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Xanthine Oxidase Inhibitor Febuxostat: Quality Comparisons and Release Kinetic Profile

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ABSTRACT

In Asian countries pharmaceutical products of same generic may differ in their quality perspectives. Such moieties offer alternative choices in respective health care deliverance setups with uneven pricing. Rationalizations of such products for prescription selection is mainly dependent of drug fate provided by the manufacturer and mostly suffer comparison details of multisource products. Furthermore drug release behaviour of oral solid dosage forms also significantly important in determining the batch to batch reliability of such formulations. These studies assures the products excellence by discerning different formulations with comparable therapeutic moieties. In the present study quality assessment of four different brands of febuxostat ($Test_1$ – $Test_4$) were carried out using various physico-chemical tests. Results were found to be in adequate limits. Also, dissolution profiles of all brands were determined using phosphate buffer pH 6.8. Data was analyzed by several statistical methods as suggested by FDA such as model – dependent, model – independent and one way ANOVA method. Results of one – way ANOVA indicated no significant difference among the release profiles of reference ($Test_1$) and test brands ($Test_1$ – $Test_4$) as P values was found to be 0.997. Similarly, results of f_1 and f_2 indicated that $Test_1$ was found to be similar with the $Test_2$ – $Test_4$. Also all the brands i.e. $Test_1$ – $Test_4$ were found to be best fitted in Weibull model.

INTRODUCTION

Febuxostat is most widely used xanthine oxidase inhibitor, which blocks the xanthine oxidase active site channels present on the surface. Since it oxidizes both hypoxanthine and xanthine to uric acid compound. As a result, febuxostat totally restrain xanthine oxidase in this way and diminishes the production of uric acid. Febuxostat is prescribed predominantly in the treatment of gout (deposition of uric acid on joints) (Bushra *et al*., 2008). *In vitro* estimation technique is applied as latent surrogate for *in vivo* biological investigations as it is amongst the significant tools to assess the quality of trial and existing products (Moore *et al*., 1996). This process decreases the potential risk and expenses during human subject's trials and speed up the implementation of supplementary developments in manufacturing and quality aspects of different products (FDA, 1995). The validation of diverse manufacturing stages can also be done in conjunction with *In vitro* studies, correspondingly, measurement of inter batch variation in quality perspective and selection of optimal formulation with enviable release kinetics is another key feature of such studies (Karmarkar *et al*., 2009). For NDAs (New Drug Applications) and ANDAs (Abbreviated New Drug Applications) approvals the consequences of *in vitro* testing are also supportive for the execution of regulatory matters when noteworthy deviation in manufacturing procedure, formula, equipments and representing batch size of final products are made. On the basis of similarity ratios in dissolution profiles between trial and innovator products, expensive bioequivalence estimation might be waived in the light of various regulatory guidelines (FDA, 1997; Costa and Lobo, 2001). It is further recommended that *in vitro* tests should be carried out following pre/post approval changes in formulation design and statistical comparisons should be drawn using various elements like difference (f_1) and similarity factor (f_2) to approximate the release model of trial and reference

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Formulations (Costa and Lobo, 2001). In present study quality attributes of four different brands of febuxostat 40 mg film coated tablets were estimated. Selected marketed brands were designated as $Test_1$ – $Test_4$, procured from local market of Karachi. A number of tests were executed. Moreover drug release parameters of different products were evaluated and statistical analysis by model -dependent and independent procedures and one way ANOVA approach was performed.

MATERIALS AND METHODS

Pharm Evo (Pvt.) Ltd gifted the febuxostat reference. Sodium hydroxide and Potassium dihydrogen phosphate were used as Merck, Damstabt, Germany grades. In the presented study, amongst selected brands, reference was chosen as $Test_1$ product owing to its preeminent physicochemical attributes whilst $Test_2$ – $Test_4$ were designated as trial/test brands.

Estimation of Physicochemical Characteristics

Febuxostat reference and test products in film coated forms ($Test_1$ – $Test_4$) were determined by diverse physicochemical in vitro tests i.e. hardness variation and friability test were carried out using hardness tester (OSK Fujiwara, Ogawa Seiki Co. Ltd., Japan), and friabilator (H. Jurgens GmbH and Co., Germany). Thickness, weight and diameter variation assessments were performed using vernier calliper and analytical balane (AUW-220, UNI Blog, Shimadzu, corp.) Basket Rack Assembly was utilized to perform the disintegration test (Erweka ZT-2 Husenstamn, Germany) (USP, 2003). For drug contents recovery (assay) evaluation, randomly selected twenty tablets from $Test_1$ – $Test_4$, were weighed and then crushed to powder form. The quantity equivalent to average weight of one tablets was dissolved in phosphate buffer pH 6.8. samples were filtered and analyzed with UV- Visible spectrophotometer (UV-1800, Shimadzu Corp., Japan) at 315 nm (Bagga *et al*., 2011). In addition, $Test_1$ – $Test_4$ brands were also estimated for drug release potential by dissolution test. For this dissolution apparatus II was used at 37^0C $\pm$ 0.5^0C; 50 rpm with 900 ml of phosphate buffer pH 6.8. percentage amount of release contents were measured spectrophotometrically in UV- Visible range with UV-1800 Shimadzu Corporation Japan. Wave length was 315 nm for the set of experiment (Bagga *et al*., 2011).

Comparison of Dissolution Profiles of different brands of Febuxostat

Febuxostat reference ($Test_1$) and test ($Test_2$ – $Test_4$) formulations were evaluated by multiple point dissolution method using apparatus II, at 50 rpm speed of rotation in 900 ml of pH 6.8 phosphate buffer.

Temperature was adjusted at 37 $\pm$ 0.5^0C throughout the experiment. Samples collection time was up to 120 minutes (5, 10, 15, 20, 30, 45, 60, 90 and 120 min). 10 mL samples were withdrawn at every point of sampling and consequently added with 10 mL fresh medium in dissolution flasks. Drug contents released were approximated by using spectrophotometer at 315 nm.

Febuxostat Release Kinetics

Model- Dependent and Model Independent Procedures:

In current study various model dependent and independent tools were applied for the evaluation of drug release patterns of reference and tests products. Numbers of authors have utilized such methods in their investigations to observe release profiles of various drugs (Hanif *et al*., 2011; Muhammad *et al*., 2012). Selected models for this study were presented in Table 3. DD-Solver software with Microsoft Excel ™ 2007 was used to calculate these model values (Microsoft Corporation, USA).

Statistical Assessment of Drug Release Kinetics

One-way Analysis of variance (ANOVA) with Tukey's Post Hoc Test was carried out to conclude the variation in release trends of various brands in phosphate buffer pH 6.8. SPSS 17.0 (SPSS Inc) was used to perform statistical evaluation.

RESULTS AND DISCUSSION

Plenty of advantages have been offered by the oral solid dosage form including mass development of stable and safe formulations. Pharmaceutical equivalent (generic) products must be in good comparisons on physical and chemical grounds. Their quality, strength, purity and bioavailability must be comparable and analogous. Moreover the other quality features like disintegration, deaggregation, dissolution and uniformity of content test should be in adequate limits of standards (USP, 2003). In another study Hussain *et al*., performed the range of quality estimation tests on various products available in market in order to evaluate the interchangeability of the brands in different conditions (Hussain *et al*., 2013). In many under developed countries effective mechanisms for the analysis of generic products were not developed. Furthermore authors also reported various brands evaluation studies and found some sub-therapeutic and counterfeit products. Such formulations may not be limited to underprivileged physicochemical attributes but also produced as sub curative outcomes (El-Sabawi *et al*., 2013; Bano *et al*., 2011). In the current study, test brands were chosen as $Test_2$ – $Test_4$ whereas $Test_1$ was considered as reference or lead brand owing to he fact of excellent quality features. The mean diameter and thickness of $Test_1$ – $Test_4$ were observed to be in the range of (0.72 $\pm$ 0.34 - 0.88 $\pm$ 0.23) and (0.33 $\pm$ 0.45 mm - 0.43 $\pm$ 0.74 mm) respectively. Similarly the average and hardness and weights values of all selected brands were in order of (6.35 $\pm$ 0.15 kg - 7.42 $\pm$ 0.27 kg) and (99.23 $\pm$ 0.14 mg - 202.47 $\pm$ 0.66 mg). Correspondingly, disintegration tests and friability results were in adequate limits (15 sec – 490 sec) and (0.59 % - 0.74 %) respectively. The dissolution and content recovery (assay) studies were performed and their values of the results were successively found in satisfactory ranges (96.24 $\pm$ 0.88 % - 97.32 $\pm$ 0.59 %) and (97.20 $\pm$ 1.23 % - 99.90 $\pm$ 1.54 %) as given away in Table 1.

Table 1: Quality Evaluation of Febuxostat Film Coated 40 mg Tablets ($Test_1$ – $Test_4$).

Febuxostat Brands	Hardness (kg)	Diameter (mm)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Weight (mg)	Assay (%)	Dissolution (%)
$Test_1$	6.35 ± 0.15	0.88 ± 0.23	0.33 ± 0.45	490	0.74	149.34 ± 0.28	97.20 ± 1.23	96.24 ± 0.88
$Test_2$	7.42 ± 0.27	0.72 ± 0.34	0.34 ± 0.82	430	0.64	99.23 ± 0.14	99.90 ± 1.54	97.17 ± 0.51
$Test_3$	6.88 ± 0.84	0.73 ± 0.58	0.43 ± 0.64	125	0.59	108.1 ± 0.34	98.63 ± 1.88	96.41 ± 0.19
$Test_4$	7.33 ± 0.41	0.78 ± 0.27	0.43 ± 0.74	15	0.62	202.47 ± 0.66	97.90 ± 1.42	97.32 ± 0.59

Table 2: Statistical assessment (ANOVA) of Dissolution profiles of Febuxostat Film Coated 40 mg Tablets.

Febuxostat Brands	Dissolution Medium	Source of variation	Sum of Squares	Df	Mean Square	F	Sig.
$Test_1$ – $Test_4$	pH 6.8	Between Groups	20.924	3	6.975	0.016	0.997
		Within Groups	13657.045	32	426.783		
		Total	13677.969	35			

Table 3: Analysis of Febuxostat Release Kinetics.

Model Independent	Difference factor (f_1)	$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100$
	Difference factor (f_2)	$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{N}\right)\sum(Ri - Ti)^2\right]^{-0.5}\right\} \times 100$
Model Dependent	First order kinetics	$\mathrm{Log\ Q = LogQ_0 - \frac{kt}{2.303}}$
	Hixson–Crowell model	$\mathrm{Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t}$
	Higuchi model	$\mathrm{Q = kt^{\frac{1}{2}}}$
	Weibull model	$\mathrm{m = 1 - exp\left[-\frac{(t-Ti)^{\beta}}{\alpha}\right]}$

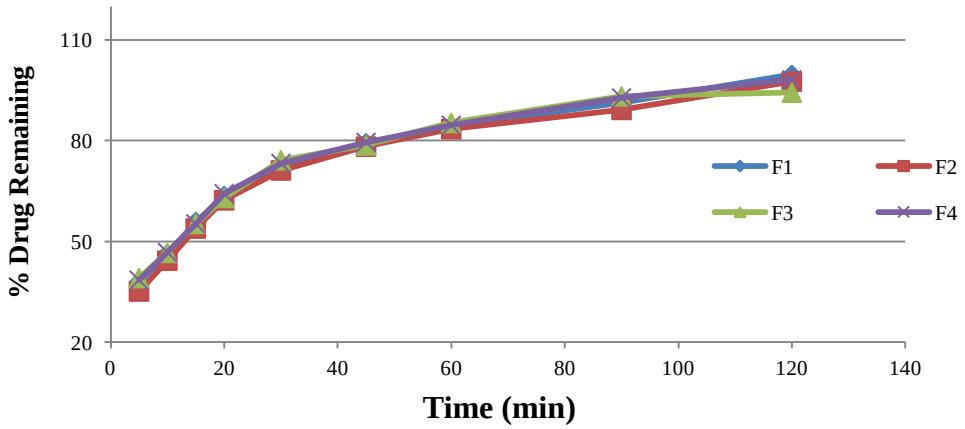

Fig. 1: % Drug Release of Febuxostat 40 mg Tablets at pH 6.8.

DRUG RELEASE PROFILES OF FEBUXOSTAT BRANDS

In present investigation, release kinetic profiles estimation of trial and reference products ($Test_1$ – $Test_4$) were carried out using phosphate buffer pH 6.8 as dissolution media (Figure1). Further examination of release kinetics were also performed by using one way ANOVA technique, different model-dependent terms and model – independent procedures as summarized in Table 3. Similarly Muhammad *et al.*, in 2012 conducted the study for the estimation of immediate release (IR) cefuroxime axetil tablets profile comparison by using various dissolution media like pH 1.2 solution, pH 4.5 and pH 6.8 phosphate buffers. Similarity factor (f_2) were calculated for subsequent analysis of release profile (Muhammad *et al.*, 2012). In vitro release kinetics estimation is significant tool in drug development and quality evaluation process.

Such studies also important in making the biowaiver decisions to control the regulatory encumber for the pharmaceutical industry (Anand *et al.*, 2011; Abdelbary *et al.*, 2009; Ali *et al.*, 2016).

Table 4: Kinetics Evaluation of Febuxostat Film Coated 40 mg Tablets.

Formulation	First Order		Higuchi		Hixson-Crowell		Weibull model		
	r^2	$K_1(h^{-1})$	r^2	K_H $(h^{-1/2})$	r^2	K_{HC} $(h^{-1/3})$	r^2	α	β
				pH 6.8					
$Test_1$	0.8084	0.050	0.9111	8.878	0.9710	0.006	0.9846	5.986	0.597
$Test_2$	0.7587	0.051	0.8968	8.639	0.9540	0.005	0.9856	5.421	0.566
$Test_3$	0.7815	0.051	0.9291	8.857	0.9854	0.006	0.9818	5.669	0.584
$Test_4$	0.8256	0.051	0.8921	8.872	0.9685	0.006	0.9892	6.038	0.604

Table 5: Evaluation of Difference Factor (f_1) and Similarity Factor (f_2) of $Test_1$ – $Test_2$.

Febuxostat Brands	f_1	f_2	Comments
	pH 6.8		
$Test_1$ and $Test_2$	0.169	91.531	
$Test_1$ and $Test_3$	0.686	89.714	
$Test_1$ and $Test_4$	0.450	92.174	Similar

Model -Independent Techniques

According to various guidelines dissolution profile estimations and comparisons can be performed by calculating the difference factor (f_1) and similarity factor (f_2) (O'hara *et al*., 1998; Yuksel *et al*., 2010). Over the past few years model – independent terms are widely utilized in numerous investigations to distinguish the similarity pattern of various drug products and to predict the artefact performance as well (Yuksel *et al*., 2010; Arshad *et al*., 2011; Hussain *et al*., 2013). Likewise, Bhardwaj *et al.* 2011 also evaluated the conventional and rapidly disintegrating tablets of Acceclofenac release profiles (Bhardwaj *et al* 2010). The current study showed the values of f_2 and f_1 ($Test_1$ – $Test_4$) in the range of (89.714 - 92.174) & (0.169 - 0.686) respectively (Table 5). Results demonstrated the similarity in the release pattern of reference ($Test_1$) product with rest of the test products ($Test_2$ – $Test_4$). In another study Koester *et al*., evaluated the carbamezapine matrix tablets release mechanism and proposition using various mathematical and statistical terms. Correspondingly, Traple *et al*., in 2014 applied the novel multivariate similarity tool for the estimation of therapeutic association of various similar brands (Koester *et al*., 2004; Traple *et al*., 2014).

Model -Dependent Approaches

In this investigation, dissolution test in multiple points manner for selected brands was conducted in phosphate buffer pH 6.8 as medium of dissolution. Various kinetic model terms are used to calculate the release profile such as, Hixon Crowell, First order, Weibull and Higuchi models. Related equations of these model terms are stated in Table 3. Zafar *et al* (2012) and Hanif *et al*. (2014) also evaluated the different formulation pattern of release kinetics including Ketoprofen and Nimesulide tablets using various model dependent terms (Zafar *et al*., 2012; Hanif *et al*., 2014). For Higuchi and First-order kinetic terms, respective r^2 values at pH 6.8 were found to be in order of (0.8921 - 0.9291) & (0.7587 - 0.8256). Hixson-Crowell model values of r^2 were tabulated in the range of 0.9540 - 0.9854. Best curve fitting was observed with Weibull model for entire formulations in selected dissolution media. As presented in Table 4. In previous years Hussain *et al*., 2013 has selected various media of dissolution in pH range of 1.2 to 6.8 to estimate the release profile of pharmaceutical products. Similarly, Rasul *et al* calculated the release kinetics of metoprolol tartrate control release formulations at different dissolution media using numerous model dependent approaches (Hussain *et al*., 2013; Rasul *et al*., 2010).

Statistical Evaluation

In present study, ANOVA in one – way manner was used to measure the release profile comparisons of the $Test_1$ – $Test_4$ products. Results showed in-significant variation between the release profiles of lead brand ($Test_1$) and test/trial brands ($Test_1$ – $Test_4$) as P values was observed to be 0.997 as shown in Table 2. Bushra *et al*., in 2016 and Zafar *et al* in 2015 also applied the Tukey's post hoc test with One way ANOVA to examined the dissimilarity amongst the release pattern of acceclofenac and Mefenamic acid tablets respectively. Results of both studies illustrated the insignificant variation in numerous dissolution media at pH 1.2, 4.5, and 6.8 with P values less than 0.05 (Bushra *et al*., 2016; Zafar *et al*., 2015).

CONCLUSION

All the selected products ($Test_1$ – $Test_4$) of febuxostat marketed tablets verified the acceptable physicochemical attributes and demonstrated the adequate drug release. Such studies not only offer excellent avenues for selection of better alternatives available in market as quality products but also facilitate the optimal care of patients in developing countries where accessibility and affordability of quality products impact the healthcare provision.

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