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A Comparative Study of the Quality Attributes of Innovator and Generic Doxycycline Tablets

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Abstract

Doxycycline is a well-known broad-spectrum antibiotic that has been artificially derived from the very well-known Oxytetracycline. The activity of Doxycycline is reported to be against a diverse range of microbes comprising of gram-negative bacteria, gram positive bacteria, anaerobic bacteria and parasites. Doxycycline is proved to be beneficial in managing RTIs, UTIs, skin and soft tissue infections. Five generic Doxycycline Hyclate 100 mg tablets from different manufacturer have been evaluated to assess their bioequivalence using in-vitro tests. Other general quality assessments of these tablets like assay, weight variation, hardness, friability, disintegration time were also determined and all these generic tablets passed compendial specifications. There were no significant differences ($p < 0.05$) in the percentage dissolution of drug from generic tablets at 15 minutes with the same from innovator brand tablet at the same time point. To compare

the dissolution profiles of all the tablet formulations and the innovator brand, a model independent approach of difference factor (f1) and similarity factor (f2) was employed with all time-points included in the dissolution studies. These results indicated that all generic Doxycycline Hyclate tablets included in this investigation were bioequivalent with the chosen innovator brand and may be used interchangeably.

INTRODUCTION

Doxycycline, a tetracycline antibiotic, has been extensively used for treating a variety of bacterial infections, including those affecting the respiratory, urinary, and gastrointestinal systems. It is well known for its broad-spectrum activity against both gram-positive and gram-negative bacteria, as well as its anti-inflammatory and immunomodulatory effects, which extend its use beyond conventional infection treatments (1). Over the years, Doxycycline has gained attention for its role in non-antibiotic applications, such as its ability to inhibit matrix metalloproteinases (MMPs), which are involved in tissue remodeling and the progression of chronic diseases like osteoarthritis and cancer (2).

In recent years, research has increasingly focused on Doxycycline's potential for treating non-infectious conditions, including cardiovascular diseases, where it has shown promise in reducing post-infarction myocardial remodeling (3). Its ability to modulate the extracellular matrix and prevent the breakdown of collagen further emphasizes its role in managing fibrosis and tissue damage, making it a potential candidate for treating conditions such as pulmonary embolism and ischemic injuries (4).

Given its high solubility and permeability, Doxycycline is classified as a Biopharmaceutics Classification System (BCS) Class I drug, allowing for bioequivalence (BE) studies to be conducted using in vitro methods rather than costly and time-consuming in vivo trials (5). This is particularly important for developing countries,

where the availability of generic formulations at lower costs can significantly improve access to essential medications (6). The introduction of generic Doxycycline formulations, which are required to demonstrate therapeutic equivalence with the innovator drug, has further reduced healthcare costs without compromising efficacy or safety (7).

This study aims to explore recent advancements in Doxycycline's pharmaceutical applications, including its non-antibiotic roles, bioequivalence considerations, and its impact on public health, particularly in resource-limited settings.

MATERIALS AND METHODS

Equipment

i. Analytical weighing balance (Shimadzu ATX224 0.01 – 220g).
ii. Disintegration apparatus (Pharmatest D-63512).
iii. Dissolution type II apparatus (Agilent 708-DS).
iv. Dryer (Black & Decker PX7).
v. Filtration assembly (Eyela A-1000S).
vi. Micropipette (Proline 100-1000 µL).
vii. Monsento tablet hardness tester.
viii. Roche Friabilator (Vankel industries 1805).
ix. Ultra sonicator (DSA150-SK_2 5.7 L).
x. UV-Visible Spectrophotometer (Jasco V-530 Double beam).

Chemicals

i. Distilled Water.
ii. Doxycycline Hyclate standard powder (English labs, Lahore).
iii. Doxycycline Hyclate 100mg tablets of innovator brand (Pfizer laboratories) and generic from five different manufacturers.

iv. Hydrochloric acid (HCl).

Glassware

v. Beakers (Pyrex 50mL, 100 mL).

vi. Volumetric flasks (Pyrex 50 ml, 100 ml, 250 ml).

vii. Pipette (Bomex 2ml, 5ml, 10ml).

viii. Graduated cylinder (Bomex 10ml, 50ml, 100ml).

ix. Glass cuvette.

x. Ependorf-tubes (1.5mL)

Softweres

i. Microsoft office 2012.

ii. SPSS 17.

Standard Doxycycline used

The standard Doxycycline Hyclate was obtained from English Pharmaceuticals Lahore, Pakistan. The details about the standard used are given in Table-1.

Table 1: Table Containing Details of the Active Ingredient Used

Name	Batch no.	% Assay	Expiry date	Supplier
Doxycycline Hyclate	HAF1212021	98.92%	December 2015	English Pharmaceuticals Lahore, Pakistan.

All the generics and innovator brand Doxycycline Hyclate 100 mg tablets as well as reference standard used in this investigation were within their shelf. Innovator brand used was Vibramycin 100mg tablets by Pfizer laboratories. All the information regarding generic tablet samples and innovator brand is mentioned in the table 2:

Table 2: Details of the Generic Tablet Samples (GS) and Innovator Brand (IB) Used

Sample	Batch no.	Expiry date	Retail Price Rs/- per 30 tabs	Supplier
GS 1	3246	September 2016	117	Pearl pharmaceuticals Islamabad, Pakistan.
GS 2	P02747	December 2016	151	Medera pharmaceuticals Islamabad, Pakistan.
GS 3	XE-03	October 2016	141	Mediceena pharma Lahore, Pakistan.
GS 4	34609	July 2016	30	Wilshire laboratories Lahore, Pakistan.
GS 5	A3684	January 2017	159	Remington pharmaceutical industries Lahore, Pakistan.
IB	E35C81	June 2017	165	Pfizer laboratories Karachi, Pakistan.

Hardness Testing

Hardness or tablet breaking force of six tablets from each of the generics and innovator brands was tested by using Monsanto hardness tester. First of all, a zero reading was taken by placing the tablet in contact with the lower plunger. After this initiatory step the upper plunger was then pushed against a spring by turning a threaded bolt around its central axis until the tablet was fractured. A pointer travelled along a measuring device in the barrel to specify the amount of force as the spring was compressed. After the force of fracture was documented, the zero reading of force was then subtracted from it. It measured the tablet breaking force in kg/cm^2.

Weight Variation Determination

20 tablets of each generic and innovator brand were weighted individually using an analytical weighing balance (Shimadzu ATX224 0.01 – 220g). The average weight of the tablets as well as their percentage deviation was calculated.

Friability

In this study the Friability of sample and innovator tablets was assessed by means of Roche Friabilator. Usually the results of friability testing are recorded in percentage (%). Analysis was carried out primarily by weighing (Wi) twenty tablets and transferring them into Friabilator through its removable side. The Friabilator then was run at the speed of 25 rotations per minute (rpm) for a time lapse of 4 minutes or in other terms operated at the frequency of 100 revolutions. Once again, the tablets were weighed (Wf). The %age Friability was finally calculated by formula;

$$\% F = Wi - Wf \times 100 / Wi$$

A maximum mean weight loss from three samples of twenty tablets must not be more than 1.0% is considered acceptable for most products (8) .

This process was repeated with all the samples of generic candidates and innovator brand.

Disintegration Test

The disintegration time for film coated tablets of Doxycycline Hyclate generic and innovator brands was sorted out by using the calibrated Disintegration apparatus (Pharm test D-63512). Individual tablet unit was retained in each of six tubes that were positioned in a beaker holding 1000 ml of distilled purified water and furthermore it was kept at 37 ± 2^0 C temperature. After the satisfactions of all the specifications the apparatus was operated (8).

The exact time taken for the tablets to disintegrate completely and pass through the mesh was recorded. This procedure was repeated three times for each five generics and one innovator brand. Hence for each sample 18 tablets were tested and for each test the resulting time in minutes was recorded.

Dissolution Studies

Dissolution analysis was executed using a USP Dissolution apparatus II (peddle type) (Agilent 708-DS).

Time = 60 minutes.

Chemicals and Solvents: The Doxycycline Hyclate tablets100 mg of both generic and innovator brand and were obtained from the local market. Doxycycline Hyclate reference standard (RS) and all the tablet samples were under expiration dates. Distilled Water used was of HPLC grade.

Dissolution Medium = 900 ml water which was maintained at 37 ± 0.5 °C at 50 rpm.

Standard Solution Preparation: A precisely weighed quantity of Doxycycline Hyclate RS was dissolved in medium and diluted quantitatively and step wise to obtain a solution containing 22µg/ml of Doxycycline.

Test Solution Preparation: 5 ml of dissolution samples were withdrawn periodically after every 5 minutes and passed by membrane filter paper (Whatman filter paper no 41) using filtration assembly (Eyela A-1000S) and suitably diluted in comparison with RS.

In all dissolution tests, 5 ml of dissolution samples were withdrawn and replaced with equal volume fresh dissolution medium at regular intervals. Attained dissolution samples were used for evaluation of released Doxycycline concentrations by using a UV-Vis spectrophotometer against standard solution. Maximum Absorbances were obtained

by scanning all samples at 276nm wavelength. Percentage of Doxycycline dissolved in samples was calculated using formula;

% dissolved = (AU / AS) × (CS / L) ×900 ×100

AU__ absorbance obtained with the Test solution.

AS__ absorbance obtained with Standard solution.

CS__ concentration of Doxycycline in the standard solution in mg / mL.

L__ Tablet label claim in mg.

900__ volume of Medium in mL.

100__ conversion factor to percentage.

Tolerances__ Not less than 85% (Q) of the labeled amount of doxycycline is dissolved in 30 minutes(8).

Assay

The content of Doxycycline Hyclate 100.0 mg per tablet (90.0 – 120.0 mg per tablet) was determined by UV-Vis Spectrophotometric assay. The content of Doxycycline Hyclate was determined by following the procedure for UV-Vis Spectrophotometer under the operation conditions like wave length (λ max) as 276 nm using water as blank (8).

Chemicals and Solvents

The Doxycycline Hyclate tablets 100mg of different generic and innovator brand were obtained from the local market and their details like batch number, manufacturing and expiry date were noted before analysis. Doxycycline Hyclate reference standard and all the tablet samples were under expiration dates properly closed and sealed. Distilled water used was of HPLC grade.

Preparation of Standard Solution: 100 mg of Doxycycline Hyclate standard was accurately weighed and then placed into a 100 ml volumetric flask. This standard was

dissolved in the solvent and diluted to make up the volume. Then it was filtered through Whatman paper No. 41. And first 5 ml of filtrate were discarded. From the rest of solution, a volume of 10 ml was diluted with the solvent to make up100 ml in the volumetric flask and 10 ml of this solution was further diluted with solvent to make the volume 100ml ((8).

Preparation of Sample Solution: A sample of 20 tablets was taken and the average weight of them was noted. The tablets were then crushed as completely as possible and the powder was weighed again. The amount of powder containing 100 mg of Doxycycline was accurately weighed and placed into a 100 ml volumetric flask. It was then dissolved in the solvent and diluted with it to make up the volume. Sample was filtered through Whatman No.41filter paper. The initial volume of about 5 ml of filtrate was discarded. From the rest or solution, a volume of 10 ml of was diluted in a 100ml volumetric flask with solvent. A volume of 10ml of this solution was further diluted to 100ml volumetric flask. For both standard and sample absorbances at 276 nm using 1cm cell were measured. Then %age assay was determined using the following formula (8).

$$\%\text{age assay of each formulation} = \frac{\text{Absorption of the formulation}}{\text{Absorption of reference standard}} \times 100$$

Statistical Interpretation of the Data

The consistency of weight was evaluated by simple statistics. For the dissolution profiles at 15 minutes, they were investigated for significant differences by using a Student - Newman- Keuls test of one-way analysis of variance (ANOVA) for all pair wise evaluations in this particular analysis. The statistical analysis was directed using SPSS 17.

RESULTS & DISCUSSION

All tablets obtained from local market were subjected to a number of tests in order to assess their in vitro bioequivalence along with other quality parameters like hardness, weight variation, friability, disintegration time, dissolution studies and assay.

Hardness Testing Profiles

The hardness test for all tablets, both generics and the innovator brand, were done to assess the capability of tablets to endure handling without cracking or chipping. As this is a factor that remarkably influence disintegration and dissolution phenomena. Hardness test was done using Monsanto hardness tester. A force of about 4 kg/cm^2 is the least requirement for a reasonable hardness of tablets (8). If the value of tablet hardness is below 4 kg/cm^2 it means that the tablet is too soft to break even in final packages and if it's too hard, it will no release its contents in time, in the body. Hence, lingering its absorption and other pharmacokinetic parameters. Hardness also affects the bioavailability of drug inside the body and this can be seen in plasma concentration versus time curves.

The results of the hardness testing showed that hardness of all generic tablets was within the range between 10.82 ± 0.11 to 12.04 ± 0.26 kg/cm^2, whereas in case of the innovator brand, it was 12.28 ± 0.33 kg/cm^2 shown in Table 3. Hence, the results of the hardness testing were satisfactory.

Weight Variation Determination

This is a test that ensures that every individual unit carries weight in acceptable limits as specified in official compendia for example USP and BP. it also testifies that none of the chosen sample is over or underweight so as to satisfy the uniformity of dosage unit. Weight variation does assist as an indicator to good manufacturing practices (GMP)

maintained by the manufacturers as well as quantity of API confined in the product. Weight variation determination was done on Analytical weighing balance (Shimadzu ATX224 0.01 – 220g.

The weight variation for all the tablets used in this study showed compliance within the official specifications (9) as concluded from table 3 and none of the products deviated by up to 7.5 % from their average weight. The weight varied between the range of 252.82 ± 0.11 to 270.30 ± 0.26 and for the innovator brand it was 272.42 ± 0.40.

Friability Testing Profiles

Friability analysis or testing is a laboratory operated procedure oftenly implemented by the pharmaceutical industries to evaluate the probability of a tablet breaking into smaller pieces during transportation and shipment. This assessment is used to test the resistance of tablet to abrasion. It involves repetitively dropping a sample of tablets over a fixed period of time using a rotating wheel with a baffle and subsequently inspecting whether any tablet is broken and what percentage of the original mass of the tablets has been fragmented off. A characteristic specification will permit a definite percentage to be lost by fragmentation or shedding and will not allow any damaged tablets. More friable the tablets are, more contents of them would be wasted during handling and vice versa.

USP and BP specify that the tablets friability should be less than 1% of average weight (8) .Friability of all the generic candidates and innovator brand was testes using, the very familiar, Roche friability tester. The %age friability of all generic tablets was within the range of 0.15 to 0.22, while the %age friability of innovator brand was 0.11 (table 3). Hence, the results of the hardness testing were satisfactory that is less than 1%.

Disintegration Time Profiles

The drug integrated in a solid drug product is unconfined quickly as the product disintegrates. Therefore, disintegration is a vital quality parameter of tablet as this is directly linked with drug dissolution and consequent bioavailability of the drug.

All the Doxycycline Hyclate 100mg tablets, both generics and the innovator brand compiled with the compendia specifications for disintegration. Results of disintegration time in minutes can be seen in Table 3. The BP specification is that the film coated tablets must disintegrate within the time span of 15 minutes (BP, 1998), while USP states that film coated tablets must disintegrate within the time span of 30 minutes (8).

Results of table 6 clearly demonstrate that all the generic candidates and innovator brand disintegrated with in the time specified. The values of disintegration time varied within the range of 5.33 ± 0.52 to 5.83 ± 0.75 min. While disintegration time for innovator brand was 5.67 ± 0.82 min.

Dissolution Profiles

According to the FDA guidance for industry, for the dissolution testing of immediate release solid oral dosage form, the BCS suggests that for class I and few class III drugs 85 % w/w dissolution of the labeled content within 15 minutes guarantee that the bioavailability of the drug is not restricted by Dissolution process (10). Doxycycline is a class I drug candidate. The amount released by all generic and the innovative brand Doxycycline Hyclate tablets was over 85 % (Table 3 and Figure 2) within 15 minutes.

No significant differences ($p < 0.05$) were found in the percentage dissolution of drug from generic tablets at 15 minutes with the same from innovator brand tablet at the same time point while comparison with all formulations evaluated by one-way ANOVA trailed by using Student- Newman- Keuls test for pair wise comparisons of all.

A model independent approach of difference factor (f_1) and similarity factor (f_2) was implemented with all time-points included in the in vitro dissolution studies to relate the dissolution profiles of all the generic samples and the innovator brand (10). Difference factor (f_1) is the percentage between the two curves expressed as:

$$f_1 = \{[\Sigma_{t=1}^{n} | R_t - T_t |] / [\Sigma_{t=1}^{n} R_t]\} \cdot 100 \ldots. (1)$$

and parameters,

n = the number of time points.

R_t = at time t, the dissolution value of reference product.

T_t = for the test product at time t, the dissolution value.

Similarity factor (f_2) can be defined as a logarithmic reciprocal square root alteration of the sum of squared error and is a determination of the similarity in the percentage (%) dissolution between these two curves and expressed as:

$$f_2 = 50 \cdot \log \{[1 + (1/ n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \cdot 100 \ldots. (2)$$

Similarity factor (f_2) has been approved as a criterion to compare the similarity of two or more dissolution profiles by FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) by the Committee for Proprietary Medicinal Products (CPMP). Similarity factor (f_2) has been included by the Centre for Drug Evaluation and Research (CDER) in their guidelines such as guidance on dissolution testing of immediate release solid oral dosage forms 15 and guidance on waiver of in vivo Bioavailability and BE Studies for IR solid oral dosage forms based on a BCS (FDA, 2000). two dissolution profiles are considered to be similar and bioequivalent if f_1 calculated is in between 0 and 15 similarly f_2 must be in the range of 50 and 100 (FDA, 1997). The calculated f_1 and f_2 values are shown in table 3. These values were found within the satisfactory range as per allowed specifications given above.

Table No. 3: Evaluation of Tablet Formulations: Hardness, Weight Variation, Friability, Disintegration Time, and Dissolution Profiles

Tablet Samples	Hardness (kg/cm^2) (Mean ± SD)	Weight Variation (mg) (Mean ± SD)	% Friability	Disintegration Time (min) (Mean ± SD)	% Dissolution at 15 min (Mean ± SD)	f1	f2
GS 1	11.52 ± 0.19	257.52 ± 0.19	0.20	5.33 ± 0.55	89.03 ± 1.92	3.33	70.45
GS 2	10.82 ± 0.11	252.82 ± 0.11	0.16	5.50 ± 0.54	86.08 ± 0.98	3.02	74.61
GS 3	11.76 ± 0.44	263.76 ± 0.44	0.17	5.33 ± 0.52	86.30 ± 1.36	3.62	70.10
GS 4	11.04 ± 0.51	258.04 ± 0.51	0.22	5.50 ± 0.58	89.01 ± 1.20	2.67	77.33
GS 5	12.04 ± 0.26	270.30 ± 0.26	0.15	5.83 ± 0.75	90.99 ± 1.63	3.29	65.35
IB	12.28 ± 0.33	272.42 ± 0.40	0.11	5.67 ± 0.82	91.13 ± 0.44	-	-

The graphical form of dissolution time versus amount of drug released is interpreted in figure 2, starting from time zero minutes to 60 minutes.

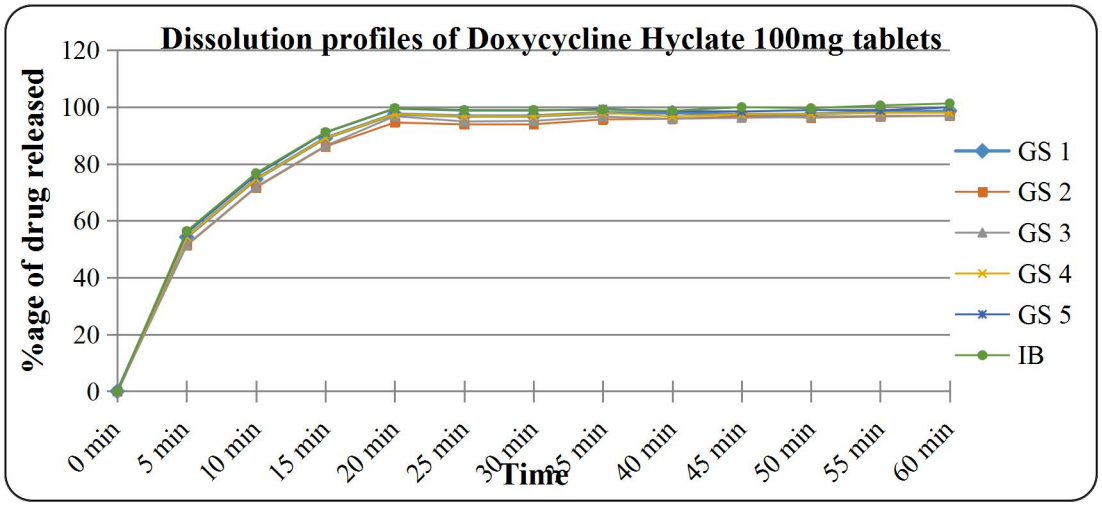

Figure 2: Dissolution Profiles of all Five Doxycycline Hyclate 100mg GS and IB for 60 Min

Determination of % Age Drug Content

Tablets of both generic and the innovator brands contained Doxycycline within the range of 100 ±10 % of their labeled claim. USP and BP provisions for assay indicate that the Doxycycline active ingredient within dosage unit must not be less than 90 % and must not be more than 110 % (USP30, 2007). Hence, the results recorded for the assay complied the compendial specifications of Doxycycline in every formulation as the lowest value of assay is 96.94 % while on the other hand highest one is 98.34%. Results of assay can be found in table 4.

Table 4: *Assay of Doxycycline Hyclate 100mg GS and IB in % Age*

Tablet samples	%age Assay (Mean ± SD)
GS 1	96.94 ± 2.46
GS 2	97.73 ± 1.89
GS 3	98.08 ± 1.68
GS 4	98.34 ± 1.53
GS 5	97.03 ± 0.59
IB	101.12 ± 1.71

CONCLUSION

As a conclusion, our results showed that all generic Doxycycline Hyclate tablet samples involved in this specific study proved to be of good overall quality with optimum dissolution rate. That is why they have good bioavailability. All of them are bioequivalent to the selected innovator brand. It is a general psychology among people that the quality of generic medicines may be poor as compared to the leading brands. As they are cheaper and they are not brand leaders. This investigation will help to change the view of people towards generic medicines.

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