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Biowaiver studies of seven generic brands of allopurinol (100 mg) tablets available in Sudanese market

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Original Research Article

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Abstract: Allopurinol is the drug of choice in the treatment of gout It reduces the concentration of urates and uric acid in tissues, plasma and urine, while increasing the concentration of xanthine and hypoxanthine. The purpose of this study was to examine the possibility of Biowaiver study for approval of generic brands of allopurinol tablets without additional in vivo bioequivalence and, to collect information on the safety and efficacy of the different allopurinol tablet brands using simple and cost effective in vitro methods. Physicochemical characteristics comprising drug content, hardness, friability, weight variation, disintegration and dissolution were evaluated for the six brands in comparison with the innovator. Dissolution test was carried under Biowaiver condition and the data analyzed by simple statistics and similarity and difference factors. The assay results showed that all the brands had active pharmaceutical ingredient within the specified official limits except Allo-4- , The crushing strength of three brands (Allo-1-, Allo-5- and Allo-7-) was out of the specified official limits, all the brands were complied with the specified limits For disintegration test, all the brands met the specified limits that stated by USP 32 for dissolution test , and according to f1 and f2 values, all the brands were similar to the innovator except Allo-4 and allo-6. From these results we can conclude that all the brands were met the specified limits for the physical tests, there is a failure of 9 % for content percent, and the brands were not accepted for Biowaiver under WHO criteria.
Keywords: Biowaiver, Allopurinol, Dissolution, Bioequivalence studies

INTRODUCTION

Allopurinol is known chemically as [1H-pyrazolo [3, 4-d] pyrimidin-4-ol], Molecular Formula: $C_5H_4N_4O$, Molecular weight: 136.1.

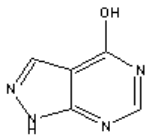


Fig-1: Chemical structure of Allopurinol

Allopurinol is on the WHO list of essential medicines [1]. Allopurinol 100 mg classified as BCS class 1 drug [2]. Being highly soluble and highly permeable across biological membrane, thus drug absorption depends on the ability of the drug to go into salvation /dissolution after oral administration and then be able to permeate biological membrane of the GIT .Thus the dissolution process is critical in prediction of in vivo events of drug[3].

Biowaiver

Is a term means that in vivo bioavailability and / or bioequivalence studies may be waived (i.e. not considered necessary for product approval). Instead of conducting expensive and time-consuming in vivo studies, a dissolution test could be adopted as the surrogate basis for the decision as to whether two pharmaceutical products are equivalent [4].

Biopharmaceutical Classification System (BCS)

It is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from Immediate Release solid oral dosage forms: (1) dissolution, (2) solubility, and (3) intestinal permeability [5].

MATERIALS AND METHOD

Materials

Allopurinol standard powder (Batch ALP-15090/06' Mfg. Date: 04/2015, Expiry Date: 03/2020, Potency: 99.9%, Loss on drying: 0.22%) was kindly gifted from Azal pharmaceutical industries, the seven brands were purchased from community pharmacies

{Table1} ,all solvents and reagents were of analytical grade and dissolution media was freshly prepared.

Method

Physical test were done according to USP method and content percent was done using reverse phase hplc method [6], the results were recorded in table [2].

In vitro dissolution study for Biowaiver

Dissolution testing is an important quality control and drug development procedure employed in the pharmaceutical industry to evaluate the in vitro drug release profiles of solid dosage forms .It is used to establish the pharmaceutical quality of a product, It will be evaluated by using similarity factor which is adopted by the FDA in its guidance [7] by using the following formula:

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

Where Rt and Tt are percent dissolved at each time point for reference and test respectively. And Difference factor (f1): It can be mathematically computed by using the following formula:

$$f_1 = \{[\sum_{i=1}^{P} |R_t-T_t|] / [\sum_{i=1}^{P} R_t]\}$$

DISSOLUTION METHOD

The media used in dissolution study were PH 1.2(0.1 N Hydrochloric acid solution), Buffer PH 4.5 (acetate buffer solution), and Buffer PH 6.8 (phosphate buffer solution) which were prepared using USP pharmacopeia method [8]. Six tablets of each of the seven generic brands were introduced on the six beakers of the paddle apparatus filled with 900 ml media at 37°c temp. The apparatus was adjusted to rotate 75 rpm for 45 mins, Samples of 5 ml volume was withdrawn at time intervals of 5, 10, 15, 30 and 45 mins, then filtered and analyzed utilizing UV spectrophotometer, at 242 nm. And the test was repeated for another 6 tablets[9] and the results was recorded in [table3].

Calibration curve preparation

A series of dilutions with concentrations of 2, 4, 6, 8, and 10 µg/ml of standard allopurinol was prepared in the three different dissolution media, using a spectrophotometer the absorbance of UV at 242 nm was measured and then plotted against the respective concentrations of the standard solutions.

Data Analysis

The uniformity of weight, disintegration, and content uniformity were analyzed with simple statistics; Percentage deviation, while differences in the in vitro dissolution profiles were evaluated using model-independent approach based on the similarity factor (f2) and difference factor (f1). For f2, values of 50 or above (50 – 100) ensure similarity of the curves and for f1, values of (0 - 15) ensures minor differences between two products [10].

Table−1: Generic brands

Brand code	Brand name	Company/country of origin	Batch №	Man. date	Exp. date
Allo-1	Zyloric	Aspan Bad OldesloeGmbH / Germany	B05415K	11 :2015	11 :2020
Allo-2	alopron	Remedica Ltd /Cyprus	61843	10 :2014	10 :2019
Allo-3	Aluric	Pharmaline S.A.L /Lebanon	A28.1	05 :2015	05 :2018
Allo-4	Azaloric	Azal Pharmaceutical industries CO. ltd /Sudan	5216	08 :2015	08 :2017
Allo-5	Cityluric	City Pharm pharmaceutical Industries/ Sudan	P12	10 :2015	10 :2017
Allo-6	No-uric	Egyptian int. pharmaceutical industries/Egypt	1409312	10 :2014	10 :2018
Allo-7	Zylonil	Blue Nile pharmaceutical factory /Sudan	ALGI	03 :2016	03 :2018

RESULTS

Table−2: Physicochemical characteristics of the seven brands of allopurinol tablets

Brand code	Average weight(gm±SD)	Disintegration time(min)	Hardness test(Kg/cm³)	Friability (%)	Assay (%)	% Dissolved In 45 mins
Allo-1	0.187±0.007	5±0.25	9.1±1.09	0.09	106.3	87.53
Allo-2	0.309±0.005	6±0.20	6.1±0.81	0.06	103.9	85.37
Allo-3	0.184±0.005	2±0.05	5.7±0.55	0.07	98.9	92.44
Allo-4	0.309±0.008	2±0.13	5.8±0.50	0.13	111.1	79.81
Allo-5	0.366±0.007	4±0.45	10.9±1.22	0.11	106.4	86.96
Allo-6	0.264±0.004	6±0.12	5.5±1.26	0.14	103.6	87.14
Allo-7	0.317±0.004	6±0.32	3.4±0.63	0.24	100.6	92.3

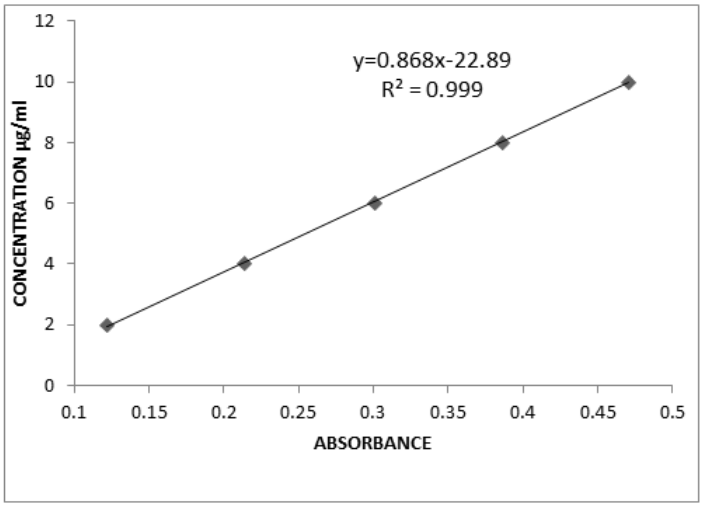


Fig-2: Calibration curve of pure allopurinol in1.2 at 242nm

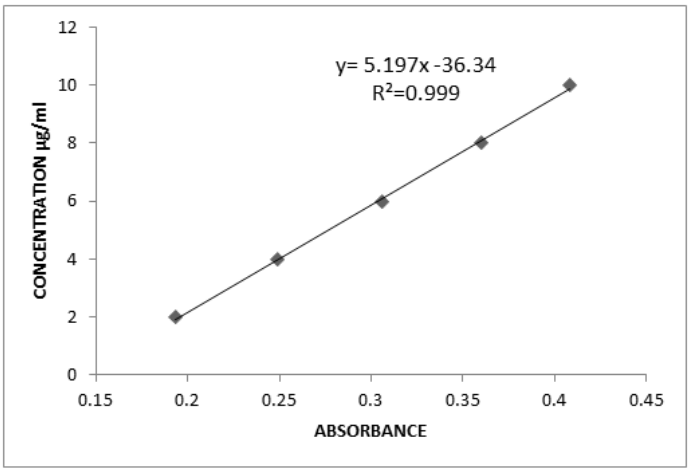


Fig-3: Calibration curve of pure allopurinol in 4.5 at 242 nm

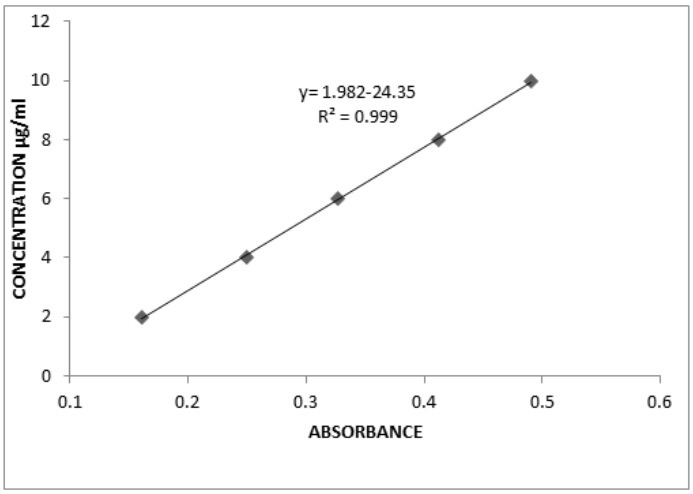


Fig 4: Calibration curve of pure allopurinol in 6.8 at 215 nm

Table-3: Dissolution test results for Biowaiver

	Drug code	Percent dissolved in:					F2	F1
		5 min	10 min	15 min	30 min	45min		
PH 1.2	Allo-1	65.37	76.59	78.88	82.79	89.67	innovator	innovator
	Allo-2	55.45	69.15	74.10	81.75	92.10	66	5
	Allo-3	5794	68.94	72.23	79.24	86.29	60	7
	Allo-4	29.93	36.05	47.48	56.66	69.00	27	34
	Allo-5	65.95	73.70	85.12	90.73	101.47	-	-
	Allo-6	49.21	56.94	64.32	72.55	83.55	43	15
	Allo-7	63.92	77.83	84.50	88.45	96.83	-	-
PH 4.5	allo-1	75.45	82.19	96.72	100.85	105.12	innovator	innovator
	allo-2	71.39	79.53	89.32	91.07	102.07	-	-
	allo-3	63.57	71.56	92.00	96.44	100.72	-	-
	allo-4	51.35	60.26	73.95	87.72	93.60	-	-
	allo-5	72.31	86.18	93.33	97.45	99.02	-	-
	allo-6	63.54	75.55	83.98	95.77	104.44	-	-
	allo-7	80.13	86.18	92.00	96.78	103.43	-	-
PH 6.8	Allo-1	59.93	67.86	75.06	80.05	85.03	innovator	innovator
	Allo-2	63.99	75.31	83.65	87.13	91.28	-	-
	Allo-3	65.57	76.63	83.21	86.69	91.95	-	-
	Allo-4	38.12	46.16	53.02	71.64	75.87	39	20
	Allo-5	50.12	59.75	75.72	82.7	90.61	57	8
	Allo-6	57.78	62.38	69.55	78.72	84.58	70	4
	Allo-7	63.05	72.02	75.94	77.61	84.36	80	3

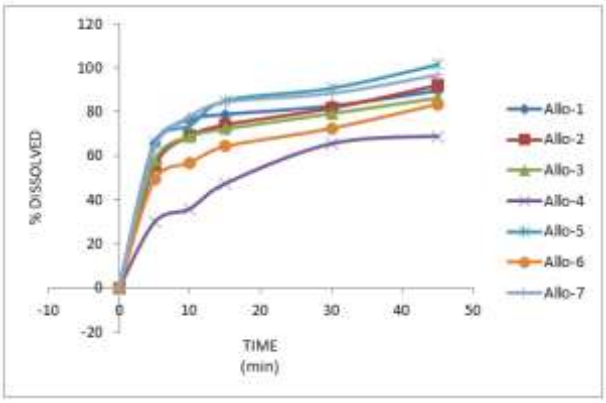


Fig-5: Dissolution profile at PH 1.2

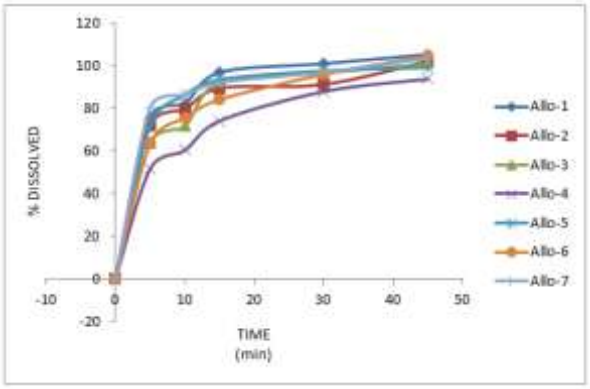
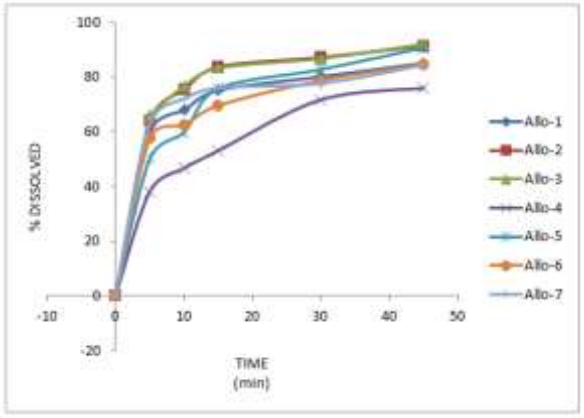


Fig-6: Dissolution profile at PH 4.5



Fig−7: Dissolution profile at PH 6.8

DISCUSSION

The aim of the present study was to collect information on the safety, efficacy and possible interchangeability of the different generic allopurinol tablets with the innovator. Previous researches in this area have shown that the post – marketing evaluation of drug products is important to develop the confidence for manufacturer in order to insure the safety and efficacy of the product [11]. As well, this kind of studies helps the health care people in interpretation between different brands of same generics. In this study, pharmacopeia standards; Disintegration time, hardness, Friability, Weight variation dissolution and Assay (Drug content) were used to compare the generics with the innovator product Allo-1-.Table [2] shows the physicochemical characteristics of the varying brands of Allopurinol tablets studied, reflecting that even though the same Active Pharmaceutical Ingredients (API) was utilized in the production of the generic form of a drug, variations in parameters existed.

The potency of the drug is a direct indication of how much API is present in the formulation and available for release. The assay results showed that all the brands had active pharmaceutical ingredient within the specified official limits except Allo-4- that reflect drug content of 111.1%, according to (USP32) Allopurinol tablets must contain not less than 93.0% and not more than 107.0 %. There was a large variation in average tablet weights amongst all the brands studied, which could be as a result of differing manufacturing processes as well utilization of varying spectrum of excipients, and varying models / mechanisms of incorporation of these excipients into the dosage form, for all the brands the individual tablet weights were within the specified limits, and no tablet in all the brands differ by more than double the percentage error. The ability of individual brands to withstand mechanical stress was evaluated via hardness test, The crushing strength of three brands (Allo-1- ,Allo-5- and Allo-7-) was out of the specified official limits ,They reflected crushing strength of (9,10 and 3 Kg/cm²) respectively , and the specified limit is (4-6 Kg/cm²) but this test is considered not official [7]. However Friability being a more objective and absolute indication of tablet strength, it was also assessed. The ability of the dosage form to resist abrasion due to mechanical handling /agitation via oscillatory tumbling motion that may be experienced during coating, packaging and necessary transportation to the end user was evaluated through friability testing. Value of 1% or less is acceptable according to USP, so all the brands were complied with the specified limits (0.09 – 0.24 %). For disintegration test, all the six brands as well as the innovator were complied with the specified limits that stated by USP 32 which gives the general requirements for disintegration for uncoated tablets as 30 minutes, and there were no large variation between the innovator brand (4.42 min) and the other brands (1.82 – 5.4 min).For dissolution test, all the brands met the specified limits that stated by USP 32 because all the brand had % release more than 75% after 45 mins.

The in vitro dissolution study is considered a fundamental requirement in the pharmaceutical industries in order to assure the quality of solid pharmaceutical dosage forms for oral use, guarantee the quality from batch to batch, orientate the development of new formulation and secure the uniformity in quality and performance of the drug even after modifications[12]. Dissolution test was carried out in the three media (ph. 1.2, 4.5 and 6.8) to cover the whole GIT environment .All the brands within their expiry dates and the possible effects of the excipients on the dissolution of the generic drugs was not evaluated because only the innovator product (ZYLORIC) listed excipients on its leaflet. Similarity factor (f2) and difference factor (f1) are simple and viable comparison approaches to assess bioequivalence between two formulations. According to FDA [13] a drug product is considered to be; very rapidly released if ≥85 %of the drug is dissolved in ≤ 15 minutes, which corresponds to gastric emptying half-life (T50%) in fasting conditions, and considered to be rapidly released

if ≥85 % of the drug is dissolved in 30 minutes. The f1 is proportional to the average difference between the two profiles, whereas factor f2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the large differences among all the time points. The similarity factor f2 measures the closeness between the two profiles [14]. Drugs of class 1 BCS are considered acceptable for Biowaiver under WHO criteria (Both the test and reference products are rapid dissolving under all physiological conditions) [15].

From the results above: At PH 1.2 only Allo-5- and allo-7- were met WHO criteria for Biowaiver acceptance. At PH 4.5, more than 85 % of the API was dissolved at 30 minutes for all the seven brands. At PH 6.8 only Allo-2 and Allo-3 were met the criteria so, we can conclude that the seven brands including the innovator (ZYLORIC) were not acceptable for Biowaiver under WHO criteria. According to f1 and f2 values, the brands Allo-2, Allo-3, Allo-5 and Allo-7 would most likely be similar to the Innovator in rate and extent of dissolution; however, they failed to meet the requirement of very rapid dissolution (more than 85% release in 15min in the three PH). While Allo-4 and Allo-6 did not meet these requirements, so they were not similar to the Innovator in rate and extent of dissolution.

CONCLUTION

From the results above we can conclude that:

- The brands were met the specified limits for the official physicochemical tests with failure of about 9% for content percent.
- The brands were not accepted for Biowaiver under WHO criteria.
- The brands Allo-2, Allo-3, Allo-5 and Allo-7 would most likely be similar to the Innovator in rate and extent of dissolution, while Allo-4 and Allo-6 are not.

RECOMMENDATIONS

In vivo bioequivalence studies are required for the brands Allo-4 and Allo-6 to ascertain brands bioequivalence with the innovator and to ensure their safety, efficacy and possible interchangeability with innovator.

ACKNOWLEDGEMENTS

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REFERNCES:

1. WHO model list of essential medicines, accessed at: www.who.int/medicines/publications/essential medicines/en/.
2. World Health Organization (WHO): proposal to waive in vivo bioequivalence requirements for WHO model list of Essential Medicines immediate-release, solid oral dosage forms. Technical Report Series, No 937,40th Report, Annex 8 of WHO Expert Committee on specification for pharmaceutical preparations. Available from: http://whqlipdoc.who.int/trs/WHO_TRS_937_ENG .PDF.
3. Staniforth, J. N. (2007). Aulton's Pharmaceutics-The Design and Manufacture of Medicines. *New York: Churchill Livingstone*.
4. www.fda.gov/cder/guidance/3618fnl.htm.
5. Amidon, G. L., Lennernäs, H., Shah, V. P., & Crison, J. R. (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical research*, *12*(3), 413-420.
6. Rajkumar, B., Bhavya, T., & Kumar, A. A. (2014). Reverse phase HPLC method development and validation for the simultaneous quantitative estimation of alpha lipoic acid and allopurinol in tablets. *International journal of Pharma Tech Research Pharmtech*, *6*, 307-312.
7. Food and Drug Administration. (2000). Guidance for industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. *Food and Drug Administration, Rockville, MD*.
8. USP 35-NF 30 Pharmacopeia. 2012. P.5773.]
9. Ammar AA, Samy AM, Marzouk MA, Ahmed MK. Formulation, characterization and biopharmaceutical evaluation of Allopurinol tablets. Int. J. Biopharm. 2011;2(2):63-71.
10. Dressman, J. B., Amidon, G. L., Reppas, C., & Shah, V. P. (1998). Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharmaceutical research*, *15*(1), 11-22.
11. Afifi, S. A., & Ahmadeen, S. (2012). A comparative study for evaluation of different brands of Metformin Hydrochloride 500 mg tablets marketed in Saudi Arabia. *Life Science Journal*, *9*(4), 4260.
12. Pal, T. K., Ghosh, U., & Panda, M. (2014). Comparative bioequivalence study of different brands of telmisartan tablets marketed in India by dissolution modeling and quality control tests. *Int. J. Pharm. Phytopharmacol*, *3*(6), 460-468.
13. Inn, H. (2005). Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research.
14. Shah VP, Tsong Y, Sathe P, Liu JP. In vitro dissolution profile comparison—statistics and analysis of the similarity factor, f2. Pharmaceutical research. 1998 Jun 1;15(6):889-96.

15. Guidance for Industry: "Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System". U.S., Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Available from: http://www.fda.gov/CDER/GUIDANCE/3618fnl.pdf.].