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SOLID DISPERSION ADSORBATE–A NOVEL TECHNIQUE FOR DISSOLUTION ENHANCEMENT OF FEBUXOSTAT

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ABSTRACT: The objective of the present investigation was to improve dissolution characteristics of febuxostat, a BCS class – II drug, by formulating it as solid dispersion adsorbate. Solid dispersion adsorbate(SDA) was prepared using labrasol, transcutol and lutrol F127 as carriers and neusilin as adsorbent. Formulation was prepared using combination of melt and adsorption technique. Optimized formulation was characterized by fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and X-ray diffraction (XRD). In-vitro dissolution profile was compared with the marketed product. SDA comprising of febuxostat, neuslin and the three carriers in a ratio of 1:2:4 was considered as optimized formulation. FTIR spectroscopy revealed intermolecular hydrogen bonding with neusilin. DSC scan showed absence of melting peak of febuxostat, which indicates solubilization of drug in carriers and conversion of crystalline to amorphous form. This point was further confirmed by XRD. The percentage yield obtained was 90% and there was 10% increase in the dissolution rate of the optimized formulation compared to the marketed product. The dissolution efficiency was found to be 37% of the optimized formulation. Significant increase in the dissolution characteristics of febuxostat was noticed. The enhancement in dissolution rate of febuxostat can be due to hydrogen bonding between the drug and neusilin, micellar solubilisation of drug in carrier, improved wettability and amorphization as confirmed by FTIR, DSC and XRD studies. The results indicated that the SDA is a promising approach for the dissolution enhancement of febuxostat and can be used for the development of suitable solid dosage form for commercialization.

INTRODUCTION: The chemical name of febuxostat (FEB) is 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid (**Fig.1**). It is indicated for the long-term management of hyperuricemia in patients with gout [1–3].

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It is a non-purine, selective inhibitor of xanthine oxidase/ xanthine dehydrogenase. According to Biopharmaceutical Classification System, FEB is a class II drug, exhibiting low solubility and high permeability.

Its oral bioavailability is hampered by low aqueous solubility and its vulnerability to enzymatic degradation in both intestine and liver. Moreover, the presence of food decreases the maximum concentration of FEB in plasma (Cmax) by 38–49%. Thus, it has undesirable dissolution profile and consequently poor bioavailability following oral administration [4, 5].

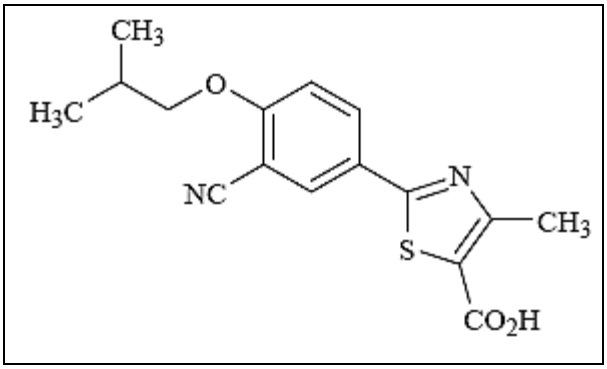

FIG.1: THE CHEMICAL STRUCTURE OF FEBUXOSTAT

The bioavailability of a poorly water-soluble drug is often limited by its dissolution rate, which in turn is controlled by the surface area available for dissolution. The fact that more than 40% of newly discovered drugs have little or no water solubility presents a serious challenge for the successful formulation development and commercialization of new drugs in the pharmaceutical industry. Micronization, nanosuspensions, polymorphs, complexation, solid dispersion, prodrugs, and salt formation can be employed to increase dissolution rate[6]. Solid dispersion has become one of the most active areas of research in the pharmaceutical field because of promises in the bioavailability enhancement of poorly water-soluble drugs [7].

Solid dispersion is defined as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent, or melting-solvent method" [8]. However, the number of marketed products derived from this approach is very limited due to problems of poor compressibility, scale-up, requirement of large amount of carrier, and stability upon storage. The processing variables of solid dispersions can be improved by the addition of adsorbent in the solid dispersion melt, thereby increasing the effective surface area of the drug leading to improved dissolution. A similar work has been reported on Ritonavir, a BCS class –II drug. It has shown a significant improvement in its dissolution characteristics by formulating it as solid dispersion adsorbate [9].

Poloxamers, a group of non-ionic surfactants, have been reported to improve the dissolution of poorly water soluble drugs from solid dispersions [10, 11]. Lutrol F127 (Poloxamer) has been successfully utilized to enhance the dissolution rate of poorly water-soluble drugs [11]. Neusilin ® was used in the present investigation as an adsorbent. It exhibits high specific area, increased surface adsorption, porosity, anti-caking and flow enhancing properties [12]. These features of Neusilin ® allow formulators to explore solid dispersion technology to improve bioavailability and overcome problems associated with processing and stability of poorly water-soluble drugs [13]. Neusilin has silanol groups on its surface, which make it a potential proton donor as well as acceptor. The hydrogen bonding potential of silanol in the local environment on silica surfaces is well documented [14, 15].

In the present investigation, a combination of solid dispersion and melt adsorption technology was utilized to prepare solid dispersion adsorbate of FEB. An attempt was made to improve the dissolution properties of FEB by preparing free-flowing solid dispersions using neusilin US2 as an adsorbent. The solid dispersions adsorbates were characterized by fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction study (XRD)[16].

MATERIALS AND METHODS:

Materials:

Febuxostat was received as a gift sample from Torrent Research Centre (Gandhinagar, India). Lutrol F127, Transcutol and Labrasol were kindly gifted by BASF Ltd. (Mumbai, India). Neusilin US2 was procured from Gangwal Chemicals Ltd. (Mumbai, India). All other reagents used were of analytical grade.

Preparation of Solid Dispersion Adsorbate (SDA):

SDA of FEB was prepared by the melt adsorption technique as reported by Kinoshita et al.[17].

Solid dispersion adsorbates of FEB were prepared with each carrier individually i.e. lutrol F127, labrasol and transcutol as well as in combination along with neusilin as an adorbent. Each carrier was melted in a porcelain dish on water bath; drug was then dispersed in molten carrier mass and stirred at temperature around 60°C. Neusilin was then added and finally the mass was allowed to cool at room temperature. Similarly, batches

containing combination of two or all three carriers were prepared with neusilin. The composition of formulated batches is shown in **Table 1**. The amount of carriers used was within IIG limits. The SDAs were then passed through sieve #40 ASTM to obtain free flowing powder of uniform size [18].

TABLE 1: FORMULATION OF SOLID DISPERSION ADSORBATES OF FEB

Batch no.	Febuxostat (mg)	Lutrol F12 (mg)	Labrasol (mg)	Transcutol (mg)	Neusilin (mg)
FEB1	40	80	----	---	80
FEB2	40	---	80	---	80
FEB3	40	---	---	80	80
FEB4	40	40	40	---	80
FEB5	40	40	---	40	80
FEB6	40	---	40	40	80
FEB7	40	53.33	53.33	53.33	80

Percentage Yield and *In Vitro* Drug Dissolution Study:

The percentage yield was calculated for SDA of each batch. Drug release studies were performed in triplicate using dissolution apparatus type II paddle method. The drug dissolution study was carried out in 900 ml of 0.05M phosphate buffer pH 6.8 at 37°C and 50 rpm. Ten ml of sample was withdrawn at 5, 15, 30, 45, and 60 min and replaced with the fresh dissolution medium. The solutions were filtered through Whatmann filter paper (0.22µm) and assayed spectrophotometrically at 315 nm. Dissolution study of marketed product was also carried out (FEBUTAX – 40 mg) for comparison with the optimized formulation.

Dissolution Efficiency:

The percentage dissolution efficiency (DE) was calculated using the eq.1[19]. Here,y is the percentage of drug dissolved. DE is then the area under the dissolution curve between time point t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same time period. The dissolution efficiency for formulated SDA product FEB7 and marketed product was calculated.

$$DE = \frac{\int_{t1}^{t2} y.dt \times 100}{y100.(t2-t1)} \quad \text{.....eq (1)}$$

Characterization Studies:

Fourier Transform Infrared (FTIR):

FTIR spectra of FEB, SDA of batch FEB7 and LLT (blank formulation without drug) were obtained using Shimadzu Biorad FT-IR system (Kyoto, Japan). Each sample was dispersed in dry potassium bromide (5 wt% of sample), ground well in mortar and pestle and disc was prepared at a pressure of 1,000 psig. The disc was placed in the FTIR sample holder and IR spectra in absorbance mode were recorded in the spectral region 4,000 to 500 cm^{-1} using the resolution 1 cm^{-1}.

Differential Scanning Calorimetry (DSC):

The melting behaviour of FEB and SDA of batch FEB7 were evaluated. Samples were sealed in aluminium pans and scanned from 30 to 200° C at a heating rate of 10° C/min in an atmosphere of nitrogen gas.

X- ray Diffraction (XRD):

The physical characterization of FEB, LLT and SDA of batch FEB7 were subjected to XRD analysis using Philip's X-ray diffractometer. The experiment was carried out at 25° C under the following conditions: scanning angle ranged from 0 to 50 of 2θ, voltage- 30 kV, current- 40 mA, counting time was 10s/step.

Stability Study:

Stability study was performed according to ICH guidelines for three months. Final formulation (SDA of batch FEB7) was kept at 45°C and 75 %RH conditions maintained in a stability chamber. Dissolution study was carried out at the end of three months to check inhibition of reversion of FEB to crystalline form.

RESULTS AND DISCUSSION: Preliminary studies were carried out to screen a suitable adsorbent. Neusilin was selected owing to good adsorptive capacity. The ratio of drug and adsorbent (1:2) was identified after evaluating the flow property. FEB was dispersed in different hydrophilic carriers like lutrol F127, labrasol, transcutol and their combination to obtain SDA. The co-melt of carrier and the drug was adsorbed

on the surface of neusilin to prepare freely flowing granules of SDA, which could be processed into a tablet or directly fill into the capsule.

Percentage Yield and *In Vitro* Drug Dissolution Study: One of the important considerations in industry is to obtain a better yield. There is considerable amount of loss in formulating solid dispersion but this problem is overcome by formulating it as solid dispersion adsorbate.

The percentage yield and percentage drug release at 30 min of batches FEB1-FEB7 are shown in **Table 2**.

TABLE 2: PERCENTAGE YIELD AND PERCENTAGE DRUG RELEASE (Y_{30})

Batches	% yield	% drug release (Y_{30})
FEB1	61±2.51	65.25±2.67
FEB2	73±1.8	55.31±2.5
FEB3	77±3.68	57.47±3.23
FEB4	75±3.22	60.36±3.65
FEB5	68±2.95	58.28±3.5
FEB6	70±3.42	54.90±2.8
FEB7	90±2.99	73.70±2.77

The dissolution curves of formulated batches and marketed product FEBUTAX are shown in **Fig.2** and **3.**

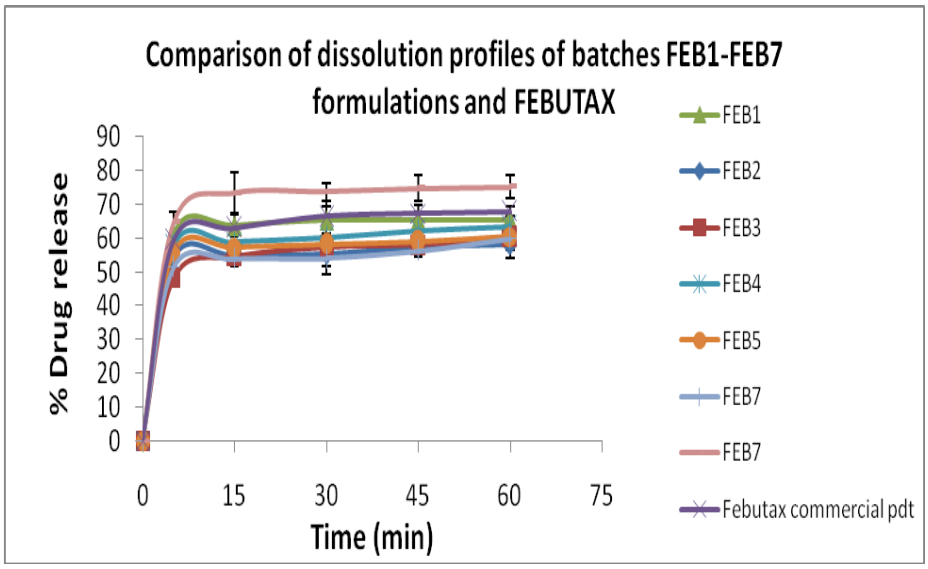

FIG.2: DISSOLUTION PROFILE OF DIFFERENT FEB FORMULATIONS

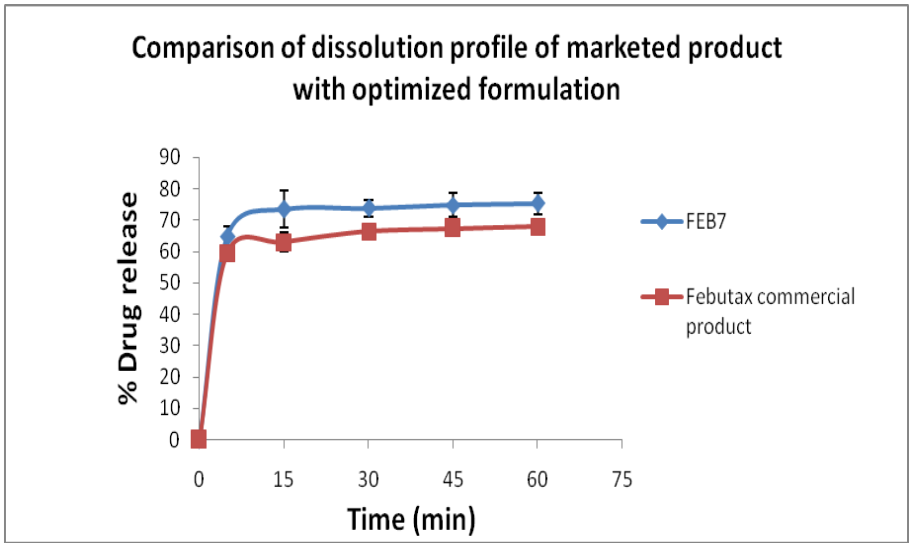

FIG. 3: COMPARISON OF DISSOLUTION PROFILE OF MARKETED PRODUCT WITH FEB7 BATCH

Dissolution efficiency of batch FEB7 and FEBUTAX, a commercial product were found to be 37 and 33.2% respectively at 30 min time interval.

The dissolution rate of SDA's comprising carrier in ratio of 2:1 (carrier: drug) showed almost similar or slightly slower dissolution rate compared to commercial product. The batch FEB7 consisting of all the three carriers within IIG limit and in ratio of 4:1 (carrier: drug) showed greater dissolution (about 11.5% increment) compared to the marketed product. This was due to synergistic effect of all the three carriers and higher ratio of carrier to drug. Thus combination of solid dispersion and melt adsorption technology resulted in enhancement in dissolution rate due to the combined effect of solid dispersion and increased surface area due to adsorption.

FTIR:

The infrared spectrum of FEB and SDA exhibited significant differences in the intensities of the absorption peaks shown in **Fig. 4** respectively. Broadening of various absorption peaks with a slight shift in the position to a lower wavelength was observed [20]. Carboxylic group of FEB is bonded with silanol group of Neusilin thus there is hydrogen bonding between them which is revealed in the graph in form of broad peak between 3000-2500 cm^{-1}. Thus, hydrogen bonding can be one of the main reasons for increase in the dissolution rate as well as stability of dosage form upon storage [21].

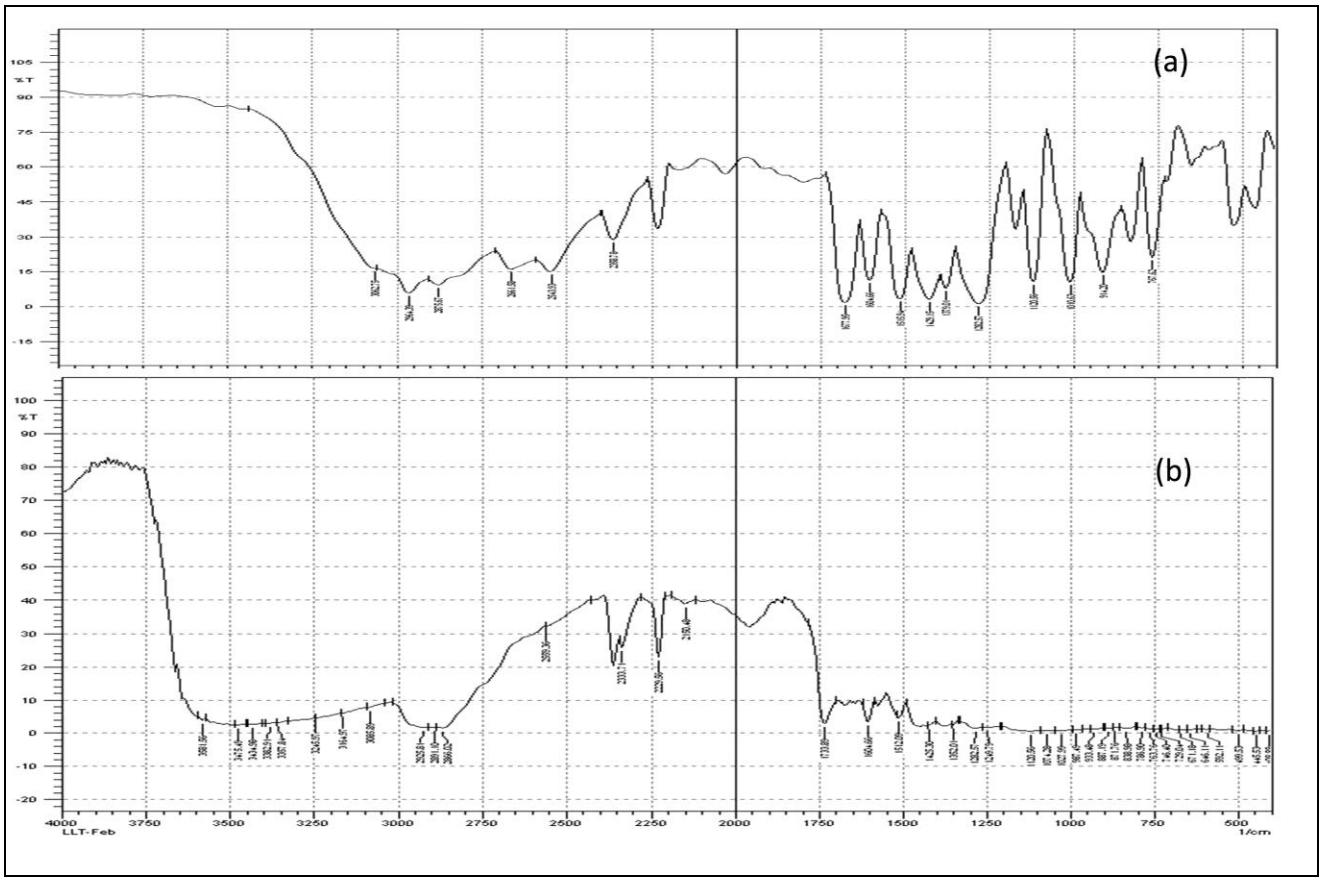

FIG. 4: OVERLAY FT-IR SPECTRA OF (a) FEB AND (b) FEB7

DSC:

DSC curves of pure FEB and the SDA are shown in **Fig.5.** DSC thermogram of FEB showed an endothermic peak at 210.13 °C, corresponding to the melting point of FEB (ΔH = -109.96 $J.gm^{-1}$). In thermogram of solid dispersion,the sharp melting peak of pure FEB was not visible; this might be because of complete dissolution of FEB in the melted polymer. Lack of melting peak of FEB in the DSC thermogram indicated that the drug might be converted to amorphous form from crystalline form. The amorphous state in comparison to crystalline form is a high-energy state and is expected to have a high absorptivity [22].

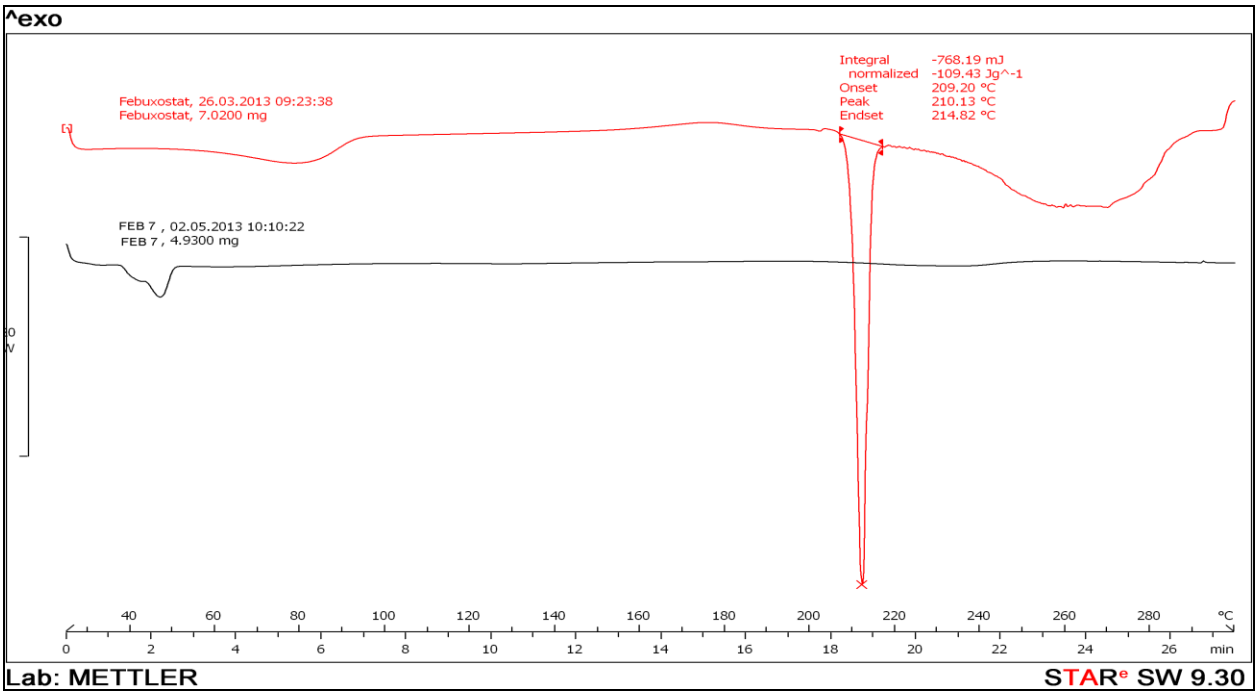

FIG.5: OVERLAY OF DSC SCAN OF FEB AND FEB7

XRD:

The X-ray diffraction patterns of FEB, FEB7 and LLT are as shown in **Fig.6**. The graph of FEB revealed high crystallinity of the drug with major diffraction peaks. Diffraction pattern of solid dispersions show absence of the characteristic peak of FEB, indicating complete drug dissolution in the carrier and thus complete, amorphization of the drug. This can also be considered as a major reason for the improvement of dissolution rate of FEB [23].

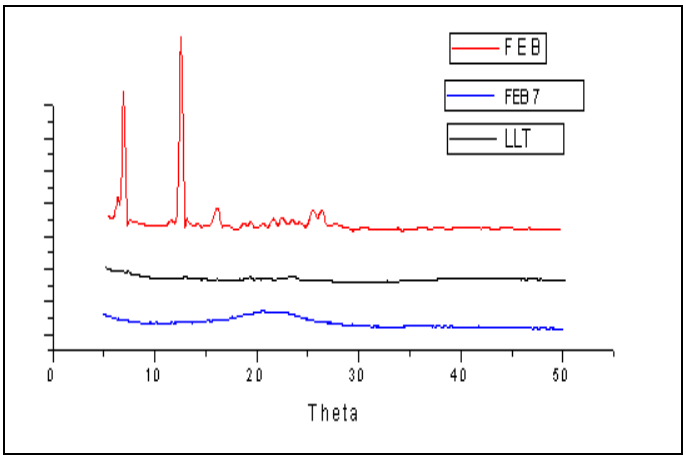

FIG.6: OVERLAY OF XRD PATTERN OF FEB, FEB7 AND LLT

Stability Study:

The solid dispersions have tendency to change the form of drug on standing. For example, amorphous drug (more soluble) is converted to crystalline drug (less soluble). In order to assure clinical response, dissolution of batch kept for stability study was carried out. Dissolution stability study of batch FEB7 performed at the end of 3 months revealed no change in the dissolution pattern as shown in **Fig.7.**

A paired t-test for two samples of means was performed to confirm these observations. The value of calculated t-statistics was 0.390. This value is less than the critical value of t-statistics, i.e. 2.896. Therefore, it may be concluded that the difference was insignificant. It may be inferred that there is no conversion of amorphous form back to crystalline form on storage.

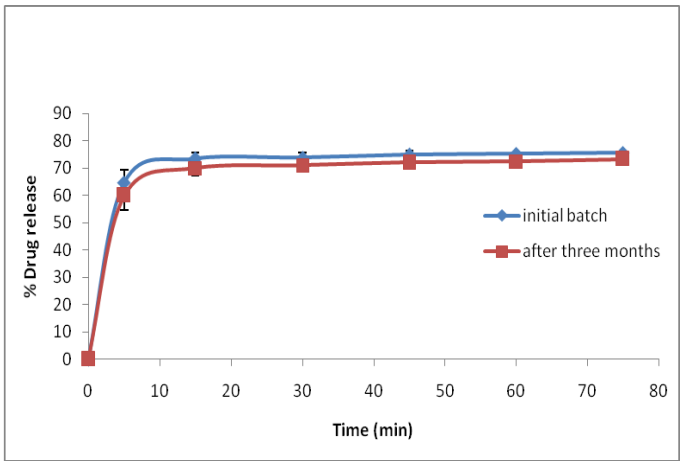

FIG.7: DISSOLUTION PROFILE OF FEB7 BEFORE AND AFTER THREE MONTHS

CONCLUSION: The prepared solid dispersion adsorbate of FEB with Neusilin and combination of three carriers lutrol F127, transcutol and labrasol in the ratio of 1:2:4 showed enhanced dissolution. About 11.5% increase in dissolution profile was observed compared to marketed product. The enhancement in dissolution may be due to hydrogen bonding between the drug and neusilin, micellar solubilisation of drug in carrier, improved wettability and reduction in crystallinity. Inhibition of reversion of amorphous form to crystalline form is the main advantage of this technique. The result indicates that the solid dispersion adsorbate is a promising and a novel approach for the dissolution enhancement of febuxostat and can be used for the development of suitable solid dosage form for commercialization. The excipients were used within the limits permitted by IIG. Further *in-vivo* study is required to be carried out to evaluate the efficiency of solid dispersion system in improving oral bioavailability of FEB. Also, further studies are needed to scale up the process.

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