**World Journal of Pharmaceutical Sciences**
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers 
Available online at: http://www.wjpsonline.org/
**Original Article**

# Effect of kollidon 90F and poloxamer188 on etoricoxib to enhance it's dissolution property by simple physical mixing and fusion techniques

A.S.M. Monjur-Al-Hossain[1*], Md. Raihan Sarkar[2], Md. Anisur Rahman[1], Shamsunnahar Khushi[1], A. B. M. Faroque[3]

[1]Pharmacy Discipline, Khulna University, Khulna 9208, Bangladesh
[2]Department of Pharmacy, Jagannath University, Dhaka, Bangladesh
[3]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka 1000, Bangladesh

**Received: 04-07-2014 / Revised: 18-07-2014 / Accepted: 26-07-2014**

## ABSTRACT

Etoricoxib Solid dispersions (SD) were prepared by simple Physical Mixing (PM) and fusion techniques using Kollidon 90 F and poloxamar 188. In case of PM Drug and carriers were used at 1: 0.5, 1:1, 1:2 ratios but in fusion methods ratios were 1:2 because in PM better results were found at that ratio. *In vitro* dissolution study was performed in distilled water for 60 minutes at 50 rpm and 37±0.5°C. In case of poloxamer 188 better dissolution was achieved at 1:2 ratios in fusion method; after first 10 minutes, dissolution was 89%. After completing dissolution for 60 minutes, release rate of etoricoxib was increased in kollidon 90F. In case of physical mixing technique, 33% etoricoxib loading (theoretical) was made possible while incorporating within the carrier mass while in case of fusion method, maximum 8.82% drug loading was found. Being a BCS class II drug, etoricoxib entails to be incorporated itself in such formulations which ensures faster dissolution and ultimately more bioavailability.

**Key Words:** Etoricoxib, physical mixing technique, fusion technique, BCS class II drug.

## INTRODUCTION

The most challenging aspects of drug development are enhancement of oral bioavailability of poorly water soluble drugs. For solid dosage form, rate and extent of absorption of the drug is the determinant of rate and extent of dissolution of the active ingredient. But in case of poorly water soluble drugs, the rate limiting step in the process of drug absorption is drugs dissolution. For poorly aqueous soluble drugs, solubility in the solvents plays the major role in dissolution of the drug. Therefore, the rate of oral absorption of these drugs is controlled by their dissolution rate in the gastrointestinal tract. Thus solubility and dissolution rate are the key determinants of oral bioavailability [1-3]. The most promising technique of enhancing drug dissolution is solid dispersion of drug in a water soluble polymer. The definition of Solid dispersion (SD) may be as the dispersion of one or more active ingredients in inert carriers at solid state prepared by physical mixtures, fusion, Solvent or solvent evaporation methods [4]. Etoricoxib (ETX), a selective COX-2 inhibitor, is being used in osteoarthritis, rheumatoid arthritis and acute gout. Etoricoxib is freely soluble in tetrahydrofuran, methanol, dimethyl sulfoxide, chloroform, dimethyl formamide, and methyl ethyl ketone. Etoricoxib is soluble in isopropyl acetate, ethanol and toluene, sparingly soluble in 2-propanol, and practically insoluble in water [5]. Various commercially viable techniques such as liquisolid, [6-8] nanomorph, [9] *in situ* micronization, [10-11] and coprecipitation using antisolvent [12] are available for improvement of solubility and dissolution rate of poorly soluble drugs. Other techniques have also been reported such as use of surfactants in the formulation, micronization of drug but both have limitations [13-14]. But ahead of all, the most promising method for formulators is solid dispersion because of its ease of preparation, ease of optimization, and reproducibility. To yield solid dispersion, poorly soluble drugs are dispersed in an inert hydrophilic

***Corresponding Author Address:** A.S.M. Monjur-Al-Hossain, Assistant Professor, Pharmacy Discipline, Khulna University, Khulna, Bangladesh; E-mail: shiplu_pharm@yahoo.com*

polymer or matrix in case of physical mixing, melting, fusion, solution formation, or solvent melting [15-17]. Solid dispersions (SDs) are prepared by the use of water soluble low melting point synthetic polymers such as polyethylene glycols (PEGs) or mannitol, polyvinylpyrrolidone (PVP) [18-19]. These polymers showed best results in drug dissolution enhancement, but the ratios of using these polymers is relatively large, around 1:2 to 1:8 (drug: polymer) [20]. It has been observed that in dissolution media, PVP and PEG get dissolved first leaving the drug back in undissolved state. In those cases, in presence of small amount of plasticizers such as water possibility of rapid reversion of amorphous drug to the more stable crystalline state is more [21]. A wide variety of poorly aqueous soluble drugs such as Nifedipine, Ketoprofen, Nimesulide, Tenoxicam, Aceclofenac, Valdecoxib is used for solid dispersion technique by the use of various hydrophilic carriers like polyethylene glycol, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, sugar, mannitol, urea etc. [22]. According to literature survey, in order to improve dissolution properties of poorly soluble drugs like etoricoxib, Kollidon 90 F and poloxamar 188 have still been unexplored to form solid dispersion.

In the present work Etoricoxib was used as a model drug and kollidon 90F and poloxamar 188 were used as carriers at 1:0.5, 1:1, 1:2 ratios to prepare solid dispersion. Drug administered in solid dispersion enhances the dissolution and immediate release, as oral administration of drug is used in osteoarthritis, acute gouty arthritis, acute pain including post-operative dental pain and primary dysmenorrhoea.

## EXPERIMENTAL

**Materials:** Etoricoxib was received as generous gift from Beximco Pharmaceuticals Ltd., Bangladesh. Kollidon 90 F and poloxamer 188 were also received.

**Preparation of Etoricoxib-Polymer Physical Mixture:** Simple physical mixtures (PMs) of ETX were prepared by mixing ETX with polymers in a mortar-pestle while drug-polymer ratio is maintained at 1:0.5, 1:1 and 1:2. Mixing was performed for 60 minutes with the interval of 10 minutes. Individual formulations were then filled in airtight vials and the vials were preserved in a desiccator until further use.

**Preparation of Etoricoxib-Polymer-Carrier Fusion Technique:** Etoricoxib solid dispersion prepared by fusion method using Poloxamer 188 and kollidon 90 F was carried out by melting Polyethylene glycol (PEG) 6000. Accurately weighed amounts of Polyethylene glycol 6000 was placed in an aluminum pan on a hot plate and melted, with constant stirring at a temperature of about below 70°C. An accurately weighed amount of Etoricoxib & excipients were incorporated into the melted Polyethylene glycol with stirring to ensure homogeneity and cooling immediately with continuous stirring to dry mass. The pan was then removed from the hot plate and allowed to cool at room temperature. Then transferred the mixture in a mortar and pestle and grinding them for about 10 minutes until a homogenous fine mixture was obtained and then stored in desiccators at a room temperature until further use. This process was repeated for other excipients. Etoricoxib carriers were used at 1:2 ratios. Each formulation was done in triplicate.

**Preparation of Calibration of Etoricoxib:** 20 mg of ETX powder was taken in 1000 mL volumetric flask containing 100 mL of methanol previously and a clear solution was made after moderate shaking. Then the volume of this solution was made up to 1000 mL using phosphate buffer solution of pH 7.4. Concentration of ETX in this solution was 20µg/mL. Then by serial dilution, 9 another solution was prepared whose concentration was 18 µg/mL, 16 µg/mL, 14 µg/mL, 12 µg/mL, 10 µg/mL, 8 µg/mL, 6 µg/mL, 4 µg/mL and 2 µg/mL. Absorbance of these solutions was measured using a UV-VIS spectrophotometer (UVmini-1240, Shimadzu Corporation, Japan) at 284 nm. Then by plotting absorbance against concentration, calibration curve was constructed. Following the same procedure, calibration curve was also constructed using distilled water.

***In Vitro* Dissolution Study:** Using a USP XXX apparatus type II (Electrolab, India), *in vitro* release study was performed for 60 minutes in 900 mL distilled water. Paddle rotation speed was 50, temperature was 37±0.5°C and withdrawn sample volume was 10 mL where sampling intervals were 10, 20, 30, 40, 50, 60 minutes. In a UV-VIS spectrophotometer (UVmini-1240, Shimadzu corporation, Japan), withdrawn samples were analyzed (either directly or after dilution) at 284 nm.

## RESULTS AND DISCUSSION

As mentioned earlier, ETX is freely soluble in ethanol. Though calibration curve was prepared using both distilled water and phosphate buffer solution of pH 7.4 where a fixed amount of ETX was dissolved in ethanol, both the curves showed almost similar extent of linearity (figure 1). So, distilled water was used finally for dissolution purpose.

Figure 2 and 3 shows the zere order and higuchi release curves of ETX in PMs Techniques. As maximum as 75% ETX was found to be released in case of physical mixtures (PMs) with poloxamar 188 (1:2 ratio) (POL 188) after first 10 minutes of dissolution. It was 65% for kollidon 90F. It was only 19% for pure ETX. After 60 minutes, cumulative percent release of ETX was 94% for POL188 and 92% for kollidon 90F. It was only 55% for pure ETX.

Figure 4 and 5 shows the zero order and higuchi release curves of ETX in fusion techniques. As maximum as 90% ETX was found to be released in case of fusion techniques with POL 188 (1:2 ratio)) after first 10 minutes of dissolution. It was 75% for kollidon 90F. It was only 19% for pure ETX. After 60 minutes, cumulative percent release of ETX was about 100% for POL188 and about 100% for kollidon 90F. It was only 55% for pure ETX.
Figure 6 shows that cumulative % release of ETX is better in fusion technique than PMs. So we can say that ETX ternary SD> ETX binary SD> Pure ETX

Figure 7 shows that release rate of Etoricoxib is better in fusion technique than PMs. The release rate for pure Etoricoxib was 7.118 mg/ml/sqrt which were increased in case of binary and ternary SD with Poloxamar 188 formulations. The release rates of these formulations were 11.29 mg/ml/sqrt and 11.89 mg/ ml / sqrt. However the release rates of binary and ternary SD with Kollidon 90F formulations were 11.48 mg/ml/sqrt and 12.36 mg/ ml / sqrt. Due to following reasons drug dissolution is increased for SDs comprising of different hydrophilic polymers:

- The drug is usually partially dissolved in melted or dissolved polymer in solid dispersions. These SDs are dried and then the drug will not nucleate to form micro crystals. The ability of rapid wetting and thereby dissolution of drug is shown by hydrophilic polymers if drug microcrystals are embedded in the water-soluble matrix [23]. Generally polyethylene glycols and polyvinyl pyrrolidone solid dispersions follow this principle.
- Higher dissolution rate is observed for solid dispersions of sodium starch glycolate, when compared with other excipients and this may be owing to their easy and rapid dispersibility in the aqueous dissolution fluids [24].
- SDs comprising of hydrophilic swellable polymers such as HPMC, Na CMC, PS, POL407 etc. becomes gelatinized in the dissolution medium. This gelatinized solid dispersion is constantly crushed by the attrition during stirring and bulk solution is diffused through the diffusion layer by these finely gelatinized SDs [25].

## CONCLUSION

Etoricoxib a selective COX-2 inhibitor used in treatment of osteoarthritis, rheumatoid arthritis provide a better therapy if better drug release is achieved by solid dispersion formulation of drug as tablet. It can be inferred that polymers like Kollidon 90F and Poloxamar 188 could be used in PMs and fusion for poorly aqueous soluble drugs like etoricoxib. From the obtained results it suggests that 1:2 ratio of ETX: polymer showed remarkable enhancement in the dissolution. Unlike other solubility enhancing compound, these swellable polymers are regularly used conventional solid dose preparations and this ensures about the availability, feasibility in use and cost effectiveness of the PMs and fusion formulations. Besides, physical mixing and fusion both are very simple in techniques and it needs very cheap tools to prepare. But fusion methods showed comparatively better results than PMs. Overall, this research work presents about a very simple but effective technique for dissolution enhancement of ETX using very common polymers. But we need to proceed with this research for *in vivo* evaluation for ensuring about the capability of PMs and fusion techniques to enhance oral bioavailability of etoricoxib.

## ACKNOWLEDGEMENT

Authors are grateful to Beximco Pharmaceuticals Ltd., Bangladesh for providing chemicals.

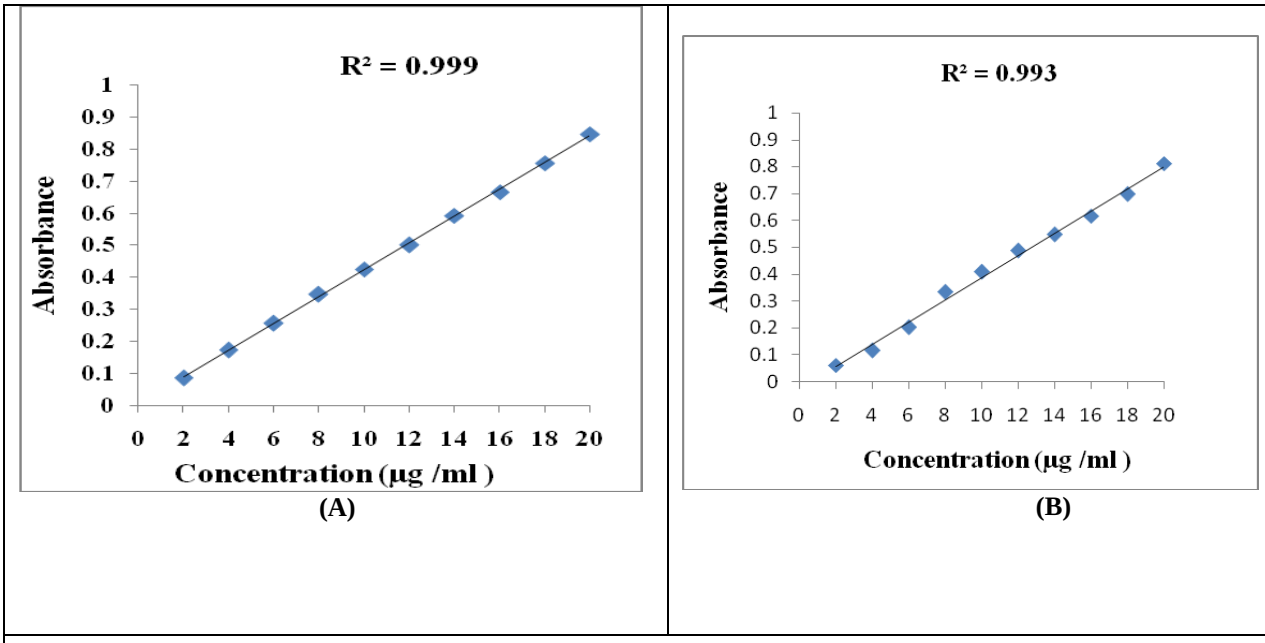



**Figure 1. Calibration curve of etoricoxib where (A) =distilled water (B)= phosphate buffer**

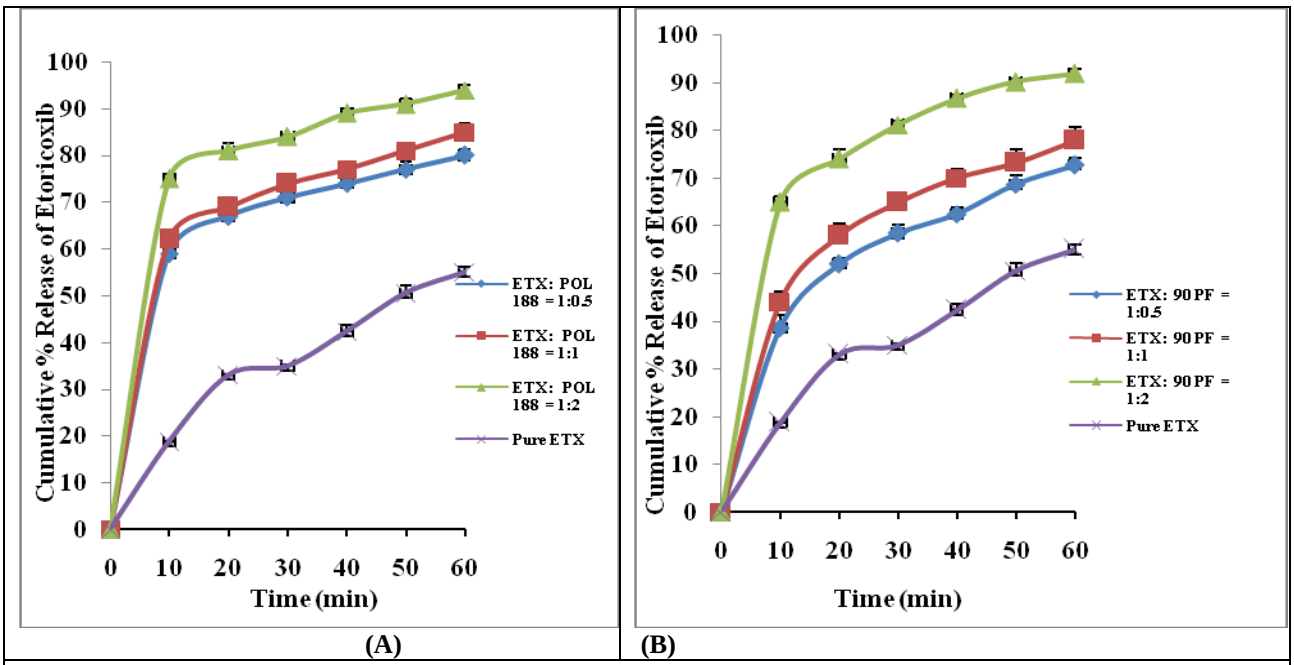
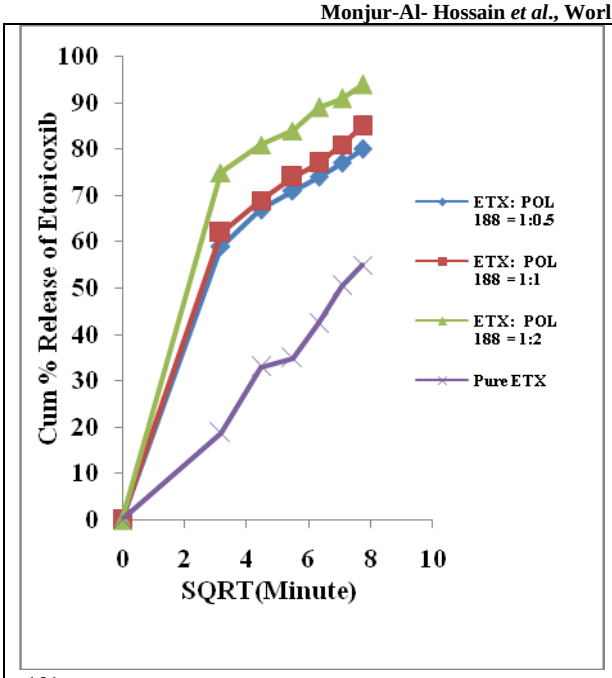
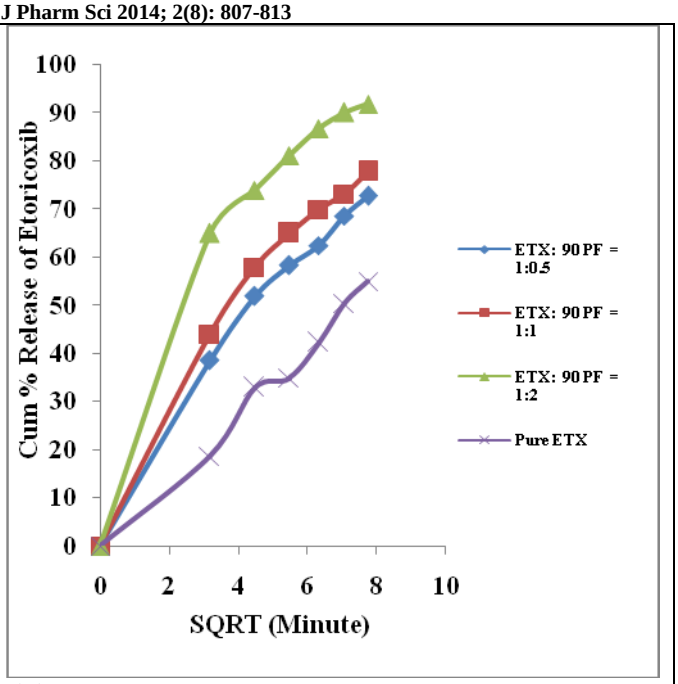



**Figure 2. Zero order release curves of ETX from physical mixtures of ETX with poloxamar 188 (A), kollidon 90F (B) (n = 6).**

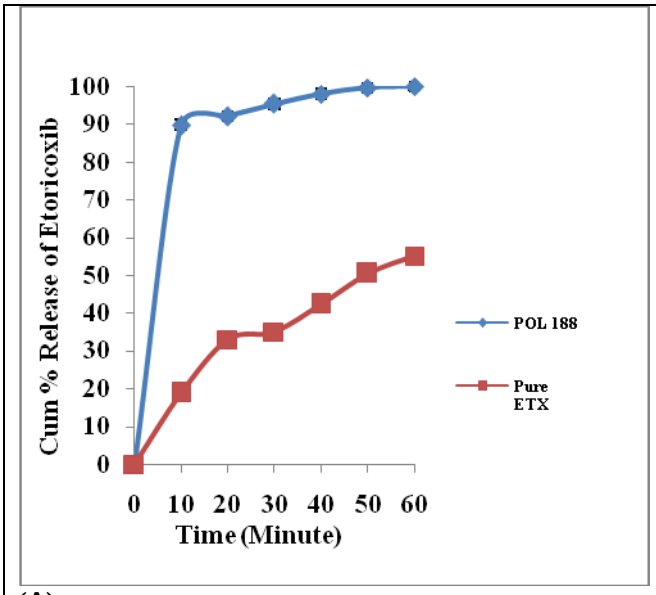



(A)

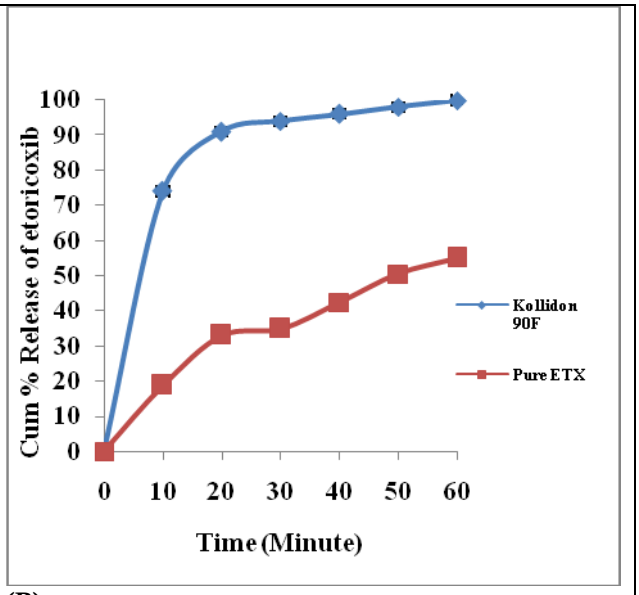



(B)

**Figure 3. Higuchi release curves of ETX from physical mixtures of ETX with poloxamar 188 (A), kollidon 90F (B) (n = 6).**




(A)




(B)

**Figure 4. Zero order release curves of ETX from fusion techniques of ETX with poloxamar 188 (A), kollidon 90F (B) (n = 6).**

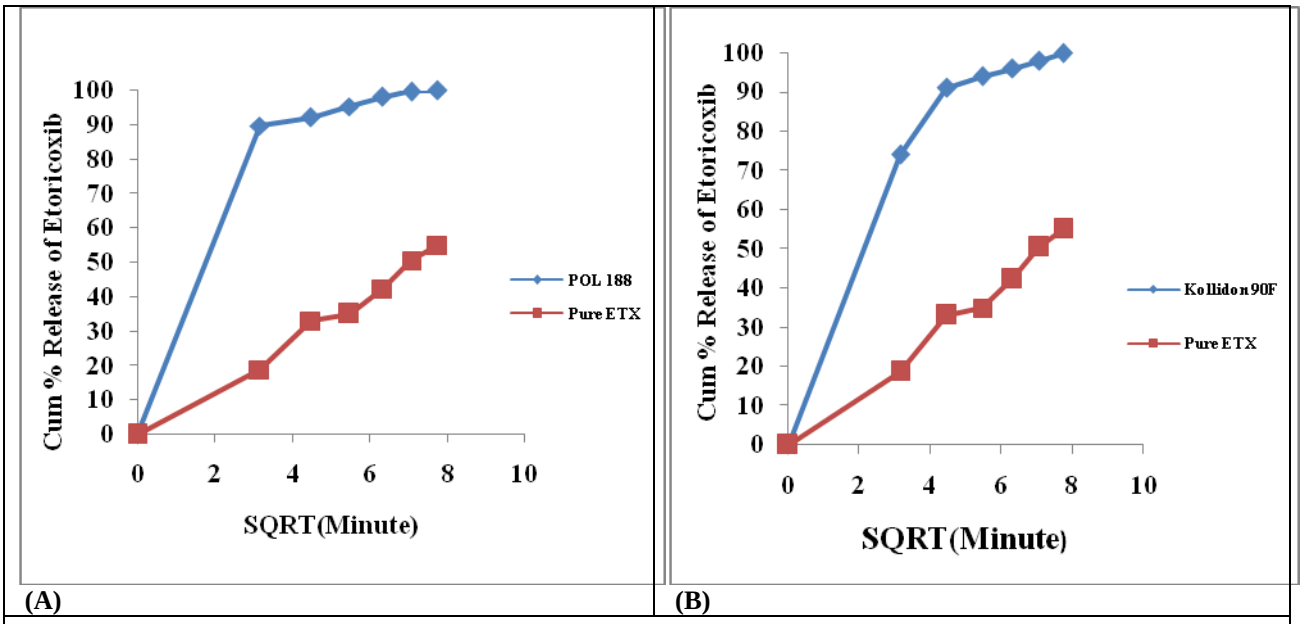



**Figure 5. Higuchi release curves of ETX from fusion techniques of ETX with poloxamar 188 (A), kollidon 90F (B) (n = 6).**

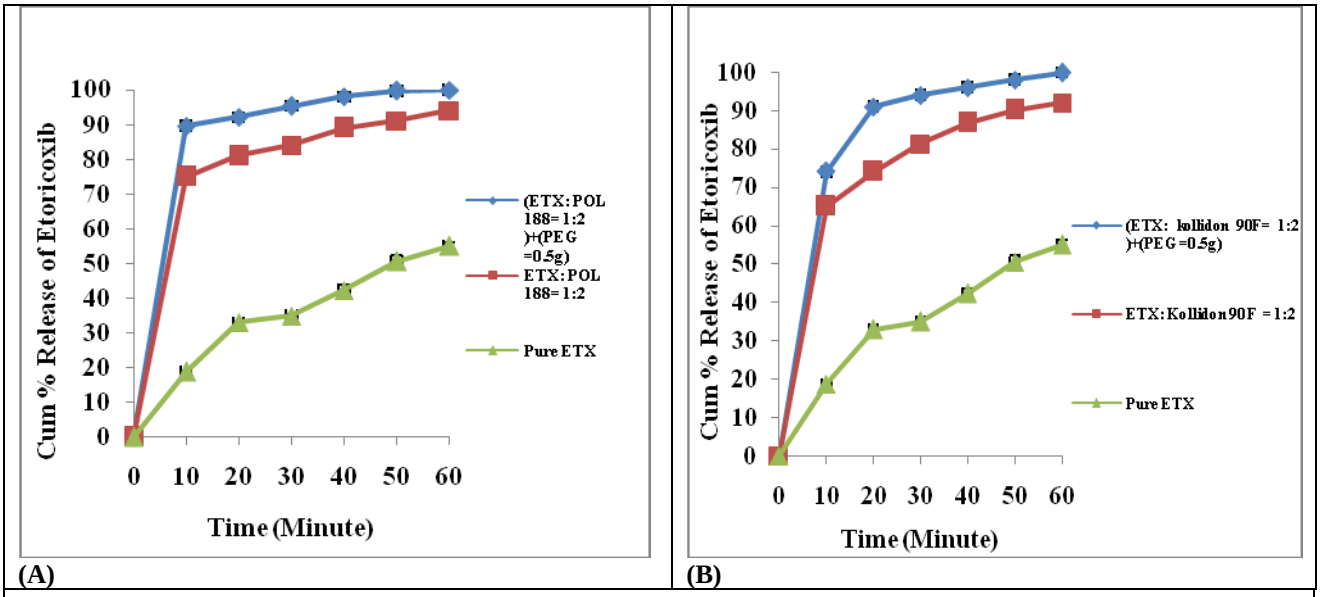



**Figure 6. Comparison of zero order release curves of ETX from PMs and fusion techniques of ETX with poloxamar 188 (A), kollidon 90F (B) (n = 6).**

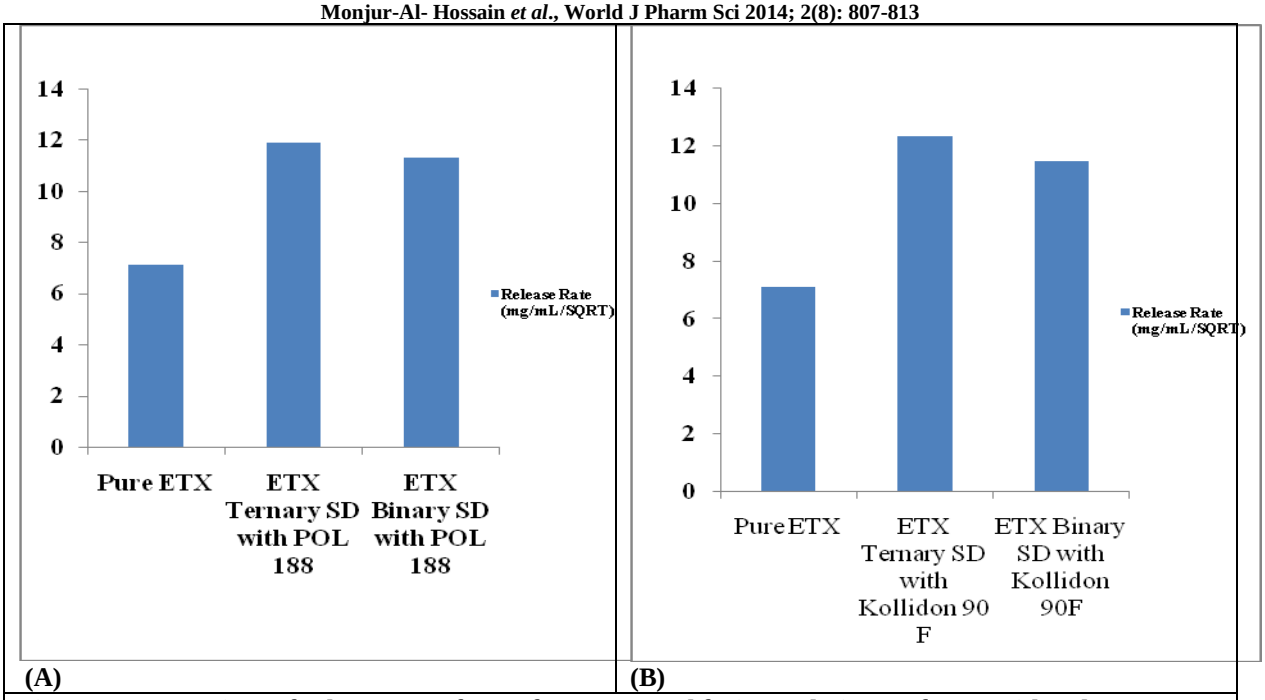



**Figure 7. Comparison of release rate of ETX from PMs and fusion techniques of ETX with poloxamar 188 (A), kollidon 90F (B) (n = 6).**

**REFERENCE**


1. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system: new scientific approaches to international regulatory standards. Eur J Pharm Biopharm. 2000;**50**:3-12.
2. Desai KGH et al. Solubility of Rofecoxib in presence of methanol, ethanol and sodium lauryl sulphate at (298.15, 303.15 and 308.15) K. J Chem Eng Data. 2003; **48**: 942-945.
3. Rawat S, Jain SK. Rofecoxib-cyclodextrin inclusion complex for solubility enhancement. Pharmazie. 2003; **58**: 639-641.
4. K. Arun Prasad et al. Preparation and evaluation of solid dispersion of terbafine hudrochloride. IJPSR 2010; 3(1): Article 27.
5. ARCOXIA Tablet PI 111109 v3 (WPC-MK0663-T-082011). https://gp2u.com.au/static/pdf/A/ARCOXIA-PI.pdf
6. Nokhodchi A et al. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharm Sci. 2005; **8**:18-25.
7. Spireas S et al. Powdered solution technology: principles and mechanism. Pharm Res. 1992; **9**:1351-1368.
8. Javadzadeh Y et al. Enhancement of dissolution rate of piroxicam using liquisolid compacts. Farmaco. 2005; **60**:361-365.
9. ABBOTT GmbH and Co. Soliqs: nanomorph technology. Accessed November 5, 2005.
10. Rasenack N et al. Microcrystals for dissolution rate enhancement of poorly water-soluble drugs. Int. J. Pharm. 2003; **254**:137-145.
11. Rasenack N, Müller BPR. Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs. Pharm Res. 2002; **19**: 1894-1900.
12. Sertsou G et al. Factors affecting incorporation of drug into solid solution with HPMCP during solvent change coprecipitation. Int. J. Pharm. 2002; **245**:99-108.
13. Bakatselou V et al. Solubilization and wetting effects of bile salts on the dissolution of steroids. Pharm. Res. 1991; **8**:1461-1469.
14. Valizadeh H et al. Physicochemical characterization of solid dispersions of indomethacin PEG 6000, Myrj 52, lactose, sorbitol, dextrin, and Eudragit E100. Drug. Dev. Ind. Pharm. 2004; **30**:303-317.
15. Chiou WL, Reigelman S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 1971; **60**:1281-1302.
16. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 2000; **50**:47-60.
17. Ford JL. The current status of solid dispersions. Pharm. Acta. Helv. 1986; **61**:69-88.
18. Goldberg AH. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. II. Experimental evaluation of a eutectic mixture: urea-acetaminophen system. J. Pharm. Sci. 1966; **55**:581-583.
19. El-Zein H et al. Enhancement of carbamazepine dissolution: in vitro and in vivo evaluation. Int. J. Pharm. 1998; **168**: 209-220.
20. Narang AS, Srivastava AK. Evaluation of solid dispersions of clofazimine. Drug. Dev. Ind. Pharm. 2002; **28**:1001-1013.
21. Hancock BC, Parks M. What is true solubility advantage for amorphous pharmaceuticals? Pharm. Res. 2000; **17**:397-404.
22. Aftab Modi, Pralhad Tayade. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS pharm sci tech. 2006; 7(3): article 68.
23. Arias MJ et al. Dissolution properties and in vivo behavior of triamterene in solid dispersions with polyethylene glycols. Pharm Acta Helv. 1996; 71:229-235.
24. Chowdary KP, Rao SS. Investigation of dissolution enhancement of itraconazole by solid dispersion in superdisintegrants. Drug Dev Ind Pharm. 2000; 26:1207-1211.
25. Okimoto K et al. Dissolution mechanism and rate of solid dispersion particles of nilvadipine with hydroxypropylmethylcellulose. Int J Pharm. 1997; 159:85-93.