Pharmaceutical and *in vitro* therapeutic equivalence studies of ketoprofen enteric coated 100 mg tablets

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Abstract: The objective of this study was to assess the quality of six different brands of enteric coated Ketoprofen 100 mg tablets, KPB_2 to KPB_6 are available in commercial market of Karachi, Pakistan, while KPB_1 was obtained from international source. We performed different physico-chemical assessments i.e. weight variation, diameter, hardness, friability, thickness, disintegration, content uniformity, assay and dissolution test. Results of all the investigations were found to be in adequate limits. Also pharmaceutical equivalence was determined by selecting different tests and assay assessment. Furthermore, *in vitro* therapeutic equivalence was also estimated at phosphate buffer pH 6.8 and 7.5. Results were evaluated by one way ANOVA, model independent and model dependent methods. ANOVA results showed that release behaviour were found to be similar as p values >0.05, also KPB_1 - KPB_6 followed Weibull model at different dissolution media. Results indicated that innovator and brands not only passes the pharmaceutical equivalence assessment but also comply with the *in vitro* therapeutic equivalence.

Keywords: Ketoprofen, Biorelevent media, model-dependent, one way ANOVA, model-independent method and Weibull model.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are mainly recommended for the management of pain, fever and inflammation (Gasparini *et al*., 2005). Ketoprofen (NSAID) is used in the management of osteo-arthritis, rheumatoid arthritis and also exhibits analgesic and antipyretic activity (Kantor, 1986; Fossgreen, 1976). Authors reported that various pharmaceutical products that are manufactured in developing countries have poor quality and also due to the elevated increase in the manufacturing of generic products obtained from different sources has developed complexity for the prescribers to choose single product among multiple comparable products (Bano *et al*., 2011). Scientists also reported that quality assessment studies of different brands evaluate inadequate and counterfeit formulations. These substandard products might not only be limited to poor physico-chemical features but also resulted in subtherapeutic outcomes (El-Sabawi *et al*., 2013).

In vitro studies are considered to be extensively effective quality evaluation tool in product development in industry. These studies predict the *in vivo* performance of different products. Release studies are also one of the important assessment methods for biowaiver studies which diminish the regulatory burden of the industry. It assesses the release pattern of generic compounds which can be used as surrogate method for bioequivalence studies (Anand *et al*., 2011). Similarly, *in vitro* release comparison studies of different products determine variations among the formulation (Hara *et al*., 1998). These comparison studies has been widely utilized during manufacturing stages of the products which are useful in developing dissolution specifications, measuring the similarity of different products and estimating *in vitro-in vivo* correlations by diminishing the need to conduct bioequivalence studies (Lue *et al*., 2008).

It is also recommended that release profiles are used for pre and post change formulations should be statistically evaluated using f_2 (similarity factor) to prove that drug release behaviour are not considerably different (USP, 2003).

Pharmaceutical equivalence is one of the universal concerns for various pharmaceutical products i.e. injectables etc. But oral formulations were only assessed for BE and pharmaceutical equivalence testings but due to the BCS system oral products are not tested by BE testings but these are only tested for pharmaceutical equivalence (Traple *et al*., 2014). In order to evaluate the *in vitro* therapeutic similarity by the help of pharmaceutical equivalence it is significantly important to assess the results of physico -chemical characteristic and similarity of generic (test) and innovator (reference) products by the help of similarity and difference factors (Koester *et al*., 2004).

The aim of this study is to evaluate different features of Ketoprofen 100mg tablets (KPB_1 to KPB_6). For this purpose we conducted different physico chemical tests on reference (KPB_1) and test (KPB_2-KPB_6) products. For

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Pharmaceutical equivalence studies various tests were included i.e. disintegration, dissolution (single point), assay and content uniformity tests while *in vitro* therapeutic assessment of different ketoprofen products were carried out by multiple point dissolution studies at phosphate buffer pH 6.8 and 7.5. Results were analyzed by using one way ANOVA method, model dependent and model – independent method. Furthermore, release profiles were also assessed using biorelevent media (Fasted state of Intestinal fluid (FaSSIF), Fasted state of gastric fluid (FaSSGF), Fed state of intestinal fluid (FeSSIF).

MATERIALS AND METHODS

Materials and Method

Ketoprofen was obtained from Aventis Pharma (Pvt.) Ltd. Five Ketoprofen brands (KPB_2 to KPB_5) were purchased from local market, Karachi Pakistan, while (KPB_1) was obtained from international source. Potassium dihydrogen phosphate, Sodium hydroxide, Methanol, Acetic acid, Glacial acetic acid, Hydrochloric acid, Sodium taurocholate, Triton X 100, Lecithin, Sodium Chloride (Merck, Damstabt, Germany).

Instruments

In present study hardness tester (OSK Fujiwara, Ogawa Seiki Co. Ltd., Tokyo, Japan), analytical balance (Mettler Toledo B204-S, Switzerland), friability tester (H.Jurgens GmbH and Co., Bremen, Germany), vernier caliper (Seikobrand, China), Basket Rack Assembly (Erweka ZT-2 Husenstamn, Germany), Dissolution Apparatus II (Erweka DT 700, Husenstamm, Germany), UV-Visible spectrophotometer (UV-1800, Shimadzu Corporation Tokyo, Japan) were used. Statistical assessment of data was performed by SPSS 20.0 (SPSS Inc) using one way ANOVA and DD-Solver (anadd in program for Microsoft Excel™ 2007, Microsoft Corporation, USA).

Assessment of pharmaceutical equivalence and quality attributes of ketoprofen tablets

Identification test (UV & Visible Spectroscopic Technique)

For the preparation of test solution 50.0mg of compound was dissolved in 96% of ethanol and further diluted to make 100mL. Take 1mL of the test solution and diluted to make 50mL using ethanol. 230-350 nm is the spectral range given in BP while at 258nm maximum absorption was determined (BP, 2004).

Physicochemical assessment

In presented work various parameters including weight variation, thickness, hardness and friability[9,12] were estimated for six brands of KPB_1-KPB_6.

Disintegration tests

Six tablets of each brand were tested in 900mL of 0.1M hydrochloric at 37±0.5°C for 2h using basket rack assembly without the discs. After specified time all tablets were examined for their state. Finally, acidic medium was replaced by phosphate buffer pH 6.8 with the addition of discs and then operated for 60 min (BP, 2004).

Dissolution studies

Dissolution specifications were in accordance of Appendix XII B1 of British pharmacopoeia. Apparatus 2 at 50 rpm was used at 37±0.5°C to determine the percent drug release of all brands. 900mL of phosphate buffer (pH 7.5) was prepared using 1.46g of potassium dihydrogen orthophosphate and 20.06g of di-sodium hydrogen ortho-phosphate in 1000mL. Absorbance of Ketoprofen was measured at 260 nm (BP, 2004).

Assay method

For assay three tablets of each brand were individually weighed and powdered. Equivalent quantity contained the mean weight of tablet was dissolved in methanol (75%) by shaking. Samples were diluted to 0.1% and filtered. Standard was also prepared in similar concentration and measured at 258 nm (BP, 2004).

Content uniformity test

Individually weighed ten tablets of each brand were crushed and dissolved in 75% methanol. Diluted and filtered to the concentration of 0.05%. Standard solution of Ketoprofen was prepared in the concentration of 0.05 % using same method. Uniformity of content of each sample was measured at 258 nm (BP, 2004).

In vitro therapeutic evaluation

In vitro therapeutic assessment of different ketoprofen products were carried out using 900mL of different media i.e., phosphate buffer pH 6.8, 7.5, also release profiles were determined at biorelevant media (FaSSGF, FaSSIF and FeSSIF) in Apparatus II at 50 rpm. Samples were taken at 5, 10, 15, 20, 30, 45, 60, 90 and 120 min and absorbance was measured at 260 nm.

Data analytical approaches

Mathematical methods

Pair Wise Procedure were used including difference factor (f_1) and similarity factor (f_2) (USP, 2003) for the estimation of closeness of test brands (KPB_2-KPB_6) with the reference brand (KPB_1) as shown in Table 1 (A).

Model- dependent methods

Different models were applied to analyze the data i.e. *First Order*, *Hixson Crowell cube root law*, *Higuchi model* and *Weibull model* as presented in Table 1 (B) (Hanson, 1982; Costa and Lobo, 2001; Hixson and Crowell, 1931; Higuchi, 1961; Langenbucher, 1972; Vudathala and Rogers, 1992).

STATISTICAL ANALYSIS

One - way ANOVA was also applied to compare the release behaviour of Ketoprofen brands (KPB_1 to KPB_6) at phosphate buffer pH 6.8 and pH 7.5.

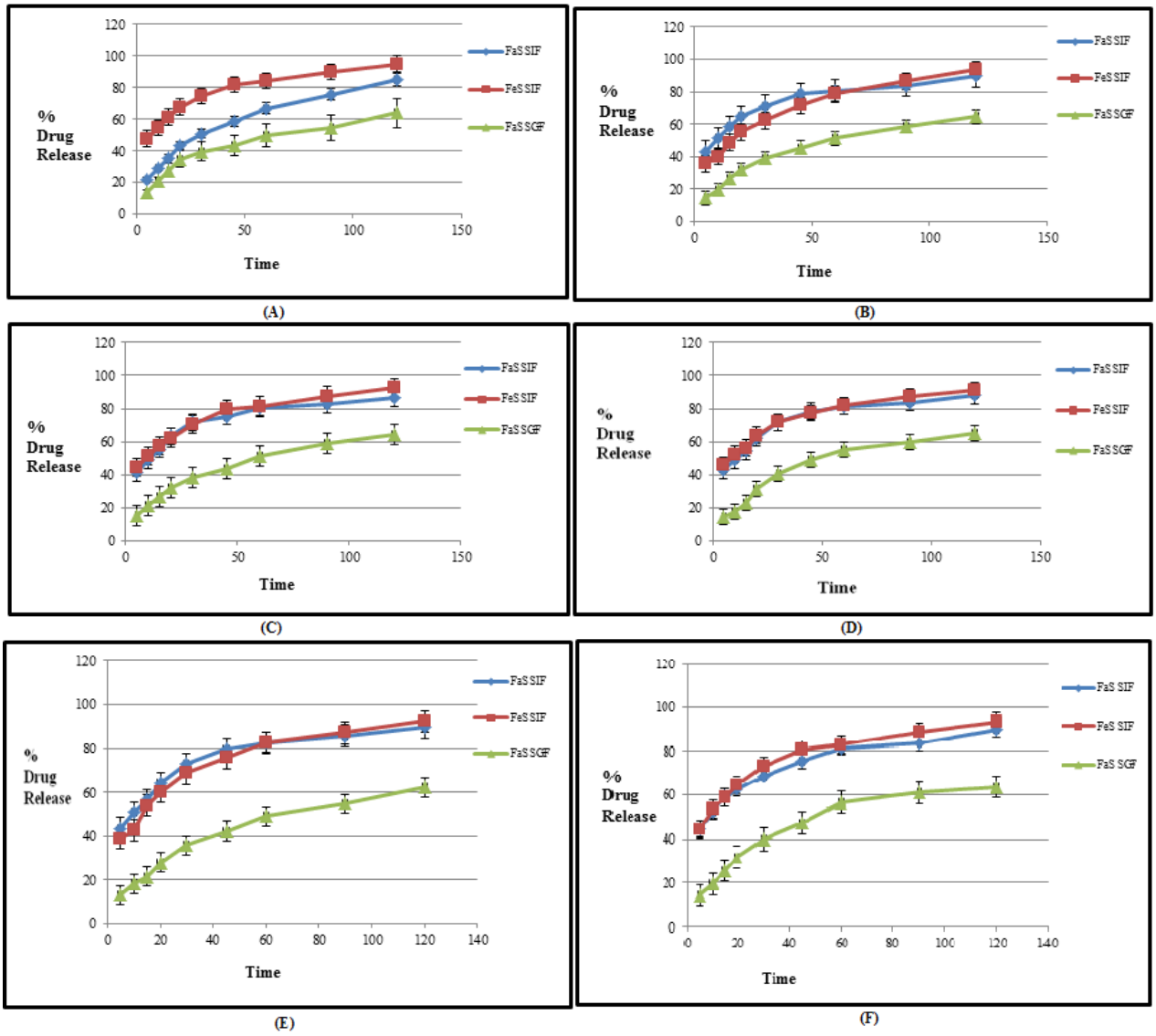

Fig. 1: Comparison of Release Pattern of KPB_1 (A), KPB_2 (B), KPB_3 (C), KPB_4 (D), KPB_5 (E) andKPB_6 (F) at FaSSGF, FaSSIF, FeSSIF media.

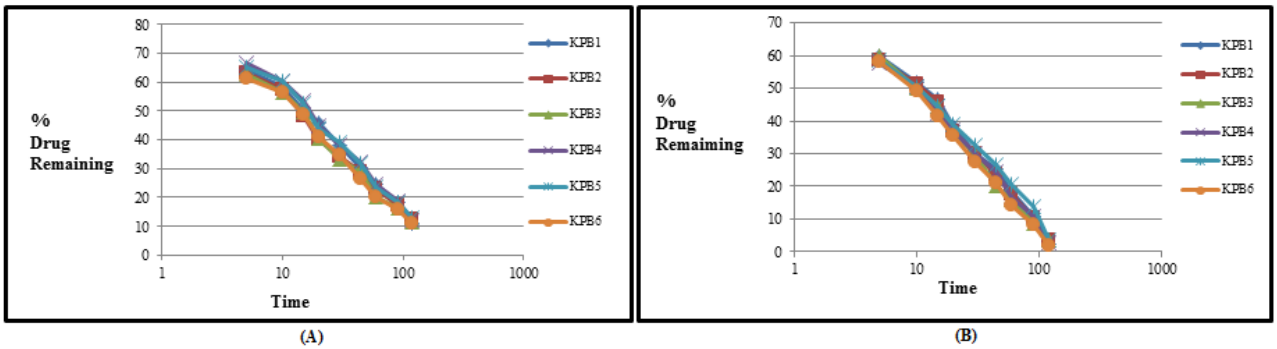

Fig. 2: First order kinetics of Ketoprofen 100 mg tablets at phosphate buffer pH 6.8 (**A**) and pH 7.5 (**B**)

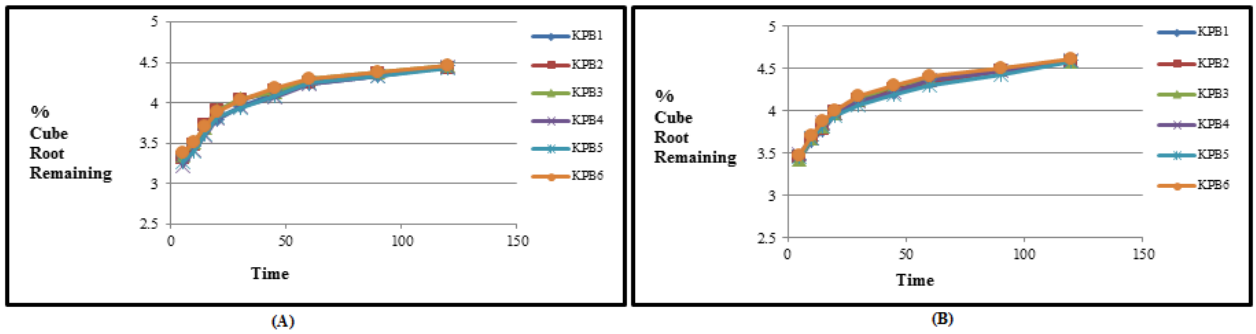

Fig. 4: Hixon- Crowell model of Ketoprofen 100 mg tablets at phosphate buffer pH 6.8 (A) and pH 7.5 (B)

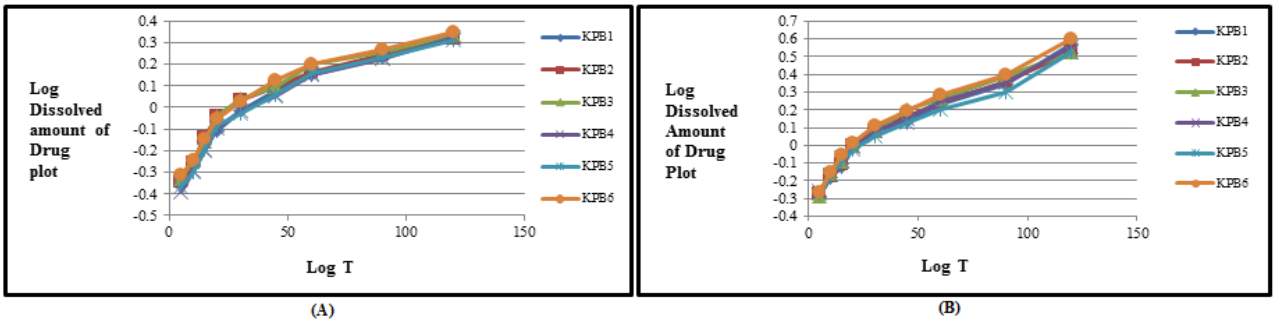

Fig. 5: Weibull model of Ketoprofen 100 mg tablets at phosphate buffer pH 6.8 (A) and pH 7.4 (B).

Table 1: Model-independent (A) and model dependent (B) equations used to assess the kinetics of KPB_1-KPB_6[13-19].

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

Table 2: Physical evaluation of KPB_1 – KPB_6

Parameters	KPB_1	KPB_2	KPB_3	KPB_4	KPB_5	KPB_6
Mean Weight (mg) (n=20)	402.34±0.12	399.68±0.33	409.64±0.58	388.76±0.76	389.25±0.55	396.87±0.57
Mean Thickness (cm) (n=20)	1.17±0.27	1.15±0.36	1.18±0.98	1.12±0.96	1.12±0.88	1.14±0.85
Mean Diameter (cm) (n=20)	0.58±0.11	0.51±0.05	0.61±0.04	0.57±0.03	0.56±0.02	0.51±0.07
Mean Hardness (kg) (n=20)	8.97±0.13	7.96±0.17	9.63±0.22	8.96±0.05	9.64±0.12	7.66±0.22
Disintegration Time (min) (n=6)	19	21	18	20	18	19
Dissolution Test (%) (n=6)	94.66±0.08	95.61±0.17	96.33±0.01	95.31±0.13	96.27±0.74	96.21±0.31
Assay (%) (n=20)	98.11±0.33	99.21±0.77	100.12±0.22	98.69±0.23	99.04±0.88	100.22±0.49
Content Uniformity (%) (n=20)	99.56±0.24	98.57±0.16	99.87±0.59	98.11±0.36	99.44±0.28	98.66±0.32

Table 3: Results of different tests and assays conducted in pharmaceutical equivalence studies among innovator and brands of Ketoprofen tablets.

Parameters (Tests and Assay)	Specifications	KPB_1 (Innovator)	KPB_2 (Brand)	KPB_3 (Brand)	KPB_4 (Brand)	KPB_5 (Brand)	KPB_6 (Brand)
Identification Test	Confirm	Confirm	Confirm	Confirm	Confirm	Confirm	Confirm
Disintegration Time (min) (n=6)	Within 60	Pass	Pass	Pass	Pass	Pass	Pass
Dissolution Test (%) (n=6)	NLT 80	Pass	Pass	Pass	Pass	Pass	Pass
Assay (%) (n=20)	90 – 110	Pass	Pass	Pass	Pass	Pass	Pass
Content Uniformity (%) (n=20)	90 – 110	Pass	Pass	Pass	Pass	Pass	Pass

Table 4: *In vitro* therapeutic evaluation using similarity and difference factors.

Reference and Tests Brands	f_1		
	pH 6.8	pH 7.5	Comments
KPB_1 and KPB_2	2.748	1.061	Pass
KPB_1 and KPB_3	3.825	2.331	Pass
KPB_1 and KPB_4	1.794	1.744	Pass
KPB_1 and KPB_5	1.391	0.874	Pass
KPB_1 and KPB_6	4.460	4.316	Pass
Tests and Reference Brands	f_2		
	pH 6.8	pH 7.5	Comments
KPB_1 and KPB_2	78.055	91.322	Pass
KPB_1 and KPB_3	75.059	79.993	Pass
KPB_1 and KPB_4	85.611	84.751	Pass
KPB_1 and KPB_5	86.577	84.417	Pass
KPB_1 and KPB_6	74.740	73.361	Pass

Table 5: *In vitro* therapeutic evaluation using kinetics models

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	A	β
pH 6.8									
KPB_1	0.9811	0.017	0.9354	7.894	0.9575	0.004	0.9921	5.720	0.509
KPB_2	0.9464	0.017	0.8759	7.775	0.9103	0.004	0.9902	5.084	0.490
KPB_3	0.9590	0.018	0.8836	7.918	0.9246	0.004	0.9879	5.220	0.504
KPB_4	0.9726	0.017	0.9254	7.966	0.9463	0.004	0.9918	6.363	0.530
KPB_5	0.9716	0.017	0.9215	7.895	0.9449	0.004	0.9882	6.073	0.519
KPB_6	0.9725	0.019	0.8975	7.971	0.9407	0.004	0.9900	5.208	0.506
pH 7.5									
KPB_1	0.9866	0.023	0.9380	8.503	0.9740	0.005	0.9763	5.251	0.541
KPB_2	0.9270	0.03	0.9241	8.431	0.9717	0.005	0.9821	4.984	0.532
KPB_3	0.9428	0.032	0.9073	8.57	0.9742	0.005	0.9899	5.215	0.555
KPB_4	0.9289	0.030	0.9339	8.357	0.9746	0.0050	0.9791	4.655	0.516
KPB_5	0.9826	0.02	0.9491	8.152	0.9715	0.0040	0.9723	4.561	0.492
KPB_6	0.9905	0.0260	0.9064	8.5550	0.9730	0.0060	0.9877	4.842	0.5460

Table 6: Statistical evaluation of release profiles of KPB_1-KPB_6.

Formulations	Dissolution Medium	Source of variation	Sum of Squares	Df	Mean Square	F	Sig.
KPB_1-KPB_6	pH 6.8	Between Groups	128.339	5	25.668	0.077	0.995
		Within Groups	16025.458	48	333.864		
		Total	16153.797	53			
	pH 7.5	Between Groups	70.619	5	14.124	0.040	0.999
		Within Groups	16964.887	48	353.435		
		Total	17035.506	53			

RESULTS

In the present study quality assessment tests were conducted on different brands of ketoprofen (KPB_2 to KPB_6) which are available in commercial market of Karachi, Pakistan, while KPB_1 was obtained from international source. Results of all physico-chemical tests were found to be in adequate limits. Mean hardness, mean weight, diameter and thickness of KPB_1-KPB_6 were consecutively found to be 7.66±0.22kg to 8.97±0.13kg, 388.76±0.76mg to 409.64±0.58mg, 0.51±0.05cm to 0.61±0.04cm, 1.12±0.88 cm to 1.18±0.98cm. In this study disintegration and dissolution tests of KPB_1-KPB_6 were found to be in the range of 18 min to 21 min and 94.66±0.08% to 96.33±0.01% respectively, also the assay and content uniformity tests were also conducted which were found to be in the range of 98.11±0.08% to 100.22±0.49% and 98.11±0.36 to 99.87±0.59% respectively as shown in table 2. Results of different tests comply with the requisites for pharmaceutical equivalence was shown in Table 3. Also, release profiles of all brands were determined using biorelevent media (FaSSGF, FaSSIF and FeSSIF) as shown in Fig. 1(A), (B), (C), (D), (E) and (F). Similarly, different kinetic models were applied as presented in Table 1 (Hanson, 1982; Costa and Lobo, 2001; Hixson and Crowell, 1931; Higuchi, 1961; Langenbucher, 1972; Vudathala and Rogers, 1992). Also, *in vitro* therapeutic evaluation of KPB_1-KPB_6 were carried out by model dependent and independent methods at phosphate buffer pH 6.8 and 7.5 as shown in Table 4-5 and Fig. 2-5. For this purpose KPB_1 (reference brand) was compared with the test brands (KPB_2-KPB_6) using difference factor (f_1) and similarity factor (f_2). Values of f_1 at phosphate buffer pH 6.8 and 7.5 were found to be in the range of 1.391 to 4.460 and 0.874 to 4.316 respectively and f_2 values at phosphate buffer pH 6.8 and 7.5 were consecutively found to be 74.740 to 86.577 and 73.361 to 91.322 as presented in Table 4. Release profiles were also assessed by model dependent method. Consecutive r^2 values for first-order and Higuchi kinetic models, were found to be 0.9464 to 0.9811 and 0.8759 to 0.9354 at phosphate buffer pH 6.8 and at pH 7.5 values were 0.9270 to 0.9905 and 0.9064 to 0.9491 as shown in table 5 and fig. 2-3 (A) and (B). For Hixon-Crowell kinetic model coefficient, r^2 values at phosphate buffer pH 6.8 were 0.9103 to 0.9575 and at pH 7.5, r^2 values were found to be 0.9715 to 0.9746 as shown in Table 5 and Fig. 4 (A) and (B). KPB_1-KPB_6 followed Weibull model at different media as shown in Table 5 and Fig. 5 (A) and (B). The release pattern of KPB_1-KPB_6 at phosphate buffer pH 6.8 and 7.5 were also assessed by One way - ANOVA method as presented in Table 6. Results indicated no significant difference among the release behaviour of different products as P values at phosphate buffer pH 6.8 and pH 7.2 were found to be 0.995 and 0.999 respectively.

DISCUSSION

The effectiveness of those product administered orally depends on the concentration of drug absorbed by the gastrointestinal tract. Physico - chemically similar products should be equivalent interms of quality and purity (USP, 2003). Formulation variations, handling techniques may produce the variation in the results (Fukami et al., 2006). That's why quality assessment studies were conducted to determine the interchangeability (Arshad *et al*., 2003). Arshad *et al*. (2011) conducted the brand evaluation studies of Gatifloxacin 200mg tablets available locally in Pakistani market. Bano *et al*. (2011) compared different brands of levofloxacin tablets. In this study different physical – chemical parameters were performed; results were found to be in adequate limits. The present regulatory guideline for pharmaceutical equivalence suggested that both reference and test brands should follow the specifications (USP, 2003; Abdelbary et al., 2009).

In vitro Therapeutic equivalence

In vitro tests are used to evaluate the release pattern of different products and also help to assess the risks associated with physiological conditions, effect of food and impact of dose dumping on the availability of product in the blood (Sungthongjeen *et al*., 1999). Different variables particularly hydrodynamics and dissolution media have been used to determine the release pattern of the compound in different regions of gastro-intestinal tract (Fotaki and Vertzoni, 2010). Vertzoni *et al.* (2005) found that in FaSSGF state the data of the compound solubility helps to determine the availability of drugs in fasted state. It was also determine that postprandial condition in the small intestine can be developed by introducing FeSSIF with FaSSIF medium (Klein, 2010).

Data analysis

Model independent method

Dave *et al*. (2004) studied the release behaviour of ranitidine hydrochloride gastroretentive products using f_1 and f_2. Shaoib *et al*. (2010) developed famotidine formulations and assess the similarity of tests with reference product using f_2. Castellanos *et al*. (2008) determine the similarity of coated and uncoated products with the marketed products.

Model dependent method

Dissolution studies at various dissolution media indicating the pattern of release *in vivo* conditions (Klein, 2010). Bravo *et al*. (2002) found that diclofenac sodium controlled products followed Zero-order, Higuchi and First-order kinetics. Ghosh and Barik (2010) found that aceclofenac (SR) tablets followed Higuchi model. Iqbal *et al.* (2011) analyzed the release kinetics of diclofenac sodium (sustained release) products using different kinetic model i.e. first order, zero order and higuchi kinetics. In

the present study Sathe *et al.* (1996), Polli *et al.* (1997) and Yuksel *et al*. (2000) described shape factor of compound release using Weibull model. Scientists reported that around the world verification of *in vitro* therapeutic equivalence is one of the important issues for regulatory bodies (Traple *et al*., 2014). In this study model dependent and independent methods showed excellent correlation with the regulatory concerns for *in vitro* therapeutic equivalence.

One way - ANOVA method

In this study Tukey test was used to compare the release pattern among and within the brands at various dissolution media.

CONCLUSION

Present study presented a statistical approach of similarity for the evaluation of *in vitro* therapeutic equivalence among different brands of ketoprofen tablets. Furthermore, such studies are helpful for the drug regulating authorities and manufacturers to continuously monitor the supply of quality medicines to the commercial market.

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