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IMPROVED SOLUBILITY AND DISSOLUTION OF ETORICOXIB VIA MULTICOMPONENT CRYSTALLIZATION WITH MEGLUMINE

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ABSTRACT

Etoricoxib, a non-steroidal anti-inflammatory drug known for its poor water solubility, faces significant challenges in achieving adequate bioavailability due to its slow dissolution rate. This study aimed to improve the solubility and dissolution rate of etoricoxib through the formation of multicomponent crystals with N-methyl-D-glucamine (meglumine) as a coformer. Multicomponent crystals were synthesized via solvent drop grinding in a 1:1 molar proportion and then analyzed for their solid-state characteristics using Differential Scanning Calorimetry, Powder X-ray Diffraction, Fourier Transform Infrared Spectroscopy, and Scanning Electron Microscopy. Thermal and diffraction analyses confirmed the formation of new crystalline phases, indicative of successful multicomponent crystal formation. Morphological studies revealed smaller and more uniform particles in the multicomponent crystals compared to the Intact etoricoxib. The multicomponent crystal exhibited a 3.2-fold increase in solubility and a 2.8-fold faster dissolution rate within 60 minutes compared to intact etoricoxib. These improvements are attributed to the reduction in crystal lattice energy, facilitated by the formation of molecular interactions between etoricoxib and the coformer. This strategy offers a promising approach to enhancing the biopharmaceutical performance of a poorly soluble drug.

Keywords: Etoricoxib, Meglumine, Multicomponent Crystal, Solubility, Dissolution Rate.

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INTRODUCTION

Poor water solubility remains a critical challenge in pharmaceutical development, with nearly 40% of marketed drugs and up to 90% of pipeline candidates suffering from limited aqueous solubility, hindering their bioavailability and therapeutic efficacy.[1,2] Etoricoxib, a selective COX-2 inhibitor used for various inflammatory conditions, is one such compound categorized under BCS Class II due to its low solubility and high permeability. Despite its therapeutic potential, its clinical effectiveness is constrained by its poor dissolution profile, especially in oral formulations.[3,4] It has a partition coefficient (Log P) of 3.9 and a saturated solubility of 78.48 ± 1.47 mg/mL in water. The low solubility of etoricoxib leads to a slow dissolution rate, reducing its absorption rate. This results in low bioavailability and may limit its therapeutic effects. Thus, improving the solubility and/or dissolution rate of etoricoxib is crucial to enhance bioavailability and reduce the required dosage.[5] Several strategies have been employed to improve the solubility of poorly soluble drugs, including particle size reduction, surfactant use, pH adjustment, cyclodextrin complexation, and solid dispersions. However, in recent years, crystal engineering, particularly through multicomponent crystal formation, has emerged as a promising and rational approach to improve solubility and dissolution without altering the drug's chemical structure. Multicomponent crystals, including cocrystals, solvates, hydrates, and salts, can be designed by selecting excipients or coformers that interact with the drug molecule through non-covalent bonds to form a new crystalline phase.[6-10] Multicomponent crystals are composed of two or more molecules, typically including an active pharmaceutical ingredient and a coformer, organized within the crystal lattice. These crystals form as a single phase consisting of molecular and/or ionic compounds combined in a defined stoichiometric ratio. Coformers are typically inactive compounds that bond with the active drug through non-ionic or non-covalent interactions. Cocrystallization is a widely used technique to enhance the physicochemical properties of solid active pharmaceutical drugs without altering their pharmacological effects through non-

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covalent interactions.[11,12] The selection of a coformer is a critical step in the formation of cocrystals. The basic requirement for coformers is that they should be non-interfering in the formulation and generally safe. Various theoretical and experimental approaches are required to select the appropriate coformer. Theoretical approaches for selecting coformers are based on potential interactions between the coformer and the active pharmaceutical ingredient molecule. These interactions aim to enhance the physicochemical properties of the active compound by facilitating hydrogen bond formation. Coformer selection may be based on functional group compatibility, pKa values, or predictive models such as the Fabian method, which evaluates cocrystal formation potential through parameters like polarity, molecular shape and size, and dipole moment.[13,14] Multicomponent crystal formation can be achieved using various methods, including solvent evaporation, solvent drop grinding, solid-state grinding, and melting.[15,16,17] In this study, N-methyl-D-glucamine (meglumine) was selected as a coformer for etoricoxib due to its biocompatibility and known capacity to improve aqueous solubility in salt or crystal complexes. Using a solvent drop grinding method, we aimed to prepare and characterize an etoricoxib–meglumine multicomponent crystal and evaluate its impact on solubility and dissolution performance. While previous studies have explored multicomponent crystals for other NSAIDs, limited data exist for etoricoxib–meglumine systems, representing a notable gap in the current literature. Addressing the formulation challenges of poorly soluble drugs such as etoricoxib contributes directly to Sustainable Development Goal (SDG) 3 – Good Health and Well-Being, by improving drug accessibility, efficacy, and patient outcomes through more effective oral delivery systems.

EXPERIMENTAL

Materials

Etoricoxib was obtained from PT Metrochem API Private Limited, Indonesia. Meglumine was purchased from Sigma-Aldrich (USA). All solvents and chemicals used in the study were of analytical grade and did not require further purification.

Preparation of Multicomponent Crystal Etoricoxib and Meglumine

The multicomponent crystals of etoricoxib and meglumine were prepared using the solvent drop grinding technique. Equimolar amounts of both components were ground together in a mortar as three drops of ethanol were gradually added during the process. The grinding continued for 10 minutes until the ethanol evaporated completely. The resulting multicomponent crystals were stored at room temperature for 24 hours and subsequently placed in a desiccator for further characterization.

Differential Scanning Calorimetry (DSC) Analysis

The thermodynamic properties of the multicomponent crystal, etoricoxib, and N-methyl-D-glucamine were analyzed using a differential scanning calorimeter (DSC; SETARAM Type EVO-131, Lyon, France), calibrated with indium. Approximately 5 mg of each sample was placed in an aluminum pan and heated from 50°C to 250°C at a consistent rate of 10°C per minute.

Powder X-Ray Diffraction (PXRD) Analysis

PXRD measurements were carried out at ambient temperature using a PANalytical PW 30/40 diffractometer (The Netherlands). The diffractograms were obtained within a 2θ range of 5° to 40° under the following operating conditions: copper (Cu) metal target, Kα filter, 45 kV voltage, and 40 mA current.

Fourier Transform Infrared (FT-IR) Spectroscopy Analysis

Molecular interactions were examined using a Perkin Elmer FT-IR spectrophotometer (USA). The samples were prepared by mixing with dry potassium bromide in a 1:100 weight ratio and compressing the mixture into pellets. Absorption spectra were recorded over a wavenumber range of 4000 cm^{-1} to 600 cm^{-1}. The analysis included intact etoricoxib, intact N-methyl-D-glucamine, and the multicomponent crystals.

Scanning Electron Microscopy (SEM) Analysis

Powder samples were placed on an aluminum sample holder and coated with a 10 nm layer of gold. The samples were then observed under various magnifications using a Scanning Electron Microscope (SEM). The voltage was set to 20 kV, and the current was maintained at 12 mA.

Solubility Test

Saturated solubility testing of etoricoxib was conducted in CO_2-free distilled water at room temperature utilizing an orbital shaker. Excess drug was added to 100 mL of the medium, stirred for 48 hours, and then filtered using standard filter paper. The etoricoxib concentration in the filtrate was measured at 234 nm using a Genesys 10S UV-Vis spectrophotometer (Madison, WI, USA).

Dissolution Rate Profile

An amount of powder equivalent to 100 mg of etoricoxib was subjected to dissolution testing using a Type II dissolution apparatus (paddle method) (Hanson SR8 Plus, USA). The dissolution medium consisted of 900 mL of phosphate buffer at pH 7. The dissolution experiment was maintained at 37°C with a paddle rotation speed of 100 rpm. Aliquots of 5 mL were collected at 5, 15, 30, and 45 minutes, with each withdrawal replaced by an equal volume of fresh medium maintained at the same temperature to preserve the total volume. Each sample was filtered using a 0.45 µm pore size Whatman membrane filter and analyzed using a UV-Visible spectrophotometer at the maximum wavelength of 234 nm.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry (DSC) analysis

DSC serves as a rapid and reliable method to identify the formation of multicomponent crystalline phases arising from interactions between solid constituents.[17,18] The DSC thermograms of intact etoricoxib, intact meglumine, and the multicomponent crystal are presented in **Fig.-1**.

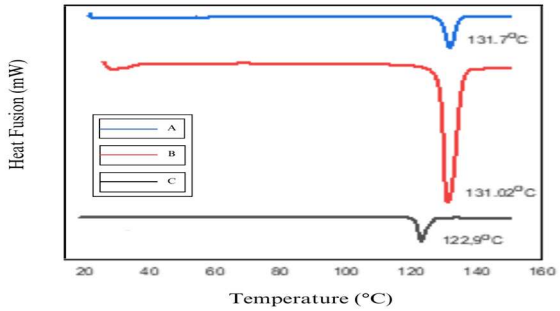

Fig.-1: DSC Thermograms of (A) Etoricoxib, (B) Meglumine, and (C) the Multicomponent Crystal of Etoricoxib-Meglumine (1:1 Molar Ratio)

The DSC thermogram of Intact etoricoxib exhibited a sharp endothermic peak at 131.7°C, corresponding to its melting point, which represents its most stable crystalline form, consistent with previous studies[6]. Intact meglumine exhibited an endothermic peak at 131.02°C, corresponding to its melting point. In contrast, the DSC thermogram of the multicomponent crystal showed a unique and sharp single endothermic peak at 122.9°C, representing the melting point of the newly formed multicomponent crystal of etoricoxib and meglumine. This melting point is lower than those of the individual components, indicating the formation of a new crystalline phase. Thermodynamically, the melting point of a crystalline phase indicates the strength of intermolecular interactions and the lattice energy within its crystal structure. These properties significantly influence the solubility and dissolution rate of the crystalline solid in aqueous environments.[18,19]

Powder X-Ray Diffraction (PXRD) analysis

PXRD is an essential method for analyzing solid-state properties, such as crystal phases, amorphization, and solid-state reaction behaviors. The formation of multicomponent crystals, including cocrystals or salts, is confirmed when the PXRD patterns exhibit distinctive diffraction peaks which are absent in the original components.

The PXRD patterns of Intact etoricoxib, Intact meglumine, and the multicomponent crystal of etoricoxib and meglumine (1:1 molar ratio) are presented in **Fig.-2**. The diffraction profile of pure etoricoxib displayed well-defined and sharp peaks at 2θ angles of 15.48°, 16.55°, 18.11°, and 22.73°, indicating a highly crystalline structure consistent with Form I etoricoxib. In contrast, intact meglumine displayed characteristic diffraction peaks at 2θ values of 12.30°, 17.10°, 17.89°, 21.89°, and 23.90°.

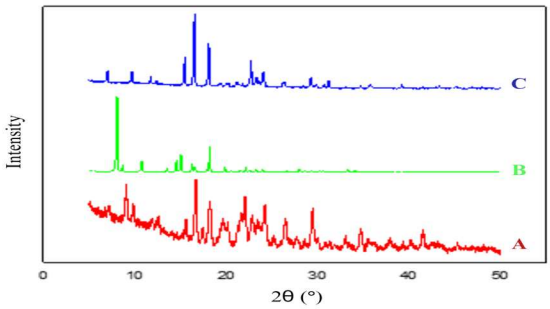

Fig.-1: Powder X-Ray Diffraction Patterns of (A) Etoricoxib, (B) Meglumine, and (C) the Multicomponent Crystal of Etoricoxib-Meglumine (1:1 molar ratio)

The PXRD pattern of the multicomponent crystal revealed a unique set of diffraction peaks at 2θ values of 9.08°, 9.86°, 12.60°, 15.71°, 16.70°, 17.53°, 19.65°, 20.20°, 21.26°, 21.69°, 22.10°, 22.87°, 24.17°, 24.34°, 26.52°, 29.35°, 29.48°, 34.67°, and 41.55°, confirming the formation of a new multicomponent crystalline phase.[8,16] Differences in these patterns suggest differences in internal crystal structures, which may indicate polymorphism.[20] Multicomponent crystals are typically categorized into two types: salts and cocrystals. Salt formation involves proton transfer between the active pharmaceutical ingredient (API) and the coformer, whereas cocrystals are characterized by the absence of such proton transfer.

Fourier Transform Infrared (FT-IR) Spectroscopy Analysis

The FTIR spectra in **Fig.-3** confirm that no new peaks are observed in the multicomponent crystal of etoricoxib and meglumine compared to the intact components. This indicates that no new functional groups are formed during the co-crystallization process, implying the interactions are physical rather than chemical. The preservation of key functional groups, such as carbonyl and sulfonyl for etoricoxib and hydroxyl and amine for meglumine, supports the formation of the crystal through non-covalent interactions. These results validate the structural stability of the drug and coformer while enhancing physicochemical properties.[4]

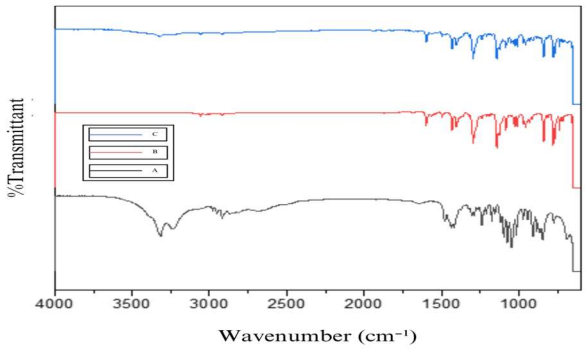

Fig.-2: Infrared Spectra (FTIR) of (A) Meglumine, (B) Etoricoxib, and (C) the Multicomponent Crystal of Etoricoxib-Meglumine (1:1 molar ratio)

Scanning Electron Microscopy (SEM) analysis

The morphology of the multicomponent crystal, shown in Fig.-4, reveals distinct differences compared to intact etoricoxib. SEM images demonstrate that the multicomponent crystals are shorter and more irregular in shape, contrasting with the elongated, well-defined crystals of Intact etoricoxib. This morphological change suggests successful formation of a new crystalline phase, which likely contributes to the improved dissolution by increasing the surface area.[21,22]

Solubility Test

The enhanced solubility and dissolution rates in multicomponent crystal phases can be attributed to several mechanisms. One key factor is the alteration of the solid phase's thermodynamic properties, particularly the melting point. A lower melting point, relative to the original compound, indicates reduced lattice energy within the crystal structure. This reduction weakens intermolecular interactions, thereby improving solubility and accelerating dissolution rates.[11,16]

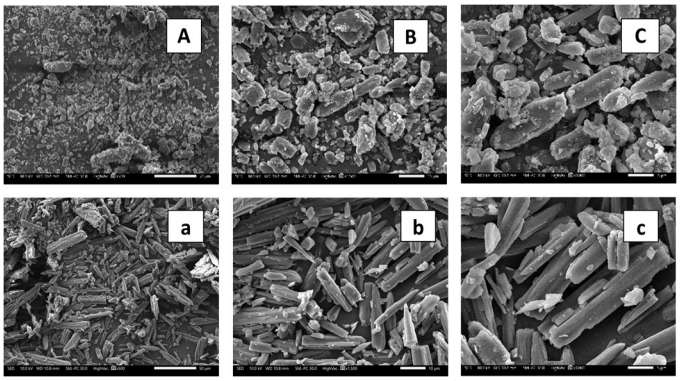

Fig.-3: Morphology of the Multicomponent Crystal of Etoricoxib-Meglumine (1:1 molar ratio) at 500x Magnification (A), 1500x Magnification (B), and 3000x Magnification (C). Morphology of Intact Etoricoxib at 500x Magnification (a), 1500x Magnification (b), and 3000x Magnification (c)

Table-1: Solubility Data

Materials	Solubility (mg/100ml)	± SD
Intact etoricoxib	4.55	± 0.144
Multicomponent crystal of etoricoxib-meglumine	23.44	± 2.295

In the case of the etoricoxib–meglumine multicomponent crystal, the enhanced solubility is attributed to the formation of a salt-type crystal structure. This form exhibits greater affinity for water, thereby improving the wetting and dispersion of etoricoxib within the crystal lattice. Consequently, this interaction weakens the intermolecular forces within the crystal lattice. The reduced strength of molecular interactions allows the tightly packed active pharmaceutical ingredient molecules to dissociate more easily, increasing their dissolution rate.[10,23,24]

Dissolution Rate Profile

The findings demonstrate that the multicomponent crystal of etoricoxib and meglumine (1:1 molar ratio) significantly enhances the solubility and dissolution behavior of etoricoxib. The solubility of the multicomponent crystal increased by approximately 5.5 times compared to pure etoricoxib, which corresponded with a marked improvement in its dissolution rate (Fig.-5). According to the Noyes-Whitney principle, a solid's dissolution rate is directly linked to its solubility, highlighting the relevance of the observed improvements.[21]

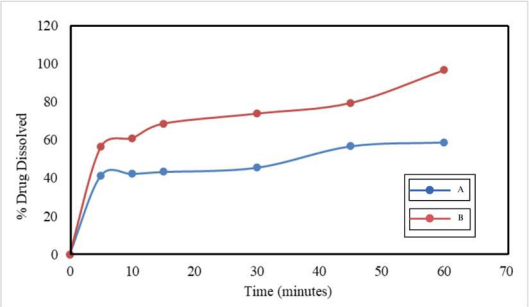

Fig.-4: Dissolution Profiles of (A) Intact Etoricoxib and (B) the Multicomponent Crystal of Etoricoxib-Meglumine

The multicomponent crystal demonstrates a significantly faster dissolution profile compared to intact etoricoxib. Within 60 minutes, 96.54% of etoricoxib from the multicomponent crystal dissolved (red line), while only 58.78% of Intact etoricoxib dissolved (blue line). This enhancement is also attributed to the solubilizing effect of meglumine in the microenvironment, which improves the wetting of etoricoxib in aqueous conditions.[25]

CONCLUSION

This study successfully demonstrated that forming a multicomponent crystal of etoricoxib with meglumine significantly enhances the drug's solubility and dissolution rate. Comprehensive solid-state characterization

using DSC, PXRD, FT-IR, and SEM confirmed the formation of a new crystalline phase with altered thermal and structural properties. These modifications, particularly the salt-type interaction between etoricoxib and meglumine, led to a 5.5-fold increase in solubility and a marked improvement in dissolution performance. The findings support the use of crystal engineering as a viable strategy for improving the biopharmaceutical properties of poorly soluble drugs without altering their chemical identity. This work aligns with Sustainable Development Goal 3 – Good Health and Well-Being by contributing to the development of more effective and accessible pharmaceutical formulations that can enhance therapeutic outcomes.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest regarding the publication of this article.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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