Section: Research Paper

MIXED HYDROTROPIC SOLUBILISATION- A NOVEL TECHNIQUE TO ENHACE THE DISSOLUTION OF FEBUXOSTAT

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ABSTACT

The aim of this study was to improve the dissolution of water insoluble drug by mixed hydrotropic solid dispersion technology. The poor dissolution characteristic of water insoluble drugs is a major challenge for pharmaceutical professionals. Mixed hydrotropic solid dispersion (HSD) technology contains the blends of hydrotropic agents, gives synergistic effect on solubility of poorly aqueous soluble drug. This technique restrict the use of large amount of individual hydrotropic agent, thus minimize the toxic effects of individual hydrotropic agent arising due to their high concentration. HSDs were prepared by using hydrotropic blend of 15% sodium benzoate, 10% Niacinamide and 5% sodium citrate by solvent evaporation method.Hydrotropic agents previously evaluated for their compatibility with drug by FT-IR study. Prepared solid dispersions were evaluated by XRD and dissolution studies, compared with the pure febuxostat power and physical mixture of drug and hydrotropic agent. The result showed no interaction between the drug and hydrotropic polymer and significant increase in the dissolution rate.

Keywords: Febuxostat, Solvent evaporation, Mixed hydrotropic solid dispersion, Dissolution, Sodium benzoate , Sodium citrate, Niacinamide

INTRODUCTION

Most of the chemical entities that are being discovered are lipophilic and have poor aqueous solubility. Because of their low aqueous solubility and high permeability, dissolution from oral delivery systems forms the rate limiting step in their absorption and systemic bioavailability. A more than 60% drug product suffers from poor water solubility. Currently number of techniques addressed the poor solubility and dissolution rate of poorly soluble drugs. Hydrotropic solubilization is one of them. Hydrotropy is a

solubilization phenomenon whereby addition of large amount of second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide/ niacinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubility of many poorly water-soluble drugs. Aqueous injection of caffeine with sodium benzoate (a hydrotropic agent) is a classic example (12). A Hydrotropes is a compound that solubilizes hydrophobic compound inaqueous solutions. Typically Hydrotropes consist of a hydrophilic part and a hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self- aggregation. Hydrotropes do not have a critical concentration above which self- aggregation suddenly starts to occur (as found for micelle forming surfactant have a critical micelle concentration). Hydrotropy is a used as solubility enhancement for different class of drugs such as anti-tumor, anti-viral, anti-pyretic, analgesic drugs, xanthine derivatives. (13)

MATERIALS AND METHODS

Material

Febuxostatis a kind gift sample from Ipca laboratories, Ratlam, Madhya pradesh. All the reagents and solvents were of analytical grade.

Selection of hydrotropic blends

As evident from the research work,() it was found that there were significant enhancement in aqueous solubility (a synergistic effect) of poorly water soluble drug by use of a combined hydrotropic blend. Keeping this point in mind and using the total dissolved concentration at least 30% w/v (at random) different blends of hydrotropic agents (sodium benzoate, niacinamide and sodium citrate) (table- 1) were made and the solubility of febuxostat was determined with them.

Table1. Composition of hydrotropic blends selected for febuxostat

S. No.	Combination	Total con. (% w/v)	Ratio
1.	B+ N + C	30%	15+ 10 + 5
2.	N+ B + C	30%	15+ 10 + 5
3.	B+ N + C	30%	10+ 10 +10
4.	B+ N + C	30%	5+ 10 + 15
5.	B+ N + C	30%	10+ 5 +15

B= SODIUM BENZOATE; N= NICOTINAMIDE; C= SODIUM CITRATE

Determination of equilibrium solubility studies in different blends of hydrotropic agents

3 ml of particular blend of hydrotropic agent was taken in a 10 ml volumetric flask and excess amount of drug was added and shaken mechanically by mechanical shaker until

saturated solution was formed. The solution wascentrifuged at 2000 rpm for 10 min in Ultra- centrifuge and resulting solution was filtered through whatman filter paper grade 41. Aliquot was suitably diluted with distilled water and analysed by using uv-spectrophotometer at 315 nm.

S. No.	Hydrotropic agent	Solubility in 30% hydrotropic agent	Solubilityenhancement ratio
1.	Nicotinamide	0.559	34.33
2.	Sodium benzoate	0.793	48.71
3.	Sodium citrate	0.097	6.06

Table 2 - Solubility studies in different blends of hydrotropic agents

Highest solubility was observed in 30% sodium benzoate. Then in order to decrease the concentration of sodium benzoate, different combination of hydrotropic agent in different ratios were made to determine enhancement in solubility.

Table 3- Different combination of hydrotropic agent in different ratios to determine enhancement in solubility

S. No.	Combination	Ratio	Solubility % w/v
1.	B+ N + C	15+ 10 + 5	4.3
2.	N+ B + C	15+ 10 + 5	3.9
3.	B+ N + C	10+ 10 +10	3.3
4.	B+ N + C	5+ 10 + 15	2.8
5.	B+ N + C	10+ 5 +15	3.0

Formulation of Hydrotropic Solid Dispersion of Febuxostatby Solvent Evaporation Method

For the preparation of hydrotropic solid dispersion containing Febuxostat and hydrotropic blend in different ratio composition described in table were weighed accurately. Minimum quantity of distilled water at 80- 85 0C contained in a 100 ml beaker was used to dissolved the B+N+C for quick dissolution. Then Febuxostat was added to this beaker at (30-40 0C) and a Teflon coated magnetic bead was dropped in it, so as to facilitate the evaporation of water. As evaporation proceeded speed of magnetic bead decreased and it stopped stirring when most of the water was evaporated and indicating the formation of wet solid dispersion.

Table 4- Composition of hydrotropic solid dispersion

S. No.	Drug hydrotropic blend	Febuxostat	Benzoate	Niacinamide	Citrate
1.	1 : 6	1 gm	3 gm	2 gm	1 gm
2.	1 : 8	1 gm	4 gm	2.67 gm	1.34 gm
3.	1 : 10	1 gm	5 gm	3.34 gm	1.67 gm

Semisolid mass so formed spread on several watch glasses in thin layers for quick drying. The watch glasses were kept in oven, at 40 0C for drying. After drying, it was triturated with the help of pestle mortar and again kept in oven for drying. After complete drying, the powder of solid dispersion was passed through sieve no. 40 and finally store in air tight glass bottle.

Physical Mixture of Febuxostat-

Drug carrier ratio 1:6, 1:8 and 1:10 were used for preparation of physical mixture. Accurate amount of ingredients were weighed and mixed intensely for 10 minutes using glass pestle and mortar with intensive trituration. Then, powder mass was shifted through sieve number 40. After this, the physical mixture was stored in air- tight glass bottle.

Determination of Drug Content in Febuxostat Formulation (HSDAnd PM)-

Powdered solid dispersion/ PM containing about 10 mg of febuxostat was accurately weighed and transferred to a 100 ml volumetric flask. About 50 ml of distilled water was added and flask wasshaken to dissolve the formulation completely. Then volume was made up to the mark with distilled water and the absorbance of this solution was measured at 315 nm against reagent blank. In each case, analysis was carried out in triplet. The drug content was determined using regression equation-

$$Y = 0.0648 X + 0.0029$$

Table 5- Drug contents of physical mixture and hydrotropic solid dispersion

S. No.	Drug : Hydrotropic blend	Percentage drug (mean ±SD)	
	BLEND	PHYSICAL MIXTURE	HYDROTROPIC SD
1.	1 : 6	65±1.417	112.4±2.557
2.	1 : 8	90.433±1.222	135.733±2.260
3.	1 : 10	97.333±2.371	106.9±1.652

POWDER X- RAY DIFFRACTION-

X- ray diffraction analysis for pure drug and hydrotropic solid dispersion of febuxostat were done by X- ray diffractometer(Figure.1-3)

Dissolution Rate Studies of Drug and their Formulations-

Solid dispersion and physical mixture of febuxostat were tested in dissolution rate studies using USP XXIV (type II) dissolution test apparatus (model TDT4P, Electrolab Mumbai, INDIA) with paddle to rotate at 50 rpm 900ml of distilled water was taken as dissolution media with temperature of 37± 0.5℃. At definite time interval 1ml of sample were withdrawn and were analysed for drug content. Withdrawn sample were also replaced with fresh dissolution media. Calculations for the amount of drug were done using respective regression equation and the results of the dissolution studies. (table- 6)

Chemical Stability Studies-

Powders of various formulation were kept in 10 ml amber coloured glass bottle which plugged and sealed. The febuxostat content of the febuxostat hydrotropic solid dispersion preparations was analyzed at 0, 1, 2, 4, and 6 months to compare the degradation over time. Bottles were kept at room temperature. The drug contents were determined by UV analysis. The initial drug content for each formulation was considered as 100%.

RESULT AND DISCUSSION

Solubility enhancement ratio of febuxostat in different hydrotropic blend like niacinamide, sodium benzoate and sodium citrate was found to be 34.33, 48.71, 6.06. The highest solubility enhancement was found in sodium benzoate. (Table 2) Percentage solubility of different hydrotropes was determined and maximum solubility was observed in blend containing sodium benzoate, niacinamide and sodium citrate in ratio 15: 10 : 5. Therefore this combination was used for the preparation of solid dispersion.

Solid dispersion of various hydrotropes with the drug was prepared in various ratio using solvent evaporation technique (Table 4). The prepared solid dispersion were further characterized by XRD and drug content. XRD analysis was performed. In the XRD of pure drug sharp peak was observed at 10-20° indicating the presence of crystalline drug while solid dispersion show sharp peak at 10-20°. The data reveals that typical drug crystalline peak was still detectable in the solid dispersion, thus confirms the presence of the littSle amount of crystalline drug in solid dispersion.However sharp peak corresponding to the drug were absent in the XRD of solid dispersion. This suggesting the crystalline nature of drug has decreased in the solid dispersion. Decrease in crystalinity of drug and hydrotrope may contribute to enhancement of dissolution of drug.

In- vitro dissolution rate study were performed at 37±0.5℃ (Table6), it showed that the bulk drug sample exhibited poor drug release profile. Initial rates of dissolution of drug from HSDs were very quick as compared with initial rates of dissolution from bulk drug sample. Drug release profile from HSDs was better than the drug release profile from PM. Also, it is indicated that as the proportions of water soluble carrier was increased in solid dispersions, there was negligible different in dissolution behavior. As the initial rates of dissolution of drug from HSDs were significantly high as compared with initial

dissolution rates from bulk drug sample, the quick onset of action and better extent of absorption is expected after oral administration of these HSD.

CONCLUSION-

In the field of pharmaceutical industries the major problem associated various drug is their poor water solubility especially for oral administration. Aqueous solubility of drug for oral preparation is very important step for better bioavailability of drug in systemic circulation. There are several approaches are used to enhanced the drug solubility of poor water soluble drugs like co- solvency, complexation and pH alteration, by chemical modification of drug and by hydrotropic solubilization etc. Among these approaches hydrotropy is suitable choice of scientist to designate the increase in aqueous solubility of various poorly water-soluble compounds (febuxostat etc.) due to the presence of a large amount of additives. Concentrated aqueous solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, sodium acetate and sodium ascorbate have been employed to enhance the aqueous solubilities of a large number of poorly water soluble drugs.Problem associated with oral formulation of febuxostat is slow solubilisation rate of febuxostat, less aqueous solubility, high cost of organic solvent, high cost of formulation, narrow therapeutic range, fluctuation in plasma concentration and serious side effects with convectional dosage form. Hydrotropic solubilization is a technique to improve the dissolution of poor water soluble drug. In this technique addition of hydrotropic agents result in the improve aqeous solubility of poor soluble drug. Various hydrotropic agents are used to enhance aqeous solubility of drug like sodium benzoate, sodium citrate, sodium acetate, niacinamide, urea etc. Aqeous injection of caffeine with sodium benzoate is a better example of hydrotropy.

Table 6- Dissolution profile of pure drug, PM and HSD in distilled water

Time (min)	**Cumulative percentage of drug dissolved (mean ± SD)**				
	Pure drug	**1 : 10 PM**	**1: 6 HSD**	**1 : 8 HSD**	**1: 10 HSD**
3	12.9±0.264	38.30±0.40	73.23±0.981	88.13±0.680	79.93±0.057
6	14.04±0.850	45.73±0.404	92.86±1.357	94.30±0.173	93.56±1.761
10	20.26±0.321	51.33±0.602	96.23±0.960	96.66±0.208	96.36±0.709
15	27.86±0.56	58.70±0.360	98.73±0.288	99.10±0.655	98.46±0.550
30	37.50±1.3	69.40±0.529	98.96±0.0507	99.83±0.057	99.73±0.152

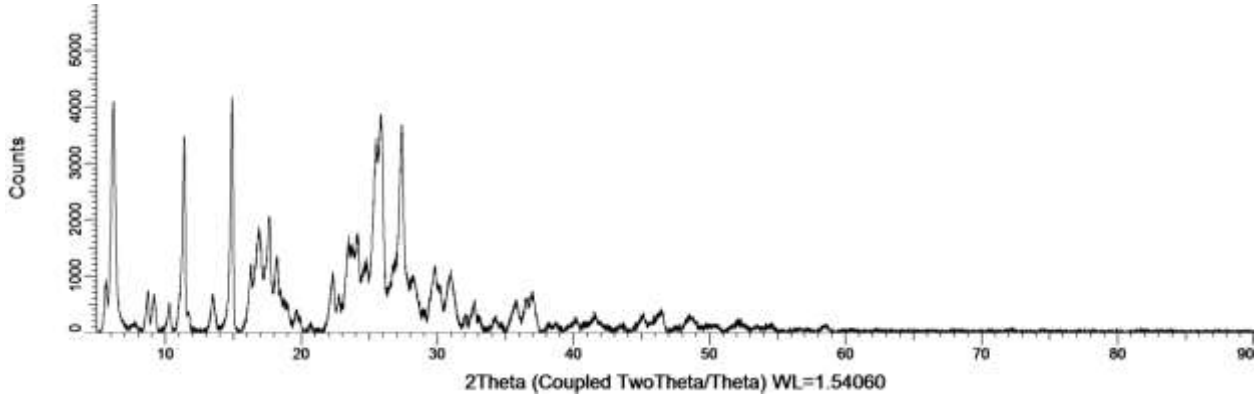

Fig 1- 1:6 HSD

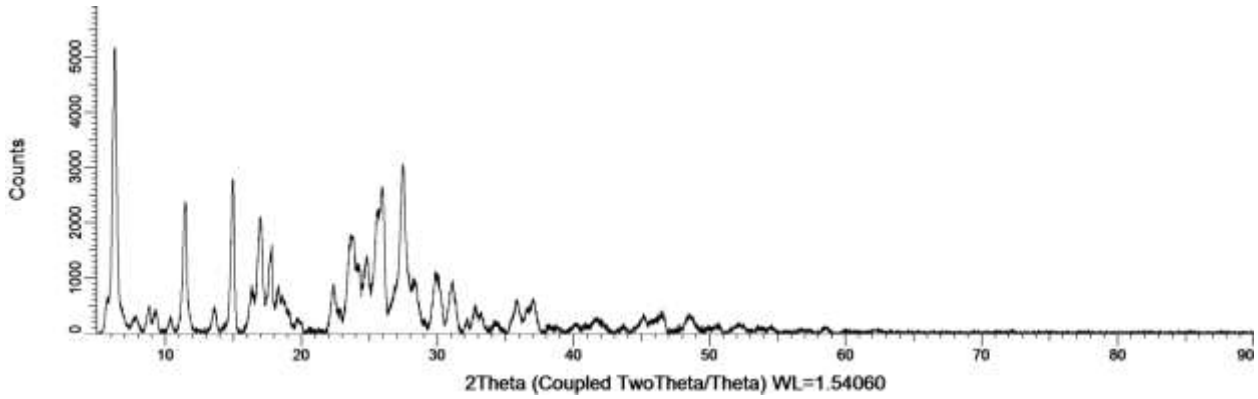

Fig 2- 1:8 HSD

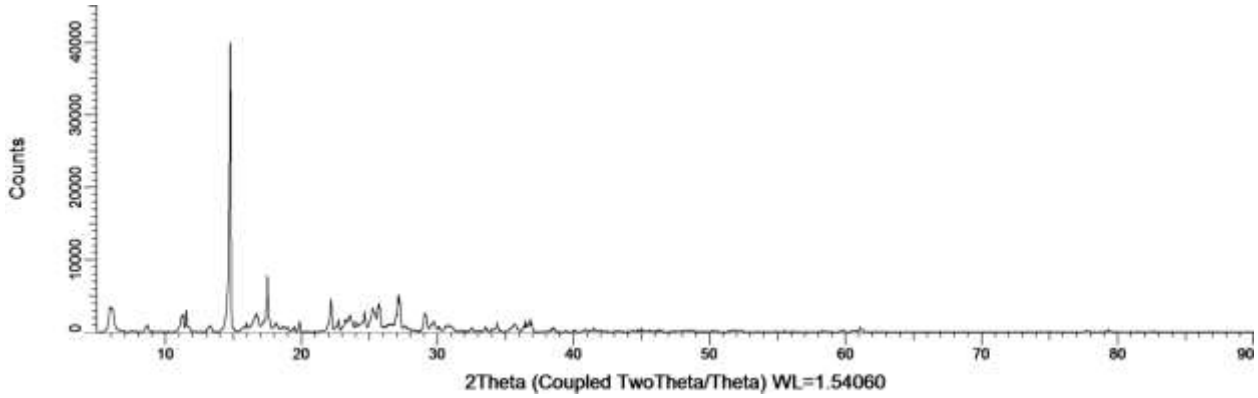

Fig 3- 1:8 PM

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