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Original Article

MODIFIED FORMULATION OF FEBUXOSTAT: IMPROVED EFFICACY AND SAFETY

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ABSTRACT

Objective: Febuxostat, a xanthine oxidoreductase inhibitor, is a drug of choice for hyperuricemia and Gout. But it also suffers from drawbacks in terms of pharmacokinetic profile and toxicity. It is available as immediate release formulation in the market. The objective is to develop a modified release formulation of febuxostat that can serve the dual purpose of increasing the efficacy and decreasing the toxicity, thereby improving safety.

Methods: Pharmacokinetic and pharmacodynamic data, including drug concentration profile, efficacy data and toxicity data have been reviewed thoroughly. Based on available data, target pharmacokinetic profile has been identified as about 50 % reduction in C_{max} and improvement in plasma drug concentration above required level during 6-24 hour. Desired *in-vitro* dissolution profile has been selected, and formulation modification has been sought to achieve the desired profile. The formulation has been prepared with a partial dose in the form of immediate release (IR) and remaining dose as an extended release (ER). IR and ER formulations have been developed separately and combined to form Inlay tablets containing ER inner tablet surrounded by IR.

Results: Based on dissolution data and Wagner-Nelson calculations, the plasma concentration profile has been predicted for the developed formulation. It reconfirms that developed formulation will achieve the desired objectives. Formulation stability has been established up to 6 months under accelerated conditions.

Conclusion: The developed formulation is a potential candidate for filing to a regulatory agency with the advantage of higher efficacy and less toxicity, which will be beneficial to the patient population and has good commercial viability.

Keywords: Febuxostat, Modified release, Gout, hyperuricaemia, Wagner-Nelson.

INTRODUCTION

Febuxostat, chemically 2-[3-cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid, is a potent, non-purine selective inhibitor of xanthine oxidoreductase. Febuxostat 40 and 80 mg once daily (QD) is approved in the United States and the United Kingdom for the chronic management of hyperuricemia in patients with gout [1, 2].

Gout is a disease that results from the deposition of urate crystals in synovial fluid and other tissues due to its saturation in blood. There are four clinical stages viz. asymptomatic hyperuricemia, acute gouty arthritis, inter-critical gout and chronic tophaceous gout [3].

Xanthine oxidoreductase enzyme can be present in two different isozymic forms [4]. In one form, the xanthine oxidoreductase enzyme is synthesized as xanthine dehydrogenase, exhibiting a very low reactivity with oxygen. However, under stress or disease conditions, such as ischemia-reperfusion injury and congestive heart failure, xanthine dehydrogenase can undergo the formation of intra-molecular disulfide bonds or proteolytic cleavage, which converts the enzyme to the second form, xanthine oxidase. Xanthine oxidase exhibits high reactivity with oxygen. Hyperuricemia is also associated with a number of disease conditions, such as renal injury and hypertension [1].

Hyperuricemia is defined as plasma or serum urate concentration greater than 70 mg/l (>420 µ mol/l) and is present in approximately 5% of the population in the world. Serum uric acid (sUA) is the primarily important risk factor for the development of gout. Sustained hyperuricemia is a risk factor for acute clinically progressive stages of gout-like gouty arthritis, tophaceous gout and uric acid nephrolithiasis. Most patients with hyperuricemia will never have an attack of gout and remain untreated. In the Normative Aging Study, the 5-year cumulative risk of gout development in subjects with sUA levels >70 mg/l or >100 mg/l was 0.6% and 30.5%, respectively [5, 6]. The higher the sUA levels greater the likelihood of developing gout.

The available treatment option is uricosuric agent, increasing uric acid excretion and xanthine oxidoreductase inhibitor (Allopurinol and Febuxostat), reducing the synthesis of uric acid. Allopurinol has been shown to prevent renal injury and hypertension associated with hyperuricemia by inhibiting xanthine oxidoreductase; thus reducing uric acid levels. In contrast, it has been found that the extent of protection against renal injury and hypertension in subjects suffering from hyperuricemia is lower in subjects treated with the uricosuric agent benziodarone. Benziodarone does not inhibit xanthine oxidoreductase activity, but instead reduces plasma uric acid levels by increasing the excretion of uric acid in the kidney [7, 8]. Therefore, there is an unmet need for new dosage forms that not only reduce uric acid levels in hyperuricemic subjects, but are also capable of maintaining a high level of (namely, at least 80%) inhibition of xanthine oxidoreductase activity in order to protect subjects receiving these dosage forms throughout their treatment regimen (i. e., Dosing interval, which is typically twenty-four h) against increasing concentrations of oxygen free radicals.

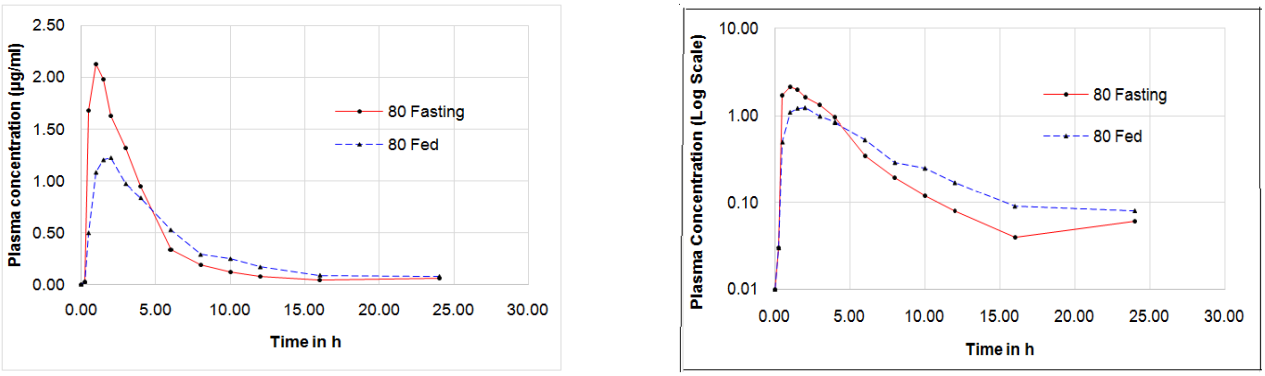
Another treatment for hyperuricemia in patients with chronic gout is with the compound febuxostat, a non-purine inhibitor of xanthine oxidase [9, 10]. Febuxostat is marketed in various countries with different brand names as immediate release tablets. In the United States of America (USA), it is marketed by Takeda Pharmaceuticals as Uloric tablets 40 & 80 mg [11]. Extensive pharmacokinetic and pharmacodynamic data have established that maintaining a concentration of febuxostat in plasma over a prolonged period of time provides similar efficacy to treatment with high doses of the drug. Generally, these studies have shown that maintaining a febuxostat plasma concentration of 0.1 µg/ml is essential to provide 95% or greater inhibition of xanthine oxidase.

Currently, the only commercially available formulations of febuxostat are immediate release tablets. Extended or delayed release formulations of febuxostat are not available. Therefore, a formulation of febuxostat that maintains the drug concentration above the critical concentration of 0.1 µg/ml for an extended period of time is expected to result in the higher efficacy of the drug, and would be a desirable treatment option for control of hyperuricemia, gout, and many other disease states.

Similar inference can also be taken from the blood concentration data of Febuxostat in fasting and non-fasting (fed) condition against the clinical effect in both conditions [12]. As shown in table 1 and fig. 1, in fed condition, there is a 49 % decrease in Maximum plasma concentration (C_{max}) level and about a 18 % reduction in Area under curve (AUC) level in comparison to fasting conditions. In clinical terms, there is a 7 % greater decrease in urate level in fed condition as compared to fasting conditions. Marginal improvement of a clinical effect can be seen in spite of the decrease in peak and total plasma exposure of Febuxostat. This is probably due to higher amount of drug availability in blood during 6 to 24 hour time period after dosing, which can be clearly seen in figure 1, log scale graphical representation.

Table 1: Pharmacokinetic and clinical data summary of febuxostat tablets 80 mg

Fbuxostat tablets 80 mg					
Condition	**Cmax**	**AUC**	**Mean serum urate level**		
			Day 1	**Day 6**	**% change**
Fasting	3.256	9.211	5.110	2.606	-51.16
Fed	1.800	7.675	5.255	2.235	-58.49
N	23	23	23	23	23



(a) **(b)**

Fig. 1: Plasma concentration profile of Febuxostat tablets 80 mg, (a): Normal scale Representation; (b): Log scale representation

Innovator, Takeda had initially conducted trials on tablets with two different strengths 80 and 120 mg and applied to the United States Food and Drug Administration (USFDA) for marketing approval. Based on the data review, USFDA had requested the withdrawal of the tablet of the strength of 120 mg and instead recommended to add the lower strength of 40 mg. Although 120 mg is the most effective strength, this decision was based on the toxicity data reported in the clinical studies conducted by Takeda [13]. Clinical data indicated that Febuxostat is more potent and effective than allopurinol, but treatment with Febuxostat is associated with higher rates of cardiovascular thromboembolic events, including death. A total of about 12 deaths had been reported along with additional non-fatal cardiac events during clinical studies. Febuxostat remains the second choice of drug for the treatment of hyperuricaemia in spite of it being more effective than allopurinol due to its toxicity.

Based on this information available from the literature, it can be inferred that (a) Febuxostat is a better choice of drug for treatment of hyperuricemia, (b) maintaining the optimal blood concentration for a longer duration is more important than achieving higher C_{max} for effective therapy in case of febuxostat.

This scenario thus presents an opportunity for some modifications in the pharmacokinetic parameters of Febuxostat driven by formulation design to achieve greater efficacy and reduced toxicity leading to the enhanced safety of a therapy for the same dose. Based on the data studied, the target had been set to achieve the required pharmacokinetic profile of a Febuxostat modified release formulation with, about 50 % reduction in C_{max} and improvement in plasma drug concentration above required level during 6-24 hour time period after dosing.

Altering the pharmacokinetic parameters of a drug is possible through the modification of the formulation where formulation and not the drug govern the requirements. Various methods of modification of drug release have been reported in the literature for different kinds of Active Pharmaceutical Ingredient (API) and the requirement of the formulation [14, 15]. Generally, conventional controlled release formulation provides good control of the release of the drug, but lacks in the quick onset of action while conventional delayed release formulation provides only delay in onset and no control after the delay. The requirement in the present case is for the first booster dose for quick onset of action and then a maintenance dose in controlled release manner. A few approaches that can render such kind of release pattern includes Multilayer tablet [16], Compression coated tablet and a mixture of variable release profile pellets in a single capsule. The approach selected in the present study is a combination of immediate release (IR) and extended release (ER) formulation, allowing an initial blood concentration (Loading dose) and then maintaining it above the therapeutically effective concentration for a longer duration (maintenance dose).

The inlay tablet formulation was proposed with an extended release inner tablet surrounded by an immediate release blend as the outer layer [7].

MATERIALS AND METHODS

Materials

Febuxostat, Microcrystalline cellulose PH 101 of Signet, Lactose Monohydrate of DEF international, Croscarmellose sodium (AC-DI-SOL), Hydroxypropyl cellulose (Klucel LF), Colloidal silicon dioxide (Aerosil 200 Pharma), Magnesium stearate (Ligamed, Veg grade),

Hypromellose 100 cps, 4000 cps and 15000 cps of Colorcon, Povidone K-30 of ISP, Isopropyl alcohol of Merck, Iron oxide Yellow of Koel.

The equipment used for the development includes Rapid mixture granulator, Fluid bed drier/Rapid drier, Mill, Stirrer, Blender, Compression machine, Moisture balance, Hardness tester, Disintegration apparatus, Vernier caliper and Friability tester.

Preparation of Immediate releases blend/tablet

Immediate release blend for the tablet was prepared by a wet granulation process. The ingredients, Febuxostat, Microcrystalline cellulose, Lactose and part quantity of croscarmellose sodium were dispensed accurately, sifted through appropriate sieves and mixed in rapid mixture granulator (RMG). Dry mix was granulated with a binder solution of hydroxyl propyl cellulose (Klucel) in water. Granules were dried in fluid bed drier/Rapid drier at 50 °C to 60 °C temperature till loss on drying (LOD) value of less than 2.0 % was achieved, as measured by a halogen moisture balance.

The dried granules were milled through a 1.5 mm sieve in the mill and any retained granules were milled through a 1.0 mm sieve. Milled granules were blended with the remaining quantity of croscarmellose sodium and aerosil and then lubricated with magnesium stearate.

Immediate release part was also separately compressed on 8 mm punch to evaluate the feasibility and study compression parameters. Table 2(a) describes various representative compositions of immediate release blend of the formulation.

Preparation of extended release inner tablet

Extended release portion of the formulation has been prepared by the wet granulation process using a non-aqueous solvent as it contains polymers which are difficult to be granulated with water. The ingredients, Febuxostat, Microcrystalline cellulose, colorant (iron oxide yellow) and hypromellose were weighed accurately and mixed thoroughly in rapid mixture granulator. Granulation was done with a solution of Povidone in isopropyl alcohol. Granules were dried in fluid bed drier/Rapid drier, at a temperature of 45 °C to 55 °C to achieve the targeted loss on drying (LOD) of less than 2.0 % measured using a halogen moisture balance.

The dried granules were milled through a 1.5 mm sieve in the mill and the retained granules were milled through a 1.0 mm sieve. Milled granules were lubricated with magnesium stearate to obtain the final blend, which was then compressed into tablets of 8 mm on the rotary compression machine. Table 2(b) describes various representative compositions of the extended release fraction of the formulation.

Table 2(a): Representative compositions of immediate release part

S. No.	Batch No.	F002	F004	F005	F006	F007	F008	F009
	Ingredients	**mg/tablet**						
1	Febuxostat	40.0	40.0	40.0	40.0	40.0	40.0	40.0
2	Microcrystalline cellulose 101	50.0	50.0	50.0	50.0	50.0	50.0	50.0
3	Lactose monohydrate	92.0	95.0	89.0	95.0	89.0	91.0	91.0
4	Croscarmellose sodium (ACDISOL)	4.0	4.0	4.0	4.0	4.0	4.0	4.0
6	Hydroxypropyl cellulose (Klucel LF)	5.0	2.0	8.0	5.0	5.0	5.0	5.0
7	Purified water	qs	qs	qs	qs	qs	qs	qs
8	Croscarmellose sodium (ACDISOL)	6.0	6.0	6.0	3.0	9.0	6.0	6.0
9	Colloidal silicon dioxide (aerosil 200)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
10	Magnesium stearate	2.0	2.0	2.0	2.0	2.0	1.0	3.0
Total		200.0	200.0	200.0	200.0	200.0	200.0	200.0

Table 2(b): Representative composition of extended release part

S. No.	Batch No.	F010	F011	F012	F013	F014	F015
	Ingredients	**mg/tablet**					
1	Febuxostat	40.0	40.0	40.0	40.0	40.0	40.0
2	Microcrystalline cellulose 101	101.0	101.0	101.0	101.0	101.0	101.0
3	Hypromellose 100 cps	50.0	-	-	25.0	20.0	30.0
4	Hypromellose K4M	-	50.0	-	25.0	30.0	20.0
5	Hypromellose K15M	-	-	50.0	-	-	-
6	Iron oxide yellow	1.0	1.0	1.0	1.0	1.0	1.0
7	Povidone K30	6.0	6.0	6.0	6.0	6.0	6.0
8	Isopropyl alcohol	qs	qs	qs	qs	qs	qs
9	Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0
Total		200.0	200.0	200.0	200.0	200.0	200.0

Preparation of Inlay tablet

Immediate release blend and extended release tablets were then combined to form inlay tablets manually. Figure 2 shows the picture of inlay tablets.

Fig. 2: Inlay tablets of febuxostat

Evaluation of IR& ER granules

The granules were characterized for physical properties like bulk & tapped density, the angle of repose, Carr's index, Hausner ratio and sieve analysis.

Physical evaluation of ER and inlay tablets

Five tablets from each formulation were randomly selected and organoleptic properties such as color, description and shape were evaluated. Thickness and diameter were also measured using Vernier calipers. The prepared tablets were evaluated for hardness, friability and uniformity of weight.

Chemical evaluation of IR, ER and inlay tablets

Uniformity of dosage unit, Dissolution, Assay, Related substance (RS) and water content were measured. HPLC methods for Assay and RS were developed in-house. Water content was measured as per the standard method using Karl Fisher apparatus.

In-vitro dissolution study

In-vitro dissolution studies are valuable and important tools to judge the quality, stability and consistency of dosage forms and are often used to predict *in-vivo* performance. Dissolution of the tablet was carried out using a paddle (USP dissolution type II apparatus) at 75 Rotation per minutes (RPM), 900 mL of Phosphate buffer pH 6.8 (OGD recommended dissolution method). Dissolution medium in a dissolution vessel was maintained at a temperature of 37±0.5°C. 5 ml of the sample was withdrawn at regular intervals and replaced with the same volume pre-warmed fresh dissolution medium. The percentage drug release was plotted against time to determine the release profile.

In-vivo prediction

In-vivo data of an immediate release reference product (Uloric 80 mg) from USFDA were utilized to generate the plasma concentration profile. Various pharmacokinetic parameters like C_{max}, $AUC_{0\text{-}t}$, AUC_{α}, absorption constant (K_{abs}), elimination constant (K_{eli}), half-life ($t_{1/2}$) etc. were also calculated. % absorption and absorption curve were defined. Wagnor Nelson (WN) values for each time point were also derived [18].

It was assumed that 100 % of the drug is available for absorption within 10 minutes since immediate release tablets were considered. Wagnor Nelson (WN) values for the developed modified formulation were calculated considering the percentage of drug available at each time point based on the results of the dissolution studies. These derived WN values were used to inversely predict the fraction of a dose absorbed. The plasma concentration of the final modified-release (MR) formulation has been derived from the prediction made using the derived WN values.

Formulation with different proportions of IR and ER part (40:60, 50:50, 60:40) and other formulations (where dissolution was faster and slower) were also treated similarly and the calculated plasma concentration were derived for all the selected formulations.

Calculation of the pharmacokinetic parameters

Table 3(a) and Table 3(b) show the plasma concentration data and other calculated Pharmacokinetic parameters for Febuxostat immediate release tablets. Figure 4 shows the plasma profile along with extrapolation for absorption and residuals.

From the plasma profile, the natural logarithm (ln) has been obtained for the concentration values. K_{eli} is the Slope of the elimination curve (preferable slope of the last four or appropriate non-zero concentrations). Intercept has also been obtained from the same.

$$\text{Half life } (t_{1/2}) = \frac{0.693}{K_{eli}}$$

Extrapolated values have been calculated using the following equation:

$$Y = mX + C$$

Since intercept is in ln format, the equation would be as follows:

$$Y = e^{(-mx+C)}$$

Where m= slope, X = time point and C = Intercept

Subtraction of Plasma concentration from Extrapolated values yields the residual concentration plot, and Slope of ln(residual) is K_{abs}

AUC is calculated using the trapezoid rule and AUC infinite (AUC_{α}) is calculated using AUC at the last time point along with concentration at last time point and elimination constant.

$$\text{Sum AUC at time t} = [Conc_t + Conc_{t-1}] \times \frac{(t) - (t-1)}{2} + \text{AUC at time } (t-1)$$

Where

$Conc_t$ = Plasma concentration at time t

$Conc_{t\text{-}1}$ = Plasma concentration at the preceding time point (t-1)

AUC infinite

$$= \text{Sum AUC at last time point} + \frac{\text{Concentration at last time point}}{K_{eli}}$$

C_{max} is the Maximum concentration achieved in profile

Absolute half-life was calculated using absorption constant and time for maximum concentration has been derived from the following equation as well as the time at which the plasma maximum plasma concentration achieved (C_{max}).

$$\text{Absolute } t_{1/2} = \frac{\text{Slope}}{K_{abs}}$$

$$T_{max} = \ln \frac{K_{abs}/K_{eli}}{(K_{abs} - K_{eli})}$$

Calculation of Wagnor-Nelson (WN) Values [19, 20]

Wagnor-Nelson values and Percentage absorption were calculated for each time point using the following equation.

$$WN = \frac{\text{Plasma conc at time t} + (K_{eli} \times \text{AUC till time t})}{AUC_{inf} \times K_{eli}} \times 100$$

$$\%\text{Absorption} = 100 - 100 \times e^{(K_{abs} \times \text{Timet})}$$

Inverse Wagner-nelson and prediction of *in-vivo* profile

The calculated WN values are based on the consideration that 100 % of the drug is available for absorption within about 10 minutes in an immediate release (IR) product. WN values were also calculated for modified developed formulation based on the dissolution of a different formulation.

$$WN = \frac{\text{Drug release at time t} \times \text{WN value for IR at time t}}{100}$$

Different dissolution values were then converted into WN values. These WN values were then converted into Predicted Fraction of Dose absorbed (Fd). Calculated Plasma concentration (CPC) values were also derived with the following equation

$$\text{Fraction of dose absorbed (Fd)} = \frac{WN}{100}$$

$$CPCt_2 = \frac{2 \times (Fd\ t_2 - Fd\ t_1) \times \text{dose in } \mu g / (Vd/F) + Conc\ t_1\{2 - [K_{eli}(t_2 - t_1)]\}}{2 + [K_{eli}(t_2 - t_1)]}$$

Where

CPC t_2 = Calculated Plasma concentration at time t2

Fd t_2 = Fraction of dose absorbed at time t2 (current time point for which we are calculating plasma concentration.

Fd t_1 = Fraction of dose absorbed at the preceding time point

Conc t_1 = Calculated plasma concentration at the preceding time point

$$\frac{Vd}{F} = \frac{\text{Dose in } \mu g}{AUC \times K_{eli}}$$

Stability studies

Stability studies at accelerated condition were performed for 6 months for the finalized prototype formulation and found to meet the standards as per the current regulatory requirements.

Excipient compatibility studies

Excipient compatibility studies were also performed on binary mixtures with 1:1 ratio of API to each excipient and exposed to 40 °C/ 75% RH and 50 °C/ 80 % RH for 1 month and analyzed for the related substance.

RESULTS

Immediate release formulation and extended release formulation have been developed separately and both have been combined in one formulation to get the desired formulation. Formulation development has been carried out using the Quality-by-design concept [21] of risk assessment and mitigation.

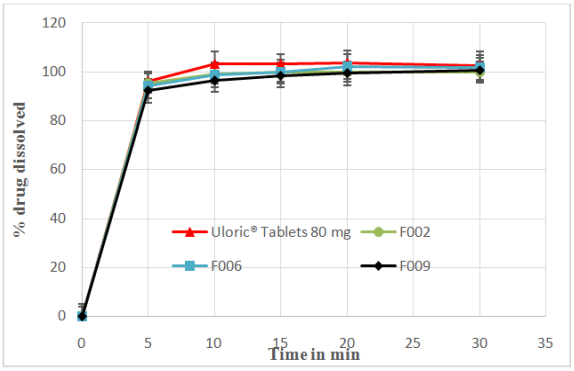
Immediate release portion of the formulation has been kept mostly similar to that of the marketed product of Takeda and dissolution

studies of the developed IR portion were also compared with the marketed formulation. A comparison of the two established the similarity between them. IR portion of the inlay tablet releases the drug within 10 minutes and dissolution is close to 100 % in the same duration in both marketed formulation as well as the developed IR formulation. Various trials have been conducted at different levels of binder, disintegrant, and lubricant. The IR formulation has been optimized based on process observations and dissolution profile. Representative composition is described in table 2(a).

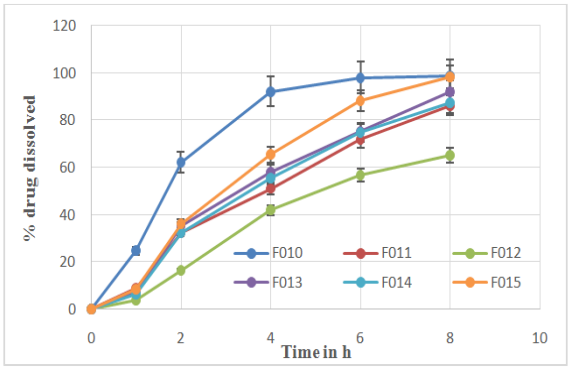
Hypromellose was selected as the polymer for the development of ER portion. Different viscosity grades (100 cps, 4000 cps and 15000 cps) were used for the development. Formulation trials were executed using different grades of polymer as well as combinations of different grades at different levels and the optimum polymer concentration has been identified to get the desired dissolution profile. Representative composition is listed in table 2(b).

The IR and ER portions were combined to form an Inlay tablet having outer immediate release granules and inner ER tablets. Dissolution studies have been performed for IR tablets, ER tablets, and Inlay tablets as well. Fig. 3 represents the data of dissolution profile achieved in different trials during the development and optimization studies.

Based on the *in-vivo* pharmacokinetic profile of Febuxostat IR formulation given in Figure 4, pharmacokinetic parameters were calculated as shown in table 3(a) and table 3(b). These parameters were further utilized for the prediction of plasma profiles of developed formulation using Wagnor-Nelson equation [22]. Fig. 5 represents the dissolution profile of different combinations of IR and ER formulation while Figure 6 shows the predicted *in-vivo* profile of a final formulation along with reference immediate release tablet.



(a)



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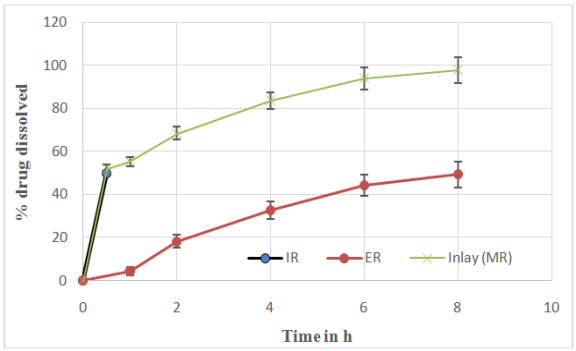


(c)

Fig. 3: Dissolution profiles of,(a): Representative IR formulations; (b): Representative ER formulation; (c): Inlay tablet in comparison with IR and ER formulations. n=6

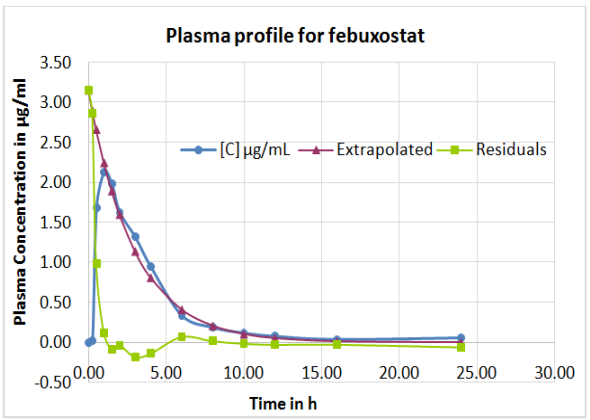


Fig. 4: Plasma profile of Febuxostat IR reference tablet

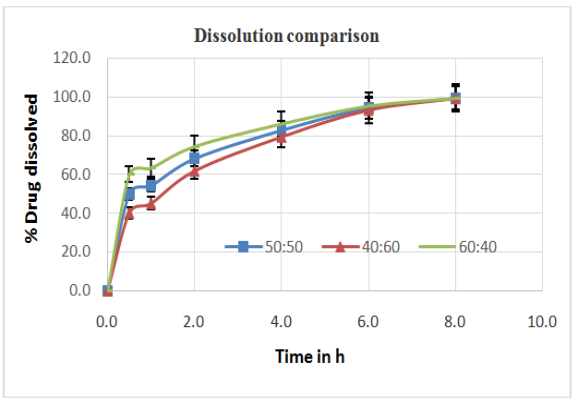


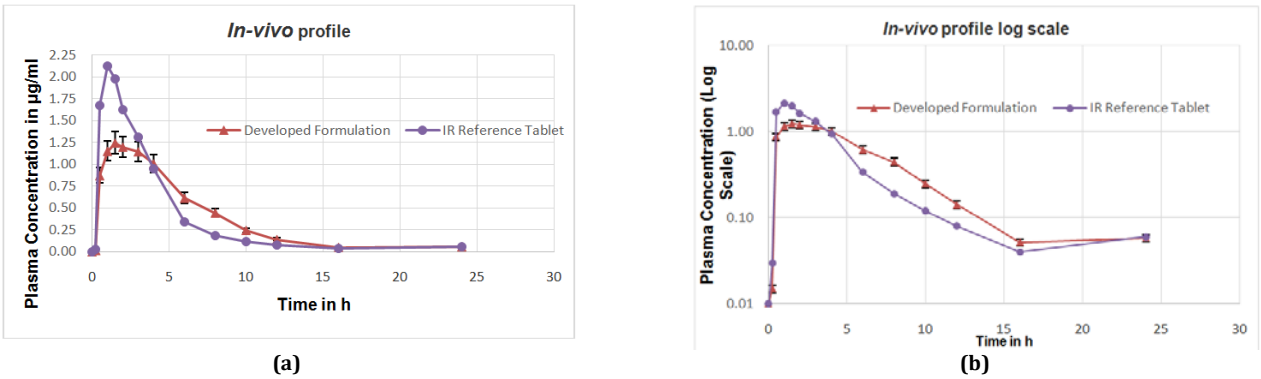
Fig. 5: Dissolution profile for Inlay tablets with different proportions of IR and ER portions. n=6

Table 3(a): Plasma concentration and plasma profile of reference product

Time	[C] µg/ml	ln [C]	Sum AUC	Extrapolated	Residuals	ln(res)
0.00	0.00	--	--	3.15	3.15	1.15
0.25	0.03	-3.51	0.00	2.90	2.87	1.05
0.50	1.68	0.52	0.22	2.66	0.98	-0.02
1.00	2.13	0.76	1.17	2.25	0.12	-2.16
1.50	1.98	0.68	2.20	1.89	-0.09	--
2.00	1.63	0.49	3.10	1.60	-0.03	--
3.00	1.32	0.28	4.58	1.14	-0.18	--
4.00	0.95	-0.05	5.71	0.81	-0.14	--
6.00	0.34	-1.08	7.00	0.41	0.07	-2.64
8.00	0.19	-1.66	7.53	0.21	0.02	-3.98
10.00	0.12	-2.12	7.84	0.11	-0.01	--
12.00	0.08	-2.53	8.04	0.05	-0.03	--
16.00	0.04	-3.22	8.28	0.01	-0.03	--
24.00	0.06	-2.81	8.68	0.00	-0.06	--

Table 3(b): Calculated pharmacokinetic parameters of reference product

Parameter	Value	Parameter	Value
k_{eli}	0.339	k_{abs}	3.503
Intercept	1.148	C_{max}	2.130
$t_{1/2}$	2.042	Abs $t_{1/2}$	0.198
AUC_{inf}	8.857	T_{max}	0.738



(a) **(b)**

Fig. 6: Predicted *in-vivo* profile for developed formulation along with reference IR tablet, (a): Normal scale representation; (b): Log Scale representation

DISCUSSION

Febuxostat is a molecule which requires modification in the formulation to change the pattern of its bioavailability at the site of action. The targeted changes in the pharmacokinetic/dissolution profile have been decided based on the available pharmacokinetic data of reference immediate release tablets.

It has been reported in the literature [23] that from 10 to 120 mg of dose it follows linear pharmacokinetics and so any changes in the dosage will be reflected linearly in the pharmacokinetic profile. Considering the pharmacokinetic profile of 80 mg dose in fasting and fed conditions, it can be inferred that plasma concentration of febuxostat above a certain level for the longer period of time is more critical rather than higher C_{max}. Also 80 mg is the strength which has been found more effective in treatment as compared to 40 mg.

The observed clinical and pharmacokinetic difference in fasting and fed conditions can also be correlated to pH dependent solubility of febuxostat. It has more solubility in pH above 6.2 and specifically above pH 6.8. In fed conditions, probably the availability of the drug to higher pH gets delayed by about 2 h. This may have reduced the C_{max} and helped to increase the blood concentration to a level above the required concentration in 6-24 h' time duration. In the proposed formulation similar delay has been achieved using modification of the formulation.

These observations resulted in keeping the target profile as, 40 to 60 % portion of the formulation needs to release the drug quickly (IR part). This target would help to achieve the C_{max} level above 1 µg/ml. The remaining 60 to 40 % of the drug in the form of Extended-release, which would slowly make the complete drug available within the next 4-8 h with less than 10 % the drug being made available in the 1st h.

The conventional controlled release formulation as reported for many of the drugs [24, 25] has the ability to retard the release of drug from the formulation and can be useful for the drugs where the initial quick onset of action is not required [26, 27]. These types of formulation are worthwhile when control of the drug release is required from the initial stage. Similar controlled release formulation is also reported for Febuxostat [28] but that will lack the initial boost required to get the plasma concentration above the required level. In comparison, the developed formulation has almost 50 % drug as immediate release, which will provide the initial surge to get C_{max} above certain required level. In the conventional controlled release formulation, it is difficult to achieve the similar level of C_{max}. Also, the time to achieve C_{max} will get delayed (T_{max}) in such conventional controlled release formulations. The T_{max} for the developed formulation will be very much similar to immediate release marketed formulation, resulting in clinically significant blood levels being achieved in time duration similar to IR formulation.

This targeted profile would have two major advantages over the conventional immediate release tablet formulation and its pharmacokinetic profile. First, it would provide better effect as compared to immediate release tablet and secondly, there will be a significant reduction in the toxicity of the drug due to the minimal amount of drug being exposed to the body at any given time point. This would, in turn, improve both safety and efficacy of the drug molecule and make it more suitable for human use.

Patent applications EP2582812 A0 and US 2011/0311620 describe a modified release formulation of Febuxostat incorporating both immediate and delayed release beads in a single pharmaceutical composition. Different beads with modification in release profile were prepared and mixed with immediate release beads. The reported formulation is more complex in terms of the formulation as well as process. Beads, because of the higher surface area, require more amount of polymer for release control as compared to tablets. Additionally, the process of preparation of the beads is also time-consuming, variable and requires sophisticated equipment.

Instead, the concept of combining IR & ER formulation in a single inlay tablet requires less effort and is more feasible and simple solution to address the need. Formulation of dual release system of combination of fast and slow release has been reported for other drugs using the concept of bilayer tablets [29] and inlay tablets [30, 31].

Few other Patent applications [32] describe controlled release formulation and the osmotic controlled formulation of Febuxostat. Unfortunately, both these formulations are deficient of the quick initial release essential in case of Febuxostat.

The developed formulation of Febuxostat is simple, but novel and has significant value in terms of market potential as well as patient safety. This has a clear advantage over other reported modified release formulations of Febuxostat.

Fig. 5 shows the dissolution of different combinations (ratio) of IR & ER portion of the modified release formulation and Figure 6 shows the predicted *in-vivo* profile for the formulation based on the calculation along with the plasma concentration profile of immediate release reference product.

Calculated plasma profiles show that the target of raising the plasma concentration after 6 h would be achieved. Plasma concentration remains above 0.25 µg/ml for more than 10 h and above 0.1 µg/ml for more than 12 h. Developed formulation has a partial quantity in the form of immediate release formulation which helps to achieve the initial boost to get the C_{max} and remaining part in the form of extended release or slow release that helps to achieve the required plasma concentration over extended periods. The modified formulation will be successful in serving the dual purpose of improving the efficacy as well as the reduction of toxicity.

Final formulation as inlay tablet was charged for stability studies at accelerated conditions. The formulation was found to be stable up to 6 months with control in related substances as well as dissolution profile.

Excipient compatibility studies have also been conducted with binary mixtures in ratio of 1:1 of API with each individual excipient. Data shows that the drug is compatible with all the excipients used. The physical appearance of the binary mixtures also remained unchanged during the exposure period.

CONCLUSION

Current study describes the preparation of a modified release formulation of Febuxostat to improve its efficacy and reduce toxicity and thereby improving safety as well. Modifications in the formulation were required to get the desired pharmacokinetic profile. Two different formulations, immediate release (IR) and extended release (ER) have been developed separately and combined to form inlay tablets. The proposed formulation will be advantageous over conventional immediate release tablets available in the market. The proposed formulation has been studied extensively and the pharmacokinetic data and *in-vivo* prediction show it to have better efficacy and safety profile.

CONFLICT OF INTERESTS

Declared None

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