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Biowaiver Study on Prednisolone Tablets 5 mg in Three Different Brands Marketed in Sudan

Safaa Mohamed*, Tilal Elsaman

Department of Pharmaceutical Chemistry, College of Pharmacy, Omdurman Islamic University, Khartoum, Sudan

***Corresponding author:** Department of Pharmaceutical Chemistry, College of Pharmacy, Omdurman Islamic University, P.O. Box 2587, Khartoum, Sudan, E-mail safaaawad89@gmail.com*

ABSTRACT

Prednisolone is widely used synthetic corticosteroids in inflammatory conditions. In the present study, the bioequivalence was studied in three different brands of prednisolone 5 mg tablets [Histacortine (Brand A, Innovtor), Crotrope Brand (B) and Cimapresone Brand (C) marketed in local Sudanese market using biowaiver. Firstly, the pharmaceutical equivalence was evaluated for the three brands, and then the biowaiver study was done using three different buffer solutions: pH 1.2, 4.5 and 6.8. The three brands complied with requirements of pharmaceutical equivalence. Brand (B) was bioequivalent to the innovator (release ≥85% in 15 min), for brand (C) less than 85% was released in 15 min so the similarity factor (f2) was calculated to evaluate the bioequivalence and it was less than 50, which mean brand (C) was failed to qualify biowaiver, therefore in vivo bioequivalence studies are required to ascertain bioequivalence.

Keywords: *Biowaiver, prednisolone, dissolution, bioequivalence*

INTRODUCTION

Biowaiver can be a good tool and thus bring benefit to society by expanding the supply of medicines effective with guaranteed security. Biowaiver can be defined as the acceptance for regulatory purpose for replacement of in vivo bioequivalence studies and bioavailability studies by in vitro assays when they are able to replace the in vivo assay reliably [1]. In 2000, the FDA issued a guidance describing the waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release (IR) solid oral dosage forms based on BCS. This guidance allows applicant to request biowaiver for highly soluble and highly permeable drug substances (class 1) in immediate-release solid oral dosage forms provided the following conditions are [2]:

1. The drug must be stable in gastrointestinal tract.

2. Excipients used in the IR solid oral dosage forms have no significant effect on the rate and extent of oral drug absorption

3. The product is designed not to be absorbed in oral cavity.

4. The drug dissolves rapidly *in vitro*.

Prednisolone is synthetic glucocorticoid, a derivative of cortisol which is used to treat a variety of inflammatory and auto-immune conditions such as asthma, multiple sclerosis, rheumatoid arthritis, and autoimmune hepatitis [3,4]. For prednisolone tablets data on its solubility, oral absorption and permeability were not totally conclusive, they strongly suggested the drug substance to be class 1, hence it was concluded that biowaiver was acceptable [5], so instead of high cost and time consuming *in vivo* study the biowaiver can be used to assess bioequivalence of different prednisolone formulations. Accordingly, the present work is an attempt to evaluate bioequivalence of three different brands of prednisolone 5mg tablets marketed in Sudan by biowaiver.

MATERIALS AND METHODS

Analysis of Prednisolone tablets was carried out on HPLC machine (SHMADZU- Japan), Dissolution tester (Pharma Test- Germany), UV spectrophotometer (SHMADZU- Japan), pH meter (Sartorius- Germany), Copley tester (Tbf 1000- United Kingdom), and Disintegration tester (Electro lab- India). Working standard of Prednisolone (Potency 99.1%, from Shanghai-Sudan Pharmaceutical Co. Ltd). All other reagents are of analytical grade. Hydrochloric acid, Potassium Chloride, Sodium acetate, glacial acetic acid, monobasic potassium phosphate and sodium hydroxide. Prednisolone tablet brands were randomly collected from the local private pharmacies. **Table 1** show brands of Prednisolone tablets, their manufacturing and expiry date.

Table-1: Prednisolone 5 mg Brands

Items	Generic name	Batch NO	Mfg. Date	Exp Date
Brand(A) (Innovator)	Histacortine	5EG012	6.2015	5.2018
Brand (B)	Corotrope	64310	5.2015	5.2018
Brand (C)	Cimapresone	1505400	5.2015	5.2017

Physicochemical parameters

The physicochemical parameters were done using US Pharmacopeia 2016 method, while the active content of generic and innovator brands was assessed using British Pharmacopeia 2016 method [6, 7]. The results were shown in **Table 2**.

Dissolution study

The dissolution profiles of Prednisolone tablets were assessed in 500mL of buffer pH 1.2, 4.5 and 6.8 using US Pharmacopeia dissolution apparatus II at 75 rpm and temperature was 37±0.5 ºC. The media used in the dissolution study were of pH 1.2 (hydrochloric acid solution), buffer pH 4.5 (acetate buffer solution) and buffer pH 6.8 (phosphate buffer solution), which were prepared using US Pharmacopeia methods [8]. In all experiments, 5 mL sample aliquots were withdrawn at 5, 10, 15, 30, 45 min

using syringe. All samples were filtered through 0.45-µm membrane filters. Drug release was determined spectrophotometrically by using calibration curve. Twelve tablets of each brand were studied to obtain statistically significant result [9].

Data analysis

Dissolution profiles were evaluated by using similarity factor which is adopted by the FDA in its guidance by using the formula [10].

$$f_2 = 50 \log \{[1+ (1/P) \sum_{i=1}^{P} (R_t\text{-}T_t)^2]^{-1/2} * 100\} \qquad \textbf{Equation 1}$$

Where Rt and Tt are, percent dissolved at each time point for reference and test, respectively. Values of 50 or above (50-100) ensure similarity of the curve.

Difference factor (*f1*): Difference factor was mathematically calculated using formula 2.

$$f_1 = \{[\sum_{i=1}^{P} |R_t\text{-}T_t|] / [\sum_{i=1}^{P} R_t]\} \qquad \textbf{Equation 2}$$

Difference factor of 0-15 ensures minor difference between two products. *f1* is proportional to profiles, whereas *f2* is inversely proportional to the average squared difference between the two profiles and it measures closeness between two profiles [29].

RESULTS

Table (2): Physicochemical properties of the three brands of prednisolone 5 mg tablets:

Items	Average Diameter (mm) ± SD	Average Thickness (mm) ± SD	Average Hardness ($Kg/cm^{2)}$ ± SD	Average Disintegration (min) ± SD	Average Dissolution (%)
Brand(A)	7.11 ± 0.02	1.93 ± 0.02	5.75 ± 0.54	0.04 ± 0.03	96.69%
Brand(B)	6.57 ± 0.01	2.64 ± 0.01	5.97 ± 0.44	0.93 ± 0.31	104.01%
Brand(C)	6.11 ± 0.02	2.77 ± 0.04	6.45 ± 0.99	0.14 ± 0.12	92.18%

Table-2: Dissolution test results of the three brands

pH	Time	Brand (A)	Brand (B)	Brand (C)
1.2	5	96.4	87.2	41.62
	10	100.89	96.99	60.46
	15	101.56	98.89	74.83
	30	103.62	100.96	90.93
	45	102.8	101.7	96.91
	f1			**23.86**
	f2			**27.81**
4.5	5	78.98	81.55	46.48
	10	88.07	90.74	64.33
	15	91.81	92.58	73.87
	30	94.62	93.39	86.28
	45	94.71	94.06	91.70
	f1			**34.82**
	f2			**19.08**
6.8	5	89.44	82.44	48.43
	10	93.87	87.39	68.28
	15	95.92	89.44	78.75
	30	98.28	93.74	91.26
	45	98.11	94.23	95.73
	f1			**31.72**
	f2			**19.59**

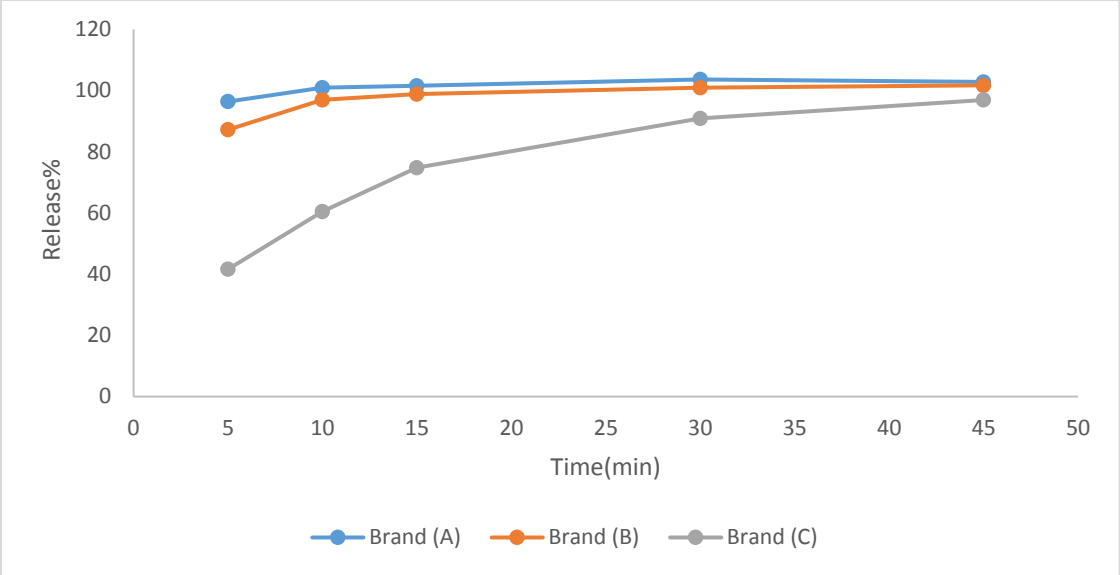

Figure-1: Dissolution profile of the three brands at HCL buffer solution pH 1.2

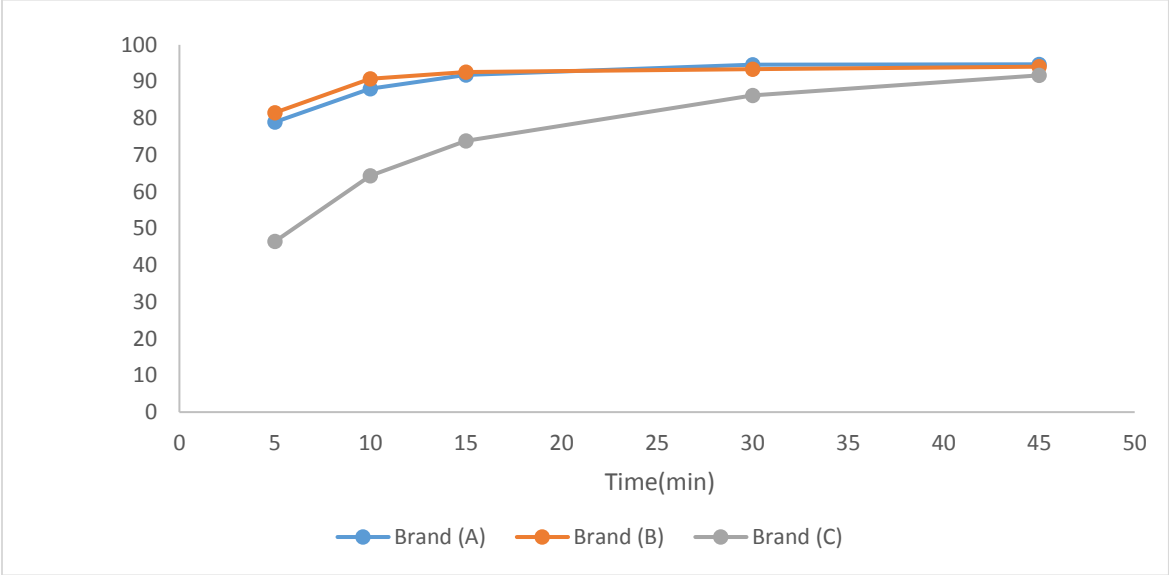

Figure-2: Dissolution profile of the three brands at Acetate buffer solution pH4.5

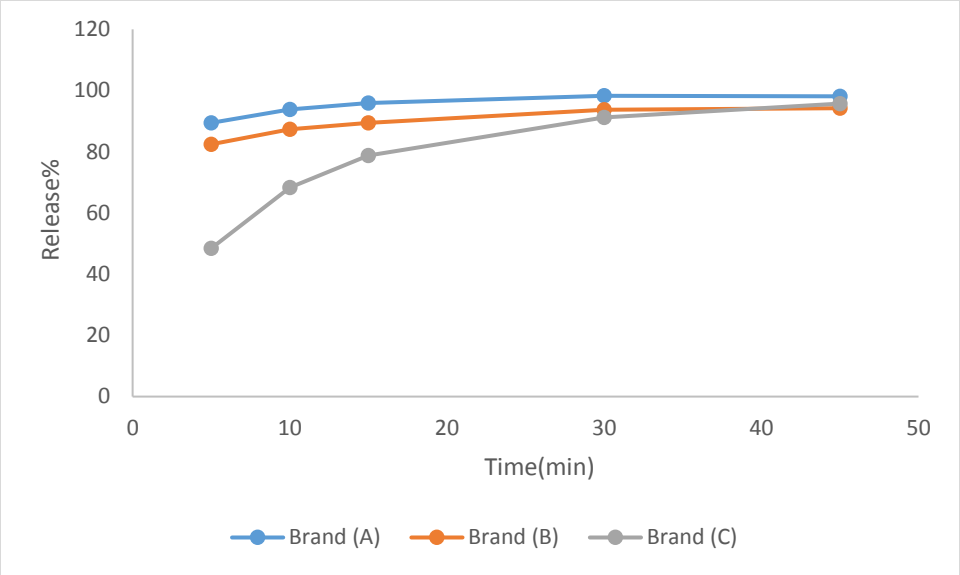

Figure-3: Dissolution profile of the three brands at Phosphate buffer solution pH 6.8

DISCUSSION

Prednisolone is corticosteroid drug; it works by modifying the body immune response to various condition and decrease inflammation. In Sudan, this drug is used widely to treat many diseases and there are many brands of it available in market. In this study three brands of prednisolone 5 mg tablets were studied to collect information on safety, efficacy, and possible interchangeability of different generic. Prednisolone tablets brands were studied by using simple and cost effective in vitro dissolution method (biowaiver).

To the best of our knowledge no biowaiver studies were done on prednisolone tablets in Sudan. In the present study, the samples of two generic brands and innovator of prednisolone 5mg tablets were collected randomly from the market, one of the generic brand is imported (brand B) and the other is locally manufactured (brand C), the three brands within their expiry dates and their physicochemical properties and content percent were studied. **Table 2** shows that all the brands studied fulfill the compendia specification for diameter, thickness, hardness, disintegration, and dissolution. Moreover, the three brands passed the assay test these means that the three brands of drug are pharmaceutical equivalents. Accordingly, dissolution test was carried out for the three brands products to establish bioequivalence among them. The test was carried out in three different buffer media (pH 1.2, 4.5 and 6.8) to cover the whole GIT environment, and then the percentage release in each point was calculated. Brand (B) exhibits very rapid dissolution (85% or more of API is released in 15 min) in the three tested buffer media, since prednisolone is class 1, according to WHO brand (B) is bioequivalent to innovator. Brand (C) exhibits rapid dissolution (85% or more of API is released in 30 min) in the three pH different buffer media, then according to WHO similarity factor (*f2*) (equation 1) was calculated to prove similarity; results are shown in **Table 3.**

They were found to be less than 50 in the three pH different buffer media which is less than WHO limit these means that brand (C) did not pass the biowaiver criteria and further *in vivo* bioequivalence studies should be done to ascertain bioequivalence. Also, the value of difference factor *f1*(equation 2) was found to be more than 15 in the three-buffer media indicating the difference between brand (C) and innovator brand (A).

CONCLUSION

It can reasonably be concluded that, branud (B) of prednisolone 5mg tablets are bioequivalent to the innovator [brand (A)]. While brand (C) of prednisolone 5mg tablets failed to meet the requirement of biowaiver according to WHO criteria for biowaiver.

REFERENCES

1. Barbosa, L., Biopharmaceutic classification system: importance an inclusion in biowaiver guidance. Braz J Pharm, **2015.** 51(1): p. 2175-9790.
2. Midha, K., FDA Bioequivalence Standards. Publisher Bing Li, Lawrence X, **2005.** p. 4-9.
3. Morshed, N., and. Sharmin, S., Comparative evaluation of prednisolone 5mg tablets marketed in Bangladesh. WJPR, **2015.** 4(5): p. 277-289.
4. Davis, M., et al., Prednisolone or prednisone for treatment of chronic active hepatitis A comparison of plasma availability, Br J Pharmac, **1978.** 5: 501-505.
5. International Pharmaceutical Federation (FIP). Biowaiver monograph, **2004.** p. 20.
6. USP 37 -NF32 pharmacopeia. **2016.** p. 4401.
7. British Pharmacopeia (BP). **2016.** P.1014.
8. USP 35-NF 30 Pharmacopeia. **2012.** P. 5773.
9. Rohila, S., Biowaivers: Criteria and Requirements. IJPBA **2012.** 3(4): 727-731.
10. http://www.fda.gov/OHRMS/DOCKETS/98fr/3657gd.pdf.