Enhancement of Aqueous Solubility and Dissolution Rate of Etoricoxib by Solid Dispersion Technique

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Abstract

Etoricoxib (EXB) is a highly selective cox-2 inhibitor which belongs to the non-steroidal anti-inflammatory drug (NSAID). EXB is a class II drug according to the biopharmaceutical classification system (BCS), which possess a very low aqueous solubility in water. In the present study, many trials were made to improve the aqueous solubility and dissolution rate of EXB by solid dispersion technique.

Eighteenth EXB formulas were formulated as a solid dispersion using a variety of hydrophilic polymers (as carriers) including poloxamer 407 (PXM 407), poloxamer 188 (PXM 188) and polyethylene glycol 4000 (PEG 4000) at different drug: polymer ratios (1:1, 1:3 and 1:5). These formulas were prepared by two methods; solvent evaporation and fusion method. The prepared formulas were evaluated for practical yield percent (PY %), drug content, saturated solubility and release rate, Fourier transforms infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and powder x-ray diffraction (PXRD).

It was found that the solubility was affected by the polymer type and the method of preparation. The polymers (as carriers) used to prepare EXB- solid dispersion showed improvement in the solubility in the following descending order; PXM 407>PXM 188> PEG 4000. The optimum formula (SD15) composed of the drug: PXM 407 at a ratio of 1:5 was prepared by solvent evaporation showed 7.76 folds (767.40%) solubility improvement as compared to pure EXB. The optimum formula showed a release rate of 99.8% through the first 15 min. The advance characterization of the selected formula indicated the possible transformation of the drug to the amorphous state.

Keywords: EXB, Solid dispersion, PXM 407, PXM 188, PEG 4000.

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Solid dispersion of etoricoxib with hydrophilic carriers

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Introduction

Etoricoxib (EXB) is a cyclooxygenase-2 (COX-2) specific inhibitor which belongs to non-steroidal anti-inflammatory drugs (NSAIDS). Cyclooxygenase-2 physiological role is the synthesis of prostanoid mediators of pain, inflammation and fever. EXB selectively inhibits the Cyclooxygenase-2(COX-2) isoenzyme action while sparing Cyclooxygenase-1 (COX-1), which is presented in the gastrointestinal tract, kidneys and platelets (1).

Therefore, the potential gastrointestinal adverse effects and impacts on platelet aggregation are less than other non-selective COX inhibitors (2).

Etoricoxib is used to relieve the symptoms of rheumatoid arthritis, osteoarthritis, acute gout, chronic musculoskeletal pain (including chronic low back pain), and primary dysmenorrhoea (3).

Etoricoxib has nomenclature is 5-chloro-6'-methyl-3-[4- (methylsulfonyl) phenyl]-2, 3'-bipyridine and a molecular weight of 358.84 g/mol (Figure 1). It has a molecular formula of C_{18}H_{15}ClN_2O_2S, a partition coefficient (LogP) of 3.9, and it presented as a whitish to creamish coloured powder (4).

Figure 1.Structural formula of EXB (5)

Etoricoxib is classified as a class II based on the biopharmaceutical classification system, due to its low aqueous solubility and thus reduced dissolution rate, which may induce challenges to the formulator (6).

Poor aqueous solubility is a significant problem that can delay the action of the drug and impart difficulties to the drug formulation. The enhancement of drug solubility has a significant impact on improving dissolution behaviour, which later on improving drug pharmacokinetics and therapeutic efficacy (7).

To enhance the low aqueous solubility of the drug and improve its dissolution, several strategies can be employed such as particle size reduction, use of surfactants, pH adjustment, and complexation with cyclodextrin and solid dispersion (8).

Solid dispersion was first introduced in 1961 by Sekiguchi and Obi as a method for enhancing aqueous solubility and dissolution rate of poorly soluble drugs. The proposed solid dispersion is an eutectic mixture of a hydrophobic drug dispersed in an inert hydrophilic carrier or matrix (9).

The purpose of the present study was to enhance the solubility and dissolution rate of EXB by solid dispersion using different carriers in different ratios and different preparation methods. The study was done to compare and investigate the best carrier type, ratio and method to enhance EXB solubility and dissolution rate.

Materials and methods

Materials

Etoricoxib (Virdev, India), Poloxamer 407 (PXM 407) and Poloxamer 188(PXM 188) from Sigma, USA), polyethylene glycol 4000 (PEG 4000) from (Ineos chemicals, Belgium), methanol (Sigma-Aldrich Co., Germany). All other reagents were of analytical grade.

Methods

Preparation of EXB-solid dispersion by the solvent evaporation method

Etoricoxib solid dispersion was prepared by solvent evaporation method using different polymers (as carriers) including PXM 407, PEG 4000, and PXM 188 at three different ratios (1:1, 1:3, 1:5) (drug: carrier ratio w:w) as shown in table (1). The carriers and drug were accurately weighed and dissolved in methanol separately by utilizing a magnetic stirrer. Then followed by mixing of the two solutions by a magnetic stirrer as well. The solvent was evaporated by leaving it in an oven at 40°C for 24 hr. The resultant dried mass was pulvrised and sieved through sieve no.60 then stored in a desiccator for further investigations (10).

Preparation of EXB-solid dispersion by the fusion method

The fusion method involved liquefying specific amounts of carriers and drug at ratios (1:1, 1:3, and 1:5) (drug: carrier ratio w:w) as shown in table (1). The carrier was first melted in porcelain petri-dish slightly above its melting point. The drug was added to the molten carrier followed by constant stirring for five minutes then cooled down using an ice bath. The dried mass was then pulvrised and sieved through sieve no.60 and stored in a desiccator for further investigations (11).
Table 1. Composition of EXB solid dispersion

| Formula Number | Carrier | Drug:carrier ratio (w:w) | Preparation method |
|----------------|---------|--------------------------|--------------------|
| SD1            | PXM 188 | 1:1                      | Fusion             |
| SD2            | PXM 188 | 1:3                      | Fusion             |
| SD3            | PXM 188 | 1:5                      | Fusion             |
| SD4            | PXM 407 | 1:1                      | Fusion             |
| SD5            | PXM 407 | 1:3                      | Fusion             |
| SD6            | PXM 407 | 1:5                      | Fusion             |
| SD7            | PEG 4000| 1:1                      | Fusion             |
| SD8            | PEG 4000| 1:3                      | Fusion             |
| SD9            | PEG 4000| 1:5                      | Fusion             |
| SD10           | PXM 188 | 1:1                      | Solvent evaporation|
| SD11           | PXM 188 | 1:3                      | Solvent evaporation|
| SD12           | PXM 188 | 1:5                      | Solvent evaporation|
| SD13           | PXM 407 | 1:1                      | Solvent evaporation|
| SD14           | PXM 407 | 1:3                      | Solvent evaporation|
| SD15           | PXM 407 | 1:5                      | Solvent evaporation|
| SD16           | PEG 4000| 1:1                      | Solvent evaporation|
| SD17           | PEG 4000| 1:3                      | Solvent evaporation|
| SD18           | PEG 4000| 1:5                      | Solvent evaporation|

Characterization of EXB-solid dispersion

Determination of EXB saturated solubility

An excess amount of EXB pure powder was added to 10 ml of distilled water, 0.1N HCl and phosphate buffer pH 6.8. The mixtures were placed in a shaking water bath at a constant temperature of 25°C for 72 hr. span. Then the mixture in suitable tubes was placed in the centrifuge for 15 min at 3000 rpm. The solutions were filtered utilizing a 0.45μm filter syringe, and concentration of the filtrate was measured by UV–spectrophotometer at λmax 234 nm to determine the solubility of EXB (12).

Determination of practical yield per cent (PY %) of the prepared EXB solid dispersion

The practical yield per cent (PY %) of the prepared EXB solid dispersion was conducted to know the efficiency of each preparation method. The (PY %) was determined by calculating the ratio of the actual weight of the obtained solid dispersion on the theoretical mass of drug and carrier (equation 1) (13).

\[
PY(\%) = \frac{\text{Practical mass(SD)}}{\text{Theoretical mass(Drug + Carrier)}} \times 100
\]

Eq. (1)

Determination of EXB content in the prepared solid dispersion

The EXB solid dispersion equivalents to 50mg of EXB was dissolved in 40 ml methanol using 50 ml volumetric flask and followed by sonication for 15 min. The volume was made up to 50 ml using methanol. After that, the resultant drug solution was diluted with methanol; the drug solution was assayed for drug content using UV-spectrophotometer at λmax 234 nm (14). The percentage of drug content in the obtained solid dispersion was determined by using the following (equation-2) (15).

Drug content% = \[
\frac{\text{Actual weight of EXB}}{\text{Theoretical weight of EXB}} \times 100\]

Eq. (2)

Determination of saturated solubility of EXB in solid dispersion

The solubility of the prepared EXB-solid dispersion was carried out in aqueous media. The solubility study was performed by adding excess amounts of EXB-solid dispersion into screw-capped vials containing 10 ml of water. The tightly sealed vials were kept in a water bath shaker at 25°C for 48hr. The saturated solutions were then analysed using UV-spectrophotometer at λmax 234 nm (16).

In-vitro dissolution studies of EXB-solid dispersion

In-vitro dissolution of EXB-solid dispersion was determined and compared with pure EXB drug by using USP XXII rotating paddle apparatus I. Etoricoxib-solid dispersion equivalents to 60 mg of the pure drug was dispersed in dissolution medium surface. The dissolution medium employed for drug release study was 900 ml of phosphate buffer (pH 6.8) containing 1% w/v sodium lauryl sulphate (SLS) to maintain sink conditions. The temperature was set at 37±0.5°C using a
thermostatic water bath with shaking by the paddle rotating at 100 rpm. Five milliliters samples were withdrawn after 5, 10, 15, 20, 30, and 45 min. Sink condition was kept by replacing every withdrawn sample with an equal volume of fresh phosphate buffer (pH 6.8 with 10% w/v SLS). The samples were filtered via a 0.45μm filter membrane and assayed using UV-spectrophotometer at λmax 234 nm.

Factors affecting dissolution behaviour of EXB from solid dispersion

Effect of polymer type
The impact of different polymer types (PXM 188, PXM 407 and PEG 4000) on the drug release of prepared solid dispersion was studied by the formulas SD12, SD15 and SD18, respectively. These formulas had the same ratio of drug: polymer (1:5) and prepared by solvent evaporation method. The results were compared to the release of pure drug. The ratio of drug: polymer (1:5) was chosen to study this effect since the highest solubility was obtained by this ratio for all the used polymers compared to other ratios.

Effect of the drug: carrier ratio
The impact of the different drug: polymer ratio on the drug release of prepared solid dispersion was studied with formulas SD13 (1:1), SD14 (1:3) and SD15 (1:5). Since all of them were prepared by solvent evaporation method using PXM 407 as a carrier. The results were compared to the release of pure drug.

Effect of preparation methods
The effect of preparation method on the drug release of prepared solid dispersion was studied with formulas SD6 which was prepared by fusion method and SD15 which was prepared by solvent evaporation method. These formulas were chosen since both of them were prepared using the same polymer (PXM 407) and with the same drug: polymer ratio (1:5) but by different methods.

Selection of the optimum formula
The selection of the optimum formula was depended on the solubility study and the dissolution profile of EXB solid dispersion.

Evaluation of the selected formula
Fourier transforms infrared spectroscopy (FTIR)
The FTIR analysis of pure EXB, PXM 407 and the selected formula was performed to investigate drug-polymer intermolecular interaction. The samples were compressed with potassium bromide (KBr) as a disc, and analyzed by FTIR apparatus (Shimadzu8000, Japan); the scanning range was 4000- 400 cm\(^{-1}\).

Differential scanning calorimetry (DSC)
Thermal characteristics of the selected formula, pure EXB and the purely related polymer were analyzed by an automatic thermal analyzer system (Shimadzu, DSC-60, and Japan). Each sample (5 mg) was placed in none hermetically aluminium pan and heated at rate 10°C/ min over temperature 5°C to 300°C. The analysis was carried out under the atmosphere flow conditions.

Powder x-ray diffraction (PXRD)
Powder x-ray diffraction was utilized to analyze the crystallinity of the pure EXB and selected formula. The PXRD measurement was performed under the following conditions: the target metals Cu, filter Kα, 45kV voltage, 30mA current. Samples scanned over a 20 range of 30-80° at a step size of 0.02°.

Statistical analysis
The results of the experiments were given as a mean for triplicate samples ±standard deviation (std) and were analyzed according to a one-way analysis of variance (ANOVA). The test level of (P < 0.05) was considered to be statistically significant, using Microsoft Excel 2010.

Results and Discussion

Characterization of EXB-solid dispersion

Determination of EXB saturated solubility
The solubility of EXB in different media (water, 0.1N HCl and phosphate buffer pH 6.8) at 25 °C was determined. Table 2 showed that the equilibrium saturated solubility for EXB was highly pH-dependent. Since, the solubility decreased from 24.23 mg/ml (sparingly soluble) at pH 1.2 of 0.1 N HCl to 0.076 mg/ml (practically insoluble) at pH 6.8 phosphate buffer. This result was in agreement with previous study.
Table 2. The saturated solubility of EXB in different media at 25°C.

| Solvent          | Solubility (mg/ml) mean±std (n=3) | Solubility definition |
|------------------|-----------------------------------|-----------------------|
| Distilled water  | 0.089 ± 0.1                       | Practically insoluble  |
| 0.1 N HCl        | 24.23 ± 0.4                       | Sparingly soluble      |
| Phosphate buffer 6.8 | 0.076 ± 0.2                      | Practically insoluble  |

**Determination of practical yield percent (PY %) and content of the prepared EXB-solid dispersion**

The (PY %) of the prepared EXB-solid dispersion was determined to investigate the best method for the preparation of solid dispersion granules. Both solvent evaporation and fusion methods gave acceptable PY % ranged from 94-99.3%, as shown in table 3.

The results elucidated that both fusion and solvent evaporation methods are comparable. The results are associated with the best entrapment of EXB particles by carrier utilized in both preparation methods. Moreover, the content of EXB loading in solid dispersion was found in a range of 94.13% - 103.9% in all prepared formulations, which was consistent with the same range of U.S. Pharmacopoeia requirements (90-110%). The above results suggested a uniform distribution of EXB particles within polymers (as a surfactant) used in all prepared formulas.

Table 3. The practical yield percent (PY %) and drug content of EXB solid dispersion using different methods

| Formula number | Preparation method | Practical yield percent (PY %) | Drug content mean±std (n=3) |
|----------------|--------------------|--------------------------------|-----------------------------|
| SD1            | Fusion             | 97.42%                         | 98.62 ±0.01                 |
| SD2            | Fusion             | 96.6%                          | 98.23 ±0.03                 |
| SD3            | Fusion             | 98.8%                          | 99.05 ±0.01                 |
| SD4            | Fusion             | 97.88%                         | 103.9 ±0.05                 |
| SD5            | Fusion             | 99.43%                         | 97.9 ±0.02                  |
| SD6            | Fusion             | 98%                            | 98.11 ±0.01                 |
| SD7            | Fusion             | 98.17%                         | 98.61 ±0.14                 |
| SD8            | Fusion             | 98%                            | 94.13 ±0.06                 |
| SD9            | Fusion             | 96%                            | 95.11 ±0.01                 |
| SD10           | Evaporation        | 98%                            | 97.56 ±0.01                 |
| SD11           | Evaporation        | 95.6%                          | 99.08 ±0.02                 |
| SD12           | Evaporation        | 99.3%                          | 99.70 ±0.12                 |
| SD13           | Evaporation        | 94%                            | 97.03 ±0.01                 |
| SD14           | Evaporation        | 94.35%                         | 95.40 ±0.04                 |
| SD15           | Evaporation        | 95.4%                          | 97.7 ±0.06                  |
| SD16           | Evaporation        | 98.8%                          | 99.03 ±0.01                 |
| SD17           | Evaporation        | 96.6%                          | 98.8 ±0.03                  |
| SD18           | Evaporation        | 96.06%                         | 99.8 ±0.12                  |

**Determination of saturated solubility of EXB in solid dispersion**

It was found that there was no significant difference among PXM 188, PXM 407 and PEG 4000 at 1:1 (drug: polymer) ratio in enhancing solubility using solvent evaporation method as shown in figure 2. While, figure 3 shows that a significant (p<0.05) enhancement in solubility was obtained by using PXM 407 at 1:3 (drug: polymer) ratio using solvent evaporation method. The best result (0.691 mg/ml) was found when PXM 407 was utilized as a carrier at a ratio of 1:5 W:W (drug: polymer) the solid dispersion was prepared by solvent evaporation method as shown in figure 4.

The enhancing in the aqueous solubility of 7.76 folds (676.40%) with PXM 407 as compared with pure EXB was due to the hydrophilic nature of the carriers and the hydrogen bonding formation between EXB and these carriers. The high hydrophilic nature of PXM 407 in comparison with other carriers is contributed to increasing the wettability and high solubility of the EXB particles.
Solid dispersion of etoricoxib with hydrophilic carriers

The use of surface-active agents (e.g. poloxamer) may overcome precipitation and the recrystallization of the drug from the amorphous state during the cooling or solvent removal step of the preparation process or storage which was considered as one of the disadvantages of solid dispersion (26).

Figure 5. Effect of polymer type of EXB-solid dispersion prepared by solvent evaporation method with the drug: polymer ratio 1:5 on the release profile of EXB in phosphate buffer pH 6.8 dissolution medium at 37°C

Effect of the drug: carrier ratio

The effect of the different drug: carrier ratio on the dissolution behaviour of EXB solid dispersion is shown in figure 6. The figure represents the release profile of EXB drug from solid dispersion prepared by the solvent evaporation method using PXM 407 as a carrier as well as pure EXB. It was observed that as the amount of PXM 407 increased in formulas (SD13, SD14, SD15), the drug release from solid dispersion was increased significantly (P<0.05). Formula SD15 exhibited the highest percent of release by (99.8%) within the first 15 min as compared with SD13 (61.3%), SD14 (74.09%) pure EXB (21.19%).

The enhanced in-vitro dissolution rate of EXB solid dispersions that were formulated with higher ratios of the water-soluble carriers was attributed to the improved drug wettability, high probability of a reduction in particle size and possible conversion to the amorphous forms which was confirmed later by DSC and PXRD (27).

In-vitro release of EXB solid dispersion

Effect of polymer type

At a constant ratio of drug: polymer (1:5), PXM 407(SD15) showed EXB release of 99.8% within the first 15 min in comparison with other the types of carriers and pure EXB. The release percentage after 15 min were 82.21%, 77.76% and 21.19% for PXM 188(SD12), PEG 4000(SD18) and pure EXB, respectively as shown in figure 5.

This significant result (p<0.05) was attributed to the enhanced solubility of EXB solid dispersion. These results were due to the increase of the wettability and possible decrease in the crystallinity of EXB. The outcome was a consequence of the interaction of EXB with many propylene oxide hydrophobic segments of PXM 407 (25).
Effect of preparation methods

The dissolution profile of EXB binary solid dispersion was affected by the preparation techniques. Figure 7 revealed the amount of EXB released from the formulas contain PXM 407 at a ratio 1:5 that formulated by solvent evaporation (SD15) and fusion (SD6) methods. The amount of EXB released after 15 min was found to be 99.8% for (SD15) and 81.5% for (SD6). Therefore the binary system of EXB and polymer (as a carrier) tend to release EXB as fine particles when it touched the dissolution medium as compared to the fusion technique. The higher release privilege was attributed to the uniform distribution of the drug and the surface activity of the PXM 407 in the molecular dispersion (28).

Selection of the optimum formula

The optimum formula was (SD15) which composed of EXB-PXM 407 solid dispersion at a ratio of 1:5 that was formulated by the solvent evaporation method. It was characterised by enhanced solubility, and the highest amount of EXB released within a short time. Therefore it was subjected to further invitro evaluation studies.

Evaluation of optimum formula

Fourier transforms infrared spectroscopy (FTIR)

The FTIR spectrum of the pure EXB (Figure 8) showed characteristic peaks of C–H stretching vibration at 2964 cm\(^{-1}\) and C = N stretching vibration at 1597cm\(^{-1}\), 1564 cm\(^{-1}\) and 1493 cm\(^{-1}\). Prominent peaks at 1431 cm\(^{-1}\), 1298 cm\(^{-1}\), 1144 cm\(^{-1}\) and 1086 cm\(^{-1}\) indicate S=O stretching vibrations. C–Cl stretching vibration was denoted by the presence of peaks at 841 cm\(^{-1}\), 775 cm\(^{-1}\) and 729 cm\(^{-1}\), these results were in agreement with previous studies (29).

The FTIR spectra of optimum formula (SD15), as shown in figure 10, was examined and compared with FTIR of EXB pure (Figure 8) powder and PXM 407 (Figure 9) spectrum separately. In SD15 spectrum all peaks of EXB were almost diffused except peaks at 777, 841 and 1599 cm\(^{-1}\), while the other peaks could no longer be noticeable. The characteristic peaks of PXM 407 were 1111 cm\(^{-1}\) (C–O intense) and 2887 cm\(^{-1}\)(C–H stretching) presented at the same position and became more intensified in the solid dispersion. However, no additional peak was observed in the solid dispersions declared the absence of any chemical interaction between EXB and carrier (30).
Figure 8. FTIR spectrum of EXB

Figure 9. FTIR spectrum of PXM 407.
**Figure 10. FTIR spectrum of the best formula (SD15)**

*Differential scanning calorimetry (DSC)*

The DSC thermograms of EXB and PXM 407 were represented in figures 11 and 12. They show a sharp endothermic peak at 138.00°C and 58.2°C, respectively. They represented the melting point of EXB and PXM 407, which revealed the crystalline nature of the drug and the polymer as previously reported (31,32). Figure 13 represented the DSC thermogram of SD15. There was a single endothermic peak at 55.9°C which was around the PXM 407 melting point. While, the absence of endothermic peak of EXB (at 138.0°C) might be attributed to the existence of EXB in an amorphous state rather than its original crystalline state (33).

**Figure 11. The DSC thermogram of EXB.**
Powder x-ray diffraction (PXRD)

Powder X-Ray Diffraction was utilized to analyze the crystallinity of the substance such as pure EXB and SD15. The degree of crystallinity was resolved (34). The PXRD analysis of EXB and optimum formula (SD15) were given in figures 14 and 15, respectively. The drug characteristic peaks were observed at 16.59°, 15.52° and 18.14° at a 2θ value with intensity 4750, 2480 and 2060, respectively. While the PXRD pattern of optimum formula (SD15) showed characteristic peaks at 19.15°, 23.28° and 22.75° with an intensity of 2320, 2120 and 700 respectively. The intensity of the characteristic peaks of the pure drug (16.57°, 15.49° and 18.13°) were markedly reduced to (600, 310 and 300) indicating the drug crystalline was converted to amorphous upon molecular dispersion (35).
Conclusions

Based on the results obtained from the present study, it can be concluded that the solubility of EXB (class II drug) was successfully enhanced by solid dispersion technique, and PXM 407 surface active agent was the best carrier at a ratio of 1:5 drug: polymer. Moreover, the solvent evaporation method was the preferred method for the preparation of EXB solid dispersion in contrast to the fusion technique.

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Figure 15. X-Ray Diffraction pattern of the SD15
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