Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Apr 25; 10(A):800-806.
https://doi.org/10.3889/oamjms.2022.9553
eISSN: 1857-9655
Category: *A - Basic Sciences*
Section: *Pharmacolgy*

Solid Dispersion of Tenoxicam – HPMC by Freeze-Drying: Solid State Properties, Dissolution Study, and Analgesic Activity in Mice

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Edited by: Sinisa Stojanoski
Citation: 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):800-806. https://doi.org/10.3889/oamjms.2022.9553
Keywords: Analgesic; Dissolution rate; Freeze-drying; HPMC; Solid dispersion; Solubility; Tenoxicam
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Received: 26-Mar-2022
Revised: 13-Apr-2022
Accepted: 15-Apr-2022

Funding: As written on acknowledgment part of the manuscript, this work was funded by the Faculty of Pharmacy, Universitas Andalas for basic grant on contract number: 13/UN16.10.D/PJ.01/2021.
Competing Interests: The authors have declared that no competing interests exist

Abstract

AIM: The aim of this study was to prepare solid dispersion of tenoxicam with hydroxypropyl methylcellulose (HPMC) to improve solubility, dissolution rate, and *in vivo* analgesic activity.

METHODS: Solid dispersion of tenoxicam with HPMC was prepared using the freeze-drying technique in three ratios of drug to carrier (1:1, 1:2, and 2:1 w/w). The solid-state properties of solid dispersion powders were characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier-transform infrared (FT-IR) spectroscopy, and scanning electron microscope (SEM). Solubility and dissolution rate studies were conducted in an aqueous medium. Analgesic activity was evaluated using the writhing method.

RESULTS: Analysis of PXRD and DSC results indicated a decreased degree of crystallinity of tenoxicam in solid dispersion powders. Solid dispersion of tenoxicam exhibited a significant improvement in solubility and dissolution rate compared to intact tenoxicam, in line to the increment on the ratio of HPMC. Analgesic activity study revealed that solid dispersion 1:2 was more effective than intact tenoxicam.

CONCLUSIONS: This study concludes that the solid dispersion technique is a promising strategy to improve the solubility and dissolution rate of tenoxicam.

Introduction

The solubility and dissolution rate of active pharmaceutical ingredients are key physicochemical properties in developing a qualified and effective solid dosage form. The dissolution rate of active pharmaceutical ingredients in gastrointestinal fluid affects the degree of absorption and bioavailability in systemic circulation [1]. The amount of pharmaceutically active ingredients that enter systemic circulation and the rate at which they do so are proportionally correlated to their therapeutic efficacy [2]. Solubility and dissolution rate influenced by various parameters including the nature of the solid phase (crystalline, amorphous, or polymorphous), size and surface area of their constituent particles, and addition of excipients that improve dissolution rates (such as hydrophilic polymers, surfactants, and cyclodextrin) [3].

The previous reports have shown that nearly 40% of active pharmaceutical ingredients in solid dosage forms have low solubility in water. Moreover, approximately 80–90% of pharmaceutical drug candidates in the research and development stage have also shown poor solubility in water [4]. Various approaches to overcome the challenge of poorly soluble drugs have been carried out, including chemical modification of molecular structure of pharmaceutically active substances and physical modification of solid state properties. One promising technique was recently developed to modify the solid state properties of active pharmaceutical ingredients by forming amorphous solid dispersions of active pharmaceutical ingredients with hydrophilic carriers [5].

One of the poorly soluble drugs is tenoxicam (TNX). TNX is a well-known non-steroidal anti-inflammation drug used to treat osteoarthritis, gout, rheumatoid arthritis, and pain [6], [7]. Unit dose per day of tenoxicam is relatively lower than other oxicam derivatives of non-steroidal anti-inflammation drugs (e.g., piroxicam and meloxicam) [8]. TNX has a solubility of just 14 mg/L in water. According to the Biopharmaceutical Classification System (BCS), tenoxicam classified under the class II drugs (low solubility and high permeability) which lead to a low bioavailability in systemic circulation [9], [10]. Therefore, dissolution rate improvements are needed to reach a more successful pharmaceutical dosage form [11], [12]. Many efforts have been reported to improve the solubility and dissolution rate of TNX previous studies, including solid dispersion with hydrophilic polymers [13], [14], [15], formation of inclusion complexes with cyclodextrin

derivatives [16], [17], a system of solubilization with cosolvents [8], and formation of multicomponent crystal phases (cocrystals and salt) with excipients [10], [18].

Here, we were interested in preparing an amorphous solid dispersion of TNX with HPMC using freeze-drying technique and characterize the solid-state properties to investigate solubility and dissolution rate improvement, as well as analgesic effectiveness. To the best of our knowledge, amorphous solid dispersion of tenoxicam with HPMC has not been explored to date.

Materials and Methods

Materials

Tenoxicam was obtained from Sanbe Farma Ltd (Indonesia). HPMC (pharmaceutical grade) was purchased from Shin-Etsu Chemical (Japan). Ethanol (pro analysis) and dichloromethane (pro analysis) were purchased from Bratachem (Indonesia). Sodium hydroxide and hydrogen chloride were obtained from Merck, Germany.

Preparation of solid dispersions of TNX-HPMC by freeze-drying

Tenoxicam (TNX) and HPMC were accurately weighed in various ratios of TNX and HPMC 2910 (1:1, 1:2, and 2:1 w/w). TNX was dissolved in dichloromethane, and HPMC was dissolved in a mixture of ethanol and dichloromethane (1:1 v/v). Magnetic stirrer mixed these solutions at 250 rpm and 60 °C until slurries were formed, and the slurries were then dried using freeze dryer apparatus (Christ Alpha 1-2 LD Plus, France) for 24 h at −50°C and 0.3 mbar. Solid dispersion powders were stored in a desiccator for physicochemical characterization and pharmacological studies.

Physicochemical properties characterization

Powder X-ray diffraction (PXRD) analysis

PXRD analysis was performed using an X-ray diffractometer (PAN Analytical, The Netherlands) with monochromatized CuKα in the laboratory of Universitas Negeri Padang. The generator voltage and current were 40 kV and 30 mA, respectively. PXRD pattern was recorded from 05 to 50° on the 2 theta at a step size of 0.02°.

Differential scanning calorimetry (DSC) analysis

A DSC thermogram of intact TNX, intact HPMC, and solid dispersion samples were evaluated using a Shimadzu DSC 06 differential scanning calorimeter (Japan). Approximately 2–3 mg of the samples were placed in aluminum pans, sealed, and heated at a rate of 10°C/min in 50–250°C.

Fourier-transform infrared (FT-IR) spectroscopy analysis

FT-IR spectra of intact TNX, HPMC, and solid dispersions of TNX-HPMC were collected using an FT-IR spectrophotometer (Shimadzu IRTracer-100 AH, Japan). About 2–3 mg of the sample was placed in Attenuated Total Reflectance (ATR) sample holder and scanned from 4000 to 500 cm^{-1}.

Scanning electron microscopy analysis

Crystalline morphology of intact TNX, intact HPMC, and solid dispersion powders was investigated by scanning electron microscope (SEM) apparatus (Hitachi model S-3400N, Japan). Samples were glued onto a metal stub with double-sided adhesive tape and sputter-coated with gold-palladium (Au 80% and Pd 20%) under a vacuum before analysis.

Solubility test

Excess amounts of intact TNX and solid dispersion powder were placed in an Erlenmeyer flask containing 50 mL of distilled water. Samples were shaken using an orbital shaker (125 rpm) at ambient temperature for 48 h. Samples were filtered by a membrane filter (0.45 µm), and TNX concentration in the filtrate determined by UV-Vis spectrophotometer (UV-Vis Shimadzu 1280, Japan) at a wavelength of 364.2 nm. Experiments were conducted in triplicate [10].

Dissolution profile studies

Dissolution profile studies of TNX and solid dispersion powder were conducted in 900 mL of 0.1 N HCl solution (pH 1.2) at 50 rpm, 37 ± 0.5°C in dissolution tester apparatus USP type-II (USP Hanson Research SR08 Dissolution Tester, USA). Samples (5 mL) were collected at definite time intervals (5, 10, 15, 30, 45, and 60 min) and replaced with a fresh dissolution medium. The amount of TNX dissolved was determined by spectrophotometer (UV-Vis Shimadzu 1280, Japan) at 361.7 nm. Data are presented in a dissolution profile curve (time versus percent dissolved of TNX). The experiment was performed in triplicate.

Analgesic activity study

Male Deutschland-Denken-Yoken mice aged 2–3 months and weighing 25–30 g were used

in this experiment. Animals were kept in standard environmental conditions at room temperature for 7 days of acclimation. The effectiveness of solid dispersion (SD 1:2) was investigated using the writhing method [19]. Mice were divided into three groups: Control group which receiving sodium carboxymethyl cellulose (Na CMC) suspension 1% (0.2 mL), those receiving intact TNX (dose equivalent 0.052 mg/kg) and those receiving solid dispersion SD 1:2 (dose equivalent 0.052 mg/kg). 13 min after oral administration of the samples, each mouse was injected with 0.5% acetic acid i.p. as a pain inductor, and writhing movements were monitored for 1 h. The numbers of writhes were calculated at definite time intervals. The Ethics Committee of the Faculty of Medicine, Universitas Andalas, Indonesia No. 149/UN.16.2/Kep-FK/2020, had approved the experiment.

Results and Discussion

PXRD is a powerful analytical method to determine the solid state properties of active pharmaceutical ingredients (API), and characterize solid state interactions between API and excipients [20]. Tenoxicam is a highly crystalline solid, as shown by sharp and intensive diffraction peaks at 2 theta: 11.57; 12.74; 14.49; 16.73; 18.53; 20.93; 25.39; 26.26; 28.36; and 29.26 (Figure 1A). The diffraction pattern of HPMC as a carrier showed a halo pattern indicating an amorphous phase, and there are no sharp diffraction peaks (Figure 1B). Figures 1C-E show the PXRD patterns of solid dispersion powders. Solid dispersions of TNX-HPMC exhibit a significant decrease in characteristic diffraction peaks. The PXRD results reveal that the crystalline phase of TNX underwent a partial amorphization in a hydrophilic polymer network. In the amorphous state, molecules of the active pharmaceutical ingredients were arranged randomly in a crystal lattice, with the lattice weaker than in the crystalline phase. Therefore, the amorphous state has a higher solubility and dissolution rate than its crystalline state [21], [22].

PXRD analysis can be used to estimate the degree of crystallinity of solid dispersion powders compared to intact TNX [23]. Figure 2 shows the degree of crystallinity of solid dispersion powders. Degree of crystallinity decreased proportionally with an increasing ratio of hydrophilic polymer. The crystallinity of solid dispersions of TNX-HPMC (SD 2:1, SD 1:1, and SD 1:2) was 70.3, 58.45, and 52.59%, respectively.

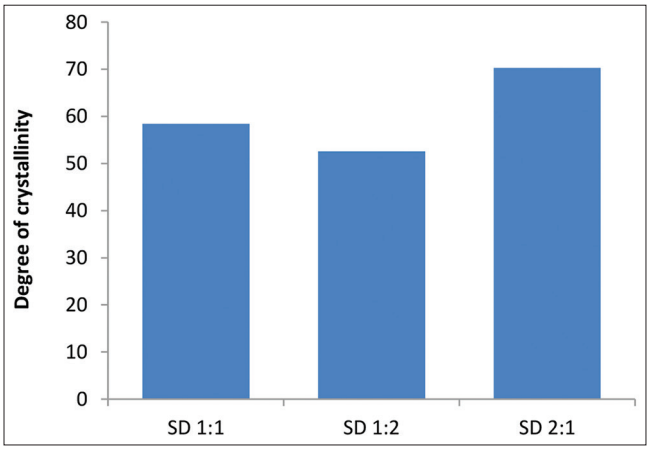

Figure 2: Degree of crystallinity of solid dispersion powders

Thermal analysis DSC is also an essential technique in characterizing the solid-state interactions between active pharmaceutical ingredients and carriers. The findings of our DSC analysis support the results of the PXRD analysis. DSC thermograms of TNX, HPMC, and SD are shown in Figure 3. TNX shows two peaks; one endothermic, followed by one exothermic peak (Figure 3A). The sharp endothermic peak at 227.36°C corresponds to the melting point of TNX, while the exothermic peak at 230.5°C is attributed to the degradation of TNX after melting. The DSC thermogram of HPMC (Figure 3B) depicts a broad endothermic event over approximately 30–90°C, which indicates a desolvation of water molecules from hydrophilic polymer HPMC [24]. Figure 3C-E displays a

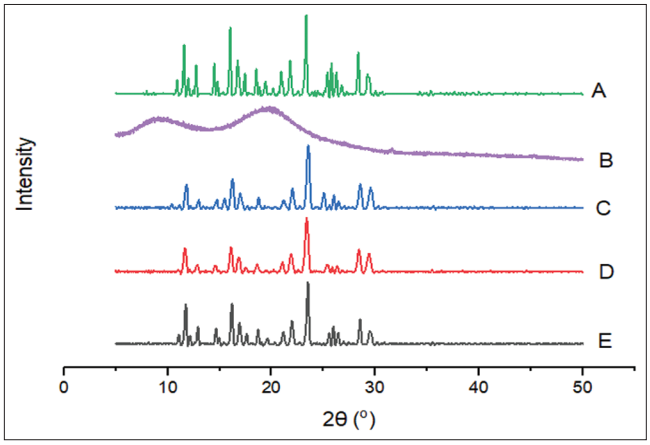

Figure 1: PXRD pattern of (A) Tenoxicam, (B) HPMC, (C) SD 1:1, (D) SD 1:2, and (E) SD 2:1

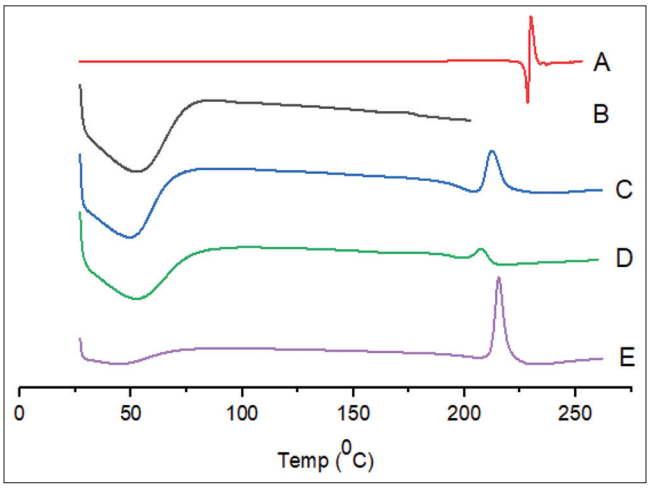

Figure 3: DSC thermogram of (A) TNX, (B) HPMC, (C) SD 1:1, (D) SD 1:2, and (E) SD 2:1

DSC thermogram of solid dispersion powders obtained by freeze-drying methods. The endothermic peaks of crystalline TNX gradually disappeared in all ratios of SD. Both the endothermic and exothermic peaks in TNX shifted to lower temperatures. This finding proves that a crystalline phase of TNX was transformed to an amorphous state and dispersed homogenously in polymer-carriers [25].

FT-IR spectrophotometry analysis was performed to assess the intermolecular interaction between TNX and HPMC [26]. FT-IR spectra of TNX, HPMC and solid dispersion powders in the range 500-4000 cm^{-1} are shown in Figure 4. TNX exhibited two specific transmittance peaks at 3091.94 cm^{-1} and 2934.74 cm^{-1}, attributed to N-H stretching and vibration of aromatic C-H. There is also a sharp band at 1595.16 cm^{-1}, caused by the stretching of amide carbonyl (C=O). FT-IR spectra of HPMC show O-H stretching vibration at 3388.99 cm^{-1} and C-H stretching vibration around 2910.63 cm^{-1}. FT-IR spectra of solid dispersion powders were a superimposition of transmittance peaks from each individual component. There were no any new peaks in the FT-IR spectra of solid dispersions, and any significant changes or shifts of peaks in the spectra. The findings prove no evidence of specific chemical interaction between TNX and HPMC [24].

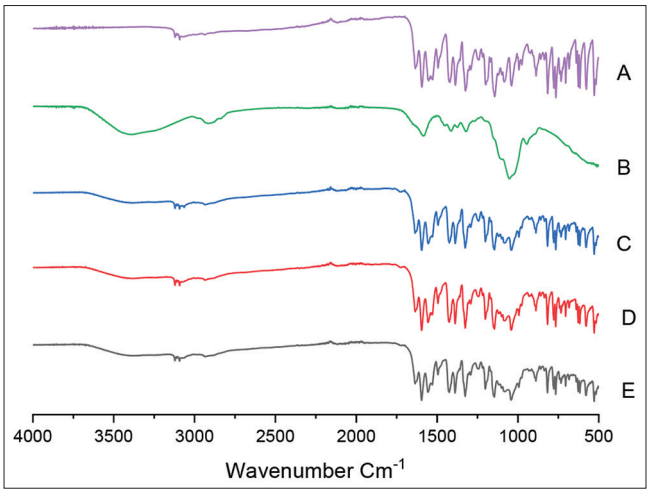

Figure 4: FT-IR spectra of (A) TNX, (B) HPMC, (C) SD 1:1, (D) SD 1:2, and (e) SD 2:1

SEM analysis is a standard tool to observe the surface and morphology of crystal habits. SEM micro photos are depicted in Figure 5: Intact TNX exhibits spherically shaped particles, HPMC shows fiber-shaped particles, while SEM micro photos of solid dispersion powders demonstrate porous, long rod-shaped particles. The freeze-drying technique in preparation for solid dispersion usually produces porous particles. Therefore, the surface area of solid dispersion powders increases compared to intact TNX [24], [27].

Solubility and dissolution rate are essential properties in the design and development of solid dosage forms. For poorly soluble drugs, dissolution rates of active pharmaceutical ingredients become

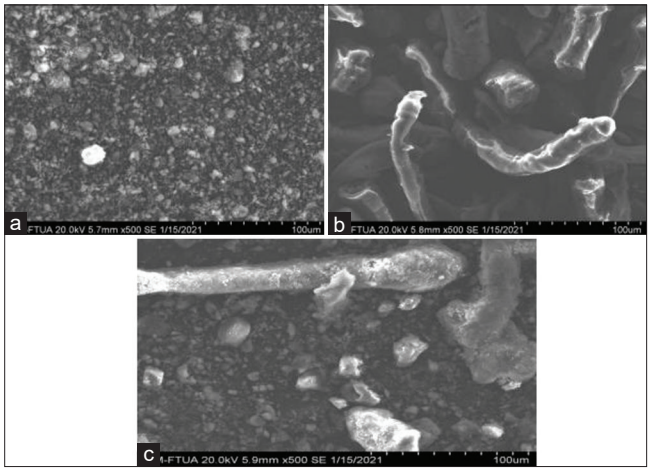

Figure 5: Scanning electron micrographs of (a) TNX; (b) HPMC; (c) SD 1:2 (all images at 500× magnification)

a rate-limiting step in absorption processes in gastrointestinal fluids. The solid active pharmaceutical ingredients must be dissolved in gastrointestinal fluid, before they permeate into the systemic circulation. For this reason, improving the solubility and dissolution rate are crucial advances in reaching optimum bioavailability of poorly soluble drugs [11], [28]. In the present study, we applied a solid dispersion prepared by freeze-drying to enhance the solubility and dissolution rate of TNX from solid dispersion with HPMC. Solubility data for TNX and solid dispersion powders are displayed in Table 1. The results show that the solubility of all solid dispersions is higher than intact TNX. Solubility of solid dispersion (SD 2:1, SD 1:1, and SD 1:2) increased 6.4, 7.1, and 8 fold, respectively, compared to intact TNX.

Table 1: Solubility data of TNX and solid dispersions (data are presented as mean ± SEM, n = 12).

Sample	Solubility (mg/100 mL) ± SEM	Solubility enhancement
Tenoxicam	3.147 ± 0.326	-
SD 1:1	22.043 ± 0.455	7.1 fold
SD 1:2	25.170 ± 0.246	8 fold
SD 2:1	20.136 ± 0.262	6.4 fold

SEM: Scanning electron microscope, TNX: Tenoxicam.

According to the Noyes-Whitney equation, dissolution rates are influenced by the specific surface area and solubility of active pharmaceutical ingredients [29]. The dissolution rate profiles of solid dispersion systems agree with the solubility data. Figure 6 depicts the dissolution rate profile of TNX and solid dispersions. The solid dispersion (SD 1:2) had the highest dissolution rate. The rate increases proportionally with the ratio of hydrophilic polymer HPMC in the solid dispersion system. The improvement of TNX solubility and dissolution rate from solid dispersion powders may be attributed to several mechanisms, including the partial amorphization of crystalline phase TNX in the polymeric matrix, and an increase in specific surface area of the solid dispersion due to the formation of porous particles. In addition, using HPMC as a hydrophilic carrier could improve the wettability of poorly soluble drugs (hydrophobic drugs). HPMC also stabilized the amorphous phase of

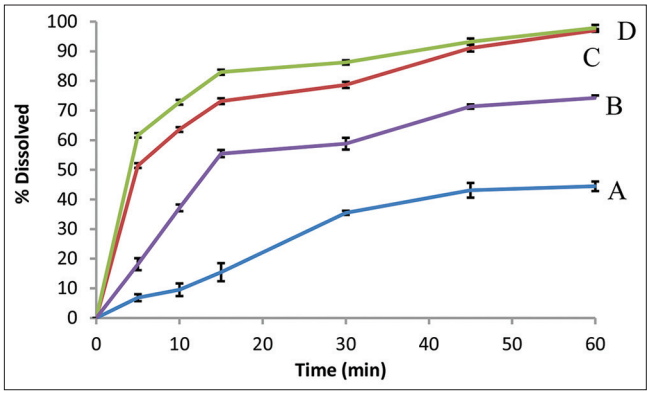

Figure 6: Dissolution rates profile of (A) TNX, (B) SD 2:1, (C) SD 1:1, and (D) SD 1:2. N = 3

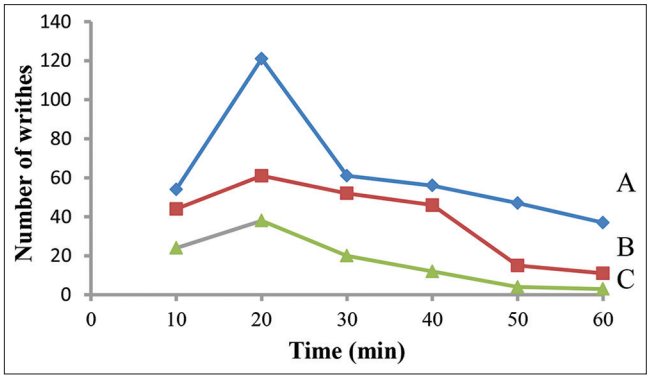

Figure 7: Writhing test result of (A) Control, (B) Tenoxicam, and (C) SD 1:2

TNX in solid dispersion systems by preventing phase transitions in the system [25], [30], [31], [32], [33].

To investigate the correlation between the solubility and dissolution rate of TNX solid dispersion (SD 1:2) and analgesic effectiveness, we conducted an analgesic activity study on animals (mice) by writhing method. Acetic acid-induced writhing response method widely used to evaluate analgesic activity of drug. Acetic acid induced pain response by prostaglandin and peritoneal mast cells pathways. When administered intraperitoneally, acetic acid enhances the release of inflammatory mediators, including prostaglandin, serotonin, histamine, bradykinin, and substance P, which responsible for abdominal constriction and pain [34]. Thus, this method could represent the efficacy of analgesic accurately. The results of this study are presented in Figures 7 and 8. The average number of writhes in the group receiving SD 1:2 remarkably decreases compared to the control group and the group receiving intact TNX. This finding reveals that SD 1:2 has better analgesic effectiveness (about 2-fold) than intact TNX. The results prove that physicochemical properties such as solubility and dissolution rate significantly affect the *in vivo* analgesic activity of TNX. Solubility and dissolution rate improvement is needed to reach an optimum bioavailability and faster onset of action of poorly soluble drugs.

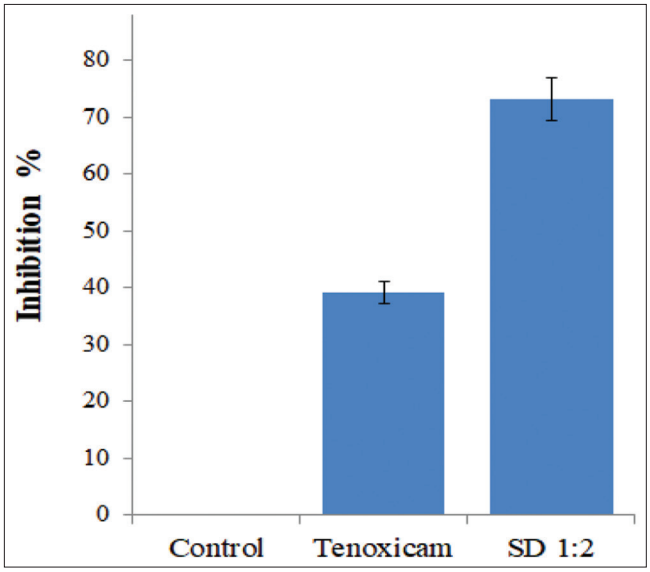

Figure 8: Analgesic activity in pain inhibition (n = 15)

Conclusions

In the present study, we conclude that solid dispersion of TNX-HPMC is successfully prepared using a freeze-drying technique. The solubility and dissolution rate of all solid dispersion powders are better than in intact TNX, where solid dispersions with ratio 1:2 (TNX: HPMC) give the best result in solubility improvement. These results were confirmed by PXRD, DSC, FT-IR, and SEM. Our *in vivo* analgesic effectiveness study shows a positive correlation with the improvement of solubility and dissolution rates. Thus, solid dispersion is a promising strategy to improve solubility and dissolution rate of tenoxicam and need further studies to confirm the positive effects.

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