Biowaiver studies of newly optimized meloxicam tablets

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Abstract: In this research work biowaiver studies of newly developed and optimized Meloxicam 7.5mg and 15mg water dispersible formulations were carried out at different dissolution media i.e. 0.1N HCl, phosphate buffer pH 4.5, pH 6.8, and pH 7.5 at 50 rpm. For this purpose reference (MA_9 and MB_9) and tests (MA_2, MA_4, MA_6, MA_7 and MA_8 (15 mg) and MB_2, MB_4, MB_6, $MB_7$and MB_8 (7.5 mg) formulations were compared. *In vitro* patterns were analyzed by using model-independent and model-dependent methods. Results indicated that all formulation at pH 0.1N HCl and phosphate buffer pH 4.5 followed Weibull model, while at pH 6.8 and pH 7.5 all formulations followed Hixson-Crowell model. Similarly results of model independent methods demonstrated that all the reference formulations were found to be similar with the tests formulations. Results indicated that Biowaiver could be granted to all the optimized water dispersible meloxicam formulations of both batches, so waiver for bioequivalence study can be allowed.

Keywords: Biowaiver, optimized, dispersible, model dependent and model-independent and Weibull method.

INTRODUCTION

Oral solid dosage form which include tablets and capsules have many advantages over other dosage form like easy manufacturing process, high stability and economical to patients (Qureshi *et al*, 2016). Different researchers stated that upto 90% of orally administered drugs exhibits systematic effect. If the drug releases from a tablet very rapidly then the drug concentration may altered. In order to avoid such problems the manufacturing methods and its formulation design should be considered and also several physico-chemical features of the additives should be assessed before developing tablet formulations (Sohi *et al*., 2004).

A large number of patients especially geriatrics and pediatrics face swallowing problem called dysphagia. Now different scientists and pharmaceutical manufacturers develop a new drug delivery system which gives maximum therapeutic effect with reduced side effects (Zafar *et al*, 2017) (Qureshi *et al*, 2017).

For generic products bioequivalence studies are very essential for product approval. In these circumstances, *invitro* studies can be significantly utilized as a surrogate for bioequivalence assessment and can be considered as "biowaiver". These biowaivers assessments can be used for further IVIVC (*in vitro-in vivo*) studies (FDA, 2000).

When drug compound present excellent understanding about their several physicochemical characteristics and parameters affecting bioavailability then these compounds are exempted from further *in vivo* studies and are regarded as "Biowaiver". Drug compound should exhibits good attributes i.e. solubility and permeability (Usman *et al*., 2014).

Biowaiver studies were evaluated by several mathematical dissolution models. Scientists reported that if the similarity was established between release profiles of reference and test products, then bioequivalence evaluation could be waived off (Zafar *et al*, 2015) (Bushra *et al*, 2016).

Meloxicam exhibits preferably a cox-II inhibition when administered in accurate dosage form. Pharmacokinetic studies of meloxicam reveal its 89% of bioavailability and excretion by both urine and feces. It is recommended in different medical conditions like osteoarthritis, rheumatoid arthritis, spondylitis and gouty arthritis (Khan *et al*, 2017). Side effects include dyspepsia, vomiting, nausea and abdominal pain (Hawkey *et al* 1998).

In this work we carried out the biowaiver studies of Meloxicam 7.5mg and 15mg water dispersible formulations at different dissolution media. Analysis was conducted by model-independent and model-dependent methods.

MATERIALS AND METHODS

Meloxicam was gifted from Hilton Pharma (Pvt.) Ltd, hydrochloric acid, sodium hydroxide and potassium dihydrogen phosphate (Merck, Damstabt, Germany).

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Formulation design

Two batches i.e. Meloxicam 7.5mg and 15mg (MA_1-MA_9; MB_1- MB_9) were manufactured using central composite design (CCRD) (Design Expert software, version 7.0.0). Two variables (independent) (Croscarmellose; X_1) (4-10%), (Microcrystalline cellulose; X_2) (50-65%) with five levels i.e. 1, -1, 0, β, -β. Selected responses were Hardness (Y_1) and Disintegration time (Y_2) (Ali *et al*., 2018).

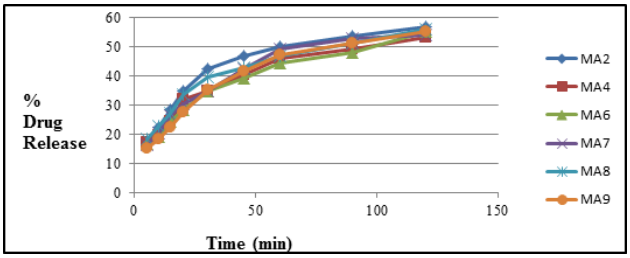

Fig. 1: Release profiles of meloxicam (15 mg) formulations AT 0.1N HCl

Biowaiver studies of meloxicam dispersible formulations

For biowaiver studies tests and reference products were compared at 50 rpm using 0.1N HCl, phosphate buffer pH 4.5, pH 6.8 and pH 7.5 dissolution media at 37±0.5°C. For both batches selected reference products were MA_9 (15mg) and MB_9 (7.5mg) and tests products were MA_2, MA_4, MA_6, MA_7 and MA_8 (15mg) and MB_2, MB_4, MB_6 $MB_7$and MB_8 (7.5mg). Ten mL sample were drawn at each time point and substituting with 10mL fresh medium. The % drug release was estimated at 359 nm.

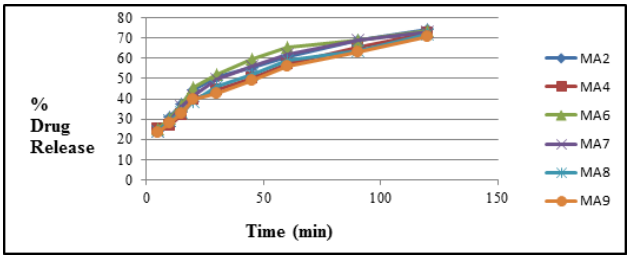

Fig. 2: Release profiles of meloxicam (15 mg) formulations at pH 4.5

Evaluation of biowaiver studies

Model - dependent and independent methods

For biowaiver assessment, results were estimated using model dependent and independent methods. Models were evaluated by using software (DD-Solver) an add in program for Microsoft Excel ™ 2007 (Microsoft Corporation, USA) while f_1 and f_2 were analyzed by Microsoft Excel™ 2007 (Microsoft Corporation, USA).

RESULTS

In this study equations of model dependent and independent methods were mentioned in table 1. Table 2 presented evaluation of release pattern using difference factor (f_1) and similarity factor (f_2). Table 3 and 4 demonstrated the assessment of release kinetics by kinetic models.

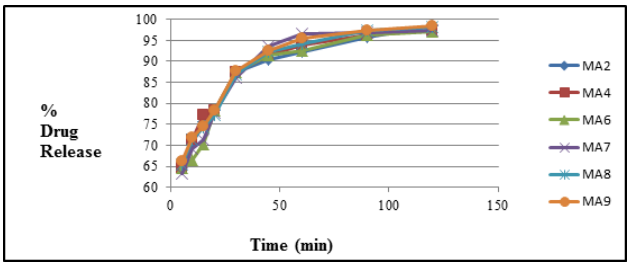

Fig. 3: Release profiles of meloxicam (15 mg) formulations at pH 6.8

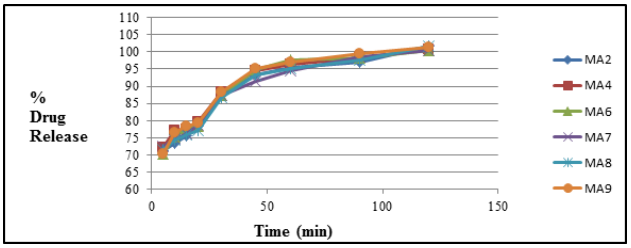

Fig. 4: Release profiles of meloxicam (15 mg) formulations at pH 7.5

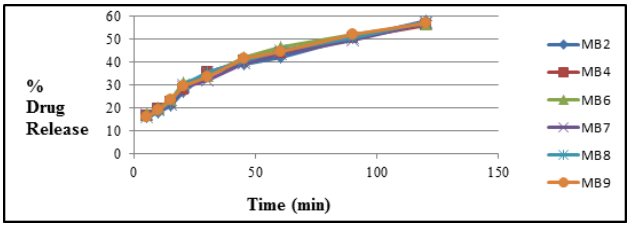

Fig. 5: Release profiles of meloxicam (7.5 mg) formulations at 0.1N HCl

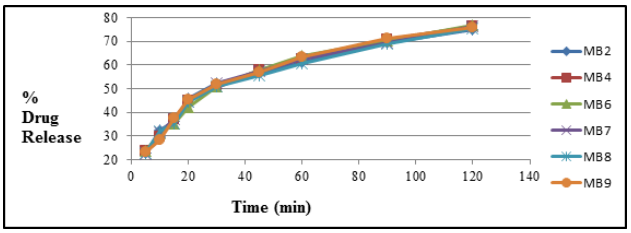

Fig. 6: Release profiles of meloxicam (7.5 mg) formulations at pH 4.5

DISCUSSION

Many researchers utilized different statistical techniques for optimization during the product development like full factorial design, Taguchi's orthogonal design and the one which is frequently used Central composite rotatable design (CCRD) (Guo *et al*, 2013). In this study dispersible meloxicam tablets were developed by CCRD. Nine different formulations of 15mg tablets (MA_1-MA_9) and other nine different formulations of 7.5mg tablets (MB_1-MB_9) were produced. Two different responses were Hardness (Y_1) and Disintegration time (Y_2) was selected.

Table 1: Model Independent and Model Dependent equations used to assess the kinetics of meloxicam formulations (Costa and Lobo, 2001) (Zafar *et al*., 2014).

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	$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{N}\right)\sum(Ri - Ti)^2\right]^{-0.5}\right\} \times 100$
Model Dependent	*First order kinetics*	Log Q= Log Q0-kt2.303
	Weibull model	M=1-exp-(t-Ti)βa
	Higuchi model	$Q = kt^{\frac{1}{2}}$
	Hixson–Crowell model	Q01/3-Qt1/3=KHCxt

Table 2: Difference factor (f_1) and similarity factor (f_2) test for test formulations with reference (15 mg and 7.5 mg) formulations

Comparison	AT pH 1.2		AT pH 4.5		AT pH 6.8		AT pH 7.5		Dissolution profile
	f_1	f_2	f_1	f_2	f_1	f_2	f_1	f_2	
MA_9 and MA_2	12.45	65.39	10.24	64.44	1.18	87.03	1.65	80.69	Similar
MA_9 and MA_4	0.84	81.64	1.72	88.42	0.65	88.41	0.14	92.60	
MA_9 and MA_6	1.01	83.58	12.82	58.91	2.86	71.11	0.70	94.92	
MA_9 and MA_7	4.06	82.83	8.63	66.64	1.38	82.89	1.05	83.55	
MA_9 and MA_8	7.70	72.17	2.89	83.19	0.69	95.72	1.06	87.81	
MB_9 and MB_2	3.16	85.02	0.28	85.22	0.05	92.70	0.77	85.38	
MB_9 and MB_4	1.09	91.77	0.09	94.73	0.64	96.12	1.09	88.54	
MB_9 and MB_6	2.03	91.08	0.16	84.71	0.63	93.84	0.61	88.98	
MB_9 and MB_7	2.59	88.27	0.03	88.49	0.94	94.02	0.36	88.11	
MB_9 and MB_8	0.07	92.54	1.57	82.46	0.10	96.09	1.38	84.54	

Table 3: Release kinetics of meloxicam formulations (15 mg)

AT 0.1N HCL									
Formulations	First Order		Higuchi		Hixon 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	β	α
MA_2	0.18	0.01	0.87	5.51	0.81	0.002	0.96	0.45	9.60
MA_4	0.23	0.01	0.92	5.06	0.87	0.002	0.97	0.45	11.34
MA_6	0.36	0.01	0.96	5.08	0.92	0.002	0.98	0.48	12.61
MA_7	0.39	0.01	0.92	5.36	0.87	0.002	0.97	0.48	12.09
MA_8	0.08	0.01	0.91	5.21	0.87	0.002	0.98	0.43	9.62
MA_9	0.57	0.01	0.95	5.40	0.90	0.002	0.98	0.53	14.96
AT pH 4.5									
MA_2	0.44	0.01	0.93	6.84	0.91	0.003	0.99	0.49	7.95
MA_4	0.53	0.01	0.97	6.58	0.96	0.002	0.98	0.51	9.80
MA_6	0.50	0.02	0.89	7.01	0.88	0.003	0.98	0.50	8.01
MA_7	0.55	0.01	0.94	6.92	0.92	0.003	0.99	0.52	8.91
MA_8	0.47	0.01	0.96	6.56	0.94	0.002	0.99	0.50	9.15
MA_9	0.47	0.01	0.97	6.41	0.96	0.002	0.98	0.50	9.52
AT pH 6.8									
MA_2	0.19	0.12	0.80	6.97	0.96	0.006	0.96	0.38	1.91
MA_4	0.28	0.12	0.75	6.90	0.95	0.006	0.97	0.39	1.94
MA_6	0.36	0.10	0.73	7.36	0.93	0.007	0.90	0.42	2.30
MA_7	0.43	0.11	0.74	7.37	0.98	0.007	0.93	0.44	2.29
MA_8	0.26	0.12	0.79	7.13	0.98	0.006	0.94	0.40	1.99
MA_9	0.27	0.12	0.78	7.09	0.98	0.007	0.94	0.40	1.95
AT pH 7.5									
MA_2	0.02	0.14	0.85	7.03	0.97	0.006	0.88	0.37	1.69
MA_4	0.41	0.06	0.28	9.23	0.90	0.01	0.85	0.72	6.72
MA_6	0.08	0.15	0.79	6.94	0.95	0.006	0.87	0.37	1.66
MA_7	0.26	0.15	0.85	6.73	0.94	0.005	0.83	0.33	1.47
MA_8	0.12	0.15	0.85	6.89	0.95	0.005	0.84	0.35	1.55
MA_9	0.16	0.15	0.81	7.005	0.96	0.007	0.87	0.38	1.68

Table 4: Release kinetics of meloxicam formulations (7.5 mg)

Formulations	First Order		Higuchi		Hixon 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	β	α
AT 0.1N HCL									
MB_2	0.62	0.01	0.98	5.31	0.95	0.002	0.98	0.54	16.24
MB_4	0.49	0.01	0.96	5.25	0.93	0.002	0.98	0.50	13.74
MB_6	0.46	0.01	0.96	5.36	0.92	0.002	0.98	0.50	12.90
MB_7	0.53	0.01	0.98	5.21	0.95	0.002	0.98	0.52	14.64
MB_8	0.53	0.01	0.96	5.37	0.92	0.002	0.98	0.52	14.10
MB_9	0.55	0.01	0.97	5.38	0.94	0.002	0.99	0.52	14.36
AT pH 4.5									
MB_2	0.50	0.02	0.92	6.97	0.90	0.003	0.98	0.51	8.23
MB_4	0.59	0.02	0.94	7.14	0.92	0.003	0.99	0.53	8.96
MB_6	0.63	0.02	0.95	7.20	0.93	0.003	0.99	0.54	9.34
MB_7	0.56	0.02	0.92	7.09	0.91	0.003	0.99	0.52	8.65
MB_8	0.51	0.02	0.93	6.93	0.92	0.003	0.99	0.51	8.50
MB_9	0.61	0.02	0.92	7.18	0.91	0.003	0.98	0.54	9.10
AT pH 6.8									
MB_2	0.43	0.11	0.76	7.33	0.95	0.007	0.94	0.43	2.23
MB_4	0.44	0.11	0.74	7.31	0.96	0.007	0.95	0.43	2.29
MB_6	0.44	0.11	0.74	7.37	0.98	0.008	0.94	0.44	2.25
MB_7	0.42	0.10	0.78	7.39	0.97	0.007	0.96	0.43	2.29
MB_8	0.43	0.11	0.79	7.49	0.99	0.007	0.94	0.44	2.28
MB_9	0.44	0.11	0.77	7.38	0.97	0.007	0.95	0.44	2.26
AT pH 7.5									
MB_2	0.51	0.11	0.78	7.68	0.98	0.008	0.93	0.46	2.44
MB_4	0.49	0.11	0.78	7.44	0.98	0.007	0.96	0.45	2.32
MB_6	0.58	0.11	0.79	7.82	0.99	0.008	0.94	0.48	2.57
MB_7	0.57	0.11	0.80	7.84	0.99	0.008	0.94	0.48	2.56
MB_8	0.58	0.10	0.77	7.74	0.98	0.008	0.95	0.48	2.61
MB_9	0.63	0.11	0.78	7.71	0.98	0.009	0.97	0.49	2.55

In-vitro studies are used during the product development process. These studies evaluate several parameters during product development i.e. it helps in modifying the composition of formulations (Zafar *et al*, 2017) (Bushra *et al*, 2016). FDA suggested the use of release profile comparison to estimate the *in vitro* release pattern of tests and reference products at specified time period. Furthermore it is considered as a significant tool in several regulatory guidelines and also helpful in the development of IVIVC studies. Thus *in vivo* drug availability can be easily predicted from its *in vitro* release pattern through the successful development of an IVIVC (FDA, 1997 a, b).

Biowaiver studies are significantly utilized for alterations in manufacturing site, equipments modification and adaptation in manufacturing procedures to develop IVIVC correlation. Furthermore researchers reported that biowaiver studies resulted in cost reduction which has been approximately reduced to be $22-$38 million/year (Polli, 2010).

The FDA explained IVIVC as a mathematical model estimating the relationship between appropriate *in vivo* response and *in vitro* features of an extended release dosage form (Cardot and Beyssac, 1993).

Model dependent method

Various models were utilized by different scientists to assess release profiles of test and reference formulations. (Zafar *et al*, 2014). In this study biowaiver assessments of both batches were carried out by using reference (MA_9 and MB_9) and tests (MA_2, MA_4, MA_6, MA_7 and MA_8 (15 mg) and MB_2, MB_4, MB_6 $MB_7$and MB_8 (7.5mg) formulations by First-order kinetic model, Higuchi Kinetics model**,** Hixson-Crowell cube root law and Weibull kinetic model at various pH i.e. 0.1N HCl, phosphate buffer pH 4.5, pH 6.8 and pH 7.5. For Higuchi Kinetics and First - order kinetic model, r^2 values for 15 mg and 7.5 mg formulations at 0.1N HCl, phosphate buffer pH 4.5, pH 6.8 and pH 7.5 were found to be in the ranged of (0.87- 0.96 and 0.96-0.98; 0.08-0.57 and 0.46-0.62), (0.89-0.97 and 0.92-0.95; 0.44-0.55 and 0.50-0.63), (0.73-0.80 and 0.74-0.79; 0.19-0.43 and 0.42-0.44)

and (0.28-0.85 and 0.77-0.80; 0.02 -0.41 and 0.49-0.63) respectively.

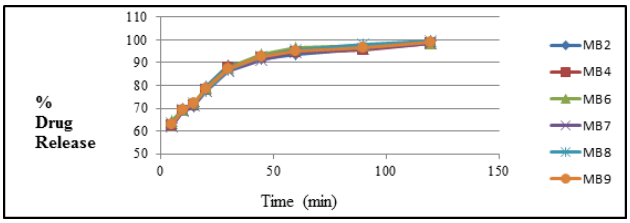

Fig. 7: release profiles of meloxicam (7.5 mg) formulations at pH 6.8

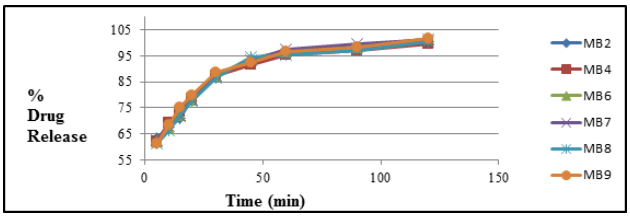

Fig. 8: release profiles of meloxicam (7.5 mg) formulations at pH 7.5

For Weibull kinetic model and Hixson-Crowell cube root law, r^2 values at 0.1N HCl, phosphate buffer pH 4.5, pH 6.8 and pH 7.5 were consecutively found to be in the ranged of (0.96-0.98 and 0.98-0.99; 0.81-0.92 and 0.92-0.95), (0.98-0.99 and 0.98 - 0.99; 0.88 - 0.96 and 0.90 - 0.93), (0.90-0.97 and 0.94-0.96; 0.93-0.98 and 0.95-0.99) and (0.85-0.88 and 0.93-0.97; 0.90-0.97 and 0.98-0.99). Ali *et al* in 2013 used several kinetic models to assess the release pattern of diclofenac potassium tablets. Similarly Zafar *et al*., in 2013 estimated the release behavior of flurbiprofen brands using different kinetic models. In this study results demonstrated that all formulation at pH 0.1N HCl and phosphate buffer pH 4.5 followed Weibull model, while at pH 6.8 and pH 7.5 all formulations followed Hixson-Crowell model .

Model independent methods

Many researchers used pair wise (f_1 and f_2) technique to compare the *in vitro* data of tests and reference formulations. In this study, reference and tests formulations were compared using similarity factor (f_2) and difference factor (f_1). Values of f_1 (difference factor) and f_2 (similarity factor) for tests and reference formulations of 15 mg and 7.5 mg at 0.1N HCl, phosphate buffer pH 4.5, pH 6.8 and pH 7.5 were consecutively found to be in the ranged of (0.8448-12.453 and 65.393-83.586; 0.078-3.166 and 85.029-92.547), (1.728-12.821 and 58.913-88.425; 0.0353-1.578 and 82.465-94.738), (0.654-2.867 and 71.113-95.726; 0.059-0.946 and 92.705-96.126) and (0.147-1.652 and 80.698- 94.922; 0.364-1.380 and 84.546 -88.989) respectively. Results indicated that Biowaiver could be granted to all the optimized water dispersible meloxicam formulations of both batches, so waiver for bioequivalence study can be allowed.

CONCLUSION

In this study, we carried out biowaiver studies on optimized formulations of water dispersible meloxicam formulations at different dissolution media. Results indicated that waiver for *in vivo* bioequivalence assessment can be granted to all newly optimized meloxicam products.

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