Possibility of extending biopharmaceutics classification system based biowaiver to BCS class IIa drug

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Abstract: Biowaiver studies have been performed to assess the bioequivalence of two drug products. Ibuprofen is a Biopharmaceutics Classification System (BCS) class IIa drug (Low solubility - High permeability) used as analgesic, antipyretic and anti-inflammatory agent. World Health Organization (WHO) placed ibuprofen in the category of biowaiver drugs but Food and drug authority (FDA) and International Council for Harmonization (ICH) has not issued yet any guidelines regarding the biowaiver of BCS class II drugs. Present study was aimed to formulate immediate release (IR) Ibuprofen 600 mg tablets with variable disintegrants. All trial film coated formulations were evaluated physicochemically with *in-vitro* bioequivalence studies in three buffer mediums (pH 6.8, pH 4.5 and pH 1.2). Samples were analyzed spectrophotometrically at 221 nm and model independent approaches (dissimilarity (f_1), similarity (f_2) and Boot strap) was applied to assess the observed similarity. The similarity factor (f_2) was achieved only in pH 1.2 in three trial formulations and met acceptance criteria (f_2, 50-100) although the amount of drug release was negligible. This investigation revealed that for BCS class IIa drug (ibuprofen), subsequent analysis of excipients used, pKa of drug and method of manufacturing should also be considered to ensure bioequivalence for a successful biowaiver study.

Keywords: Biowaiver, BCS, ibuprofen, bootstrap, bioequivalence.

INTRODUCTION

Biowaiver studies are principally constructed on the BCS classification of the drugs (Hofsass and Dressman, 2019) which governs that the absorption of drugs is based on the solubility and permeability of drugs. Therefore, those active pharmaceutical ingredients which possess high solubility and high permeability (BCS Class I) can be easily accredited as a successful biowaiver candidate. For a drug to be biowaiver the *in-vivo* bioavailability or bioequivalence testing is not prerequisite and only the *in-vitro* dissolution profile is applied to determine whether the two pharmaceutical products are equivalent or not. In December 2017, FDA issued guidance for industry on waiver of *in-vivo* bioavailability, based on BCS classification, only for immediate release solid oral dosage forms (FDA, 2017). Later in June 2018, draft of M9 guidelines of ICH was released regarding the BCS based biowaivers (ICH, 2018). Both have discussed the immediate release dosage forms containing API belonging to BCS class I and III. However, WHO extended the scope of biowaiver to other classes of drugs (BCS class II and III drugs) if their dose/solubility ratio is 250 ml or less at pH 6.8. If biowaivers are extended to BCS class II, in support of sufficient scientific basis and evidences, then the development of generic product and subsequent approvals from regulatory authorities will become easier in economically developing nations (WHO, 2006).

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WHO proposed guiding principle which establish interchangeability of BCS class I, II and III biowaivers; if the multisource product dissolves rapidly (more than 85% of drug release in 30 minutes) in phosphate buffer (pH 6.8), acetate buffer (pH 4.5) and 0.1N HCl (pH 1.2) (WHO, 2006). Further, regulatory authorities like Food and Drug Administration (FDA) and European Medicine Agency (EMA) permitted only BCS class I and III as biowaiver following 85% of the drug release in 30 minutes at pH values stated above (FDA, 2017; EMA, 2010) given in table 1. While to the best of our knowledge no guideline is available to consider the film coated tablets for biowaivers.

Ibuprofen is a propionic acid derivative ($C_3H_{18}O_2$) (WÖhrl, 2018) and a non-steroidal anti-inflammatory drug (NSAID) used for relieving pain associated with rheumatoid arthritis, osteoarthritis, primary dysmenorrhea, fever and reducing inflammation. Ibuprofen is available in 200 mg to 600 mg tablets for oral administration (Irvine *et al*, 2017). According to biopharmaceutic classification it falls in BCS class II (low solubility-high permeability). Regardless of class II drug and low solubility at lower pH values ibuprofen is highly permeable as it shows rapid absorption soon after dissolution (Rinaki *et al*., 2004). The lowest solubility of ibuprofen was stated at pH 1.2 which was not recognized by other researchers as the isomers showed acceptable solubility at pH 1.5 as compared to racemates of ibuprofen (Gosh *et al.,* 1998). On the other hand, complexation of ibuprofen resulted in improved

wettability which enhanced rapid dissolution (Charoenchaitrakool *et al*., 2002; Imai *et al*., 1990). Some authors recommended ibuprofen in "intermediate solubility class" proposed for weak acidic drugs that are soluble at pH 1.2 or 6.8 (Yazdanian *et al.,* 2004). Literature revealed that different studies have been performed by following WHO biowaiver guidelines. Alvarez *et al*., 2011 evaluated *in-vitro* and *in-vivo* studies of ibuprofen 600mg IR formulations, and compared with reference product. The formulations were failed as biowaiver because *in-vitro* dissolution study did not detect variation in the rate of absorption of drug whereas *in-vivo* study determined inequivalency in C_{max}. Shohin *et al.,* 2011 found two ibuprofen 200 mg marketed brands as bio-inequivalent because they showed similarity only in acetate buffer (pH 4.5) but not in phosphate buffer (pH 6.8) with negligible release at pH 1.2 acidic medium at 246 nm. Potthast *et al.,* 2005 revealed specific excipients in specific amount for ibuprofen formulation can affect on its rate of absorption but it does not effect on the extent of absorption which can be detected easily by *in-vitro* dissolution test. The resulted test product showed similarity with reference product among the dissolution profiles at pH 1.2, 4.5 and 6.8.

Investigation was also reported on the most sensitive wavelength for ibuprofen UV measurements in biowaiver buffer mediums (pH 6.8, 4.5 and 1.2). Calibration curves were plotted at two different wavelengths 264/272nm (Ph. Eur.wavelength) and 220/221nm (USP wavelength). It was concluded that maximum sensitivity was found at 220/221nm and could be used in biowaiver analysis to obtain differentiation between the dissolution profiles because Ph.Eur. wavelength was not sensitive enough to detect 10% difference required for similarity testing (Vidal and Alegre, 2013).

The aim of current study was to formulate ibuprofen 600 mg IR film coated tablets using direct compression method. The biowaiver suitability was evaluated by comparing with innovator brand using WHO guidelines at 221nm.

MATERIALS AND METHODS

Chemicals

Ibuprofen a white crystalline powder, was a gift by Abbott laboratories, Karachi, Pakistan. Ibuprofen 600mg tablet innovator brand was purchased from local market in Karachi. Microcrystalline cellulose (Avicel PH-102), pregelatinized starch, magnesium stearate, aerosil, talc, croscarmellose sodium, hypromellose, crospovidone, PVP-K30, HPMC 5cps, titanium dioxide, talc, PEG 6000 were purchased from Merck (Germany).

Equipment/Apparatus

High Performance Liquid Chromatography (HPLC) (Shimadzu, Japan), Spectrophotometer UV-1800 (Shimadzu, Japan), Dissolution apparatus Type II (Erweka GmbH, Germany), Disintegration apparatus (Erweka, Germany), Friability tester (Erweka GmbH, Germany), Homogenizer (Ogawa Seiki Co., Ltd, Japan), Sonicator (AFD, USA), pH Meter (Jenway 3505, Germany), Hardness tester (Fujiwara Seisukusho Corporation, Japan), Single punch compression machine (Korsch Erweka, Frankfurt, Germany), Vernier caliper (Seiko brand, China), Coating pan (Erweka GmbH, Frankfurt, Germany), Weighing balance (Shimadzu, Japan), Spray gun (F-75-G, China), Dryer (Sonashi, France).

Methodology

Calibration curve plotting

For pH 7.2 and 6.8 phosphate buffers, standard stock solutions were prepared by dissolving 50mg of ibuprofen in 100ml buffers (0.5mg/ml). For pH 4.5, ibuprofen 15mg was weighed and dissolved in 500ml of acetate buffer (0.03mg/ml) while 10mg of ibuprofen was taken and dissolved in 500ml buffer of 0.1N HCl buffer (pH 1.2) (0.02mg/ml). Calibration curves were plotted to determine the sensitivity at 221nm. Mean regression values were calculated in all four buffer solutions of pH 7.2, 6.8, 4.5 and 1.2. Concentration versus absorbance curves are shown in fig. 1-4.

Development of Ibuprofen IR tablets

Three ibuprofen 600mg formulations were developed consuming conventional excipients already in use in marketed formulations (Potthast *et al*, 2005). All the excipients and ibuprofen were exactly weighed in pre-labelled polythene bags. Formulation F1 was manufactured using croscarmellose sodium, hypromellose, avicel, aerosil, talc and magnesium stearate. Same composition followed in remaining formulations except povidone and crospovidone (F2) and pregelatinized starch (F3). The tablets were compressed by direct compression technique on single punch machine.

Pre-formulation Testing

Pre- compression properties of the formulation blends were evaluated. The flow behavior of above powder mixtures was calculated by angle of repose, Hausner's ratio and compressibility index. The following parameters were calculated by equation a, b and c:

$\tan(\theta) = height/0.5\ base$ (a)

Carr's compressibility Index= 100 x (Tapped bulk density - Poured bulk density)/Poured bulk density (b)

Hausner's ratio = Tapped bulk density/Poured bulk density (c)

Film Coating of Ibuprofen (600mg) tablets

After compression next phase was the film coating of compressed tablets using conventional coating pan, a spray gun and dryer.

Table 1: Biowaiver authorization among different regulatory authorities

Biopharmaceutics Classification for Biowaiver Consideration	Regulatory Agency		
	WHO	FDA	EMEA
	Dissolution apparatus rotating at; Paddle; 75 rpm Basket; 100rpm	Dissolution apparatus rotating at; Paddle; 50 rpm Basket; 100rpm	Dissolution apparatus rotating at; Paddle; 50 rpm Basket; 50rpm
BCS Class I (high solubility- high permeability)	Biowaiver allowed at pH 1.2, 4.5 and 6.8 at 37°C.	Biowaiver allowed at pH1.2, 4.5 and 6.8 at 37°C	Biowaiver allowed at pH1.2, 4.5 and 6.8 at 37°C
BCS Class II (low solubility- high permeability)	Biowaiver allowed at pH 1.2, 4.5 and 6.8 at 37°C and if dose: solubility ratio is 250ml or lower at pH6.8	Biowaiver not allowed	Biowaiver not allowed
BCS Class III (high solubility – low permeability)	Biowaiver allowed at pH 1.2, 4.5 and 6.8 at 37°C	Biowaiver allowed at pH1.2, 4.5 and 6.8 at 37°C	Biowaiver allowed at pH1.2, 4.5 and 6.8 at 37°C
BCS Class IV (low solubility – low permeability)	Biowaiver not allowed	Biowaiver not allowed	Biowaiver not allowed

Table 2: Pre-Compression properties of different powder blends

Formulation blend	Angle of Repose°	Carr's Index (%)	Hausner Ratio	Flow Performance
F1	28.36*	19.75	1.24	Fair
F2	32.00	14.39	1.16	Good
F3	30.96	14.81	1.17	Good

*Excellent flow as per angle of repose

Table 3: Physicochemical features of ibuprofen innovator and trial formulations (F1-F3)

Formulation Code	Physical appearance	Weight variation (mg)	Hardness (Kg)	Thickness (mm)	Length (mm)	Width (mm)	Friability (%)	Disintegration (min.)	Assay (%)
Innovator	White, coated caplet shaped	936.50 ±4.89	9.92 ±0.07	6.14 ±0.009	20.03 ±0.04	9.04 ±0.05	0.10 ±0.005	6.55 ±0.09	102.64 ±0.24
F1	White, coated caplet shaped	1024.50 ±13.16	9.88 ±0.08	7.41 ±0.01	17.72 ±0.06	8.64 ±0.07	0.10 ±0.005	5.36 ±0.15	103.59 ±0.52
F2	White, coated caplet shaped	1043.25 ±20.53	9.95 ±0.06	7.96 ±0.43	18.85 ±0.05	8.81 ±0.05	0.21 ±0.01	5.56 ±0.09	100.45 ±0.42
F3	White, coated caplet shaped	1039.0 ±13.72	9.83 ±0.09	6.50 ±0.16	18.12 ±0.08	8.78 ±0.04	0.28 ±0.01	4.46 ±0.13	102.69 ±0.15

Table 4: Cumulative *in-vitro* release profiles of ibuprofen innovator and trial formulations (F1-F3)

Dissolution mediums	Tablet formulation	15 minutes	30 minutes	45 minutes	60 minutes
Phosphate buffer (pH7.2)	Innovator	50.74 ± 3.00	77.69 ± 1.74	87.28 ± 1.33	92.90 ± 2.16
	F1	39.37 ± 6.97	59.73 ± 9.09	74.62 ± 8.69	85.06 ± 7.52
	F2	37.29 ± 6.63	69.58 ± 11.86	85.48 ± 11.37	92.37 ± 9.10
	F3	39.54 ± 2.49	59.51 ± 3.17	72.40 ± 8.59	85.77 ± 7.61
Phosphate buffer (pH6.8)	Innovator	38.04 ± 0.24	59.61 ± 0.96	70.79 ± 1.48	86.97 ± 1.66
	F1	6.83 ± 0.17	21.02 ± 0.66	23.31 ± 0.18	25.44 ± 0.16
	F2	27.54 ± 2.22	44.20 ± 0.90	48.56 ± 0.60	62.79 ± 0.28
	F3	15.62 ± 0.81	23.80 ± 0.33	28.05 ± 0.83	31.69 ± 0.18
Acetate buffer (pH4.5)	Innovator	7.40 ± 0.05	14.81± 0.03	18.51 ± 0.03	22.22 ± 0.03
	F1	1.85 ± 0.04	2.96 ± 0.06	3.33 ± 0.03	3.70 ± 0.04
	F2	1.11 ± 0.05	1.85 ± 0.04	2.22 ± 0.07	2.59 ± 0.04
	F3	2.22 ± 0.04	2.96 ± 0.06	3.33 ± 0.06	3.70 ± 0.06
0.1N HCl (pH1.2)	Innovator	5.86 ± 0.08	7.81 ± 0.15	10.21± 0.48	11.50 ± 0.05
	F1	2.68 ± 0.04	3.29 ± 0.12	3.83 ± 0.04	5.75 ± 0.02
	F2	2.93 ± 0.11	3.93 ± 0.11	4.52 ± 0.08	4.79 ± 0.03
	F3	1.67± 0.10	3.94 ± 0.11	7.19 ± 0.21	7.88 ± 0.17

n = 12, Mean ± SD ; $p < 0.05$

Table 5: Similarity (f_1) and Dissimilarity (f_2) values of Ibuprofen innovator and trial formulations

Phosphate buffer (pH 6.8)	f_1	f_2
Innovator vs F1	72.81	20.59
Innovator vs F2	27.20	40.95
Innovator vs F3	59.12	24.16
Acetate buffer (pH 4.5)		
Innovator vs F1	76.69	47.97
Innovator vs F2	87.31	46.32
Innovator vs F3	78.21	48.12
0.1N HCl (pH 1.2)		
Innovator vs F1	55.51	67.60
Innovator vs F2	53.39	68.04
Innovator vs F3	51.60	70.50

f_1 was failed in all buffers
f_2 was failed in acetate buffer and phosphate buffer but not in HCl buffer.

Table 6: Similarity Assessment by Bootstrap Technique

Dissolution medium	Observed *f*2	*f*2 distribution 500 bootstrap 1000 bootstrap	500 bootstrap 5% Percentile 5% Percentile	1000 bootstrap 5% Percentile 95% Percentile
Phosphate buffer (pH 6.8)				
Innovator vs F1	20.59	20.57 20.57	20.48 20.67	20.47 20.66
Innovator vs F2	40.95	40.95 20.57	40.56 41.29	20.47 20.67
Innovator vs F3	24.16	24.15 24.15	24.02 24.26	24.02 24.27
Acetate buffer (pH 4.5)				
Innovator vs F1	47.97	47.96 47.96	47.94 47.98	47.94 47.98
Innovator vs F2	46.32	46.34 46.34	46.32 46.37	46.32 46.37
Innovator vs F3	48.12	48.13 48.13	48.10 48.15	48.10 48.16
0.1N HCl (pH 1.2)				
Innovator vs F1	67.60	67.71 67.71	67.47 67.97	67.44 67.96
Innovator vs F2	68.04	68.49 68.49	68.21 68.73	68.19 68.75
Innovator vs F3	70.50	70.63 70.63	70.37 70.89	70.37 70.91

Preparation of coating solution and coating procedure

HPMC was placed in beaker and dissolved in distilled water. In another beaker, titanium dioxide, talc and PEG 6000 was added and dissolved in distilled water completely. Both the solutions were mixed together and homogenized and filtered prior coating. Coating pan was filled with tablets maintained at 40^{o}C. The tumbling tablet ground was coated by spraying and alongside dried with the help of dryer. Coating was continued until the tablets attained even appearance.

Dissolution studies

Dissolution profiles were conducted in official mediums phosphate buffer pH 7.2 and WHO biowaiver mediums; phosphate buffer (pH 6.8), acetate buffer (pH 4.5) and 0.1N HCl (pH 1.2). 900ml of dissolution medium was filled in all the six vessels and maintained at 37±0.5°C and paddles rotated at 50 rpm. Samples of 5ml were withdrawn at stated time intervals (5, 10, 15, 20, 30, 45 and 60 minutes) then every time substituted with same amount of buffer solution to maintain the sink condition. Same method was adopted for biowaiver buffer solutions with altered rotational speed at 75 rpm as proposed by WHO. Every sample was filtered through 0.45 µm filter paper, diluted with desired buffer solution and analyzed at 221 nm (USP, 2015) the most sensitive wavelenght as per Vidal and Alegre, 2013. Previously same experiments were carried out at 226 nm as per European pharmacopeia (Alvarez *et al*., 2011; Shohin *et al*., 2011). The entire dissolution was performed by collecting triplicate readings to confirm the consistency of the data. Data were analyzed by using Microsoft Excel® 2016. Analysis of

Variance (ANOVA) was applied to dissolution samples collected at each time interval, at 0.05 level of significance.

Model independent approach for fit factors

Dissolution profiles of multisource products is compared by dissimilarity factor ($f1$) and similarity factor (f_2) and considered equivalent if values of $f1$ ranges between 0 and 15 and $f2$ between 50 and 100 respectively (FDA, 2017). Difference factor (f_1) is the mean percentage difference in the quantity of test and reference product dissolved at all time points. When indistinguishable profiles of reference and test products were obtained the f_1 value is 0 whereas dissimilarity increases the value consistently. It is calculated by (Anderson *et al*., 1998);

$$f_1 = \{[St=1^n |Rt - Tt|]/[St=1^n Rt]\}\times 100 \quad (d)$$

$$f_2 = 50^* \log \{[1 + (1/n)\Sigma t=1\ n\ (Rt - T)^2]^{-0.5} *100\} \quad (e)$$

The differences between the means whether they are statistically significant or not were observed by one-way analysis of variance. Similarity among the dissolution profiles were compared by model-independent approach to assess the fit factors (Costa *et al.,* 2003; Cascone, 2017) performed by software DD Solver® an add-in program in excel. Another methodology was applied such as model-independent multivariate confidence region method; it is a boot strap method to simulate the confidence interval (Shah *et al*., 1998). Bootstrapping allows the assessment of observed similarity in the dissolution profiles and serve as an important guide in simulating future formulation development (Mendyk *et al*., 2013).

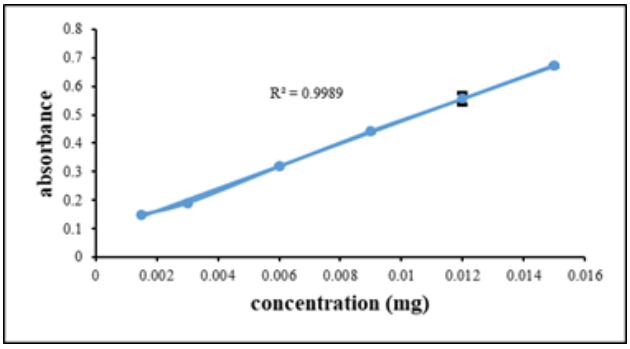

Fig. 1: calibration curve of ibuprofen at pH 7.2 (Phosphate buffer)

RESULTS

Physicochemical evaluation

The powder blends displayed acceptable flow behaviors with different composition of excipients are shown in table 2. The tablets manufactured (F1-F3) were film coated, caplet shaped white in color with smooth, glossy and shiny appearance. The weight of the tablets ranged from 950 mg – 1050 mg and innovator: 930 mg – 940 mg. All the trial formulations showed enough hardness ranged from 9.43-9.95 Kg and innovator: 9.80 Kg-10.12 Kg with friability values from 0.10-0.28% and innovator: 0.10%-0.11%. Assay of the trial formulations showed up to 100.45%-103.59% of drug content equivalent to innovator: 102.36%-102.84%. Compressed formulations showed earlier disintegration as compared to innovator (trial: 4.46 minutes-5.56 minutes and innovator: 6.48 minutes 6.66 minutes) given in table 3.

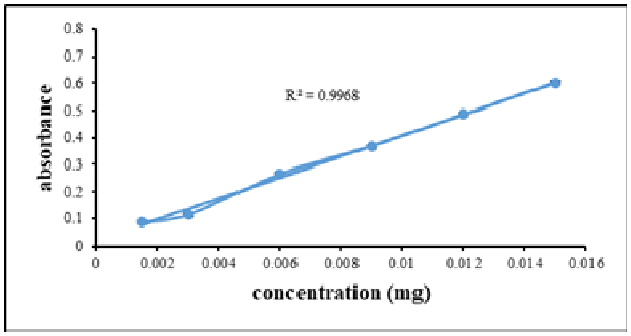

Fig. 2: calibration curve of ibuprofen at pH 6.8 (Phosphate buffer)

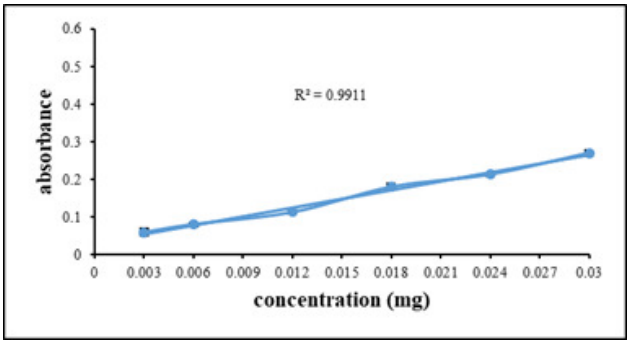

Fig. 3: calibration curve of ibuprofen at pH 4.5 (Acetate buffer)

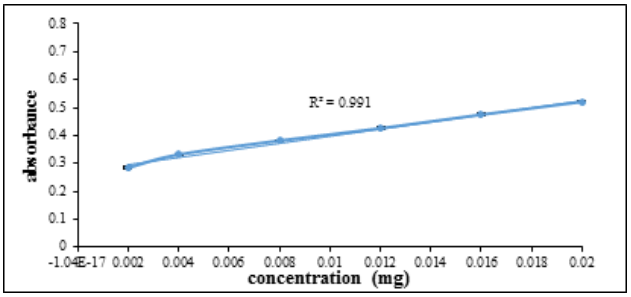

Fig. 4: calibration curve of ibuprofen at pH 1.2 (0.1N HCl)

In-vitro dissolution profile comparison

The drug release profile of all the trial formulations was first compared with innovator in official medium (Phosphate buffer pH 7.2). All the formulations complied USP standards and greater than 80 % of drug was released in 60 minutes. The release pattern was identical for both test and innovator, though innovator released maximum API at all sampling times as compared to trial formulations. Release profiles of innovator over formulation F2 was superimposed at 60 minutes.

Cumulative profiles showed maximum dissolution of innovator followed by F2, F1 and F3. Significant difference was detected by ANOVA at multiple time points ($p<0.05$) given in table 4 and fig. 5. In Phosphate buffer pH 6.8, slow release was observed at initial time points where 18 % innovator release was observed at 5 minutes followed by F2 (14 %), F3(9 %) and F1(3 %). Until 60 minutes, innovator released 87 % of API whereas, F2 released 63 % drug as compared to F3 (32%) and F1 (25%). A significant difference in release profiles at all sampling times were observed by ANOVA ($p<0.05$) given in table 4 and fig. 6. Inadequate dissolution was observed in Acetate buffer (pH 4.5) where innovator showed only 7 % release at 15 minutes followed by F3, F1 and F2 and no improvement in drug release were observed among trial formulations. A slight increase in innovator release was obtained at 60 minutes around 22 % as compared to trial formulations that displayed maximum 4 % of API release. Significant difference in release profiles was detected by ANOVA ($p<0.05$) shown in table 4 and fig.7. Analogous low drug release was obtained in 0.1N HCl (pH 1.2), as in case of acetate buffer (pH 4.5). Innovator released only 4 % of drug at 5 minute followed by F2, F1 and F3 respectively. The drug release pattern at other time points (10 minutes and onwards) displayed no change and improvement in the release. Approximately, 11 % of innovator release was obtained followed by F3 (8%), F1(6 %) and F2(5 %) respectively. A significant difference was detected when ANOVA was applied at all time points ($p<0.05$) given in table 4 and fig. 8.

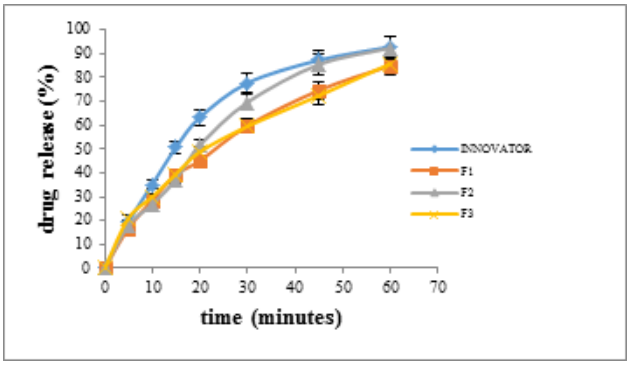

Fig. 5: Cumulative dissolution profile of Ibuprofen innovator and trial formulations in Phosphate buffer (pH 7.2)

f_2 and f_1 determination Difference between the values of the two curves of the innovator and trial formulation was evaluated by Fit factors hence it is a quantitative method. If the profile is positioned above or under the reference curve, the deviation between the curves was not recognized by these fit factors (Costa *et al.,* 2003). Fit factors quantify the errors at each time point and sensitive to the differences at >85% of drug release so, they basically showed cumulative outcome. To use these fit factors efficiently minimum three time points should be compared, and dissolution time points should be similar. Only one value should be considered after 85% release. Mean values used when the difference at the earlier time points is < 20%, and other time points < 10% (Shah *et al.,* 1998). Similarity and dissimilarity between the dissolution profiles were also calculated in different dissolution mediums by comparing innovator with trial formulations. Dissolution profiles in Phosphate buffer pH 6.8 was not considered equivalent when $f1$ and $f2$ value found for formulation F1(73) (21); F2 (27) (41), and F3 (59) (24) did not met the biowaiver acceptance criteria. In Acetate buffer pH 4.5 again factor $f1$ and $f2$ for formulation F1 (77) (48), F2 (87) (46) and F3 (78) (48) did not endorse similarity between the dissolution profiles. Similarity was observed only in case of 0.1N HCl (pH 1.2) where calculated $f1$ and $f2$ values found for F1 (55) (68), F2 (53) (68) and F3 (51) (71) met the biowaiver acceptance criteria (f_2; 50-100) given in table 5.

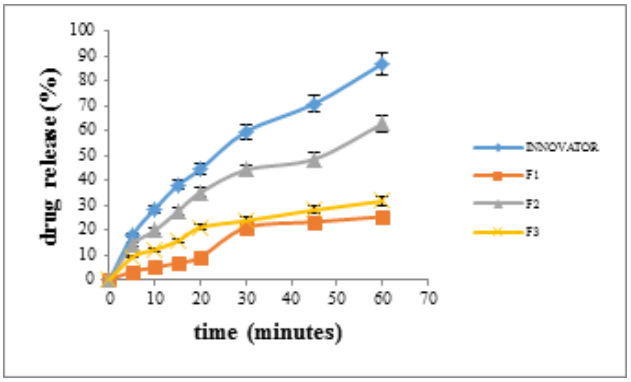

Fig. 6: Cumulative dissolution profile of Ibuprofen innovator and trial formulations in Phosphate buffer (pH 6.8)

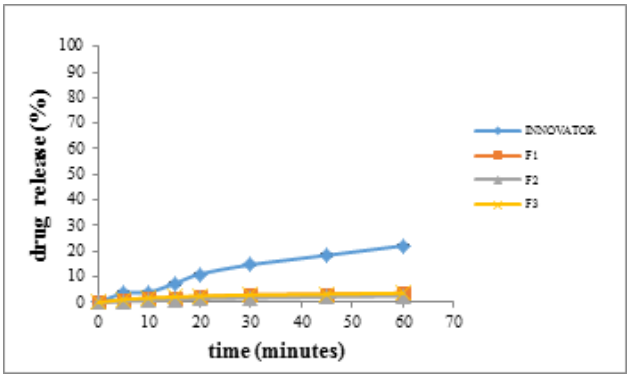

Fig. 7: Cumulative dissolution profile of Ibuprofen innovator and trial formulations in Acetate buffer (pH 4.5)

Bootstrap evaluation

The dissolution data also subjected to non-parametric bootstrap f_2 methodology for re-evaluating the similarity between two dissolution profiles. The bootstrapping is the practice of estimating properties of an estimator by measuring those properties when randomly sampling from an approximating distribution (Mendyk *et al.,* 2013). For

example, an empirical distribution function of the observed data. A bootstrap sample is generated with replacement many times creating large number of bootstrap samples. It was applied to all biowaiver mediums using 500 and 1000 bootstrap samples. The *f*2 value equivalent to 50 was considered as cut-off point for similarity between reference and test batches. The results indicated that only one bio-waiver dissolution medium i.e. pH 1.2 showed similarity while remaining (pH 4.5 and 6.8) failed to produce similarity between reference and test samples. The observed *f*2 value was approximately close to bootstrap *f*2 in all three bio-waiver mediums shown in table 6.

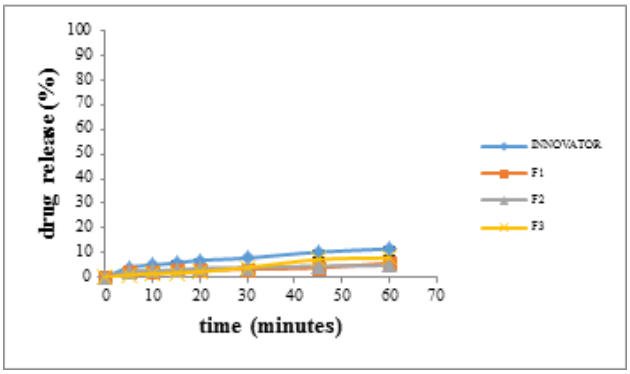

Fig. 8: Cumulative dissolution profile of Ibuprofen innovator and trial formulations in 0.1N HCl (pH 1.2)

DISCUSSION

Ibuprofen dissolution profiles showed variation due to pH dependent solubility. In phosphate buffers innovator and trial formulations exhibited remarkable performance whereas in acetate and HCl buffer ibuprofen demonstrated insignificant release due to decreased solubility of ibuprofen as pH shifted from basic to acidic. At pH 6.8, F-2 showed better drug release as compared to F-1 and F-3 shown in table 4 fig. 6 which might be due to presence of crospovidone in this formulation. Cross linking not only make the crospovidone insoluble, but it also quickens the uptake of water without noticeable swelling (Quadir and Kotler, 2006). It is reported that croscarmellose sodium has the tendency to form a gel when encounters with water (Rojas, 2011). Therefore, retarded release at early time point was observed. Similarly, pregelatinized starch showed the same behavior at pH 6.8. This trend was not continued as pH was lowered to 4.5 and 1.2. The reason could be the conversion of the carboxymethyl sodium salt moiety to its free acid form, which has lower water holding capacity, under low pH environment (Rojas and Ruge, 2012). Due to low solubility of Ibuprofen, it was difficult to determine the effect of disintegrants at lower pH. These results are in agreement with Alvarez *et al*. and Alhatem *et al.* who have also studied the dissolution behavior of Ibuprofen tablets in different pH (Alvarez *et al.,* 2011; Alhatem *et al.,* 2018).

For biowaiver acceptance similarity factor was calculated between innovator and trial formulations at 221 nm. Compliance was observed only in case of HCl buffer where *f*2 criteria was met whereas, non-compliance was observed in phosphate and acetate buffer. These findings contrast with the previous studies which were performed at 264 nm (Alvarez *et al.,* 2011; Shohin *et al*., 2011). Enhanced dissolution and biowaiver acceptance for ibuprofen did not improve by change in wavelength (264nm to 221nm) as suggested by previous study (Vidal and Alegre, 2013). According to WHO standards each formulation should satisfy the f_2 criteria for biowaiver acceptance (WHO, 2006) in all biowaiver media. So, in the present study ibuprofen trial formulations failed to meet biowaiver requisite. There was no significant change observed when applying similarity factor *f*2 and bootstrap *f*2 approach. The bootstrap approach did not produce successful results in pH 4.5 and 6.8 biowaiver media which might be due to small variability (low RSD) found between dosage units in two dissolution profiles.

BCS class II drugs are divided into subclasses according to their pKa value; (a) acidic, (b) basic and (c) neutral (Tsume *et al.,* 2014). Findings of this study might be considered in suggesting the biowaiver criteria to BCS class II subclass (a) drug substances, like ibuprofen, which can be better tested in a medium of a biologically related pH value closer to their pKa value. Mediums closed to pKa values can better highlight the differences between two distinct formulations. It was also reported by Alvarez *et al*. and Alhatem *et al.* who have conducted the biowaiver studies on ibuprofen 600 mg and 400 mg tablets respectively (Alvarez *et al*., 2011; Alhatem *et al*., 2018). We can also suggest the testing of BCS class II a drug at 3 pH levels i.e, pH = pKa, pH=pKa + 0.5, pH=pKa-0.5, instead of testing at pH 1.2, 4.5 and 6.8 for IR tablets having non-functional coating. Results presented in this manuscript may provide some evidences for the consideration of non-functional coated tablets as candidates for biowaivers. Because on the basis of results obtained from our work the suggested testing mediums will be more biorelevant and biopredictive. Biowaiver studies are significant for scale up and post approval changes, batch to batch drug release uniformity, stability studies, monitoring of systemic absorption and for prediction of *in-vivo* behavior. Dissolution tests is an important tool in predicting the bioavailability and formulation factors that affect the bioavailability of the drugs. Some excipients which are used commonly like lubricants, surfactants, coating materials, suspending agents etc. may disrupt the drug release either by changing the dissolution medium or by reacting with the drug itself and so they must be used with caution as they may modify the drug dissolution. For this reason, excipients should be pharmacodynamically inert (Shargel, 2005).

CONCLUSION

It is difficult to extend the existing criteria for the biowaiver of BCS class I and III, as suggested by FDA, ICH and WHO to BCS class II drugs. Therefore, testing in medium having pH equal to pKa value, in medium having pH = pKa +0.5 and pH = pKa -0.5 is suggested for BCS class IIa drugs. More work is required to assess the effect of ionic strength of dissolution media. We further suggest conducting *in vivo* bioequivalence testing to get the concrete scientific evidence, which is beyond the scope of current research work.

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REFERNCES

Alvarez C, Nunez I, Torrado JJ, Gordon J, Potthast H and García Arieta A (2011). Investigation on the possibility of biowaivers for Ibuprofen. *J. Pharm. Sci.,* **100**(6): 2343-2349.

Alhatem M, Zaheer K, Potthast H and Langguth P (2018). Intact versus shredded tablets Biopharmaceutical evaluation of metformin and ibuprofen containing finished medicinal products. *Krankenhauspharmazie.*, **39**(8): 343-350.

Anderson NH, Bauer M, Boussac N, Khan-Maleck R, Munden P and Sardaro M (1998). An evaluation of fit factors and dissolution efficiency for the comparison of in-vitro dissolution profiles. *J. Pharm. Biomed. Anal.,* **17**(4-5): 811-822.

Cascone S (2017). Modeling and comparison of release profiles: Effect of the dissolution method. *Eur. J. Pharm. Sci*., **106**: 352-361.

Charoenchaitrakool M, Dehghani F and Foster NR (2002). Utilization of supercritical carbon dioxide for complex formation of ibuprofen and methyl-beta-cyclodextrin. *Int. J. Pharm*., **239**(1-2): 103-112.

Costa FO, Sousa JJS, Pais AACC and Formosinho SJ (2003). Comparison of dissolution profiles of Ibuprofen pellets. *J. Control. Release,* **89**(2): 199-212.

European Medicine Agency (2010). Committee for medicinal products for human use. Guidelines on the investigation of bioequivalence. http://www.ema. europa.eu/docs/en_GB/ document_library/Scientific_ guideline/ 2010/01/WC500070039/

Food and Drug Administration (2017). Guidance for industry. Waiver of *in vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. https://www.fda.gov/downloads/ Drugs/Guidances/ucm070246.

Ghosh LK, Gosh NC, Chatterjee M and Gupta BK (1998). Product development studies on the tablet formulation of ibuprofen to improve bioavailability. *Drug. Dev. Ind. Pharm*., **24**(5): 473-477.

Hofsass MA and Dressman JB (2019). The discriminatory power of the BCS-Based Biowaiver: A retrospective with focus on essential medicines. *J. Pharm. Sci.,* pp.1-14.

ICH M9: Biopharmaceutics Classification System-Based Biowaivers (2018).

Imai T, Kimura S, Iijima T, Miyoshi T, Uneo M and Otagiri M (1990). Rapidly absorbed solid oral formulations of ibuprofen using water-soluble gelatin. *J. Pharm. Pharmacol*., **42**(9): 615-619.

Irvine J, Afrose A and Islam N (2017). Formulation and delivery startegies of ibuprofen: Challenges and opportunities. *Drug. Dev. Ind. Pharm.,* **44**(2): 173-183.

Mendyk A, Paclawski A, Szlek J and Jachowicz R (2013). PhEq_bootstrap: Open-Source software for the simulation of f2 distribution in cases of large variability in dissolution profiles. *Dissolut. Technol*., **201**: 13-17.

Potthast H, Dressman JB, Junginger HE, Midha KK, Oeser H, Shah VP, Vogelpoel H and Barends DM (2005). Biowaiver monographs for immediate release solid oral dosage forms: Ibuprofen. *J. Pharm. Sci.,* **94**(10): 2121-2131.

Quadir A and Kolter K (2006). A comparative study of current superdisintegrants. *Pharm. Technol*., **10**: 1-4.

Rinaki E, Dokoumetzidis A, Valsami G and Macheras P (2004). Identification of biowaivers among Class II drugs: Theoretical justification and practical examples. *Pharm. Res.,* **21**(9): 1567-1572.

Rojas J, Guisao S and Ruge V (2012). Functional assessment of four types of disintegrants and their effect on the spironolactone release properties. *AAPS Pharm. Sci. Tech*., **13**(4): 1054-1062.

Rojas J (2011). Assessment of co-processing of cellulose II and silicon dioxide as a platform to enhance excipient functionality. PhD thesis. The University of Iowa, Iowa City.

Shah VP, Tsong Y, Sathe P and Liu JP (1998). *In vitro* dissolution profile comparison statistics and analysis of the similarity factor, f_2. *Pharm. Res.,* **15**(6): 889-986.

Shohin IE, Kulinich JI, Vasilenko GF and Ramenskaya GV (2011). Interchangeability evaluation of multisource Ibuprofen drug products using biowaiver procedure. *Indian J. Pharm. Sci*., **73**(4): 443-446.

Shargel L, WuPong S and Yu ABC (2005). Applied Biopharmaceutics and Pharmacokinetics, fifth ed. McGraw-Hill Co.Ins.

Tsume Y, Mudie DM, Langguth P, Amidon GE and Amidon GL (2014). The Biopharmaceutics classify-cation system: Subclasses for *in vivo* predictive dissolution (IPD) methodology and IVIVC. *Eur. J. Pharm. Sci.,* **57**(16): 152-163.

United States Pharmacopoeia (2015). USP38/NF33. The United States Pharmacopoeial convention.

Vidal NLG and Alegre MEG (2013). UV analytical method suitability for investigation of BCS class 2 biowaivers: Ibuprofen case. *Dissolut. Technol*., **20**(1): 44-48.

World Health Organization (2006). Proposal to waive *in-vivo* bioequivalence requirements for WHO Model list of essential medicines immediate-release, solid oral dosage forms. http://www.who.int/medicines /areas/ quality_safety/quality_assurance/Annex7-TRS992/.

WÖhrl S (2018). NSAID hypersensitivity recommen-dations for diagnostic work up and patient management. *Allergo. J. Int.,* **27**(4): 114-121.

Yazdanian M, Briggs K, Jankovsky C and Hawi A (2004). The“ high solubility” definition of the current FDA Guidance on Biopharmaceutical Classification System may be too strict for acidic drugs. *Pharm. Res.,* **21**(2): 293-299.