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Research Paper

Enhancing the Solubility and Dissolution Rate of Tenoxicam through Co-Amorphous Formation with Meglumine by a Solvent Dropped Grinding Method

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Abstract
Tenoxicam is a non-steroidal anti-inflammatory drug (NSAID), one of the oxicam group. It is categorized as Biopharmaceutical Classification System class II, as its low solubility and high permeability. The aims of this research were to enhance the solubility and dissolution rate of tenoxicam by its modification into a co-amorphous phase with meglumine at a molar 1:1 ratio. The co-amorphous form of tenoxicam-meglumine was prepared by a solvent drop grinding method, and characterized by thermal analysis using differential scanning calorimetry (DSC), solid phase by powder X-ray diffraction (PXRD), identification of functional group by Fourier-transform infrared (FT-IR) spectroscopy, and morphology by polarized light microscopy (PLM) and scanning electron microscopy (SEM). The solubility test was conducted in water, whereas the dissolution test was performed in 0.1 N HCl solution and water. The DSC thermogram demonstrated a decrease in the endothermic peak of the co-amorphous tenoxicam-meglumine. The PXRD diffractogram revealed a reduction in the peak intensity of the X-ray diffraction, which formed a halo pattern. The FT-IR spectroscopy analysis indicated the formation of the co-amorphous system. The co-amorphous of tenoxicam-meglumine solubility's increased by 42.71-fold as compared to intact tenoxicam. The co-amorphous tenoxicam-meglumine exhibited a dissolution rate of 92.71% and 100% in 0.1 N HCl and distilled water, respectively, after 60 minutes, and resulting in separate increases in dissolution efficiency by 3.05 and 9.12-times in 0.1 N HCl and distilled water. In summary, the formation of the co-amorphous phase of tenoxicam and meglumine successfully enhanced the solubility and dissolution of tenoxicam.

Keywords
Tenoxicam, Meglumine, Co-Amorphous, Solubility, Dissolution Rate

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1. INTRODUCTION

Tenoxicam is a one of non-steroidal anti-inflammatory drug (NSAID) that derived from phenothiazine and belongs to the oxicam group, drugs that are commonly used in the treatment of osteoarthritis, gout, rheumatoid arthritis, ankylosing spondylitis, and various rheumatic conditions (Todd and Clissold, 1991). The mechanism of action of tenoxicam is inhibition of cyclooxygenase enzymes and prostaglandins that impede the formation of metalloproteinase enzymes, which can induce cartilage damage (Syggelos et al., 2007; Todd and Clissold, 1991).

Based on the Biopharmaceutical Classification System, teno xicam is categorized as a class II enzyme with low solubility and high permeability (Xie et al., 2022). The solubility of tenoxicam is approximately 14 mg/L in water, with dissociation constant (pKa) values of 1.1 and 5.3 (Bolla et al., 2013; Olkkola et al., 1994; Patel et al., 2012). As a weak acid, molecules of tenoxicam are primarily nonpolar and cannot readily penetrate water's lattice structure, thus it has low solubility in water (Manal and Manal, 2009). Generally, a drug with low solubility in water is problematic during dissolution, which becomes the rate-limiting step for absorption process in gastrointentinal tract (Khadka et al., 2014). Therefore, drugs with low solubility but high permeability, such as tenoxicam, can disrupt the drug absorption process (Abdulbaqi et al., 2021).

Various techniques have been employed to enhance the solubility of tenoxicam including particle size reduction (Abdulbaqi et al., 2021), amorphization through solid dispersion (Umar et al., 2022), inclusion complex formation with cyclodextrins (Suta et al., 2012), solubilization using polymeric micelles (Hussein and Maraie, 2022), and the formation of multi-component crystals with glycolic acid, α-ketoglutaric acid, succinic acid, maleic acid, malonic acid, oxalic acid, salicylic acid, saccharin, pyrogallol, catechol, resorcinol, salicylic acid, and benzoic acid (Bolla et al., 2013; Patel et al., 2012). Manipulation of the amorphous phase of a drug is one of the

most effective approaches for the refinement of drug solubility and dissolution rate (Lutfiyah et al., 2022; Shi et al., 2019). If a drug has high solubility and a high dissolution rate, it leads to an enhancement in bioavailability (Lutfiyah et al., 2022).

A co-amorphous phase consists of active pharmaceutical ingredients with one or more coformers that frequently have lower molecular weights. The use of coformers in a co-amorpho us formation can enhance physical stability, solubility, and the dissolution rate of the co-amorphous form as compared to the amorphous phase (Dengale et al., 2016). Generally, co-amorphous phases (prepared by stoichiometric ratio), have strong hydrogen bonds between the active ingredient and co-formers, which markedly improves drug solubility and dissolution rates as compared to the crystalline phase (Wicaksono et al., 2022). Several studies have been conducted on the formation of co-amorphous phases and enhancement of solubility including indomethacin-nicotinamide (Fael and Demirel, 2021), atorvastatin calcium-maleic acid (Wicaksono et al., 2022), simvastatin-nifedipine (Martínez-Jiménez et al., 2018), and indomethacin-naproxen (Wang et al., 2024).

In this study, a co-amorphous phase of tenoxicam was prepared with meglumine. Meglumine, or N-methyl-D-glucamine, is an organic base composed of D-glucose and methylamine, used as a pH regulator, and improves the solubility of other substances (Sheskey et al., 2020; Zaini et al., 2019). Moreover, meglumine readily dissolves in water with a solubility of 1 g/mL and is a safe, non-toxic, and inert excipient (Zaini et al., 2019). The melting point of meglumine is 128-132°C with a pKa of 9.5 (Sheskey et al., 2020). The co-amorphous tenoxicam-meglumine was prepared using a solvent dropped grinding method, followed by solid state characterization using thermal analysis by differential scanning calorimetry (DSC), solid phase by powder X-ray diffraction (PXRD), identification of functional groups by Fourier-transform infrared (FT-IR) spectroscopy, morphology by polarized light microcopy (PLM) and scanning electron microscopy (SEM) and solubility and dissolution tests.

2. EXPERIMENTAL SECTION

2.1 Materials

Tenoxicam (TCI, Japan), meglumine (Sigma-Aldrich, USA), analytical grade ethanol (Merck, Germany) and HCl (Merck) were used without further purification, and distilled water.

2.2 Methods

2.2.1 Preparation of Co-Amorphous Tenoxicam and Meglumine

The preparation of a co-amorphous form of tenoxicam and meglumine was formulated at a molar 1:1 ratio. Tenoxicam (0.337 grams) and meglumine (0.195 grams) were ground continuously for 10 minutes, and 2 drops of methanol were added during the process (Hasanah et al., 2024). The co-amorph of tenoxicam and meglumine produced was kept in an air-tight container and stored in a desiccator.

2.2.2 Preparation of a Physical Mixture of Tenoxicam and Meglumine

A simple physical mixture of tenoxicam and meglumine was prepared, at the same amount as its co-amorph form, in which both materials were mixed physically until homogeneity was achieved without using any solvent or employing the grinding process. The mixture was then kept in an air-tight container in a desiccator.

2.2.3 Solid State Characterizations

For the analyses listed below, the samples processed included tenoxicam, meglumine, the co-amorphous form, and the physical mixture, unless otherwise specified.

2.2.4 Powder X-Ray Diffraction Analysis

The PXRD analysis was conducted using a Rigaku RINT-2500 diffractometer (Tokyo, Japan). The measuring conditions were set at 40 kV voltage, 40 mA current, and analysis occurred in the 2-theta range of 5–50°C at room temperature. Prior analysis the instrument was conditioned using Cu metal target and Kα filter (Hasanah et al., 2024).

2.2.5 Differential Scanning Calorimetry Analysis

The thermal analysis of the samples were characterized using a calibrated Setaram DSC 131 Evo (France). About 3 mg of each sample were placed in an aluminum pan and instrument was set at a temperature range of 30-300°C with heating rate of 10°C/min (Hasanah et al., 2024).

2.2.6 Fourier Transform – Infrared Spectroscopy Analysis

Each sample was prepared by grinding it with KBr at a 1:9 weight ratio. The resulting powder was then evenly distributed on the attenuated total reflectance surface. Subsequently, the sample was compressed until a transparent layer was formed. The spectra were acquired by scanning the samples using FT-IR spectroscopic analysis (Thermo Scientific, USA) at the wavenumber range of 4000-400 cm^{-1} (Hasanah et al., 2024).

2.2.7 Polarization Light Microscopy Analysis

A Zeiss Axioscope 5 (Baden-Württemberg, Germany) was employed to visually examine each sample under polarized light at a magnification of 10× (Fitriani et al., 2023).

2.2.8 Scanning Electron Microscopy Analysis

The morphology of tenoxicam and co- amorphous of tenoxica m-meglumine was carried out using scanning electron microscope (Carl Zeiss EVO 10, Germany). A small amount of each sample was dispersed in the sample holder and the instrument was set at 7 kV.

2.2.9 Solubility Evaluation

The solubility tests for intact tenoxicam, the physical mixture and the co-amorphous form of tenoxicam-meglumine were performed in CO_2-free distilled water. An excess quantity of each sample was added into 10 mL of CO_2-free distilled water and sonicated for 30 minutes. Before measurement, the

samples were filtered using 0.45-μm Whatman filter paper. The amount of tenoxicam dissolved was determined using a UV-Vis spectrophotometer (Shimadzu UV-1700, Japan) at a wavelength of 368 nm (Hasanah et al., 2024).

2.2.10 Dissolution Rate Test

A dissolution rate test of intact tenoxicam, the physical mixture, and the co-amorphous form of tenoxicam-meglumine was conducted using a type 2 dissolution apparatus at 37 ± 0.5°C with a stirring speed of 50 rpm. Two different dissolution media were utilized in this test, 0.1 HCl and CO_2-free distilled water. A sample equivalent to 20 mg of tenoxicam was introduced into the media, and samples were collected at 5, 10, 15, 30, 45, and 60 minutes, followed by filtration of each using 0.45-μm Whatman filter paper. A UV-Vis spectrophotometer (Shimadzu UV-1700, Japan) was used to measure the amount of dissolved tenoxicam at wavelengths of 361 nm and 368 nm, respectively (Hasanah et al., 2024).

3. RESULT AND DISCUSSION

In this study, PXRD analysis was performed to confirm the crystalline phase intact material and the formation of amorphous structures through diffractograms result. As seen in Figure 1 and Table 1, diffractogram of tenoxicam presented specific peak at 2θ of 14.455°, 16.766°, 20.970°, 21.807°, 23.328°, 25.332°, 28.284°, and 29.327°. Meglumine also exhibit particular peak at 2θ of 8.928°, 17.153°, 17.283°, 17.924°, 19.484°, and 21.940°. These result amplify that both tenoxicam and meglumine are crystalline phase. The intensity peaks of the physical mixture are exhibited by the superposition of the two intact components, tenoxicam and meglumine, and do not present a new peak or a halo pattern. Meanwhile, the formation of a co-amorphous form of tenoxicam with meglumine was observed in the diffractogram, which formed an amorphous solid represented by the disappearance of crystalline peaks of the compound, which results in diffracted halo patterns in the diffractogram (Fael and Demirel, 2021). Generally, a decrease in the peak intensity indicates a reduction in the degree of crystallinity, which can also lead to an enhancement in the solubility of tenoxicam (Fael and Demirel, 2021; Manal and Manal, 2009).

Thermal analysis is a technique for measuring changes in the physochemical properties of a sample as a response to temperature changes which can be determined by DSC analysis (Zaini et al., 2016). As illustrated in Figure 2, the DSC thermogram indicates that tenoxicam exhibited an endothermic peak (absorbed heat) and followed by an exothermic peak (release heat). In contrast, the co-amorphous phase of tenoxicam-meglumine displayed an exothermic peak followed by an endothermic peak. It was also observed that meglumine had a lower endothermic peak as compared to tenoxicam. The decline in melting point of the co-amorphous form of tenoxicam-meglumine, as demonstrated by the endothermic peak, also indicated a reduction in the crystallinity of the co-amorphous form as described in the x-ray diffraction results.

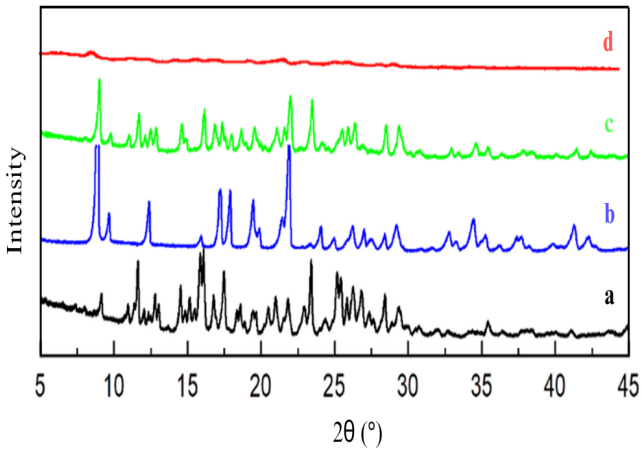

Figure 1. Diffractogram Overlay of (a) Tenoxicam, (b) Meglumine, (c) the Physical Mixture of Tenoxicam and Meglumine and (d) Co-Amorphous Tenoxicam-Meglumine

Table 1. Peak Intensity of Tenoxicam, Meglumine, Physical Mixture and Co-Amorphous of Tenoxicam -Meglumine

2θ(°)	Peak Intensity			
	Tenoxicam	Meglumine	Physical Mixture	Co-Amorphous
8.928	-	20531.16	1301.09	-
14.455	1413.68	-	886.13	-
15.9502	1507.33	862.86	1008.23	-
16.7663	1411.1	-	-	-
17.1533	-	4868.26	403.41	-
17.2838	-	4607.6	-	-
17.924	-	4440.03	-	-
19.4843	-	4183.83	865.39	-
20.9705	1216.32	-	669.48	-
21.8077	1529.45	-	808.53	-
21.9405	-	9578.31	-	-
23.3286	3395.21	-	-	-
25.3323	1464.88	-	607.85	-
28.284	1086.93	-	-	-
29.3273	1297.83	-	-	-

Table 2. Thermogram Data of Tenoxicam, Meglumine, and Co-Amorphous

Samples	Melting Point (°C)
Tenoxicam	223.29
Meglumine	132.38
Co-amorphous	184.91

A decrease in the melting point of tenoxicam was observed when it was transformed into a co-amorphous state using the solvent drop grinding method. The melting point declined to approximately 40°C, as presented in Table 2. The alter-

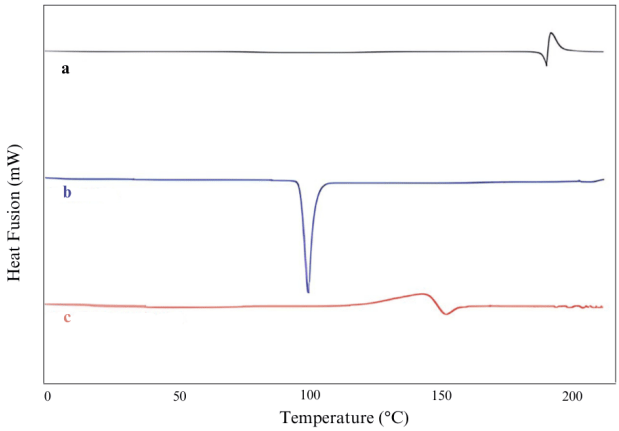

Figure 2. Thermogram Overlay of (a) Tenoxicam, (b) Meglumine and (c) Co-Amorphous Tenoxicam-Meglumine

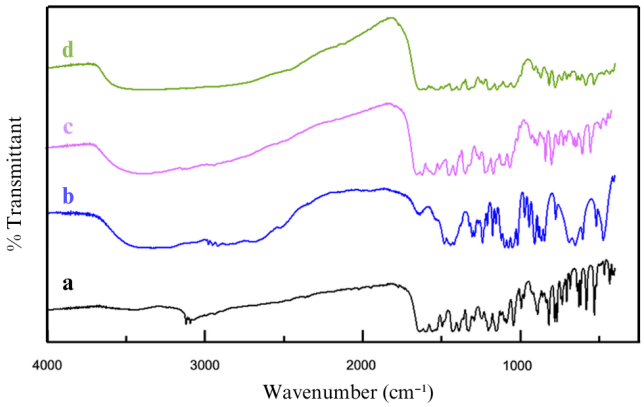

Figure 3. FTIR Spectra Overlay of (a) Tenoxicam, (b) Meglumine, (c) the Physical Mixture of Tenoxicam and Meglumine, and (d) Co-Amorphous Tenoxicam-Meglumine

ation in the endothermic peak indicates an interaction between tenoxicam and meglumine as a coformer, resulting in a lower melting point than that of intact tenoxicam. This reduction in the melting point also signified a reduction in the degree of crystallinity which is associated with an increase in the solubility of tenoxicam (Manal and Manal, 2009; Wairkar and Gaud, 2016).

The infrared analysis was conducted to confirm the interaction between the drug and the coformer used, which support the solubility results (Febriyenti et al., 2020). The IR spectrum findings revealed wavelength shifts for tenoxicam, the physical mixture, and co-amorphous forms, wherein these shifts remain within the range of the same functional groups. This outcome implies that there was no chemical interaction occurring between tenoxicam and meglumine. In the stretching band, it was observed that both the physical mixture and co-amorphous forms exhibited hydrogen bonding. Through intermolecular hydrogen bonding, an enhancement in solubility and dissolution is facilitated and may be attributed to the stabilization of the amorphous form of the drug and coformer (Chavan et al., 2016). The overlay of the FT-IR spectra for tenoxicam, physical mixture, and co-amorphous forms are depicted in Figure 3.

Table 3 presents the wavenumber stretching observed in the physical mixture and co-amorphous forms of tenoxicam-meglumine. The infrared spectra reveal the characterization of tenoxicam at wavenumbers 3448 cm^{-1} ($-OH^-$), 1152 cm^{-1} (S=O), 1559 cm^{-1} (C−N), and 1323 cm^{-1} (C−H). Changes in the wavenumber occurred in the co-amorphous form of tenoxicam and meglumine, as well as in the physical mixture, particularly in the $-OH^-$ region, where values were 3331 cm^{-1} and 3354 cm^{-1}, respectively. For the S=O group, there was an alteration in the wavenumber for the co-amorphous form of tenoxicam and meglumine to 1247 cm^{-1}. The shifts in wavenumber remained within the same functional groups, indicating the interaction between tenoxicam and meglumine.

The polarization microscopy analysis revealed differences in the morphology between the physical mixture and the co-amorphous form of tenoxicam-meglumine as observed in Figure 4. In the physical mixture, tenoxicam and meglumine were separate and dispersed from each other. In contrast, the co-amorphous form of tenoxicam and meglumine, prepared with the solvent drop grinding method, are present in smaller particle sizes due to the milling process. In addition to the size reduction, tenoxicam and meglumine appeared to be likely integrated and not dispersed.

Another foremost morphology analysis for solid state characterization is scanning electron microscopy (SEM) analysis, which support to view surface details with high resolution. The magnification of this instrument depends on the type and quality of the sample being observed. The morphology of tenoxicam and co-amorphous of tenoxicam-meglumine is seen in Figure 5. Tenoxicam (Figure 5a) shows almost spherical shape and tend to agglomerate which also seen in another study (Albadri et al., 2021). Meanwhile, Figure 5b presents irregular shape which indicate that tenoxicam and meglumine was succeed to fuse in the co-amorphous phase, which also exhibit in another study (Liu et al., 2021).

The solubility test results, as displayed in Figure 6, present an enhancement of the solubility of tenoxicam in the physical mixture by 5.401 times and in the co-amorphous form of tenoxicam-meglumine by 42.715 times. Several factors likely influenced the solubility enhancement. In this study, the increased solubility of tenoxicam in the co-amorphous form was attributed to the reduction in the crystallinity of tenoxicam mixed with meglumine as depicted in the PXRD results. The decrease in diffraction peak intensity signified a reduction in crystallinity that improved the solubility (Manal and Manal, 2009). Moreover, the increase in solubility of tenoxicam is supported by DSC results confirming a shift in the endothermic

Table 3. Some Functional Group's Wave Number Observed in FTIR Analysis for Tenoxicam, Meglumine, the Physical Mixture and the Co-Amorphous

Functional Groups	Wave number (cm^{-1})			
	Tenoxicam	Meglumine	Physical Mixture	Co-amorphous
$-OH^-$	3448	3330	3331	3354
S=O	1152	-	1146	1247
C=O	1636	-	1636	1636
C−N	1559	1492	1528	1523
C−H	1327	1323	1327	1326

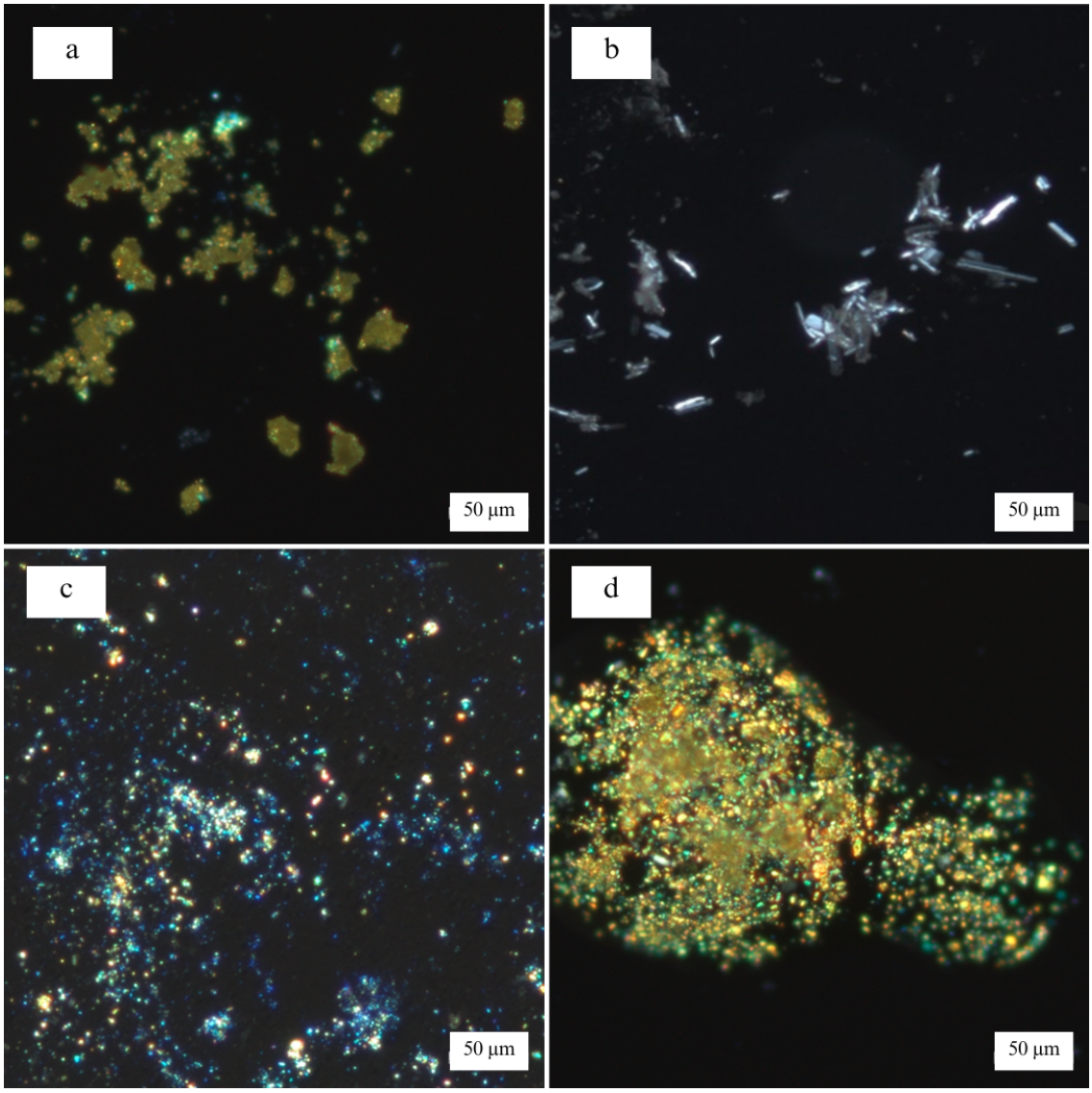

Figure 4. Polarized Microscope Images for (a) Tenoxicam, (b) Meglumine, (c) the Physical Mixture and (d) Co-Amorphous Tenoxicam-Meglumine (Magnification 10×, scale 50μm)

peak, and a reduction in the crystallinity of the co-amorphous form of tenoxicam and meglumine. Co-amorphous tenoxicam and meglumine exhibit hydrogen bonding between molecules, as evident from the FTIR analysis. The hydrogen bonding in the co-amorphous tenoxicam and meglumine enhanced solubility and dissolution rate through the stabilization of the amorphous form of the drug and conformer (Chavan et al., 2016).

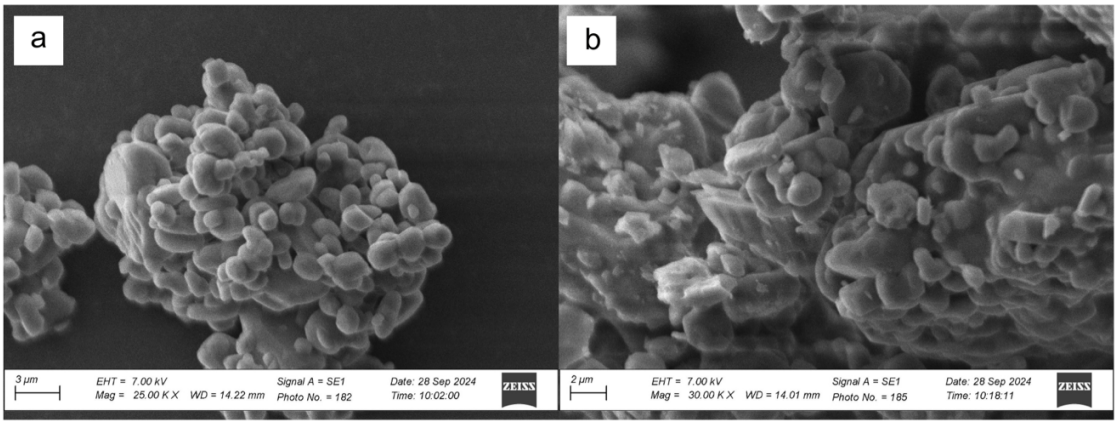

Figure 5. SEM Morphology of (a) Tenoxicam and (b) Co-amorphous Tenoxicam-Meglumine)

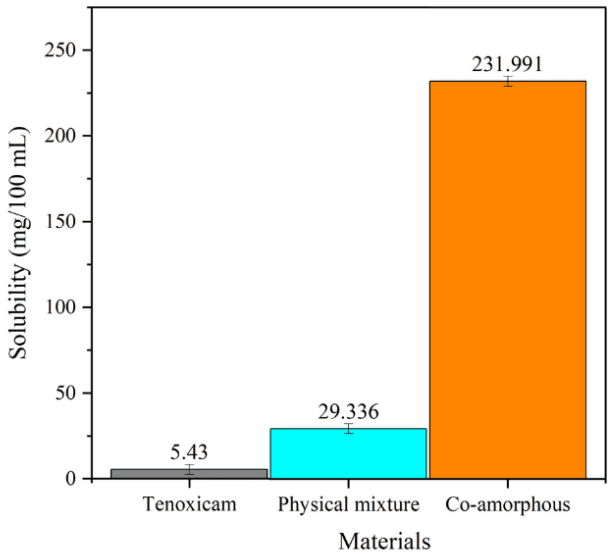

Figure 6. Solubility Data for Tenoxicam, Physical Mixture of Tenoxicam-Meglumine and the Co-Amorphous Tenoxicam-Meglumine in CO_2-Free Distilled Water

The solubility of tenoxicam in the co-amorphous form, prepared using the solvent drop grinding method, was significantly greater ($p < 0.05$) as compared to the physical mixture. This difference in solubility is attributed to a higher degree of crystallinity in the physical mixture as compared to the co-amorphous form, as established in the diffractogram. The variation in crystallinity resulted in the improvement of solubility between the physical mixture and the co-amorphous form. The noteworthy increase in solubility of tenoxicam in the co-amorphous form, by 42.715 times, surpasses the improvements observed for other forms, including multicomponent crystals with benzoic acid (0.4 times), catechol (5.8 times), resorcinol (10.1 times), pyrogallol (7.5 times), and solid dispersion with skimmed milk, which increases solubility by 23 times (Bolla et al., 2013; Topaloglu et al., 1999).

Strongly alkaline conditions cause the degradation of tenoxicam; therefore, our dissolution rate study was conducted in HCl solution and distilled water. Based on the dissolution rate study results represented in Figure 7, both the physical mixture and the co-amorphous form of tenoxicam-meglumine demonstrated a significant increase ($p < 0.05$) as compared to intact tenoxicam in 0.1 N HCl. The amount of tenoxicam dissolved after one hour were 44.172% ± 1.59, 64.642% ± 0.15, and 92.709% ± 0.84, for the intact tenoxicam, the physical mixture, and the co-amorphous form respectively. The increased percentage of dissolved tenoxicam in the physical mixture and the co-amorphous led to a marked enhancement in dissolution efficiency by 2.08 and 3.05 times, respectively. The escalation noted for the dissolved content of co-amorphous tenoxicam is in accordance with the solubility test results (Manal and Manal, 2009; Wairkar and Gaud, 2016).

In addition, the dissolution rate study results also indicated that the physical mixture and the co-amorphous form were also improved as compared to the intact tenoxicam in the dissolution medium of CO_2-free distilled water. The dissolved percentages of tenoxicam after 60 minutes for intact tenoxicam, the physical mixture, and the co-amorphous form of tenoxicam-meglumine were 31.699% ± 1.46, 62.507% ± 2.00, and 100% ± 0.87, respectively. The significant elevations in dissolution efficiency for both the physical mixture and the co-amorphous form of tenoxicam-meglumine prepared using the solvent drop grinding method were 5.56 and 9.12 times, respectively. This amount of tenoxicam dissolved in water was greater as compared to that dissolved in HCl medium. This dissolution result was as expected, based on the solubility test results (Manal and Manal, 2009; Wairkar and Gaud, 2016). Moreover, the percentage of tenoxicam dissolved in both types of dissolution media depicted a notable enhancement in the physical mixture and the co-amorph forms, as supported by the thermogram and diffractogram data. The role of meglumine as the coformer which has high solubility in water also

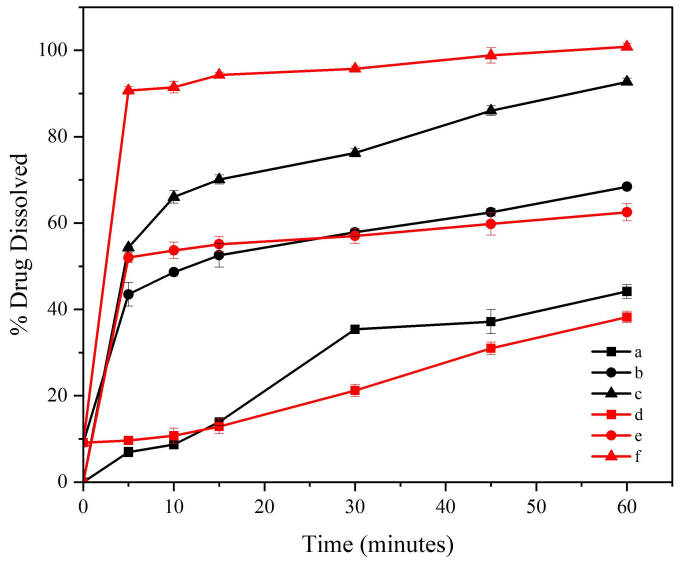

Figure 7. Dissolution Profile of (a) Tenoxicam, (b) Physical Mixture, (c) Co-Amorphous in HCl 0.1 N and (d) Tenoxicam, (e) Physical Mixture, (f) Co-Amorphous in Distilled Water

contributed to the positive dissolution results.

4. CONCLUSIONS

Tenoxicam and meglumine were successfully prepared into a co-amorphous phase in a 1:1 molar ratio using solvent drop grinding methodology. This co-amorphous form resulted in a 42.715-fold augmentation of tenoxicam solubility in water. Additionally, tenoxicam dissolution efficiency was significantly enhanced by 3.05- and 9.12-times in 0.1 N HCl and CO_2-free distilled water, respectively.

5. ACKNOWLEDGMENT

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