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Original Article

TENOXICAM-TROMETHAMINE MULTICOMPONENT CRYSTAL: PHYSICOCHEMICAL CHARACTERISTICS, SOLUBILITY, AND DISSOLUTION EVALUATION

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ABSTRACT

Objective: Tenoxicam is classified as a nonsteroidal anti-inflammatory drug employed for managing musculoskeletal conditions. However, its effectiveness is obstructed by its restricted ability to dissolve in water. This investigation aims to create a multicomponent crystal involving tenoxicam and tromethamine to augment tenoxicam's solubility and dissolution rate.

Methods: Using the solvent drop grinding technique, the multicomponent crystal was synthesized by combining tenoxicam and tromethamine in equimolar proportions. The physicochemical properties of multicomponent crystal were assessed through powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and FT-IR spectroscopy. Solubility test and dissolution rate profile were conducted to evaluate the effectiveness of multicomponent crystal formation in compared to intact tenoxicam. The solubility test occurred in CO_2-free distilled water over 48 h and was quantified using UV spectrophotometry at 368 nm. Dissolution rate profiles were conducted using a USP type II dissolution apparatus in HCl 0.1 N, and CO_2-free distilled water as the dissolution media.

Results: The multicomponent crystal displayed distinctive characteristics in the diffractogram, including altered melting points, and shifts in the FT-IR spectrum peaks. Within the multicomponent crystal system, the solubility of tenoxicam exhibited a notable increase, specifically by a factor of 11.130. Moreover, the dissolution efficiency of tenoxicam in HCl 0.1 N solution and CO_2-free distilled water showed substantial enhancements, with respective increases of 2.600-fold and 8.605-fold observed at the 60-minute mark.

Conclusion: In conclusion, the tenoxicam and tromethamine multicomponent crystal formation using a solvent drop grinding technique resulted in a novel crystalline structure, enhancing the solubility and dissolution of tenoxicam both in CO_2-free distilled water and HCl 0.1 N.

Keywords: Tenoxicam, Tromethamine, Multicomponent crystal, Solvent drop grinding, Solubility, Dissolution

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INTRODUCTION

Oxicam group anti-inflammatory drugs are potent and active in managing pain associated with musculoskeletal diseases such as rheumatoid arthritis, osteoarthritis, and other joint conditions [1]. In contrast to numerous other nonsteroidal anti-inflammatory drugs (NSAIDs), tenoxicam presents specific benefits as it can be conveniently taken once a day, and there is no need for dose adjustments in older individuals or those with kidney or liver issues [2]. Although there are advantages to tenoxicam, it poses a challenge for formulation due to its low solubility in water, measuring just 0.072 mg/ml [3].

The solubility of a substance plays a vital role in the dissolution process [4]. Various approaches have been devised to tackle solubility and dissolution-related challenges in pharmaceuticals. These methods entail the alteration of the active drug compound, either physically or chemically [4]. Multiple techniques have been documented to improve tenoxicam's solubility and dissolution rate. These include creating salt [5], loaded to polymeric micelles material [6], solid dispersion formation [7], employing solid deposition [8], and implementing crystal engineering strategies to generate multicomponent crystals [5, 9, 10]. Multicomponent crystals are systems comprising two or more molecules combined into a single crystal phase [11], which can take the form of co-crystals, salts, or solvents [4, 12]. Previously reported multicomponent crystals of tenoxicam include co-crystals with glycolic acid, 4-hydroxybenzoic acid, α-ketoglutaric acid, succinic acid, maleic acid, malonic acid, oxalic acid, salicylic acid, saccharin, catechol, resorcinol, and pyrogallol, as well as salts with piperazine, hydrochloric acid, methane sulfonic acid, and ethanolamine [5, 9, 10].

In this study, we have formed a multicomponent crystal of tenoxicam with tromethamine, a weak base compound that readily dissolves in water with a pKa of 8.07 [13]. Tromethamine, a safe co-former classified as Class II (low toxicity) according to the Handbook of Pharmaceutical Salts Class [14], was chosen due to its prior use in several methods for enhancing solubility, including the formation of salt with indomethacin [15] and the construction of multicomponent crystals with gliclazide [16] and mefenamic acid [13], also the formation of pelubiprofen-tromethamine [17]. The purpose of forming the multicomponent crystal of tenoxicam and tromethamine is to enhance the solubility of tenoxicam and, consequently, improve its dissolution. The resulting multicomponent crystal was characterized through powder X-ray diffraction pattern analysis, thermal analysis using differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy analysis, and solubility and dissolution rate profile.

MATERIALS AND METHODS

Materials

Tenoxicam (TCI, Tokyo, Japan), tromethamine (Merck, Darmstadt, Germany), methanol analytical grade (Merck, Darmstadt, Germany), NaOH (Merck, Darmstadt, Germany), HCl (Merck, Darmstadt, Germany), distilled water.

Multicomponent crystal preparation

The multicomponent crystal of tenoxicam and tromethamine was prepared by the liquid-assisted grinding (LAG) as follows: tenoxicam (337 mg, 1 mmol) and tromethamine (121 mg, 1 mmol), both substances, in a 1:1 stoichiometric ratio, were individually measured and placed in a mortar. They were then meticulously ground with 0.1 ml of methanol for approximately 10 min. For comparison, a physical mixture of tenoxicam and tromethamine was prepared by thoroughly mixing equimolar amounts of powder using a vortex mixer. All sample powder was subsequently placed in a desiccator for storage until it was ready for further analysis.

Physicochemical of solid-state characterization

Solid-state characterization was conducted for at least three samples: intact tenoxicam, tromethamine, and the multicomponent crystal of tenoxicam-tromethamine. X-ray diffraction analysis (PAN analytical MPD PW3040/60 XPert Pro, the Netherlands) was conducted to determine crystallinity, employing Cu Kα radiation at an operational voltage of 40 kV and a current of 40 mA within the 2-theta range of 10–50 degrees. The thermal characteristics of each sample were assessed using DSC (DSC EVO 131, Setaram, France) over the temperature range of 30-250 °C, with a heating rate of 10 °C per minute. FT-IR spectroscopic analysis (Thermo Scientific, USA) was performed to identify the chemical groups present in each sample. This involved preparing a sample-KBr plate and analyzing it within the 4000-500 cm^{-1} wave number range.

Solubility test

Solubility testing was conducted for intact tenoxicam, physical mixture of tenoxicam-tromethamine, and a multicomponent crystal of tenoxicam-tromethamine. The solubility was observed in CO_2-free distilled water by subjecting samples to agitation on an orbital shaker. Excess amount of samples and 50 ml of solvent were combined in a 100 ml Erlenmeyer flask, followed by 48 h of orbital shaking at 125 rpm, maintaining a 25±0.5 °C temperature. Before measurement, the solution underwent filtration using 0.45 µm Whatman filter paper to eliminate excessive particles. The quantification of tenoxicam was carried out using a UV-Vis spectrophotometer (Shimadzu UV-1700, Japan) at a wavelength of 368 nm.

Dissolution rate profile

Dissolution profiles were examined for the multicomponent crystal, physical mixture, and intact tenoxicam. The dissolution test was conducted using an Apparatus 2 dissolution tester (SR8 Plus Dissolution Test Station, Hanson Virtual Instrument, USA) in two different media: HCl 0.1 N and CO_2-free distilled water, encompassing both acidic and neutral pH environments. The testing was conducted at a controlled temperature of 37 °C±0.5 °C, with a rotation speed of 50 rpm. Each sample, consisting of 20 mg of tenoxicam, was weighed and put into the dissolution medium. Dissolution samples were withdrawn at 5, 10, 15, 30, 45, and 60 min, with each sample measuring 10 ml. Subsequently, the samples were filtered through a 0.45 µm Whatman filter paper and analyzed using a UV-Vis spectrophotometer at 368 nm.

RESULTS

X-ray diffraction patterns for tenoxicam, tromethamine, the physical mixture, and the multicomponent crystal observed in fig. 1 shows that the diffraction pattern of the tenoxicam-tromethamine multicomponent crystal differs from that of the active ingredient and co-former. Tenoxicam exhibits diffraction peaks at 2θ values of 11.62°, 12.86°, 16.12°, 25.46°, and 28.45°, while tromethamine displays peaks at 2θ values of 14.10°, 17.89°, and 20.08°. The X-ray diffraction pattern of the physical mixture of tenoxicam and tromethamine presents a pattern in which the diffraction peaks correspond to the interference between the diffraction peaks of the two individual substances, albeit with a decrease in peak intensity. Conversely, the X-ray diffraction pattern of the tenoxicam-tromethamine multicomponent crystal reveals distinct diffraction patterns. New diffraction peaks emerge at 2θ values of 13.13°, 21.53°, and 24.01°. In comparison, there is a significant decrease in the diffraction peaks of tenoxicam at 2θ values of 12.86°, 25.46°, and 28.46°, as well as a significant reduction in the diffraction peaks of tromethamine at 2θ values of 14.10° and 20.08°.

The divergence between the X-ray diffraction pattern of the multicomponent crystal and those of tenoxicam and tromethamine suggests the formation of a novel crystalline phase distinct from the original substances (tenoxicam and tromethamine). This new phase is afterward characterized through thermal analysis, FT-IR spectroscopy, and evaluations of solubility, and dissolution.

The presence of interactions among the samples is indicated by alterations in the melting points of the analyzed materials, which are used to evaluate interactions between the active and carrier substances [18]. The thermograms of tenoxicam, tromethamine, the physical mixture, and the multicomponent crystal are displayed in fig. 2.

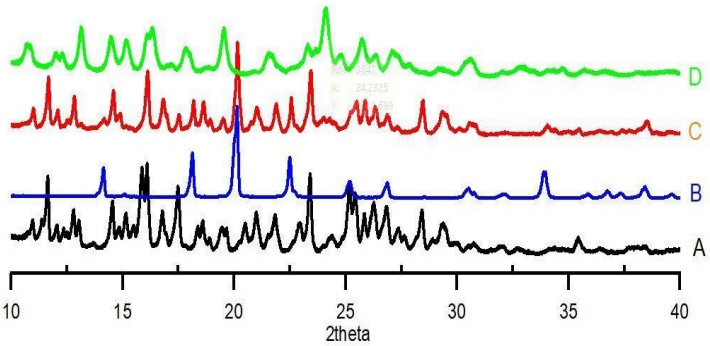

Fig. 1: X-Ray diffractogram of tenoxicam (A), tromethamine (B), physical mixture of tenoxicam-tromethamine (C), and multicomponent crystal of tenoxicam-tromethamine (D)

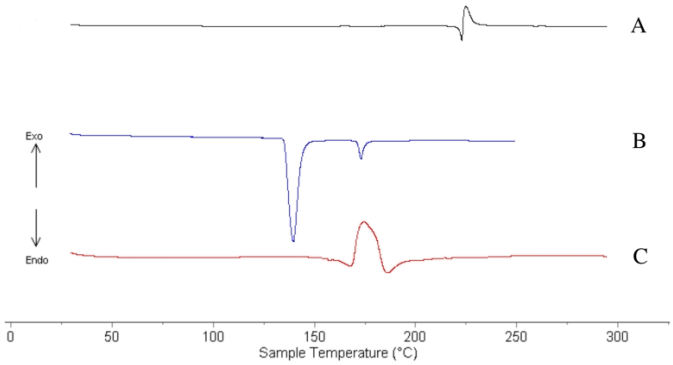

Fig. 2: Differential scanning calorimetry thermogram of tenoxicam (A), tromethamine (B), and multicomponent crystal of tenoxicam-tromethamine (C)

It can be observed that the melting point of tenoxicam is 223.290 °C (fig. 2). The thermogram of tenoxicam displays an endothermic peak, followed by an exothermic peak, indicating a decomposition event [19]. On the other hand, tromethamine exhibits two melting points: 139.075 °C, which represents the temperature associated with a polymorphic transition, and 173.347 °C, which corresponds to the melting point of tromethamine itself. The multicomponent crystal of tenoxicam-tromethamine exhibits a decrease in its melting point to 168.331 °C, followed by an exothermic peak at 174.868 °C, possibly indicative of a recrystallization event that re-melts at 186.387 °C. The exothermic peak in tenoxicam and the multicomponent crystal system prevents the calculation of fusion enthalpy for characterizing the formed multicomponent crystal [19]. Consequently, physical interactions in the DSC thermal analysis are observed by monitoring the changes in the melting points of each sample.

The reduction in the melting point in the tenoxicam-tromethamine multicomponent crystal system suggests the occurrence of physical interactions between the two temperature-dependent components. These physical interactions correlate with X-ray diffraction analysis, indicating the formation of a new crystalline phase formation in the multicomponent crystal system.

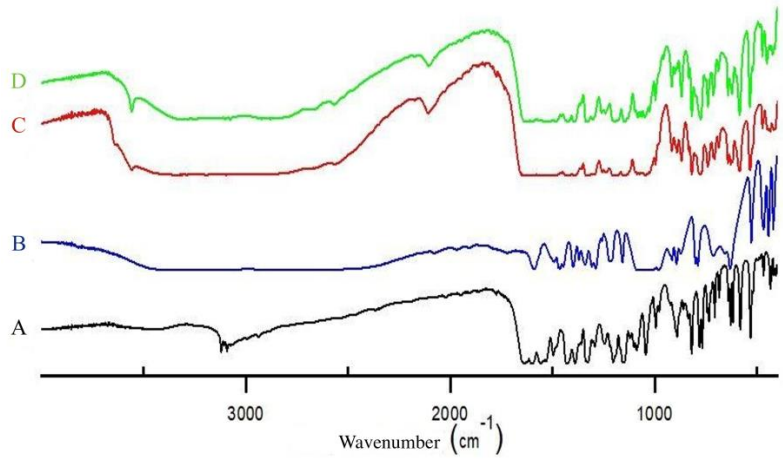

Fig. 3: FTIR spectrum of tenoxicam (A), tromethamine (B), physical mixture of tenoxicam-tromethamine (C), and multicomponent crystal of tenoxicam-tromethamine (D)

Interactions between components within a multicomponent crystal system are characterized by the appearance of new peaks or shifts in peak positions [20]. Changes in the wavenumber indicate the formation of hydrogen bonds between the two substances [9]. The FT-IR spectra of tenoxicam, tromethamine, the physical mixture, and the multicomponent crystal are depicted in fig. 3.

It can be observed that tenoxicam exhibits several absorption peaks at wavenumbers of 3120.58 cm^{-1} (-OH), 3448.58 cm^{-1} (-NH), 1152.04 cm^{-1} (-SO), 1597.84 cm^{-1} (-CO), 1559.34 cm^{-1} (-CN), and 1327.82 cm^{-1} (-CH). Additionally, as shown in table 1, there are changes in the wavenumbers of tenoxicam within the multicomponent crystal, specifically in the-NH group, which shifts from 3448.58 cm^{-1} to 3558.56 cm^{-1}, the-CO group, which shifts from 1597.84 cm^{-1} to 1520.82 cm^{-1}, and the-OH group, which shifts from 3120.58 cm^{-1} to 3077.31 cm^{-1}. These wavenumber changes in the multicomponent crystal system are assumed to result from physical interactions between the two components involving hydrogen bonding, leading to protonation within the multicomponent crystal system [13].

Table 1: Absorption peaks of tenoxicam, tromethamine, the physical mixture and multicomponent crystal

Functional group	Wavenumber (cm-1)			
	Tenoxicam	Tromethamine	Physical mixture	Multicomponent crystal
OH	3120.58	3319.99	3187.84	3077.31
NH	3448.58	3346.94	3558.17	3558.56
S=O	1152.04	-	1150.16	1146.82
C=O	1597.84	-	1636.38	1520.82
C-N	1559.34	-	1559.23	1559.23
C-H	1327.82	1339.55	1331.63	1335.20

One of the parameters supporting the occurrence of protonated hydrogen within the multicomponent crystal system is the significant difference in pKa values (>3) between tenoxicam and tromethamine, which results in the formation of a salt-type multicomponent crystal. This is substantiated by DSC analysis data indicating a decrease in melting point and XRD analysis, which reveals new diffraction patterns within the multicomponent crystal system.

Table 2: Solubility test result

Sample	Solubility±SD (mg/100 ml) (n=3)
Tenoxicam	7.694±0.326
Physical mixture	81.350±0.680
Multicomponent crystal	85.631±1.547

In table 2, it can be observed that the solubility of tenoxicam increased by a factor of 10.574 in the physical mixture and by a factor of 11.130 in the multicomponent crystal. The improved solubility of tenoxicam in the multicomponent crystal is supported by DSC analysis data indicating a decrease in the melting point and XRD analysis data showing the formation of a new crystal form. Similarly, in the physical mixture, the increased solubility of tenoxicam is corroborated by XRD analysis data, which indicates a reduction in peak intensity, signifying a decrease in crystallinity.

Previous research had involved the formation of multicomponent crystals of tenoxicam with catechol, resorcinol, pyrogallol, and piperazine, which increased the solubility of tenoxicam by factors of 5.8, 10.1, 7.5, and 5.5, respectively [9]. Conversely, the formation of multicomponent crystals with benzoic acid, salicylic acid, hydrochloric acid, and methane sulfonic acid did not increase solubility. Hence, the

construction of the tenoxicam-tromethamine multicomponent crystal demonstrates significantly improved solubility compared to prior research on the formation of tenoxicam multicomponent crystals.

Dissolution profile tests were conducted to compare the dissolution profiles of tenoxicam with the newly formed multicomponent crystal. Dissolution profile tests were carried out on tenoxicam, the physical mixture, and the multicomponent crystal in two media: HCl 0.1 N and CO_2-free distilled water. The dissolution profile tests in these two media were designed to observe the variation in tenoxicam dissolution between acidic and neutral pH conditions.

Based on the results of the dissolution profile tests conducted using HCl 0.1 N medium, as shown in fig. 4, it can be observed that the physical mixture and the tenoxicam-tromethamine multicomponent crystal affect the dissolution rate of tenoxicam. The average percentage of tenoxicam dissolved in HCl 0.1 N medium at the 60-minute mark for tenoxicam, the physical mixture, and the multicomponent crystal was 44.428%, 49.196%, and 82.053%, respectively, indicating an increase in dissolution efficiency for the physical mixture and multicomponent crystal by a factor of 1.347 and 2.600, respectively.

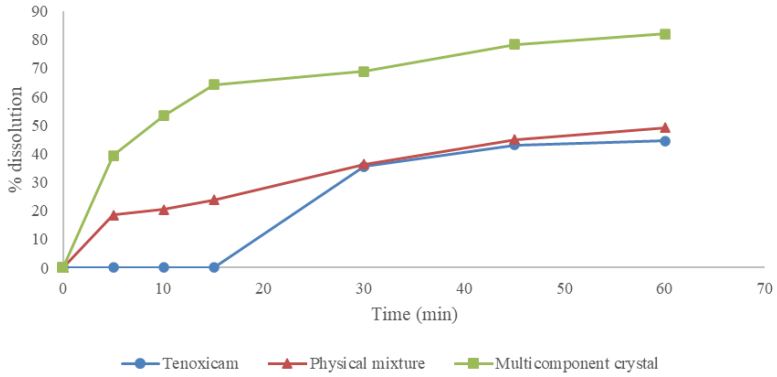

Fig. 4: Dissolution profile of tenoxicam in 0.1 N HCl

In the dissolution profile tests conducted using CO_2-free distilled water as the medium (fig. 5), it is evident that both the physical mixture and the tenoxicam-tromethamine multicomponent crystal significantly impact the dissolution rate of tenoxicam. The average percentage of tenoxicam dissolved in CO_2-free distilled water at the 60 min mark for tenoxicam, the physical mixture and the multicomponent crystal was 31.535%, 49.394%, and 93.552%, respectively.

These results highlight a substantial increase in dissolution efficiency for the physical mixture and the multicomponent crystal by factors of 3.495 and 8.605, respectively, when compared to tenoxicam alone. Notably, this significant enhancement in dissolution efficiency demonstrates the potential of the tenoxicam-tromethamine multicomponent crystal as a promising formulation to improve the solubility and dissolution of tenoxicam, particularly in CO_2-free distilled water. These findings provide valuable insights into the potential applications of multicomponent crystals in enhancing the dissolution characteristics of poorly soluble drugs across different pH.

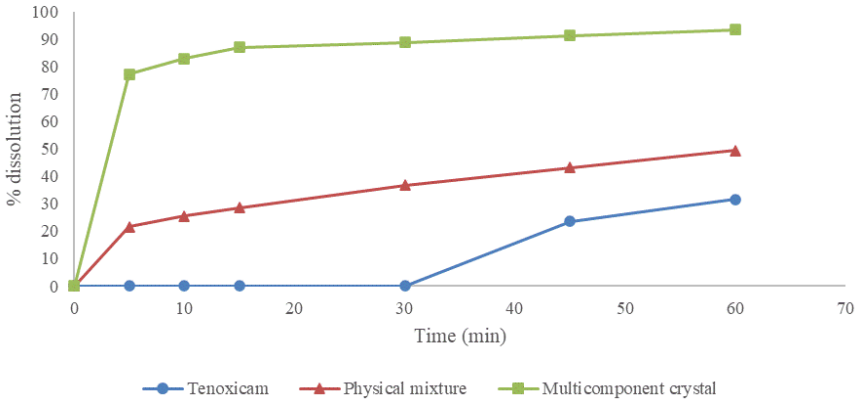

Fig. 5: Dissolution profile of tenoxicam in CO_2-free distilled water

DISCUSSION

In prior research, multicomponent crystals of tenoxicam were formed with glycolic acid, saccharin, salicylic acid, and succinic acid. These multicomponent crystals displayed similar or lower dissolution rates than the active substance, tenoxicam [10].

Conversely, the formation of multicomponent crystals with benzoic acid, catechol, resorcinol, pyrogallol, piperazine, hydrochloric acid, and methane sulfonic acid exhibited successive increases in dissolution rates by factors of 2.0, 3.1, 4.2, 2.4, 2.5, 1.3, and 1.2, respectively [9]. Consequently, the tenoxicam-tromethamine multicomponent crystal formation has demonstrated an improved on dissolution rate compared to the previously formed multicomponent crystals.

The characterization data supports the increase in the dissolution amount of tenoxicam-tromethamine multicomponent crystal, including a decrease in melting point, a reduction in peak intensity, and solubility test data indicating improved solubility. However, in the dissolution test, the increase in dissolution at the 60 min mark in the physical mixture is not as prominent as the increase observed in the solubility test. This difference is attributed to the testing conditions and the duration of the tests. The solubility test is conducted until equilibrium is reached, while the dissolution profile test lasts 60 min.

Dissolution tests using 0.1 N HCl and CO_2-free distilled water showed different outcomes. The selection of dissolution media comprising HCl 0.1 N and CO_2-free distilled water was deliberate, encompassing both acidic and neutral pH environments. This strategic choice allows for a comprehensive evaluation of tenoxicam dissolution under conditions that simulate the diverse pH ranges encountered in the gastrointestinal tract. The dual-media approach enables a nuanced assessment of dissolution behavior, providing insights into the potential performance of the tenoxicam-tromethamine multicomponent crystal across varying physiological pH environments. In an acidic environment, the increase in dissolution is not as significant as in a normal pH. This is predicted to be due to ionic equilibrium events at acidic pH, resulting in a less pronounced increase in dissolution compared to normal pH. Additionally, the enhanced dissolution of the multicomponent crystal mechanism is influenced by the properties of the co-former (tromethamine), which readily dissolves in water. When the multicomponent crystal system, with tenoxicam encased by the co-former, meets the solvent, the co-former, being highly soluble, dissolves first. This subsequently leaves tenoxicam to dissolve, contributing to increased solubility and dissolution of tenoxicam.

The observed improvements in solubility and dissolution efficiency play pivotal roles in enhancing drug bioavailability, aligning with fundamental principles in dissolution science. The degree of solubility directly influences the dissolution rate, a crucial factor governing drug absorption and bioavailability. Mathematical expressions such as the Noyes–Whitney, Nernst–Brunner, and Hixson–Crowell equations highlight the significance of diffusion, surface area, and temporal changes in the dissolving substance's surface in the dissolution process [21]. A drug with optimal aqueous solubility is more likely to readily dissolve in the watery environment, facilitating efficient absorption through membranes. In summary, the ability of a solid drug to dissolve in a watery environment emerges as a key determinant of its overall bioavailability upon administration.

CONCLUSION

The tenoxicam and tromethamine multicomponent crystal formation using a solvent drop grinding technique resulted in a novel crystalline structure, enhancing the solubility and dissolution of tenoxicam both in CO_2-free distilled water and HCl 0.1 N

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AUTHORS CONTRIBUTIONS

Each author contributed equally to the research and article preparation. E. Z, L. F and U. H designed the experiments and interpreted the data. Y. A assisted the experiment, U. H and Y. A performed the characterization. U. H and Y. A wrote the manuscript in consultation with E. Z and L. F.

CONFLICT OF INTERESTS

The authors declared that there is no conflict of interest.

REFERENCES

1. Erbas M, Simsek T, Kiraz HA, Sahin H, Toman H. Comparacao da eficacia de tenoxicam administrado por via oral e intra-articular a pacientes com osteoartrite de joelhos. Braz J Anesthesiol. 2015 Sep 1;65(5):333-7. doi: 10.1016/j.bjan.2013.12.003.
2. Eren OT, Armagan R, Talmaç MA. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. In: Musculoskeletal research and basic science. Springer International Publishing; 2015. p. 683-93.
3. Osman SK, Yassin TM, Mohammed AM, Alfayomy AM, Abdellatif AA, Mahdi WA. A novel approach for the availability and ocular delivery of tenoxicam potassium: synthesis, characterization, and *in vivo* application. AAPS PharmSciTech. 2023 Jan 1;24(1):44. doi: 10.1208/s12249-022-02487-3, PMID 36703092.
4. Bashimam M, El-Zein H. Pharmaceutical cocrystal of antibiotic drugs: a comprehensive review. Heliyon. 2022 Dec 1;8(12):e11872. doi: 10.1016/j.heliyon.2022.e11872, PMID 36478792.
5. Xie Y, Yuan P, Heng T, Du L, An Q, Zhang B. Insight into the formation of cocrystal and salt of tenoxicam from the isomer and conformation. Pharmaceutics. 2022 Sep 19;14(9):1-18. doi: 10.3390/pharmaceutics14091968, PMID 36145717.
6. Abdul Hussein HA, Maraie NK. Tenoxicam-loaded polymeric micelles material: formulation, optimization, and evaluation. Mater Today Proc. 2022 Jan 1;61(3):672-80. doi: 10.1016/j.matpr.2021.08.218.
7. Umar S, Usman H, Salsabila H, Zaini E. Solid dispersion of tenoxicam-HPMC by freeze-drying: solid-state properties, dissolution study, and analgesic activity in mice. Open Access Maced J Med Sci. 2022 Apr 25;10(A):800-6. doi: 10.3889/oamjms.2022.9553.
8. Aboud HM, Ali AA, Abd Elbary A. Formulation and optimization of tenoxicam orodispersible tablets by solid deposition technique. J Drug Deliv Sci Technol. 2012 Jan 1;22(6):555-61. doi: 10.1016/S1773-2247(12)50096-1.
9. Bolla G, Sanphui P, Nangia A. Solubility advantage of tenoxicam phenolic cocrystals compared to salts. Cryst Growth Des. 2013 May 1;13(5):1988-2003. doi: 10.1021/cg4000457.
10. Patel JR, Carlton RA, Needham TE, Chichester CO, Vogt FG. Preparation, structural analysis, and properties of tenoxicam cocrystals. Int J Pharm. 2012 Oct 15;436(1-2):685-706. doi: 10.1016/j.ijpharm.2012.07.034, PMID 22841852.
11. Lutfiyah DS, Fitriani L, Taher M, Zaini E. Crystal engineering approach in physicochemical properties modifications of phytochemical. Sci Technol Indones. 2022 Jul 28;7(3):353-71. doi: 10.26554/sti.2022.7.3.353-371.
12. Gryl M, Kozieł M, Stadnicka KM. A proposal for coherent nomenclature of multicomponent crystals. Acta Crystallogr B Struct Sci Cryst Eng Mater. 2019 Feb 1;75(1):53-8. doi: 10.1107/S2052520618015858, PMID 32830778.
13. Izadihari R, Rosaini H, Zaini E, Yuliandra Y. Multicomponent crystals of mefenamic acid-tromethamine with improved dissolution rate. Sanat. 2019;23(6):988-96. doi: 10.35333/jrp.2019.63.
14. Stahl PH, Wermuth CG. Handbook of pharmaceutical salts: properties, selection and use. Chem Int. 2002;24:21.
15. Bookwala M, Thipsay P, Ross S, Zhang F, Bandari S, Repka MA. Preparation of a crystalline salt of indomethacin and tromethamine by hot melt extrusion technology. Eur J Pharm Biopharm. 2018 Oct 1;131:109-19. doi: 10.1016/j.ejpb.2018.08.001, PMID 30086393.
16. Bruni G, Berbenni V, Maggi L, Mustarelli P, Friuli V, Ferrara C. Multicomponent crystals of gliclazide and tromethamine: preparation, physico-chemical, and pharmaceutical characterization. Drug Dev Ind Pharm. 2018 Feb 1;44(2):243-50. doi: 10.1080/03639045.2017.1386208, PMID 28956461.
17. Park JY, Oh DH, Park SW, Chae BR, Kim CW, Han SH. Development of pelubiprofen tromethamine with improved gastrointestinal safety and absorption. Pharmaceutics. 2021 May 18;13(5):745. doi: 10.3390/pharmaceutics13050745, PMID 34070062.
18. Zaini E, Azhari D, Fitriani L. Identification and characterization of solid binary system of quercetin-nicotinamide. Orient J Chem. 2016 Jun 1;32(3):1545-50. doi: 10.13005/ojc/320330.
19. Fitriani L, Firdaus WA, Sidadang W, Rosaini H, Putra OD, Oyama H. Improved solubility and dissolution rate of ketoprofen by the formation of multicomponent crystals with tromethamine. Crystals. 2022 Feb 17;12(2):275. doi: 10.3390/cryst12020275.
20. Cantera RG, Leza MG, Bachiller CM. Solid phases of tenoxicam. J Pharm Sci. 2002 Oct 1;91(10):2240-51. doi: 10.1002/jps.10207, PMID 12226851.
21. Alladi S, Shastri NR. Semi solid matrix formulations of meloxicam and tenoxicam: an *in vitro* and *in vivo* evaluation. Arch Pharm Res. 2015 May 1;38(5):801-12. doi: 10.1007/s12272-014-0396-3, PMID 24752862.
22. Viswanathan P, Muralidaran Y, Ragavan G. Challenges in oral drug delivery: a nano-based strategy to overcome. In: Nanostructures for oral medicine. Elsevier; 2017. p. 173-201.