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Original Article

Etoricoxib Co-Crystals: Unlocking New Frontiers in Drug Solubility

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ABSTRACT

The classification of etoricoxib (ETX), a nonsteroidal anti-inflammatory drug, under the Biopharmaceutics Classification System as a model class II drug is based on its low solubility and slow dissolution rate, which limits its bioavailability and therapeutic efficacy. This study aimed to improve the dissolution rate and consequently the anti-inflammatory efficacy of etoricoxib. A mixture of etoricoxib with different co-formers, L-alanine, L-glycine and sucralose, has been developed in three ratios (1:1, 1:2, and 1:4) by the liquid assisted grinding. All formulations underwent in-vitro dissolution testing to assess their effectiveness in improving drug solubility. Among the tested co-formers, sucralose demonstrated a significant enhancement in etoricoxib dissolution. The in-vitro characterization revealed enhancement in the solubility properties of ETX, which may have led to a better dissolution profile. The formula consisting of etoricoxib and sucralose at a 1:4 ratio was identified as the targeted formula with the desired characteristics, making it the ideal formulation for further investigation.

Keywords: Co-grinding, Dissolution, Etoricoxib, Solubility.

1. INTRODUCTION

Etoricoxib (ETX), 5-chloro-6′-methyl-3 [4-(methylsulfonyl) phenyl]-2, 3′–bipyridine is a highly selective second-generation cyclooxygenase-2 (COX-2) inhibitor [1] that is taken orally [2] as a nonsteroidal anti-inflammatory drug (NSAID) [3] and painkiller [4] (Figure 1) [5].

Osteoarthritis, rheumatoid arthritis, gouty arthritis, postoperative dental pain, chronic musculoskeletal pain (including persistent low back pain) [6], and primary dysmenorrhea are among the medical conditions for which etoricoxib has been licensed [7]. In comparison to traditional non-COX-selective NSAIDs, it is generally well tolerated and has greater GI tolerance [8]. Etoricoxib is categorized as a class II medicine under the Biopharmaceutics Classification System [9] because of its restricted aqueous solubility, which limits its potential for therapeutic use [10].

As a result, the oral absorption rate of etoricoxib is limited by its dissolution rate [11], so increasing both its solubility and the dissolution rate will increase its oral bioavailability [12,13].

The efficient delivery of active pharmaceutical ingredients (APIs) with low water solubility has proven to be a challenge for pharmaceutical scientists [14]. It is now evident that pharmaceutical co-crystals can be logically generated through crystal engineering to achieve this objective [15].

Pharmaceutical co-crystals are multi-component systems [16] that are kept together by H-bonding and consist of two or more molecules [17]. Co-crystals enhance the physical properties of active pharmaceutical ingredients, such as

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solubility, stability, processability, and bioavailability, without compromising their pharmacological effect [18], thereby providing the pharmaceutical industry with exciting opportunities to develop and manufacture new medications [19]. The reclassification that occurred recently indicates that co-crystals are now considered drug polymorphs rather than novel active pharmaceutical ingredients (APIs), which significantly influence drug development [20].

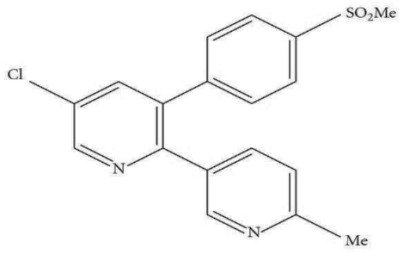

Figure 1. Chemical structure of etoricoxib

This approach has been involved in boosting the dissolution of different pharmaceuticals, including hydrochlorothiazide [21] and nateglinide [22].

The co-grinding of medicines with amino acids as excipient has been extensively advanced. In addition to enhancing the physicochemical properties of the active pharmaceutical ingredient (API), amino acids are less hazardous than chemical co-formers such dicarboxylic acids and are easy to manage[23].

Amino acids of low molecular weight, such as L-alanine and L-glycine, form a co-amorphous system. The use of amino acids as co-formers in co-amorphous formation has been extensively investigated. It has been demonstrated to improve the stability and dissolving profile of APIs with solubility issues. Amino acids are co-formers because they have amino and carboxylic groups that can act as donors and acceptors of hydrogen bonds[23].

Also sweetener, as sucralose can be used as a potential co-former for increasing the dissolution rate of a poorly water-soluble model medication. Sucralose is an artificial sweetener made by structurally modifying sucrose and selectively replacing three hydroxyl groups with chlorine atoms. It is characterized as a non-caloric, non-nutritive sweetener, which is beneficial to diabetes people[24]. The Food and Drug Administration (FDA) has allowed its use in pharmaceuticals and food products, with an acceptable daily dose of 5 mg per kilogram body weight [25].

Therefore, the present study aims to develop novel co-grinding of etoricoxib with different excipients to enhance its solubility and dissolution rate, thereby potentially improving its oral bioavailability.

2. METHODS

2.1. Materials

Etoricoxib was received as a donation from Rameda Pharmaceutical Co. (Egypt). L-alanine, L-glycine and sucralose were purchased from El Nasr Pharmaceuticals Chemicals CO., Cairo, Egypt. Acetone was supplied by EL Nasr Pharmaceuticals Chemicals CO., Cairo, Egypt.

2.2. UV spectroscopic assay of etoricoxib

Briefly, methanol was used to prepare an etoricoxib standard stock solution with a concentration of 200 µg/ml, and phosphate buffer solution with a pH of 7.4 was used to appropriately dilute this stock and prepare a range of concentrations between 3 and 13 µg/ml.

Using a UV spectrophotometer (Thermo Fisher Scientific, Evo300pc, USA), the absorbance value of each concentration was measured at a wavelength (λ) of 235 nm [26]. This method was validated to ensure reliability and reproducibility. The calibration graph was drawn by plotting the recorded absorbance values against drug concentration.

2.3. Preparation of etoricoxib co-grinding mixture

The co-ground composite was prepared by acetone-drop grinding. This was carried out in accordance with the composition shown in Table (1). Using a mortar and pestle, both ETX and either L-alanine, L-glycine and sucralose were mixed and then co-ground with the dropwise addition of acetone until a thin paste was obtained. The paste was continuously ground until the organic solvent evaporated and a dry, flowable powder was formed. This process was repeated three times. To make sure all traces of leftover solvent were eliminated, the powder was left overnight [27]. The formulations were selected to be a ratio between the molecular weights of the materials used in the test [33]. As a result, for every excipient listed, three created formulae were evaluated. The selected drug excipient concentration were 1:1, 1:2, and 1:4 based on molar ratio.

Table 1. The composition of etoricoxib formulations using different excipients

	Etoricoxib (mg)	**1:1**	**1:2**	**1:4**
L-alanine (mg)	358.842	89.09 (F1)	178.18 (F2)	356.36 (F3)
L-glycine (mg)	358.842	75.067 (F4)	150.34 (F5)	300.268 (F6)
Sucralose (mg)	358.842	397 (F7)	794 (F8)	1588 (F9)

2.4. In-vitro characterization of the formulated preparations

The USP dissolution apparatus type 2 (paddle type) (Copley Scientific Dis 6000, Nottingham, United Kingdom) was employed to investigate the *in-vitro* dissolution of etroicoxib from the formulated preparations and its pure form. The paddle speed was established at 50 rpm, and the

dissolution media consisted of 900 mL of 7.4 phosphate buffer maintained at 37°C±0.5°C, according to the published procedure[28]. An amount of etoricoxib co-grinding formulations equivalent to 60 mg was put into the dissolution vessels. Samples (5 ml) were collected at designated scheduled times (5, 10, 15, 20, 30, 45, 60, 90, and 120 minutes) and were subsequently replenished with fresh dissolving media to maintain sink conditions [29]. The samples were promptly filtered using membrane filters with a pore size of 0.45 µm [30]. The initial 2 ml of the filtrate was thrown away, and the samples were assessed for drug concentration via UV spectrophotometry at 235 nm [26] after adequate dilution with the dissolution media. The dissolution studies were carried out in triplicate. The cumulative drug release amounts (expressed as percent (%) of the total drug added) were plotted against time to establish dissolution profiles, which were applied to calculate dissolution parameters for comparison purposes [31]. The amount of the active pharmaceutical ingredient dissolved in the first 5 minutes (Q5) and the dissolution efficiency (DE) were employed to compare the overall dissolution profiles [32]. Dissolution efficiencies were calculated from the area under the dissolution plot compared to the corresponding area obtained assuming 100% dissolution at the first time point [25].

3. RESULTS AND DISCUSSION

3.1. Determination of the calibration curve

The absorbance pattern of the drug showed a good recovery at the selected wavelength. The test was repeated several times to validate the results. The result is shown in Figure 2. The results were plotted in a linear chart with a regression of 0.9999, and the linear equation was:

$$y = 0.06x + 0.0531 \quad (2)$$

Y represents the absorbance, while X is the drug concentration (µg/ml).

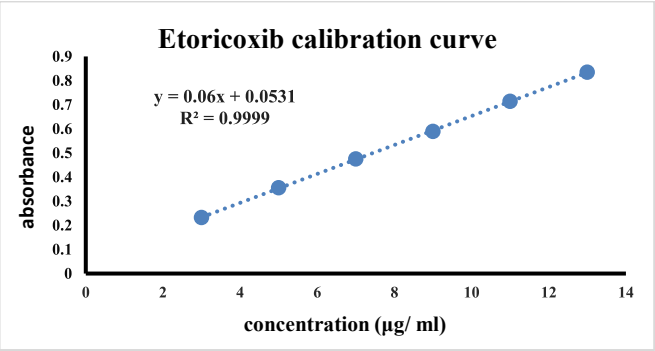

Figure 2. Calibration curve of Etoricoxib

3.2. In-vitro characterization of prepared formulations

Dissolution studies were conducted to assess the impact of co-processing etoricoxib with L-alanine, L-glycine and sucralose. Details of the formulation are provided in (Table 1). Figures 3, 4, 5 illustrates the dissolving profiles of pure etoricoxib and its various formulations in a phosphate buffer at pH 7.4. Dissolution parameters were calculated from the dissolution data to compare various formulations and are listed in (Table 2) as the percentage of medication released after 5 minutes (Q5), 10 minutes (Q10), and 60 minutes (Q60), and dissolution efficiency (%DE).

Furthermore, dissolution profiles were examined utilizing the similarity factor test, which calculates the F2 value using the following equation:

$$F2 = 50.log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}\right\}.100$$

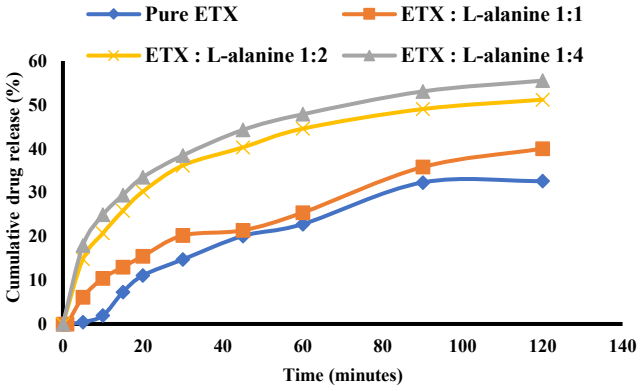

Figure 3. In-vitro dissolution of pure etoricoxib and L-alanine containing formulations at different ratios

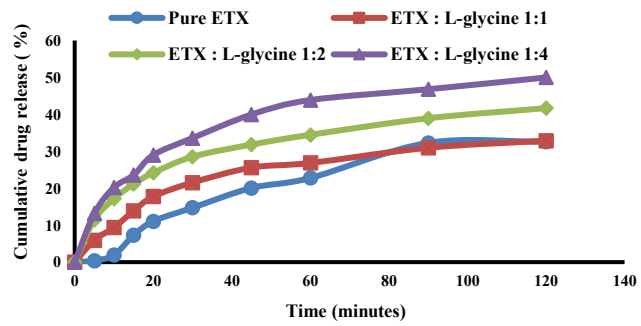

Figure 4. In-vitro dissolution of pure etoricoxib and L-glycine containing formulations at different ratios

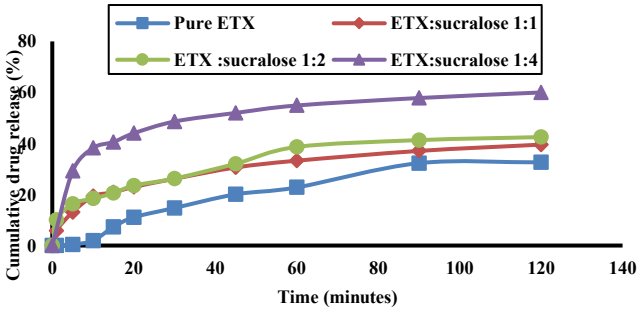

Figure 5. In-vitro dissolution of pure etoricoxib and sucralose containing formulations at different ratios

Table 2. The dissolution characteristics of etoricoxib from different formulations and its pure form. The quantity of drug released at 5 minutes (Q5), 10 minutes (Q10), and 60 minutes (Q60), in addition to the dissolution efficiency of etoricoxib in different formulations [Values between brackets represent standard deviation with a sample size of 3 (n=3)

Formulations	Q5 min (%)	Q10 min (%)	Q60 min (%)	DE (%)
Pure etoricoxib	0.41 (0.16)	1.92 (1.01)	22.78 (1.8)	21.55 (1.4)
F1	6.13 (2.7)	10.42 (4.5)	25.40 (5.4)	25.68 (1.2)
F2	14.79 (1.1)	20.70 (1.6)	44.56 (1.2)	40.25 (0.81)
F3	17.91 (2.4)	24.91 (1.33)	47.84 (2.3)	43.82 (1.9)
F4	5.95 (1.01)	9.35 (1.6)	26.85 (2.1)	24.65 (0.73)
F5	11.44 (1.7)	17.16 (3.4)	34.47 (3.5)	31.94 (1.3)
F6	13.18 (2.1)	20.20 (1.5)	43.88 (1.9)	38.86 (1.2)
F7	13.10 (3.3)	19.28 (4.4)	37.25 (3.7)	33.92 (1.8)
F8	16.35 (1.5)	20.41 (1.9)	40.64 (0.96)	37.48 (0.67)
F9	29.18 (1.8)	38.20 (0.66)	54.88 (0.37)	51.04 (0.48)

Where *F*2 is the similarity factor, n the number of data points, Rt is the amount (%) dissolved from the reference at time t. Tt is amount dissolved (in percentage) from the test, at the same time. F2 values less than 50 indicates dissimilar release profiles, while F2 > 50 indicates similar profiles [25]. The similarity factor between pure etoricoxib and the tested formulations is shown in table (3).

Table 3. The similarity factor between etoricoxib and the tested formulations

Drug Formulations	Similarity Factor (F2)
Etoricoxib - Formulation 1:1 L-alanine (F1)	57
Etoricoxib - Formulation 1:2 L-alanine (F2)	29
Etoricoxib - Formulation 1:4 L-alanine (F3)	25
Etoricoxib - Formulation 1:1 L-Glycine (F4)	54
Etoricoxib - Formulation 1:2 Glycine (F5)	41
Etoricoxib - Formulation 1:4 Glycine (F6)	38
Etoricoxib - Formulation 1:1 Sucralose (F7)	36
Etoricoxib - Formulation 1:2 Sucralose (F8)	30
Etoricoxib - Formulation 1:4 Sucralose (F9)	17

The dissolution profile of pure etoricoxib exhibited inadequate slow release, with just 0.41% of the administered dose released after 5 minutes. This, coupled with a dissolution efficiency of merely 21.55%, underscores the hydrophobic characteristics of etoricoxib. This may be attributable to inadequate wettability of the particles [34].

The acetone-assisted grinding of etoricoxib with L-alanine in a 1:1 molar ratio (F1) demonstrated dissolution parameters like those of pure etoricoxib, indicating that the grinding of the drug at this ratio was insufficient for better dissolution. This assumption is confirmed by a similarity factor greater than 50. Increasing L-alanine content to 1:2 and 1:4 molar ratio (F2 and F3) improved dissolution parameters that were superior to F1. The supremacy is evidenced by a similarity factor of less than 50. The observed upgrading change may result from modifications in crystalline structure due to wet grinding and the solubilizing effects of amino acids. Amino acids enhance drug solubility due to their hydrophilic properties, which function as counter ions, thereby improving solubility [35].

The grinding of etoricoxib with L-glycine, assisted by acetone, yielded dissolution parameters comparable to those observed in the dissolution profile of L-alanine. The 1:1 molar ratio (F4) did not produce a significant alteration in the dissolution pattern of ETX (F2 value > 50). In contrast, the co-ground mixture at elevated molar ratios of 1:2 and 1:4 (F5 and F6) released the drug substantially faster ($P < 0.05$) than the 1:1 molar ratio (F4) (F2 value < 50). A notable difference was observed in the comparison of Q5, Q10, and dissolution efficiency. The arguments for the improved etoricoxib from formulations incorporating L-alanine can be applied here.

The grinding of etoricoxib with sucralose using acetone produced varying dissolution behaviors in the tested formulations (F7, F8, and F9). The rise of the sucralose molar ratio seemed to have a notable change in drug dissolution. 1:1 and 1:2 formulations (F7 and F8) showed low dissolution profiles, but still, they showed better dissolution profiles than pure ETX (F2 value <50). On the other hand, 1:4 sucralose-containing formulations had good dissolution profiles, releasing a remarkable amount of loaded drug in the crystalline system (F2 value <50). The enhanced dissolution rate can be explained based on the formation of co-crystallization between etoricoxib and sucralose.

4. CONCLUSION

Sucralose as a guest molecule, significantly improved etoricoxib dissolution. The *in-vitro* characterization revealed enhancement in the solubility properties of etoricoxib, which may have led to a better dissolution profile. The co-grinding of etoricoxib and sucralose, produced at a drug: carrier molar ratio of 1:4 (F9), exhibited better solubility and drug release within five to ten minutes from the formula with desired dissolution efficiency. These findings suggest that the Etoricoxib–sucraose co-grinding formulation could serve as a promising candidate for further development, with the potential to enhance oral bioavailability.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to the submitted work.

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