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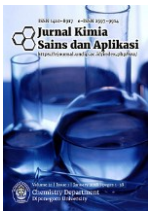

The Effect of Meloxicam Nanocrystal Formation with the Addition of PVP K-60 and Decyl Glucoside as Stabilizers on Its Solubility

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Abstract

Meloxicam (MLX) is a non-steroidal anti-inflammatory drug that has low bioavailability when administered orally due to its low solubility, and efforts have been made to improve drug delivery to improve solubility. The aim of this study was to prepare and characterize Meloxicam nanocrystals (MLX-NC) and evaluate them with the addition of polyvinylpyrrolidone K-60 (PVP K-60) and decyl glucoside (DG) to prevent nanoparticle aggregation. MLX-NC preparation by a combination of ultrasonic homogenization and the freeze-drying method. The particle size analysis results ranged from 9.76 to 12.73 nm with a polydispersity index <0.5, indicating a homogeneous and stable size distribution. PXRD and DSC characterization revealed the disappearance of the characteristic crystalline peaks of MLX, indicating a transformation to an amorphous form. Additionally, based on saturated solubility studies, the solubility of MLX-NC increased by up to 173 times compared to pure MLX. This study shows that the formulation, initially intended as nanocrystals, resulted in an amorphous solid dispersion due to the influence of stabilizer concentration. This transformation, along with reduced particle size, contributed synergistically to the enhanced solubility of MLX.

1. Introduction

One of the important parameters to be determined in pharmaceutical preparation manufacture, in particular with oral administration, is solubility. Oral drug delivery is the most common route of administration due to its advantages in safety, storage stability, and relatively low cost. Meloxicam is one of these orally applied drugs. Meloxicam (MLX) is an NSAID with pharmacological functions for the treatment of pain and inflammation as a preferential cyclooxygenase-2 (COX-2) inhibitor. MLX is a BCS class II molecule with low solubility and high permeability [1]. Because of its low solubility in water, however, it displays low oral bioavailability, which constitutes a significant problem [2]. This problem was tackled by developing a delivery system beneficiary of a nanocrystal technology that enhances solubility and bioavailability [3].

Nanocrystals (NC) are a novel technology that involves nano-scale crystallites (1–500 nm). These nanocrystals have specific physicochemical properties that are suggested to correlate with increased solubility and bioavailability [2, 3, 4]. However, the instability and particle size control are still the main challenges in the construction of these delivery systems [5]. Thus, a suitable stabilizing agent may be crucial for maintaining the stability of the system of such nanocrystals. One of the effective stabilizers used is PVP K-60.

Polyvinylpyrrolidone (PVP), a polymer commonly used as a stabilizer, has the ability to coat the surface of the particles with a protective film to reduce agglomeration of the nanocrystals and to improve their stability to achieve drug solubility [6, 7, 8]. However, PVP K-60 has the disadvantage of its long-term stability, and it is believed to have potential interactions with other formulation ingredients affecting its stability [9]. Moreover, when high stability of nanocrystals is required, the PVP K-60 with decyl glucoside serves as a stabilizer.

Decyl glucoside (DG) is a non-ionic surfactant that lowers surface tension, enhances particle dispersibility in nanocrystal systems, and improves drug solubility due to its biocompatibility[2]. Due to the hydrophilic properties of PVP K-60 and the emulsification properties of decyl

glucosides, this combination can give rise to a more consistent and efficient system in drug delivery [10]. This synergy helps establish a balanced interaction between the drug and the polymer matrix, which in turn enables better and more controlled drug release [11]. It is anticipated to accomplish a better stability condition and solubility of nanocrystals by using only a stabilizer, PVP K-60 [7]. Moreover, this formulation approach may reduce side effects commonly associated with conventional drug forms [12]. Ultimately, this strategy offers a promising solution to the solubility limitations of MLX, thereby enhancing its therapeutic efficacy.

Previous studies mostly investigate a single type of stabilizer, while in this study, the mutual effect of PVP K- 60 and DG is highlighted. The objective of this study is to investigate a novel process concerning the formation of meloxicam nanocrystals (MLX-NC) using a mixture of PVP K-60 and DG as stabilizers. The present study was anticipated to shed more light on the effects of the combinations of stabilizers on the properties and solubility of MLX and ultimately serve as a great stepping stone for better and safer drug-loaded nanocrystals.

2. Experimental

2.1. Materials

The materials used consisted of meloxicam (MLX) purchased from Swati Spentose Pvt. Ltd., India, polyvinylpyrrolidone (PVP) K-60, decyl glucoside (DG), and water. All materials used were of pharmaceutical quality, and solvents were of analytical quality.

2.2. Raw Material Inspection and Initial Characterization

The inspection of MLX, PVP K-60, and DG raw materials included organoleptic as well as initial characterization of PXRD and DSC analysis, and determination of MLX calibration curves.

2.3. Preparation of Meloxicam Nanocrystals (MLX-NC)

The preparation of MLX-NC uses a combination of ultrasonic homogenization and freeze-drying methods, with several modifications. The sonication process involves various physical mechanisms that assist in breaking down larger particles into nano-sized particles. Meanwhile, the freeze-drying technique was employed to dry the resulting nanosuspension (detailed in the subsequent procedure). MLX was weighed in 20 mg and then dispersed in 100 mL of water. Stabilizers were added with a combination of PVP K-60 (3%) and DG (3%). Then the liquid suspension was homogenized using an Ultrasonic Homogenizer Probe Sonicator (Biostellar BSD-250 W, China) at 70% power and maintained at a constant temperature of 90°C for 40 minutes [13].

2.4. Production of Dry Nanocrystals

The freeze-drying method, also known as lyophilization, was used for the purpose of freezing and drying by causing a phase change from liquid to solid or powder under vacuum conditions at low temperatures. The nanosuspensions formed were frozen at -40°C for 24 hours, followed by drying for 72 hours at a pressure of 0.01 mbar using a Lyophilizer Freeze Dryer (Biobase BK-FD12S, China). Drying was carried out by adding 3% (w/v) mannitol [14, 15].

2.5. In Vitro Characterization of MLX-NC

2.5.1. Particle Size Analysis and Polydispersity Index

Particle size analysis of nanocrystals was determined by the Dynamic Light Scattering (DLS) principle using a Nanoparticle Analyzer (Horiba SZ-100V2, Japan). The measurement results were the average particle diameter and the range of particle size distribution [16].

2.5.2. Differential Scanning Calorimetry (DSC) Analysis

Thermal analysis was carried out using a Differential Scanning Calorimeter (Shimadzu DSC-60 Plus, Japan) based on the principle of measuring heat flow into or out of the sample during heating or cooling. Samples weighing 2-5 mg were placed in an aluminum pan and heated in the temperature range of 30–350°C at a heating rate of 10°C/min [17].

2.5.3. Powder X-ray Diffraction (PXRD) Analysis

PXRD analysis was performed to determine the crystalline structure of MLX and MLX-NC. The diffraction patterns were obtained using Powder X-ray Diffraction with Cu Kα radiation (λ = 1.5406 Å) at 40 kV and 40 mA and a scanning speed of 10°/min over a 2θ range of 5–45° [18].

2.6. Saturation Solubility Study of MLX-NC

The saturation solubility of pure MLX and MLX-NC was optimized and tested in water. Excess amounts of each sample were placed in 10 mL vials containing water as the solvent. The mixture was shaken using an Orbital Shaker (IKA KS 260, Germany) at a temperature of 25 ± 0.5°C for 24 hours, then filtered using a 0.22 µm filter paper, and the filtrate was diluted appropriately. The solutions were measured using a UV-Visible Spectrophotometer (Shimadzu UV-1800, Japan) at the maximum wavelength (λ_{max}) of 362.20 nm to determine the absorbance of each sample [19].

3. Results and Discussion

3.1. Raw Material Inspection

The analysis started with the identification of the raw materials used—MLX, PVP K-60, and DG—which included organoleptic examination and initial characterization using PXRD and DSC analyses. It also included the development of an MLX calibration curve and solubility testing of unmodified MLX prior to its conversion to nanocrystals. This is to ensure that the excipients utilized are consistent with those documented in the official compendia and other supporting literature. According to the examination results and literature review, all the raw materials met the specified standards, with supporting Certificates of Analysis (CoA) provided [20, 21]. The λ_{max} of MLX in water was determined by preparing a 10 µg/mL solution and scanning within the range of 200–400 nm. The resulting λ_{max} was 362.20 nm, which is consistent with earlier findings [22].

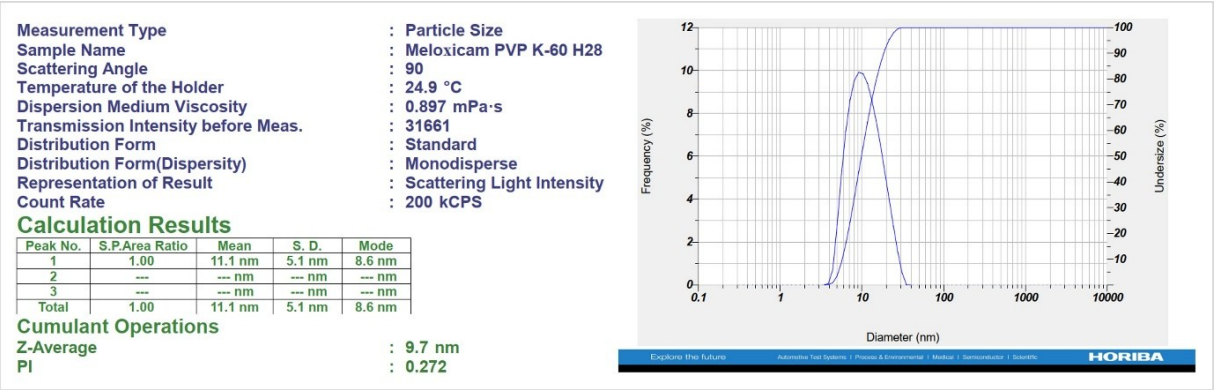

Figure 1. Data representing the results of particle size analysis and polydispersity index of nanosuspension solutions on the 28th day of measurement

3.2. Preparation and Production of Dry MLX-NC

The formation of MLX-NC was achieved through a combination of ultrasonic homogenization and freeze-drying methods, with several modifications. The ultrasonic homogenizer facilitates particle size reduction by employing high-frequency ultrasonic waves to generate acoustic cavitation forces within the liquid medium, effectively breaking down larger particles into the nanoscale range [23, 24]. Meanwhile, freeze-drying is performed to dry the resulting nanosuspension solution, which undergoes a phase change from liquid to solid or powder in a vacuum at low temperatures [25].

This research formulated MLX-NC, consisting of the active pharmaceutical ingredient MLX, stabilized by a combination of polymeric (PVP K-60) and surfactant (DG) stabilizers. These stabilizers function to inhibit particle aggregation, which is a common challenge in nanoscale systems due to the high surface energy of small particles. By inhibiting aggregation, the stabilizers help maintain the stability and uniformity of the nanosuspension dispersion system [26, 27]. The use of combined stabilizing agents in nanoparticle formulations remains relatively underexplored. Therefore, the concentrations of PVP K-60 and DG employed in this study were selected based on a comprehensive review of the literature, focusing on optimal concentrations of individual stabilizers known to produce nanoparticles with desirable size and stability characteristics [28, 29].

The process in the formation of MLX-NC begins with the preparation of MLX by incorporating PVP K-60 and DG to produce a nanosuspension, facilitated by an ultrasonic homogenizer. After obtaining the expected particle size based on the analysis of size characterization and particle distribution, the nanosuspension underwent a drying process via freeze-drying (lyophilization) using a freeze dryer. During this step, 3% mannitol was added to serve as a cryoprotectant, aimed at preventing aggregation and protecting the nanocrystals from potential damage caused by high vacuum pressure during the drying process [30, 31].

3.3. Particle Size and Polydispersity Index Analysis of MLX-NC

Determination of nanoparticle size analysis is carried out using the particle size analysis method, which is one of the important characterizations for confirming the successful reduction of a material to the nanoscale. The results of the physical characterization of MLX-NC can be seen in Table 1. The nanoparticle size obtained from particle size and distribution analysis after 28 days of storage at room temperature ranged from 9.76 to 12.73 nm, with a polydispersity index between 0.1 and 0.3. Thus, the preparation meets the criteria of nanocrystals, with a particle size of < 800 nm and a polydispersity index value of < 0.5, indicating good particle size distribution and homogeneous size [32].

Throughout the 28-day storage period, the particle size decreased but remained relatively stable. The decrease in particle size may have been due to internal restructuring during storage. This was caused by the relaxation of internal tension in the particle matrix, which can lead to a decrease in particle size over time [33, 34]. The particle size analysis data and polydispersity index on the 28th day of measurement can be seen in Figure 1. Furthermore, the topography of the developed MLX-NC particles was observed to be spherical based on morphological analysis using a SEM at 750× magnification with a 20 µm scale and an acceleration voltage of 15 kV, as shown in Figure 2. The topographical appearance of the MLX-NC particles shows that the particles are dispersed in the PVP-K60 matrix, which appears as a film-like layer, serving as its primary function.

Table 1. Results of physical characterization of MLX-NC particle size

Time (days)	Particle size (nm)	Polydispersity index
0	12.73 ± 0.98	0.24± 0.06
7	10.5 ± 0.12	0.18± 0.03
14	10.13 ± 0.25	0.24± 0.09
21	9.76± 0.15	0.21± 0.03
28	9.76± 0.11	0.30± 0.06

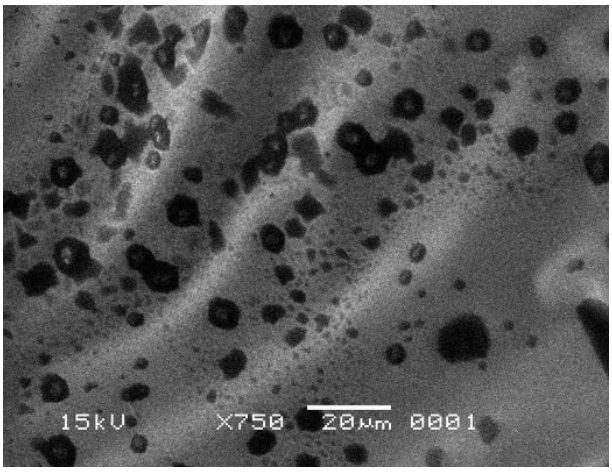

Figure 2. SEM images of MLX-NC illustrating the surface morphology of the particles

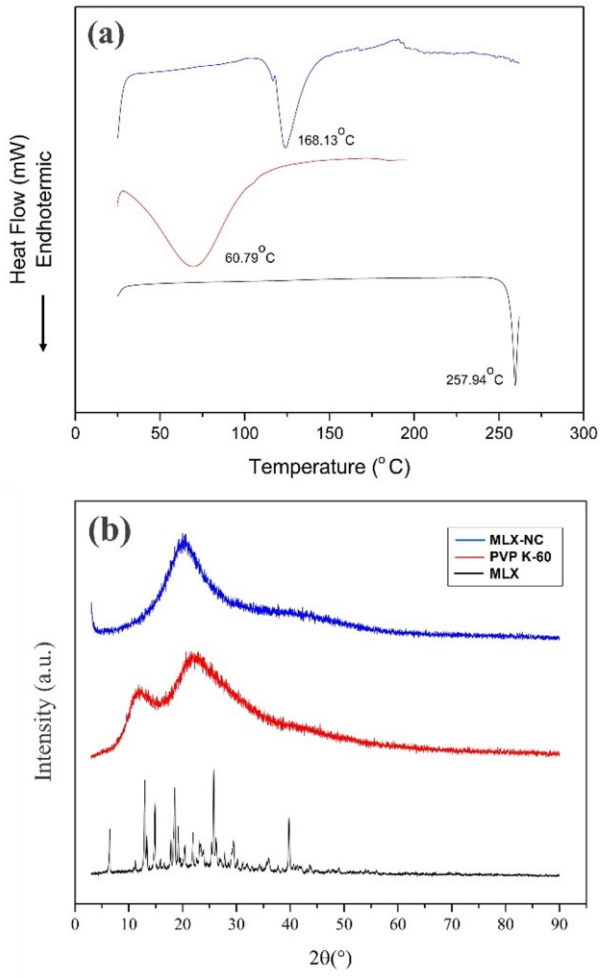

Figure 3. Solid-state characterization using (a) DSC thermograms and (b) XRD diffractograms of MLX, PVP K-60, and MLX-NC

3.4. Differential Scanning Calorimetry (DSC) Analysis

DSC is a thermal analysis technique with the ability to characterize the presence of multicomponent crystal formation by analyzing the melting point difference between the product and its constituent components [15]. The results of the DSC analysis characterization can be seen in Figure 3a, showing the thermogram patterns of MLX, PVP K-60, and MLX-NC. The DSC thermogram pattern of MLX shows a sharp endothermic transition at 257.94°C, which is characterized by melting according to the melting point of MLX and the occurrence of an optimal degradation process [35].

The presence of a sharp peak confirms the crystalline nature of MLX, as seen and evidenced also in the PXRD diffractogram. The thermogram pattern of PVP K-60 shows a broad endothermic peak around 60.79°C; this peak is related to the glass transition of PVP K-60, which is typical of amorphous materials. The thermogram pattern of MLX-NC does not show a noticeable endothermic peak at around 257°C, which means that pure MLX has lost its crystal structure [36]. This indicates that there is a change in energy that occurs during the nanocrystal synthesis process, where MLX is in amorphous form, dispersed in a PVP K-60 matrix [37].

The MLX-NC thermogram pattern, an endothermic transition occurred at a temperature of 168.13°C, which formed between the melting points of pure MLX and PVP K-60, caused by intermolecular interactions and changes in the thermal energy of the mixture of components in the formula, as well as a shift in the peak [38, 39]. It can be seen that the MLX-NC thermogram pattern formed with a broad endothermic peak indicates a tendency toward an amorphous phase. This is related to the use of excessive stabilizer concentrations, which can affect the MLX-NC thermogram pattern and enable crystallinity changes and phase transitions [40, 41].

3.5. Powder X-ray Diffraction (PXRD) Analysis

PXRD diffractogram analysis can provide information about changes in crystal structure and the formation of new crystal phases or the transformation of new structural states of a material. The results of the PXRD analysis characterization can be seen in Figure 3b, showing the diffractogram patterns of MLX, PVP K-60, and MLX-NC. The PXRD pattern of MLX clearly exhibits a crystalline structure, with sharp diffraction peaks observed at 2θ angles of 6.46°, 12.9°, 14.9°, 18.64°, 20.9°, 25.76°, 29.5°, and 39.68°, consistent with previous reports [35]. Whereas the PXRD pattern of PVP K-60 shows a diffraction pattern with a broad or 'halo' shape, arch-like peaks or non-sharp peaks with low intensity, which is characterized as an amorphous structure [37].

Interestingly, the PXRD pattern of MLX-NC shows a significant reduction in peak intensity compared to the original MLX pattern, with the absence of sharp peaks. This indicates the possibility of transformation from a crystalline state to an amorphous state. The formation of MLX-NC lowers the crystallinity of MLX, which leads to the fading of most sharp diffraction peaks. This change is linked to the increased solubility of MLX-NC [42, 43]. It can also be caused by the use of stabilizers at concentrations higher than the active substance, which can suppress the crystallinity of pure MLX. Increasing the concentration of polymers such as PVP, as stabilizers in nanocrystals, can eliminate the crystallinity of pure MLX, which is clearly visible in the PXRD diffraction pattern, indicating that a transformation occurs in the formation of the amorphous phase [44, 45].

DSC and PXRD analyses of DG were not conducted due to its physical form—a viscous, cloudy liquid—which poses limitations for such characterizations. Both DSC and PXRD analyses require samples in the form of smooth, homogeneous solids or powders [46, 47].

3.6. Saturation Solubility Study of MLX-NC

The final achievement of this research is that the formation of MLX-NC is expected to increase the solubility of MLX, which is a crucial factor in oral drug administration. A saturation solubility study was conducted to determine the maximum amount of MLX and MLX-NC that can dissolve in water under specific conditions. As shown in Figure 4, the solubility of pure MLX was 0.006 ± 0.87 mg/mL, consistent with previous reports [48, 49], while the solubility of MLX-NC produced is 0.989 ± 0.74 mg/mL at 25°C. The nanocrystalline form has a solubility increase of up to 173 times compared to its pure form. The difference in solubility values obtained indicates that smaller particle size changes can have a better solubility effect because they have a larger surface area for the solvent to work on, thereby accelerating the process and increasing solubility.

In this study, the main functions of PVP K-60 and DG are expected to act as physical stabilizers, but these two excipients can also indirectly contribute to increased solubility, not only through physical stabilization of nanocrystals, but also due to the intrinsic solubilizing effects of both excipients. PVP K-60 is known to enhance solubility through hydrogen bonding and increased wettability [29, 37], while decyl glucoside, as a nonionic surfactant, can improve solubility through micelle formation [50, 51]. It is recognized that these conditions may also contribute to solubility enhancement beyond particle size reduction.

This increase in solubility can also be correlated with the results of PXRD and DSC characterization data, which show the absence of characteristic MLX diffraction peaks in the PXRD analysis, as well as the disappearance of endothermic melting peaks in the DSC curve. This indicates that MLX in the formulation has undergone a transformation from a crystalline form to an amorphous form [52, 53].

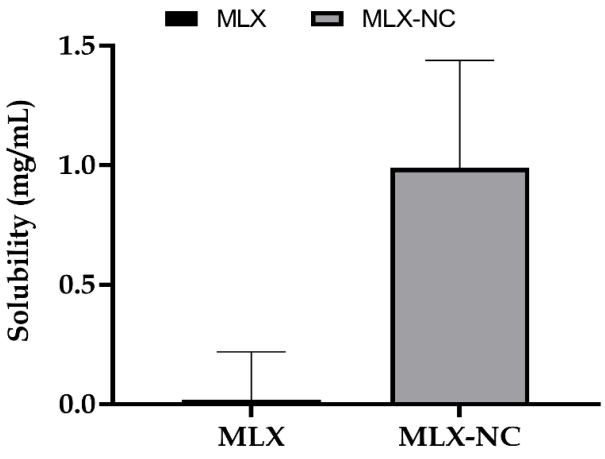

Figure 4. Represents the solubility comparison of pure MLX and MLX-NC in aqueous media

However, although the initial formulation process was intended to produce nanocrystals, the actual results show that the resulting system is more appropriately categorized as an amorphous solid dispersion. This transformation is likely influenced by the high concentration of stabilizers (PVP K-60 and decyl glucoside) and the processing conditions used, such as mechanical energy or local solubility changes. Thus, the increased solubility obtained is not only due to particle size reduction but also from the contribution of amorphous properties that enhance the free energy and intrinsic solubility of the active ingredient.

4. Conclusion

The MLX formulation in the form of nanocrystals (MLX-NC) was successfully developed using a combination of ultrasonic homogenization and freeze-drying methods, with the addition of PVP K-60 and decyl glucoside as stabilizers. Although the particle size is in the nanoscale range and shows good physical stability, the results of PXRD and DSC characterization analysis indicate the loss of MLX crystallinity and the formation of an amorphous form. This transformation is likely caused by the high concentration of stabilizers. In addition to preventing aggregation, PVP K-60 and DG also indirectly contribute to the increased solubility of MLX. Test results showed a solubility increase of up to 173 times compared to its pure form. Therefore, the resulting system is more appropriately classified as an amorphous solid dispersion, which remains effective in significantly enhancing the solubility of MLX.

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