DDDT.S159965
64. Li J, Wang Z, Zhang H, Gao J, Zheng A. Progress in the development of stabilization strategies for nanocrystal preparations. *Drug Deliv*. 2021;28(1):19-36. doi:10.1080/10717544.2020.1856224
65. Tao J, Chow SF, Zheng Y. Application of flash nanoprecipitation to fabricate poorly water-soluble drug nanoparticles. *Acta Pharm Sin B*. 2018;9:4-18. doi:10.1016/j.apsb.2018.11.001
66. Li G, Chen L, Ruan Y, Guo Q, Liao X, Zhang B. Alkyl polyglycoside: a green and efficient surfactant for enhancing heavy oil recovery at high-temperature and high-salinity condition. *J Pet Explor Prod Technol*. 2019;9(4):1-10. doi:10.1007/s13202-019-0658-1

67. Ghani L, Kim S, Ehsan M, Liu X, Im W, Chae PS. Melamine-cored glucosides for membrane protein solubilization and stabilization: importance of water-mediated intermolecular hydrogen bonding in detergent performance. *Chem Sci*. 2023;14(45):13014-13024. doi:10.1039/d3sc03543c

68. Gigliobianco MR, Casadidio C, Censi R, Di Martino P. Nanocrystals of poorly soluble drugs: Drug bioavailability and physicochemical stability. *Pharmaceutics*. 2018;10(3). doi:10.3390/pharmaceutics10030134

69. Uddin A, Halder S, Deb N, Das H, Shuma ML, Hasan I, Shill M, Haider SS. Impact of Methods of Preparation on Mechanical Properties, Dissolution Behavior, and Tableting Characteristics of Ibuprofen-Loaded Amorphous Solid Dispersions. *Adv Pharmacol Pharm Sci*. 2024;2024. doi:10.1155/2024/2303942

70. Silva JFC, Rosado MTS, Maria T, Silva PSP, Silva M, Eusébio M. Introduction to Pharmaceutical Co-amorphous Systems Using a Green Co-milling Technique. *J Chem Educ*. 2023;100(4):1627-1632. doi:10.1021/acs.jchemed.3c00036