WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 4, 1576-1585. Research Article ISSN 2277–

ASSESSMENT OF LUDIFLASH AS A SUPERDISINTEGRANT IN FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLET OF FEBUXOSTAT

Deepali B. Rajpure*, Sagar D. Kore, Makarand V. Puri and Parag A. Kulkarni

Department of Pharmaceutics, Siddhant College of Pharmacy, Sudumbare, Pune, 412109-India.

Article Received on
15 Feb. 2017,

Revised on 11 Mar. 2017,
Accepted on 31 Mar. 2017

DOI: 10.20959/wjpr20174-8277

***Corresponding Author'**
Deepali B. Rajpure
Department of Pharmaceutics, Siddhant College of Pharmacy, Sudumbare, Pune, 412109-India.

ABSTRACT

Febuxostat is drug used in the treatment of gout. This drug has very poor bioavailability about 49% due to its poor solubility. The present research work was aimed to minimize these two limitations i.e. poor bioavailability and poor solubility. This research work involves incorporation of β-Cyclodextrin & Ludiflash as excipients to improvise rate of disintegration & solubility of Febuxostat. Assessment of In-vitro studies depict that the solubility and dissolution rate of Febuxostat was significantly improved by complexion with β-Cyclodextrin & Ludiflash as a superdisintegrant. The formulation was prepared with β-Cyclodextrin, Ludiflash & other additives by kneading method which exhibit remarkable solubility. The Febuxostat containing tablets was prepared by direct compression method using other ingredients such as kollidon CL-SF, kollidon CL-F, microcrystalline cellulose. The formulation of Ludiflash as a superdisintegrant in the concentration of (20 %) i.e. F4 batch gives best results as this formulation required minimum disintegration time & wetting time as compared to formulations of kollidon CL-F and kollidon CL-SF with same concentration. So it can be conclusively stated that Febuxostat fast disintegrating tablet can be formulate with β-Cyclodextrin & Ludiflash.

KEYWORDS: Febuxostat, β-Cyclodextrin, Ludiflash, Gout, kollidon CL-SF, Kollidon CL-F.

INTRODUCTION

Fast dissolving Tablets are disintegrating or dissolving rapidly in the saliva without need of water; some tablets are designed to dissolve in saliva remarkably fast, within few seconds and are true fast dissolving tablets. Other contain agents to enhance the rate of tablet disintegration in oral cavity and are more appropriately termed fast disintegrating tablet as they may take up minute to complete disintegration.[1-3] Chemically febuxostat is (2-[3-cyno-4-(2methyl propoxy)phenyl]-4-methylthiazole-5-carboxylic acid. It is freely soluble in dimethyl formamide, soluble in dimethyl sulphoxide; sparingly soluble in methanol and acetonitrile and practically insoluble in water .Febuxostat is practically insoluble in water, chemically stable, half-life -5 to 8 hours. It undergoes first pass effects so it selected as a drug candidate for fast disintegrating tablet.[4] Solid dispersion is defined as dispersion of one or more active ingredients in inert carrier in solid state, by fusion, solvent or solvent fusion method. The physical state of drug is often transformed in solid dispersion from crystalline to amorphous and dissolution surface increases because of particle size reduction.[5] Febuxostat prepared by kneading method using hydoxy propyl β-Cyclodextrin 1:1. Kneading method is cheap, simple, no wastage and less time consuming as compared to co-evaporation method.[6] The objective of present research work is to improve rate of disintegration with the incorporation of ludiflash as a superdisintegrant & incentivizing the increase in the solubility of drug through complexion with β-Cyclodextrin by kneading method and to formulate the fast disintegrating tablet by incorporating the prepared complexes by direct compression method using various superdisintegrant.

MATERIAL AND METHOD

Material

Febuxostat was received as a gift sample form Excel Industries Ltd, Mumbai, India. The complexing agent β- cyclodextrin was purchased from S.D. Fine Chemicals Pvt. Ltd., Mumbai. All other chemicals and solvents used were of analytical grade.

Preparation of solid dispersion

Solid dispersions of febuxostat in 3 different weight ratios (1:1 and 1:0.5, 1:1.5) were prepared by the kneading method. Febuxostat, β-Cyclodextrin other ingredients were weighed according to predetermined ratios. The mixture of febuxostat and excipients was prepared by using ethanol as a wetting agent and kneaded thoroughly for sufficient time in a mortar. The paste formed was dried in hot air oven for 24 h. Dried powder was allowed to get

passed through sieve no. 30. Solid dispersion made by another technique is solvent evaporation method in which drug and excipients were kept in petry dish and dish was put on hot plate to evaporate moisture. Third method was physical mixture in which the mixture of drug and excipient was taken in mortar and triturated by pestle.[7]

Phase solubility study[8]

Phase solubility studies were performed as directed by the methods described in Higuchi and Connors.

Determination of drug content

Mixture of drug & other additives equivalent to 10 mg of drug was mixed with 100 ml of methanol. From this the concentration of 10µg/ml was prepared and the drug content was determined spectrophotometrically at 315 nm using methanol as blank reading.

Saturation solubility studies

Excess amount of drug, physical mixture and inclusion complexes were added to 250 ml conical flask containing 25 ml of double distilled water. The sealed flasks were shaken for 24 h at room temperature followed by equilibrium for 3 days .Then; the aliquots were withdrawn through whatman filter paper. The concentration of febuxostat was determined by UV spectrophotometer at 315 nm

Characterization of the physical mixture

UV spectroscopic study[4]

Mixture of febuxostat and cyclodextrin was studied by UV spectroscopic method. 10 mg febuxostat was weighed accurately and dissolved in 100ml methanol. Diluted suitably and spectra of drug recorded at 315 nm.

Fourier Transform Infrared spectrophotometry [FT-IR]

FT-IR spectrophotometry was used to investigate the drug-excipient interaction.

Differential Scanning Calorimetry

The thermo gravimetric data for analysis was extracted in the form of thermo grams from DSC.

In-vitro dissolution studies

Dissolution study was performed in one dissolution media (phosphate buffer pH 6.8), both on pure drug (40 mg) and the combination. Aliquots of regularly taken samples analyzed spectrophotometrically, and equal volume of dissolution medium was replaced.[7, 9]

Preparation of tablets[10, 11]

Tablets were prepared by the direct compression method from an optimized batch of kneaded 1:1 febuxostat-β Cyclodextrin solid dispersion by taking in consideration dissolution and saturation solubility results for the solid dispersions, by adding one of three different superdisintegrants ludiflash, kollidon CL-F, kollidon CL-SF. Formulation of Fast dissolving tablets was performed in two steps firstly formulation of tablets for that accurately weighed quantity of ingredients as mentioned in table 1 and it was prepared by direct compression to form tablets using 8 mm diameter flat punches on rotary 8 stations tablet machine (Karnavati Press, India). In second step formulation of fast dissolving tablet by accurately weighed quantity of all ingredients as mentioned in table 1. Magnesium stearate and talc were passed through sieve no 64. Then all the ingredients were mixed thoroughly for 30 min in mortar. Tablets were compressed into the tablets using 8 mm diameter punches on rotary tablet machine. The tablets were prepared separately in the proportions given in Table 1.

Table No.1. Formulae used in the preparation of tablets.

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug –β-CD Complex	80	80	80	80	80	80	80	80	80
SLS	10	10	10	10	10	10	10	10	10
K-CL-SF	30	40	50	-	-	-	-	-	-
LF	-	-	-	30	40	50	-	-	-
MCC	20	10	00	20	10	00	30	40	50
K-CL-F	-	-	-	-	-	-	20	10	00
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
TiO2	1	1	1	1	1	1	1	1	1
Vanillin	1	1	1	1	1	1	1	1	1
Total Wt.	150	150	150	150	150	150	150	150	150

***weight in mg**

D-BCD- dug+ beta cyclodextrin,(equivalent to dose i.e. 40 mg), SLS- sodium lauryl sulphate, K-CL-SF-kollidon -CL-SF, LF-ludiflash, MCC-microcrystalline cellulose, K-CL-F-kollidon-CL-F, MgS-Magnesium Stearate, T- Talc, TiO2-Titanium dioxide, V-vanillin

Evaluation of super disintegrating tablets[12]

Powder blend were evaluated for flow properties. Different tests that were carried out are angle of repose, hardness, friability, disintegrating time, wetting time, in-vitro release bulk density, tapped density, compressibility index, and Hausner's ratio.

Disintegration time

The in vitro disintegration time for all formulations was determined by tablet disintegration test apparatus. The time for tablet samples were recorded for further assessment.

Drug content

Drug content uniformity test was conducted by powdering ten tablets & extracting the drug in phosphate buffer. The absorbance was taken at 315 nm on spectrophotometer .The drug content was determined using standard calibration curve.

Wetting time[4]

The method was followed to analyze wetting time of tablet.

In- vitro dissolution study[13]

The release rate of drug from formulated fast disintegrating tablets was determined using dissolution testing apparatus USP II. Absorbance of solutions was measured at 315nm spectrophotometrically.

RESULT AND DISCUSSION

The tablet formulated by solid dispersion of febuxostat with β-Cyclodextrin by kneading method in the ratio of 1:1 was found to increase the solubility of drug. Compared with the pure powdered drug, the presence of ludiflash increases rate of disintegration & β-Cyclodextrin increases the dissolution of febuxostat from the solid dispersions. The prepared solid dispersions increase the dissolution rate up to 82.06%. All the release profiles showed two different phases of drug release. An initial rapid release phase followed by a slower one. These results could be attributed to the general phenomenon of particle size reduction during the dissolution process and use of ludiflash as superdisintegrant enhances the dissolution of the drug in phosphate buffer pH 6.8. he solubility of febuxostat in phosphate buffer 6.8 pH at 25^{o}C was found to be µg/ml The influence of β- Cyclodextrin upon the solubility of febuxostat can be stated as an increase in solubility was linear with respect to the weight fraction of the carrier.

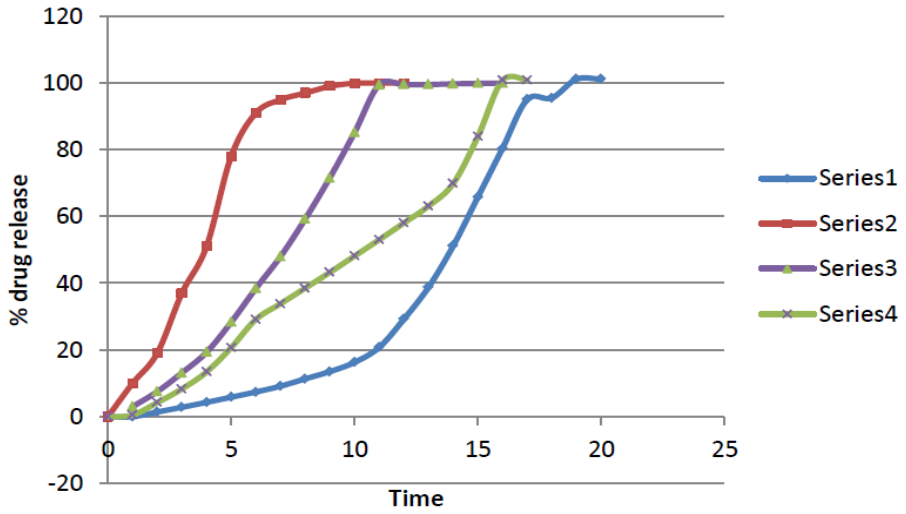


Figure No.1. Dissolution release profile of pure drug and from solid dispersions at 37 C.

Series 1- Drug with: β-Cyclodextrin (1:1.5), Series 2- Drug with: β-Cyclodextrin (1:1), Series 3- pure drug, Series 4- Drug with β-Cyclodextrin (1:0.5).

Table No. 2: Dissolution release profile of pure drug and from solid dispersions.

Time(min)	Pure drugs	SD1(1:0.5)	SD2(1:1)	SD3 (1:1.5)
0	0	0	0	0
5	5.777554	25.2086	33.44929	20.20
10	10.74427	27.83386	44.59905	30.83
15	12.67016	29.54687	59.80328	49.54
20	15.81237	36.18605	66.79722	51.63
25	17.94093	47.6399	74.19661	60.19
30	20.57632	49.86985	82.30553	65.30

*Data are as mean ± expressed S.D. (n=3)

The chemical interaction between the drug and the cyclodextrin often leads to identifiable changes in the infrared profile of dispersion (Figure No. 2). Drug spectrum shows prominent peaks at 2928 cm-1 for CH, 2231cm-1 for C=N, 1714 cm-1 for C=O, 1629 cm-1 for C=N and 1516 cm-1 for C=C. The physical mixture of drug with ß-CD (1:1) complexes shows the prominent peaks of drug, but there was reduction in peak intensity of drug peak which was obscured by cyclodextrin peak indicating formation of complexes. In this fast dissolving tablet formulation used here different excipients like superdisintegrant, binding agent, flavoring agent, lubricant, surfactant, diluents stabilizing agent and solubility enhancing agent.

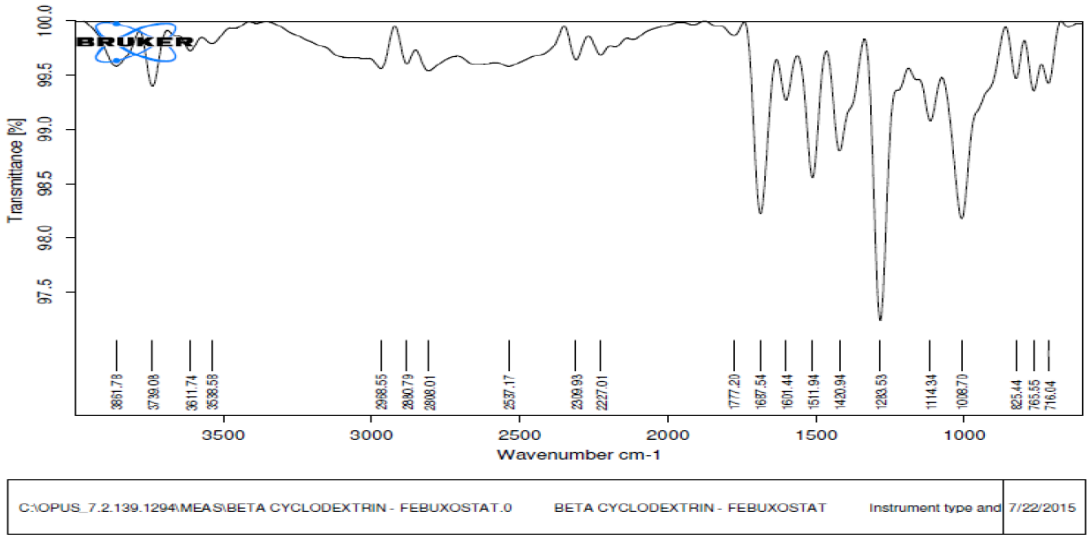


Figure No.2. FTIR spectra of solid dispersion1:1 of Febuxostat with ß-cyclodextrin.

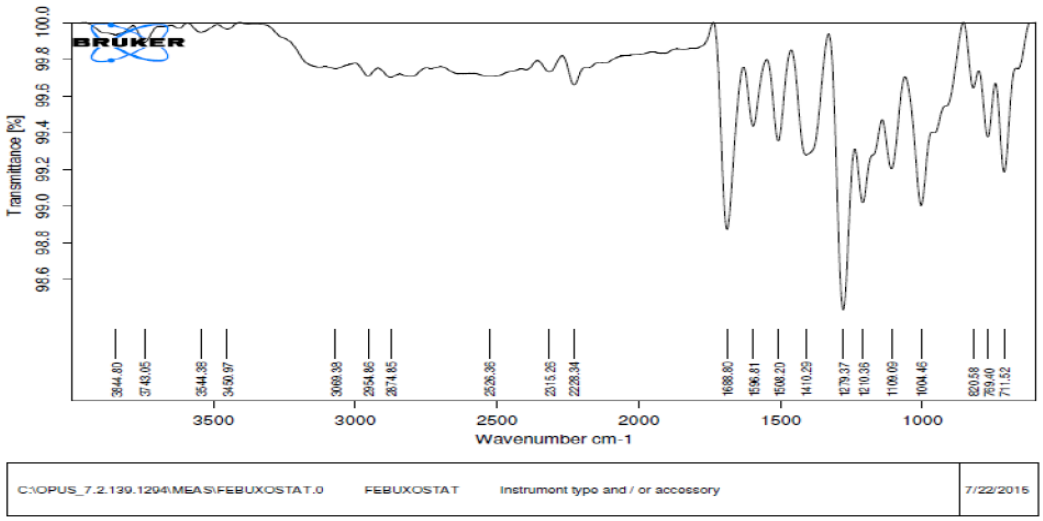
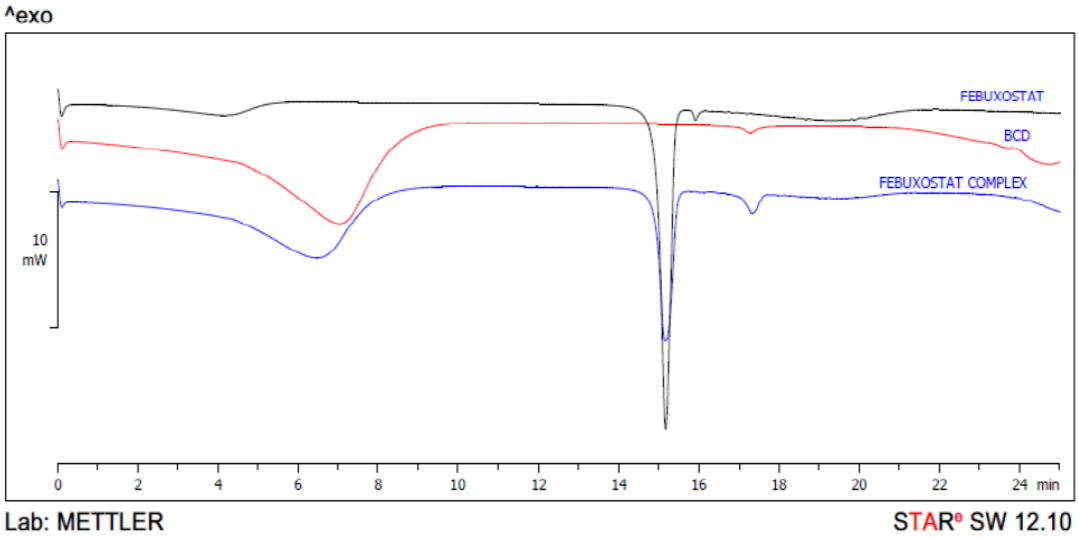


Figure No.3. FTIR spectra of pure Febuxostat.

DSC studies showed that endothermic peaks for pure febuxostat, β-Cyclodextrin were obtained at 200 °C, 85.11°C and 280 °C respectively. Thermogram of drug: β-Cyclodextrin (1:1) complex showed reduction in the intensity of peak of febuxostat and shift of endothermic peak of β- Cyclodextrin. These indicate successful complexation with β-Cyclodextrin. Thus, DSC studies confirm the inclusion complexation of drug with β-Cyclodextrin.

Figure No.4. DSC pattern of pure febuxostat, pure ß-cyclodextrin and solid dispersion of febuxostat ß- cyclodextrin.



In order to select the best superdisintegrant, preliminary trials were conducted (Table No.3).All the prepared tablets were characterized by uniform thickness, diameter and weight. Based on the disintegration and dissolution results, the investigated superdisintegrant can be ranked according to their ability to swell in water as ludiflash>kollidon CL-SF>Kollidon CL-F. The wicking and capillary action are postulated to be major factor in the ability of these superdisintegrant to function. As a result, the superdisintegrant Ludiflash exhibited faster disintegration and dissolution release. Hence they were selected for further studies.

Table No.3. Evaluation of Powder Blend of febuxostat

Formulation codes	Bulk density(g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility	Angle of repose(°)
F1	0.417±0.002	0.476±0.002	1.14±0.000	12.41±0.066	29.14±0.536
F2	0.403±0.002	0.470±0.003	1.17±0.011	14.18±0.830	29.56±1.368
F3	0.400±0.002	0.472±0.003	1.18±0.011	15.16±0.0817	30.39±0.501
F4	0.399±0.002	0.457±0.005	1.15±0.013	10.43±1.299	32.20±0.996
F5	0.417±0.002	0.464±0.003	1.14±0.000	12.41±0.066	29.14±0.536
F6	0.403±0.002	0.476±0.002	1.17±0.011	14.18±0.830	29.56±1.638
F7	0.407±0.004	0.461±0.003	1.13±0.016	11.71±1.270	28.33±0.608
F8	0.414±0.002	0.472±0.003	1.14±0.011	12.31±0.857	27.52±1.031
F9	0.419±0.002	0.446±0.004	1.12±0.016	13.20±0.993	25.77±0.996

*Data are as mean ± expressed S.D. (n=3)

Table No.4.Evaluation of Febuxostat Fast Disintegrating Tablet.

Formulation Codes	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm 2)	Friability (%)	Wetting Time (sec)	Disintegration Time(sec)	Drug Content (%)
F1	147.9±2.12	3.053±0.187	3.083±0.069	0.77	71.00±2.94	135.67±2.87	99.35±0.73
F2	148.3±1.98	3.020±0.091	3.200±0.058	0.61	56.67±1.70	108.67±1.69	99.46±0.21
F3	148.4±1.98	3.030±0.083	3.467±0.095	0.52	34.67±2.87	67.48±2.05	99.49±0.57
F4	148.3±2.25	3.006±0.094	3.033±0.111	0.81	26.00±0.82	100.67±1.24	99.11±0.77
F5	148.7±1.85	3.027±0.088	3.117±0.090	0.68	34.33±1.24	67.33±1.25	99.20±0.43
F6	148.3±2.16	3.007±0.086	3.183±0.090	0.59	57.67±1.25	92.33±0.47	99.90±0.33
F7	149.0±1.54	3.018±0.089	3.267±0.094	0.74	62.00±0.81	98.00±0.82	99.53±0.52
F8	148.8±1.76	3.016±0.086	3.334±0.094	0.63	43.33±0.47	82.33±1.24	99.35±0.88
F9	148.3±2.07	3.018±0.090	3.300±0.100	0.56	98.33±0.94	60.00±2.45	99.17±0.84

*Data are expressed as mean S.D. (n = 3)

Table No. 5. In vitro release of Febuxostat Fast Disintegrating Tablet.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	20.7	10.6	8.55	48.15	26.52	52.40	22.10	27.60	20.39
10	48.15	64.79	67.61	100	67.02	87.84	71.16	64.50	62.01
15	69.86	98.90	100		99.99	100	98.99	97.96	84.50
20	100	100			100		100	100	100

CONCLUSION

Assessment of the results brings us to a conclusion that as the concentration of superdisintegrant increases thus there is increase in drug release rate. The influence of β-Cyclodextrin upon the solubility of febuxostat is depicted in Figure 1which illustrate that the increase in solubility was linear with respect to the weight fraction of the carrier. The increase in the solubility with increasing β-Cyclodextrin concentration indicates the solubility enhancement potential of β-Cyclodextrin. It can probably be explained by increased wettability of febuxostat. Indeed, it can be conclusively stated that ludiflash improvises the rate of disintegration & β-Cyclodextrin causes a decrease of the interfacial tension between the drug and the dissolving solution resulting in increased solubility. The formulation developed through present research work proves successful in achieving an improvised rate of disintegration & dissolution subsequently contributing to improved bioavailability which conforms to the objective.

REFERENCES

1. Shekhar R, Vedavathi T. Recents trends of oral fast disintegrating tablets-an overview of formulation and taste masking technology, Res. J. Pharm. Bio and Chem. Sci, 2012; 772-792.

2. Divate S., Kavitha K., Sockan GN., Fast disintegrating tablets. An emerging trend, Int. J. Pharm Sci. Rev. & Res, 2011; 18-22.
3. Bhanudas S Kuchekar., Varsha B Devkar., Swati C Jagdale. Solubility enhancement and formulation of Rapid Disintegrating Tablet, Bio Med Rx, 2013; 1(2): 168-175.
4. Rahul Dass, Sandhya Jaiswal, G.D Gupta. Formulation and evaluation of febuxostat fast disintegrating tablet. Indo American Journal of Pharm. Research, 2014.
5. Van den Mooter G., Wuyts M., Blaton N., Physical stabilization of amorphous ketoconazole in solid dispersions with polyvinylpyroliddone K25, Eur. J Pharm Sci, 2001; 12: 227-230.
6. Ghareeb MM., Abdulrasool AA., Hussein AA. Noordin MI., Kneading Technique for Preparation of Binary Solid Dispersion of Meloxicam with Poloxamer 188, AAPS Pharm Sci Tech, 2009; 1206-1215.
7. Choudhary A., Rana AC., Aggarwal G., Kumar V., Zakir F., Development and characterization of an atorvastin solid dispersion formulation using skimmed milk for improved oral bioavailability, Acta Pharmaceutica Sinica B.
8. Higuchi T., Connors KA., Phase solubility techniques, Adv Anal Chem. Instrum, 1965; 4: 117-210.
9. Modi A., Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) techniques, AAPS Pharm Sci Tech, 2006: 203-211.
10. Shirsand S; SarasijaSwamy P.V. formulation design and optimization of fast dissolving clonazepam tablet, Indian journal of Pharmaceutical sciences 2009; 71: 567-572.
11. Palkhede MB., Amrutkar SV., Erande KB, formulation, optimization and evaluation of fast disintegrating tablet of mebeverine HCl, Int. J. Pharm. & Phrm. Sci, 2012; 923-935
12. Naluri B, Chowadary K., Murthy K., Satyanarayana V. Hayman A., Becket G., Inclusion complexation and dissolution properties of nimesulide and meloxicam-hydroxypropyl- β-cyclodextrin binary systems. Journal of inclusion Phenomena and macrocyclic Chemistry, 2005; 53: 103-110.
13. Vanshiv S., Rao R., Physiochemical characterization in vitro dissolution of oxacarbazepine and β-cyclodextrin inclusion complexes. Indian Drug, 2008; 45: 816-820.
14. Setty M.c., Prasad D., Gupta V., Development of fast dispersible aceclofenac tablets: Effect of functionality of superdisintegrant. Indian journal of pharmaceutical sciences, 2008; 70, 180: 185.