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PHARMACEUTICAL STUDIES ON THE EFFECT OF DIFFERENT POLOXAMERS ON THE DISOLUTION RATE OF BSC CLASS II ANTIGOUT MODEL DRUG (FEBUXOSTAT)

Ahmed A. El Shenawy[1*], Wael A. Abdelhafez[1], Ahmed Ismail[1], Alaa A. Kassem[2]

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt.
[2]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Nasr City, Cairo, Egypt.

***Corresponding Author: Dr. Ahmed A. El Shenawy**
Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar University, Assiut, Egypt.

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ABSTRACT
The aim of the present work was to increase the dissolution rate of febuxostat (FXT) (Xanthine oxidase enzyme inhibitor), a practically water-insoluble drug using solid dispersion with hydrophilic polymers. Two commercially available poloxamer grades (poloxamer 188 and poloxamer407) were selected, and solid dispersions containing different weight ratio of poloxamers and FXT were prepared by kneading method. The kneading method was used to prepare FXT/ poloxamer solid dispersions due to the good results obtained in previous researches reported by many researchers. FXT has low, variable oral bioavailability and poor water solubility with slow dissolution and peripheral degradation. The prepared solid dispersions was characterized by drug content, in vitro release study, Fourier Transform Infra-Red (FT-IR), Scanning electron microscopy (SEM) and Differential scanning calorimetry (DSC). The results revealed that FXT solid dispersion using poloxamer 188 and poloxamer 407 increased the dissolution rate in comparison to unprocessed FXT. Further, the thermal analysis showed that the FXT enhanced dissolution was due to FXT crystal pattern changes. Moreover, the results revealed that, FXT dissolution rate was inversely proportional with poloxamer ratio as its increase, drug dissolution decreased. SEM image revealed that the solid dispersion granules did not have a perfect spherical shape and a rugged surface. It could be concluded that, solid dispersion technique was a powerful method that enhanced the dissolution rate of FXT utilizing kneading method and poloxamer 188 in 1:1 drug/ polymer w/w ratio was effectively enhanced the dissolution rate of FXT more than poloxamer 407.

KEYWORDS: Febuxostat, Solid dispersions, Poloxamer.

INTRODUCTION
FXT "Fig. 1" is a xanthine oxidase (XO) inhibitor drug used in the management of chronic hyperuricaemia for gouty cases.[1] According to biopharmaceutical classification system (BCS), FXT is considered as class II chemical compound with high permeability and poor solubility. So the dissolution rate of FXT is the only limiting step in its absorption following its administration via oral route.[2] The bioavailability of FXT is very low (49 %) as a result to poor dissolution that leads to inadequate, variable bioavailability[3] and hepatic presystemic metabolism in the cytochrome P450 enzyme system producing acylglucuronides[4] transolid dispersionermal delivery of FXT is thus expected to enhance its bioavailability.[5]

The low solubility of FXT and consequently the dissolution result in variations in bioavailability. So, enhancement of dissolution of FXT is useful for acceptable bioavailability. Many studies have been done to enhance the solubility of FXT by using co-solvents[6] as well as by using other techniques.[7] Solid dispersion method seems to be the most promising for solubility enhancement, as they overcome the limitations of other techniques. When solid dispersions of microcrystalline drug particles, are exposed to aqueous media, the carrier dissolves and the drug is released as a fine colloidal dispersion, thus resulting in higher surface area and consequently, solid dispersions of many poor water soluble drugs by incorporating them into a water-soluble polymer matrix have been considered as an effective method for improving drug dissolution rate and their saturation solubility in the gastrointestinal fluids.[8] Poloxamers are polyoxyethylene-polypropylene block copolymer nonionic surfactants that have been widely used as wetting and solubilizing agents and surface adsorption excipients.[9] They have been employed to enhance the solubility, dissolution, and bioavailability of

many poorly water-soluble drugs using various techniques including melting, kneading and melting agglomeration.[10] For some drugs, the improvement in solubility using poloxamers is higher compared to the other meltable polymers such as polyethylene glycol or complex-forming agents such as cyclodextrins.[11] Poloxamer 188 and poloxamer 407 were empirically selected to prepare solid dispersions because of its low melting point, surfactant properties, and oral safety. Kneading method is used to prepare valdecoxib-polyvinyl pyrrolidone binary systems, and results showed that the dissolution rate of valdecoxib can be enhanced to a great extent by solid dispersion technique using an industrially feasible kneading method.[12]

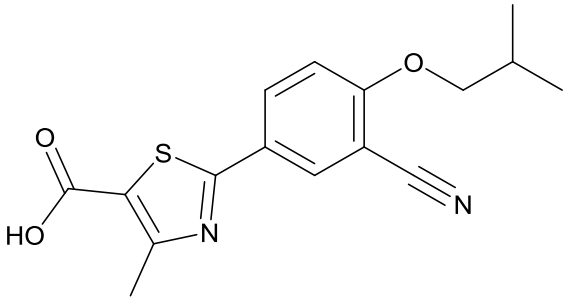

Figure 1: The chemical structure of febuxostat.

MATERIAL AND METHODS

Materials

Febuxostat (kindly provided by MASH Pharmaceuticals, Egypt), Poloxamer 188 and 407 (FLUKA Chemika, Switzerland) Methyl alcohol, Ethyl alcohol (ELNASR Pharmaceutical chemicals co., Egypt), Potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate (NICE Chemicals (p) LTD, India) and Filter membrane, diameter pore 0.2 µm (Germany).

Preparation of FXT solid dispersions using kneading method

Solid dispersions of FXT were prepared by mixing defined weight of FXT with poloxamer (188 and 407) drug/ polymer ratio of 1:1, 1:3, and 1:5 (w/w) for ten minutes using glass mortar and pestle. The mixtures were pasted using mixture of ethanol-water (1:1) solution (5ml) to give a paste; the mixture was kneaded for 30 minutes followed by drying in a hot oven (60°C). The dried past was grinded, the final powder passed through 40 # sieve size, the powder was kept in a desiccator (48 hours), weighed and packed in a well closed brown glass container.[13]

Preparation of physical mixtures

Physical mixtures were prepared by efficient blending of FXT with poloxamer 188 or 407 with using porcelain mortar and a pestle. The physical mixtures were sieved and stored in a well closed brown glass bottle.

Characterization of the prepared solid dispersions

Drug content

The practical FXT content of the prepared Solid dispersions and PHMs was investigated using USP guidelines.[14]

Assessment of in vitro dissolution rate

Accurately weighed formulations (40 mg equivalent of FXT) were dispersed in phosphate buffer solution pH 7.4 (900 ml) with 0.35% w/v Tween 20 added to ensure sink conditions in each cell of dissolution test apparatus ((SR II, 6 flasks (paddle type) (Hanson Research Co., USA)) with a speed of 50 rpm at 37 ± 1 °C. Five ml. samples were withdrawn at 5, 10, 15, 20, 30, 45, 60, 90, 120, 150 and 180 minutes and the samples were filtered using a 0.45 mm membrane filter and the samples were suitably replaced by the same volume. The samples were UV spectrophometrically analyzed after suitable dilution at 315 nm against the prepared blank. Unprocessed FXT was investigated similarly. The in vitro release resulted data was analyzed for FXT cumulative % dissolved at different time intervals. Each in vitro dissolution test was done in triplicate manner and the means were used for assessment.[15]

Fourier Transform Infra-Red spectroscopy (FT-IR)

FT-IR spectra of FXT, poloxamer, solid dispersions and physical mixtures were done for the sample prepared in KBr disks (Two milligrams sample in 200 mg KBr) using Shimadzu FT-IR spectrophotometer utilizing scanning range of 400-4000/cm with a resolution of 4/cm.[16]

Differential scanning calorimetry (DSC)

Thermograms of the samples (FXT, poloxamer, solid dispersion and physical mixture) were obtained utilizing a differential scanning calorimetry (DSC-60, Shimadzu, Kyoto, Japan) after calibration. Samples of 4 mg of FXT, poloxamer, solid dispersion or physical mixture were charged into appropriate aluminum pans sealed with lids. DSC thermograms of the samples were assessed under nitrogen at 10 °C/min and 25–300 °C.[17]

Scanning Electron Microscopy (SEM)

The morphology of the selected FXT solid dispersion was carried out using scanning electron microscope (JSM 6100, Jeol, Japan). Samples of unprocessed FXT, poloxamer 188 and the selected solid dispersion were mounted onto the stubs using double-sided adhesive tape and then coated with a thin layer of gold palladium alloy (150–200A°). The scanning electron microscope was operated at an acceleration voltage of 20 KV, working distance (12–14 mm). The selected magnification was ×500.[18]

RESULTS AND DISCUSION

Drug content

The drug content assessment results showed that the range of drug content ranged from 95.4 – 98.5% indicating the acceptability of kneading method for

preparation of solid dispersions. FXT content was found to be the same among all the prepared solid dispersions and physical mixtures of different FXT/ poloxamer ratios.

In vitro FXT dissolution rate studies

The in vitro dissolution profiles of the unprocessed FXT, various solid dispersions using poloxamer 188 and poloxamer 407 and their corresponding physical mixtures utilizing phosphate buffer solution (pH 7.4) for 180 minutes are represented by figures 2- 4. By the end of 180 minutes, 33.33 %, 51.77 %, 66.57 %, 100 %, 51.1 %, 60.52 %, 67.17 %, 46.11 %, 58.15 % and 61.81 % FXT was released from unprocessed FXT sample, 1:5 FXT/ poloxamer 188 SOLID DISPERSION, 1:3 FXT/ poloxamer 188 solid dispersion, 1:1 FXT/ poloxamer 188 solid dispersion, 1:5 FXT/ poloxamer 407 solid dispersion, 1:3 FXT/ poloxamer 407 solid dispersion, 1:1 FXT/ poloxamer 407 solid dispersion, 1:5 FXT/ poloxamer 188 physical mixtures, 1:3 FXT/ poloxamer 188 physical mixtures and 1:1 w/w FXT/ poloxamer 188 physical mixture respectively. All of the physical mixture and Solid dispersions showed enhanced dissolution rate of FXT over unprocessed FXT. With regarding to the used poloxamer 188 and 408, all of the prepared solid dispersions revealed higher enhancement of FXT dissolution rate than their corresponding physical mixtures. These results indicated that the improved dissolution rate of FXT from solid dispersion due to conversion of FXT into the amorphous state as compared to FXT/ poloxamer physical mixtures and unprocessed FXT, where FXT is present in the crystalline state.[19] Physical mixtures could increase the solubility due to the increase in FXT particles surface area of that dissolved in the dissolution medium. The lowering of surface tension effect of polymer may result in improvement of the wettability of hydrophobic drug of crystalline surface. The underlying mechanism may be possible for the improved dissolution rate of FXT in solid dispersions formulation that could be attributed to the reduction of crystallinity of FXT resulting in enhanced dissolution.[20] The results of in vitro dissolution profile of FXT solid dispersions with poloxamer 188 and 407 also showed that, the larger ratios of poloxamer (188 and 407) in Solid dispersions were not effective in increase of FXT dissolution rate to when compared to the smaller ratios, which was more observed in the prepared Solid dispersions with poloxamer 407. It could be expected that larger amount of poloxamers in Solid dispersions resulted in good conditions for gel layer formation when putted in the dissolution medium, which acts as a diffusion barrier and retards drug release. Poloxamer 407 shows a temperature depending gelling effect, which cause the delayed dissolution of FXT [21]. The results also showed that the solid dispersion formed with poloxamer 188 and FXT (1:1 w/w) had the best enhancement in dissolution rate. When poloxamer 188 compared to poloxamer 407, it was has the lesser effective polymer as a FXT solubilizer. The results could be attributed to the higher M.wt. and larger proportion of hydrophobic polyoxypropylene part of poloxamer 407.[21]

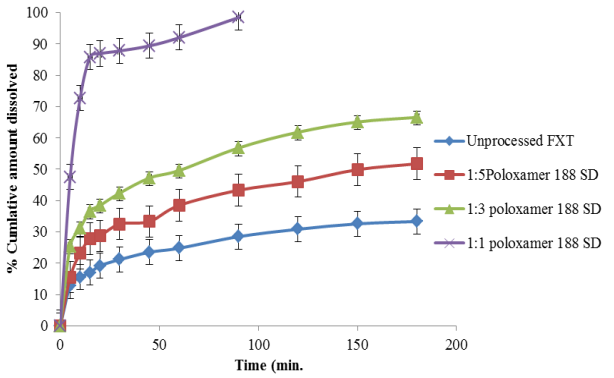

Figure 2: Dissolution profiles of unprocessed FXT, 1:1 FXT/ poloxamer 188 solid dispersion, 1:3 FXT/ poloxamer 188 solid dispersion and 1:5 w/w FXT/ poloxamer 188 solid dispersion (n = 3).

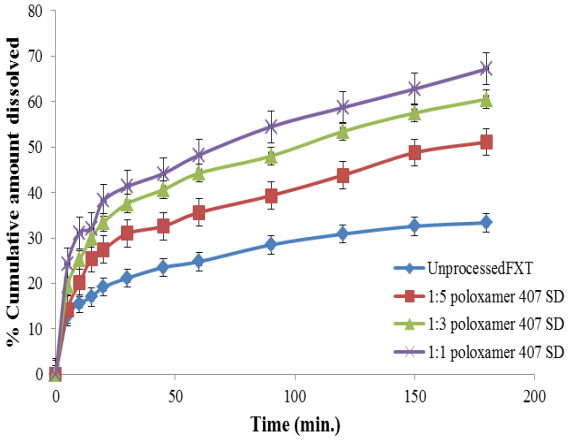

Figure 3: Dissolution profiles of unprocessed FXT, 1:1 FXT/ poloxamer 407 solid dispersion, 1:3 FXT/ poloxamer 407 solid dispersion and 1:5 FXT/ poloxamer 407 solid dispersion (n = 3).

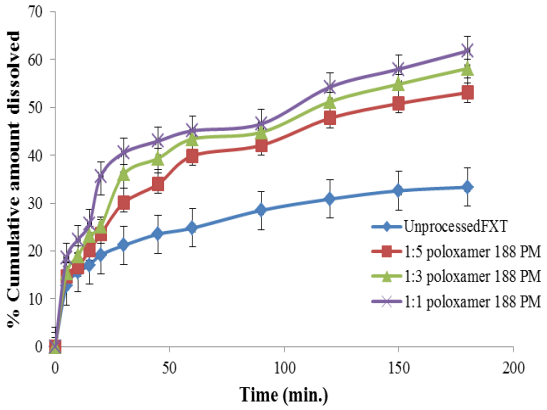

Figure 4: Dissolution profiles of unprocessed FXT, 1:1 FXT/ poloxamer 188 physical mixture, 1:3 FXT/ poloxamer 188 physical mixture and 1:5 FXT/ poloxamer 188 physical mixture (n = 3).

FXT Solid dispersions solid state characterization

Fourier Transformer Infra- Red (FT-IR) spectroscopy

The FT-IR spectrum "Fig. 5" was conducted in order to detect the interaction between FXT and poloxamer 188 solid dispersion (1:1, w/w). The FT-IR spectra of unprocessed FXT, unprocessed poloxamer 188, 1:1 w/w (drug: polymer solid dispersion) and their corresponding physical mixtures. Unprocessed FXT spectrum showed peaks at 2961, 2231, 1512 cm^{-1} which corresponding to the O-H stretch of carboxylic group, C≡N stretch and the C=N stretch of the thiazole ring respectively. After forming FXT/ poloxamer 188 solid dispersion, they were shifted to 2885, 2229, 1508 cm^{-1}, respectively. The peak of 1678 cm-1 corresponding to the C=O stretch of FXT was up-shifted to 1683 cm^{-1} in the solid dispersion as shown in Fig.4. The COOH group of FXT molecule does not act as donor participating in the formation of hydrogen bonds as usual, so the state of this group is more close to the free carboxyl. Poloxamer 188 molecule exhibits specific peaks at 2886, and 1114 cm−1 due to stretching of O-H and C-O groups respectively. The spectrum of FXT/ poloxamer 188 (1:1, w/w FXT: poloxamer ratio) physical mixture was equivalent to the addition of spectrum of FXT and poloxamer indicating no interaction occurring in physical mixture.

The spectrum of solid dispersion exhibited significant decrease in intensity of C=N stretching vibrations and C≡N stretching vibrations which may be due to intermolecular hydrogen bonding. The FXT/ poloxamer 188 Solid dispersions spectrum did not show any other peaks indicating that there is no any interaction between FXT and poloxamer 188. The spectra peaks of FXT are almost unchanged in the optimized formula of solid dispersion which indicates that the overall symmetry of molecule is not significantly affected. The total band shift was considered to be non-significant. These results indicate that there is no significant interaction has been occurred between FXT and poloxamer 188.[22]

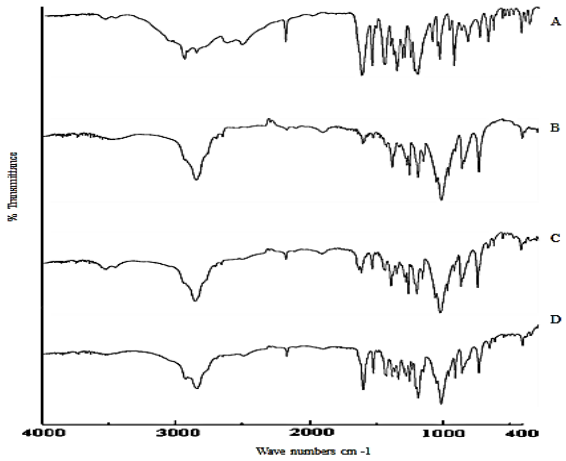

Figure 5: FT-IR spectrum of (A) unprocessed FXT, (B) poloxamer 188, (C) 1:1 w/w FXT/ poloxamer 188 solid dispersion and (D) 1:1, w/w FXT/ poloxamer 188 physical mixtures.

Differential scanning calorimetry

To explore the possible mechanisms of improved dissolution and possible interaction between FXT and poloxamer 188, Solid dispersions was characterized by DSC. Unprocessed FXT "Fig. 6A" has a sharp endothermic peak at 209.55 °C, equal to its melting point which attributed to its non-amorphous nature. The showed FXT endothermic peak comes in accordance with the product pamphlet of the production company which listed that the melting point of FXT is in the range of 207 - 211°C. The melting point of poloxamer 188 was resulted at 55.99 ◦C "Fig. 6B". FXT as well as poloxamer 188 peaks were disappeared in 1:1 w/w Solid dispersions and corresponding PHMs. For 1:1 w/w solid dispersion there is an appearance of new endothermic peak at 72.8 °C for solid dispersion "Fig. 6C". Similarly, 1:1 w/w PHM showed an expanded peak at 61.72 ◦C "Fig. 6D". The complete disappearance of the endothermic peak of FXT in its solid dispersion with poloxamer 188 may be resulted due to the formation of amorphous FXT form. Similar finding were obtained by Madhuri *et al.* [23] who noticed complete disappearance of the endothermic peak of ibuprofen in its solid dispersion with poloxamer 188. They explain this phenomenon on the basis that solid dispersion resulted in an amorphous form of ibuprofen.

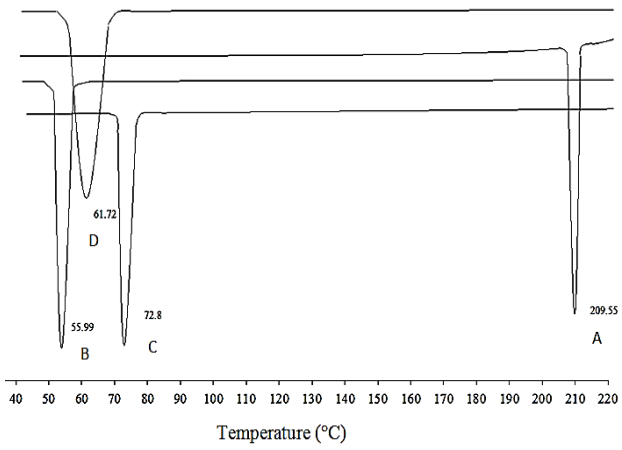

Figure 6: DSC peaks of: FXT/ poloxamer 188 (1:1 w/w) PHM (D), unprocessed FXT (A), pure poloxamer 188 (B) and FXT/ poloxamer 188 (1:1 w/w) solid dispersion (C).

Scanning Electron Microscopy (SEM)

The SEM images for unprocessed FXT, poloxamer 188 and 1: w/w FXT/ poloxamer solid dispersion are shown in "Fig. 7". Unprocessed FXT image showed an aggregate of large and small crystals, poloxamer 188 consist of spherical particles with smooth surfaces [24] whereas SEM image of solid dispersion of FXT does not show any crystalline material. The results of SEM imaging confirmed the irregular shape of the granules.[25]

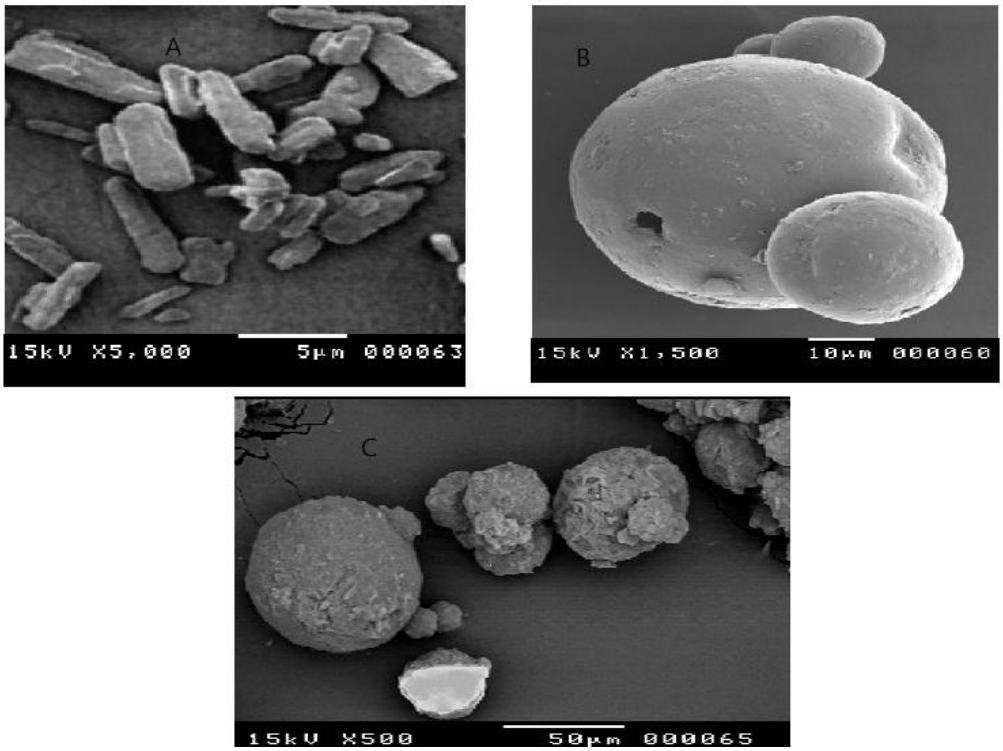

Figure 7: Scanning Electron Microscopy images of (A) Febuxostat, (B) poloxamer 188and (C) solid dispersion. The magnification is 5000, 1500 and 500 in febuxostat, poloxamer 188 and solid dispersion, respectively.

CONCLUSION

The obtained results indicate that poloxamers 188 and poloxamer407 are suitable for the preparation of Solid dispersions with FXT by kneading method. Solid dispersions with both poloxamer 188 and poloxamer 407 have increased the dissolution rate of FXT, with poloxamer 188 showing a greater solubilization capability. Increased poloxamer ratio in Solid dispersions decreased the dissolution rate of FXT because of the gelling characteristic of poloxamers.

CONFLICT OF INTEREST: The authors declare that they have no competing interests.

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REFERENCES

1. Michael E, Michelle A. Febuxostat: A Selective Xanthine Oxidase/Xanthine- Dehydrogenase Inhibitor for the Management of Hyperuricemia in Adults with Gout. Clin Therap, 2009; 31(1): 2503 – 18.
2. Mayer M, Khosravan R, Vernillet L, Joseph-Ridge N, Mulford D. Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. Am J Ther, 2005; 12(4): 22–34.
3. Mei Z, Xiaohui D, Lin X, Juan X, Yongge Y, Nan J, Lixue S, Xueting X. Pharmacokinetics and pharmacodynamics of febuxostat under fasting conditions in healthy individuals. Exper Therap Med, 2014; 7(1): 393-96.
4. Bishoy K, Garry G, Kenneth M, Kevin D, Richard O. Clinical Pharmacokinetics and Pharmacodynamics of Febuxostat. Clin Pharm, 2017; 56(1): 459 – 75.
5. Tatsuo H, Kenjiro K, Sadayoshi I, Masaaki I. The effect of febuxostat to prevent a further reduction in renal function of patients with hyperuricemia who have never had gout and are complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study. Trials, 2014; 15(3): 26 – 35.
6. Naidu NB, Chowdary K, Murthy K, Satyanarayana V, Hayman A, Becket G. Physicochemical characterization and dissolution properties of meloxicam-cyclodextrin binary systems. J Pharm Biomed Anal, 2004; 35(1): 75–86.
7. Vijaya S, Mishra N. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. Int J Pharm Sci., 2006; 126(2): 93–7.
8. Vijaya S, Mishra DN. Preparation, characterization and in vitro dissolution of solid dispersion of meloxicam with PEG 6000. Int J Pharm Sci., 2006; 126(8): 657–64.
9. Collett J, Popli H, Kibbe AH, editors. Poloxamer: Handbook of Pharmaceutical Excipients, 3rd ed. London, UK: Pharmaceutical Press: 2000, p. 386–8.
10. Hang Y, Myung C, Hoo-Kyun C. Preparation and characterization of piroxicam/poloxamer solid

dispersion prepared by melting method and solvent method. J Korean Pharm Sci., 2007; 37(3): 1–5.
11. Chutimaworapan S, Ritthidej G, Yonemochi E, Oguchi T, Yamamoto K. Effect of water-soluble carriers on dissolution characteristics of nifedipine solid dispersions. Drug Dev Ind Pharm, 2000; 26(11): 1141–50.
12. Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. Amer Ass Pharm Sci PharmSciTech, 2006; 7(3): 68-75.
13. Mowafaq M, Alaa A, Ahmed A, Mohammed I. Kneading Technique for Preparation of Binary Solid Dispersion of Meloxicam with Poloxamer 188. Amer Assoc Pharm Sci PharmSciTech, 2009; 10(4): 1206 – 15.
14. Sharma A, Jain CP. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res Pharm Sci., 2010; 5(1): 49–56.
15. Natalija Z, Obrezaa A, Marjan B, Stane S. Physical properties and dissolution behavior of nifedipine/mannitol solid dispersions prepared by hot melt method. Int J Pharm, 2005; 291(1): 51–8.
16. Vikrant V, Pankajkumar S, Poonam K, Manali S. Physicochemical characterization of solid dispersion systems of tadalafil with poloxamer 407. Acta Pharm, 2009; 59(6): 453–61.
17. Van den G, Augustijns P, Blaton N, Kinget R. Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. Int J Pharm, 1998; 164(5): 67–80.
18. Huyen T, Jun Bom P, Ki-Hyuk, Han-Gon C, Hyo-Kyung H, Jaehwi L, Kyung T, Beom-Jin L. Preparation and characterization of pH-independent sustained release tablet containing solid dispersion granules of a poorly water-soluble drug. Int J Pharm, 2011; 415(2): 83– 8.
19. Sang-Chul S, Cheong-Weon C. Physicochemical characterizations of piroxicam-poloxamer solid dispersion. Pharm Delve Techno, 1997; 2(4): 403-7.
20. Choudhary D, Kumar S, Gupta G. Enhancement of solubility and dissolution of glipizide by solid dispersion (kneading) technique. Asi J Pharm, 2009; 1(1): 245- 51.
21. Madhuri N, Krishna H, Dong X, Tae-Hyub K, Jung A, Bong K, Jong S, Won S, Chul S, Han G. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188. Int J Pharm, 2007; 343(1): 228–37.
22. Patel B, Parikh R, Swarnkar D. Enhancement of dissolution of Telmisartan through use of solid dispersion technique - surface solid dispersion. J Pharm Bioallied Sci, 2012; 4(1): S64–8.
23. Madhuri N, Krishna H, Dong X, Tae-Hyub K, Jung A, Bong K, Jong S, Won Seok L, Chul S, Han Gon C. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188, Int J Pharm, 2007; 343(4): 228–37.
24. Madhuri N, Krishna H, Dong H, Young R, Joon H, Jong O, Jong S, Han G, Chul S. Enhanced Dissolution of Ibuprofen Using Solid Dispersion with Poloxamer 407. Arch Pharm Res, 2008; 31(11): 1497-507.
25. Nadia P, Beatrice A, Marisa L, Cristina C. Preparation and characterization of ibuprofen–poloxamer 188 granules obtained by melt granulation. Euro J Pharm Sci., 2002; 15(4): 71 - 8.