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RESEARCH ARTICLE
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PHARMACEUTICAL EQUIVALENT STUDY OF DICLOFENAC SODIUM TABLET FORMULATIONS AVAILABLE IN GUJRAT, PAKISTAN

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ABSTRACT
This study aims to check pharmaceutical equivalents of different brands of Diclofenac sodium tablets available in Gujrat, Pakistan. Two different brands of diclofenac sodium tablets (500mg) were investigated in the study. Five quality control parameters; weight variation test, hardness test, friability test, disintegration test and dissolution test were carried out as specified by BP/USP (British Pharmacopeia, United State Pharmacopeia). The result of the study revealed that all the parameters such as the weight variation test, hardness test, friability test, disintegration test and dissolution test were following USP/BP.

Keywords: Pharmaceutical Equivalent, Diclofenac Sodium, Quality Control parameters, Bioequivalence, Pharmacopeial standards.

1. INTRODUCTION

1.1. Bioequivalence Study
A bioequivalence study is a type of clinical trial designed to assess whether a generic version of a drug is equivalent to the innovator or brand-name version in terms of pharmacokinetic and pharmacodynamic properties (Jalali & Rasaily, 2018). The goal is to demonstrate that a generic product is essentially the same as the reference product in terms of safety and efficacy (De Mora, 2015). They allow for cost-effective alternatives to be introduced into the market while maintaining the same therapeutic benefits (De Mora, 2015).

1.1.1. Purpose
The primary purpose of a bioequivalence study is to demonstrate that the generic version of a drug is absorbed into the bloodstream at a rate and extent similar to that of the innovator product (Chow, 2014; Jalali & Rasaily, 2018). This ensures that there are no significant differences in the performance of the generic drug compared to the reference product (Meredith, 2003; Nation & Sansom, 1994).

1.2. Pharmacokinetics
Pharmacokinetics focuses on pharmacokinetic parameters, which include the absorption, distribution, metabolism, and elimination of the drug (Benet et al., 1996; Mannhold et al., 2012). Blood samples

are taken at various time points to measure the concentration of the drug in the bloodstream (Kang & Lee, 2009).

1.3. Pharmaceutical Equivalents

Drug products are deemed pharmaceutical equivalents when they consist of the same active ingredient(s), share the same dosage form and route of administration, and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules) (Cristofoletti et al., 2018). These equivalents are designed to contain an identical amount of active ingredient in the same dosage form and adhere to the same compendial or other relevant standards (such as strength, quality, purity, and identity) (Cristofoletti et al., 2018). However, they may exhibit variations in characteristics like shape, scoring configuration, release mechanisms, packaging, excipients (including colours, flavours, and preservatives), expiration time, and, within specified limits, labelling (Kefalas et al., 2011).

1.4. Diclofenac Sodium

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID), which is used for inflammation, joint stiffness, and rheumatic and non-rheumatic conditions. It has a potentially short half-life (approx. 2 hours) (Meretskyi & Meretska, 2023).

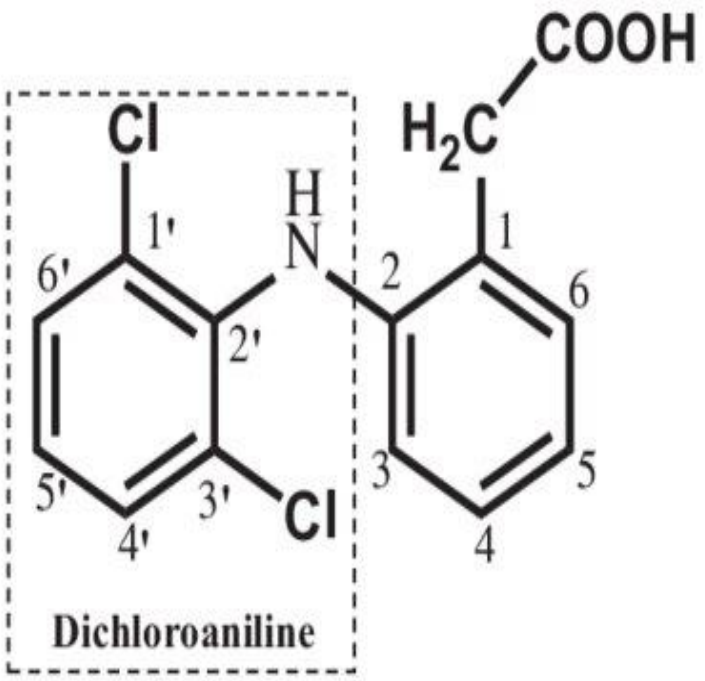

Figure 1.1: Chemical Structure of Diclofenac

Studies show that diclofenac sodium inhibits cyclooxygenase (COX). It also inhibits the N-methyl-D-aspartate (NMDA) receptor, substrate P, and peroxisome proliferator-activated receptor gamma (PPAR-γ or PPARG) (Gupta et al., 2020). It leads to reduced pain perception or the transduction of neuropathic pain. Diclofenac sodium tablets are associated with anti-inflammatory and analgesics, as they inhibit COX1, COX2, prostaglandin, prostacyclin, and thromboxane (Gupta et al., 2020). Prostaglandin is produced during the inflammatory process and its inhibition aids in reducing inflammation (Scher & Pillinger, 2009).

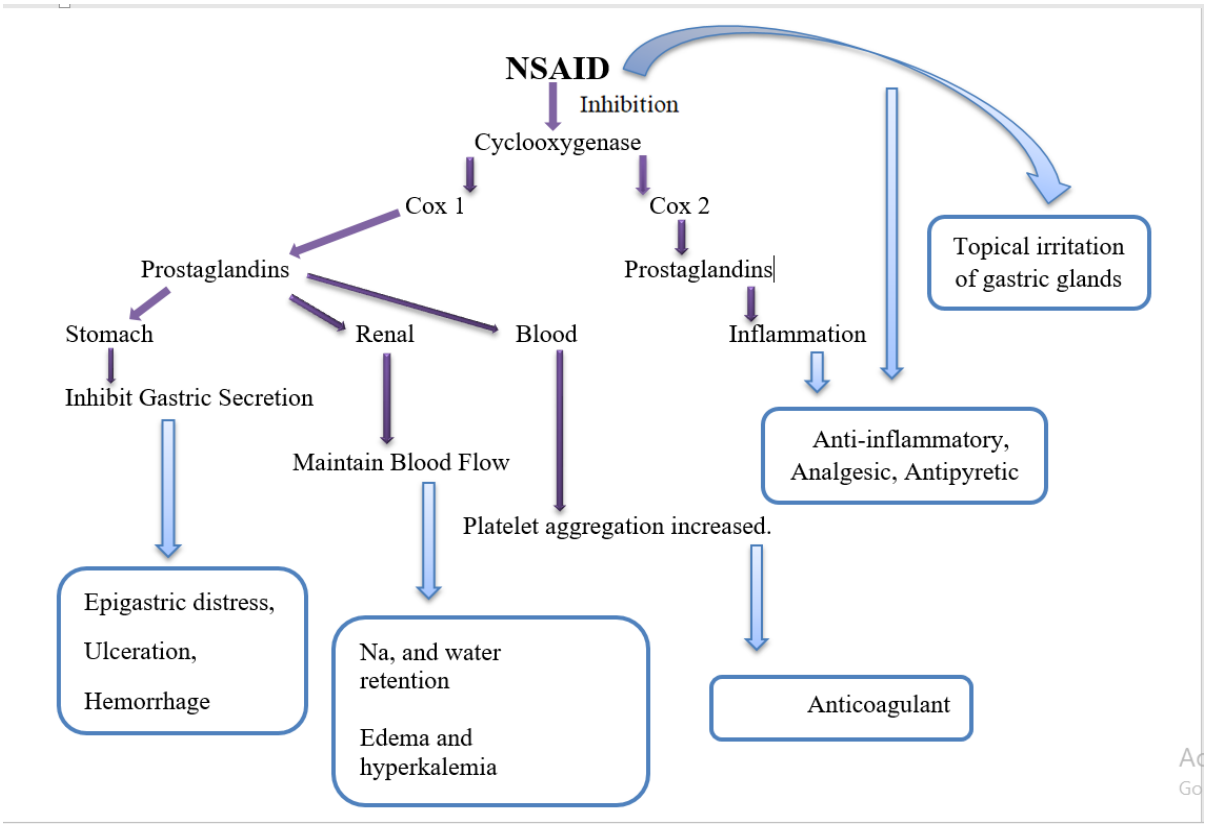

Figure 1.2: Mechanism of action of Diclofenac

1.5. Statistical Analysis

Statistical methods are used to analyze the data collected from the study (Martin & Bridgmon, 2012). The most common metric is the area under the concentration-time curve (AUC) and the maximum concentration (C_{max}) (Medellín-Garibay et al., 2014). If the 90% confidence interval of the ratio of the generic to the reference product falls within the predefined bioequivalence limits (usually 80-125%), the products are considered bioequivalent (Davit et al., 2013).

1.6. Regulatory Requirements

Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have specific guidelines and requirements for bioequivalence studies. Generic drug manufacturers must demonstrate bioequivalence to obtain regulatory approval for their products (Sullivan et al., 2018).

2. Types of bioequivalence studies

Bioequivalence studies can take various forms, depending on the specific goals, characteristics of the drug, and regulatory requirements. Some common types of bioequivalence studies are;

2.1. Single-Dose Crossover Study

Design: Participants receive a single dose of the test (generic) and reference (innovator) products in a randomized order with a washout period between doses.
Purpose: Assess the bioequivalence of a single dose of the generic drug compared to the reference drug (Nam et al., 2015).

2.2. Multiple-Dose Crossover Study

Design: Similar to a single-dose study, participants receive multiple doses of the test and reference products over a specified period (Huang et al., 2018).
Purpose: Evaluate the bioequivalence of multiple doses, especially relevant for drugs with a cumulative or delayed effect.

2.3. Parallel Design Study

Design: Participants are divided into two groups, with one group receiving the test product and the other the reference product. There is no crossover between groups (Lui, 2016).
Purpose: Assess bioequivalence without the need for a washout period, suitable for drugs with long half-lives or when a crossover design is impractical.

2.4. Replicate Design Study

Design: Participants receive multiple doses of the test and reference products in separate periods, with each period treated as an independent study (Nix & Gallicano, 2011).
Purpose: Provides additional data to enhance the robustness of bioequivalence assessment.

2.5. Food Effect Study

Design: Participants receive the test and reference products under both fasting and fed conditions to evaluate the impact of food on bioavailability (Graefe-Mody et al., 2011).
Purpose: Assess whether the generic product behaves similarly to the reference product under different nutritional states.

2.6. Dose-Proportionality Study

Design: Investigates bioequivalence at different dose levels to determine if the relationship between dose and systemic exposure is proportional (Sheng et al., 2010).
Purpose: Ensures that bioequivalence is maintained across various doses of the drug.

2.7. Steady-State Study

Design: Participants receive multiple doses of the test and reference products until a steady state is achieved, with measurements taken at this point (Yuen et al., 2004).
Purpose: Relevant for drugs that require time to reach a consistent concentration in the body.

2.8. Topical Bioequivalence Study

Design: Assess the bioequivalence of topical formulations, such as creams or ointments, by comparing the systemic exposure of the active ingredient (Yacobi et al., 2014).
Purpose: Determines whether the generic and reference topical products are equivalent in terms of absorption and systemic exposure (Raney et al., 2015).
These study designs aim to provide comprehensive data on the bioequivalence of generic and reference products, addressing different aspects such as single or multiple doses, food effects, and steady-state conditions (Cristofoletti et al., 2018). The specific design chosen depends on the characteristics of the drug and the requirements of regulatory agencies.

Experimental

2.9. Tablet specification

All parameters (weight variation test, hardness test, friability test and disintegration) of different brands were carried out.

2.10. Weight variation test:

This test examines uniformity with each batch's tablet composition, which shows its content. We chose twenty diclofenac sodium pills from Brand A for our investigation, and we weighed each tablet separately as well as the group. The data were entered into a tabular format to compare the USP limits. For Brand B, the identical process was carried out once again. The following formula is used to determine the upper and lower control limits for weight variation:
Upper control limit: Mean + 3x Standard Deviation
Lower control limit: Mean – 3x Standard Deviation

2.11. Disintegration test

The disintegration test was carried out through a DST-3C automated disintegration tester. Six random samples of each formulation were tested using 0.1 N HCL for 2 hours, followed by a phosphate buffer with a pH of 6.8 for disintegration. The samples were placed in a basket rack inside a 1000 ml vessel containing 900 ml of the disintegration liquid, kept at a temperature of 37 ± 2 °C. The basket rack moved up and down within a 5-6 cm range, at a speed of 31 cycles per minute. During the upward movement, the samples stayed 1.5 cm below the surface of the liquid, and during the downward movement, they remained 2.5 cm above the bottom of the vessel. The time taken for the samples to completely disintegrate (when no particles were left on the basket) was recorded (Hammami et al., 2020).

2.12. Friability test

As per USP standards, the friability test was performed using the Roche friability subjecting them to uniform tumbling motion for a specified time (25 rotations per minute for 4 minutes). It examines the tendency of the tablet to chip, crumble, or break upon compression or abrasion. It is essential to test the friability of a tablet for complete dissolution in the gastrointestinal tract. A tablet's durability is tested, and during the procedure, a 1% mass loss is permitted.

2.13. Hardness test

To find the tablet's strength under mechanical stress, ten tablets of each brand are put through this test. A tablet must be sturdy enough to withstand pressure. With the LTHT-A11 Hardness Tester, the hardness of every brand is examined. Every tablet's hardness value was assessed, and the average value was computed and compared.

2.14. Dissolution study:

A Type 2 dissolution instrument, specifically a paddle apparatus, was selected for the dissolution study of the tablet as per its monograph. This test is crucial for establishing a correlation between in vitro and in vivo results and assessing the dosage form's efficacy. The dissolution beaker was filled with 900 ml of phosphate buffer at pH 6.8, maintained at a temperature of 37±0.5°C. A single tablet from Brand A was placed in each beaker and stirred at 75 rpm. Samples of 5 ml were withdrawn at intervals of 5, 10, 15, 30, 45, 60, and 75 minutes, with an equivalent volume of buffer solution replenished after each sampling. The absorbance of diclofenac sodium was measured using a UV-visible spectrophotometer at these specific intervals (Gupta, 2020).

These samples were then analyzed spectrophotometrically at 276 nm using a UV/Visible spectrophotometer Shimadzu 1800, Japan. The amount of drug diffused at specific time intervals was determined and plotted against time. The same procedure was conducted in triplicate and the % drug release was calculated**.**

Table. 1: Tablet of different brands Specifications.

	Result for diameter (mm)	**Result for thickness (mm)**	**BP/USP Specification**	**Deviation from BP/USP**
Brand A	8mm	3mm	Thickness 1-3mm	PASS
Brand B	9mm	4mm	Diameter 4-8mm	PASS

Table. 2: Weight of 20 Tablets of Two Different Brands (mg) of diclofenac sodium.

Tablets	**Brand A**	**Brand B**
1	220mg	260mg
2	230mg	250mg
3	220mg	260mg
4	220mg	250mg
5	220mg	280mg
6	230mg	280mg

7	230mg	250mg
8	230mg	260mg
9	220mg	260mg
10	230mg	250mg
11	230mg	250mg
12	210mg	250mg
13	220mg	260mg
14	220mg	260mg
15	220mg	250mg
16	220mg	270mg
17	220mg	260mg
18	220mg	260mg
19	210mg	270mg
20	210mg	260mg

Table. 3: Statistical weight variation of different brands of diclofenac sodium.

Tablets	Average (mg)	Standard Deviation	Upper limit (x+3 S.D)	Lower limit (x-3 S.D)
Brand A	221.5mg	6.708	241.6	201.38
Brand B	259.5mg	9.445	287.84	231.17

Table. 4: Weight variation test of two brands of different brands of diclofenac sodium.

Tablets	Result (mg)	BP/USP specification	Deviation from BP/USP specification
Brand A	221.5	Deviation should be ±7.5%	Within specified limit
Brand B	259.5	Deviation should be ±7.5%	Within specified limit

Table. 5: Friability test of different brands of diclofenac sodium tablets.

Tablets	Friability	BP/USP specification	Deviation from BP/USP specification
Brand A	0.43%	Not more than 1%	PASS
Brand B	0.37%	Not more than 1%	PASS

Table. 6: Disintegration test of different brands of diclofenac sodium.

Tablets	Disintegration time (minutes)	Limits	Deviation from USP
Brand A	30 minutes	Not more than 30 minutes for uncoated tablets	Pass
Brand B	30 minutes	Not more than 30 minutes for uncoated tablets	Pass

Table 7: Hardness of 10 tablets from optimized formulation.

Tablets	Veloft	Voveron
1	16.4kg	16.3kg
2	16.4kg	16.4kg
3	16.4kg	16.2kg
4	16.4kg	16.3kg

5	16.4kg	16.3kg
6	16.5kg	16.3kg
7	16.3kg	16.2kg
8	16.4kg	16.4kg
9	16.4kg	16.4kg
10	16.5kg	16.3kg

Tablets	**Average hardness**	**S.D**
Veloft	16.41kg	±0.2
Voveron	16.31kg	±0.2

Table 8: % Drug release for Brand A and Brand B.

SR.#	Sampling time (mins)	Brand A % Drug release	Brand B % Drug release
1	0	0	0
2	5	42.20	30.67
3	10	50.60	39.48
4	15	66.70	46.70
5	30	73.02	58.12
6	45	78.42	67.91
7	60	81.14	74.46
8	75	80.23	78.52

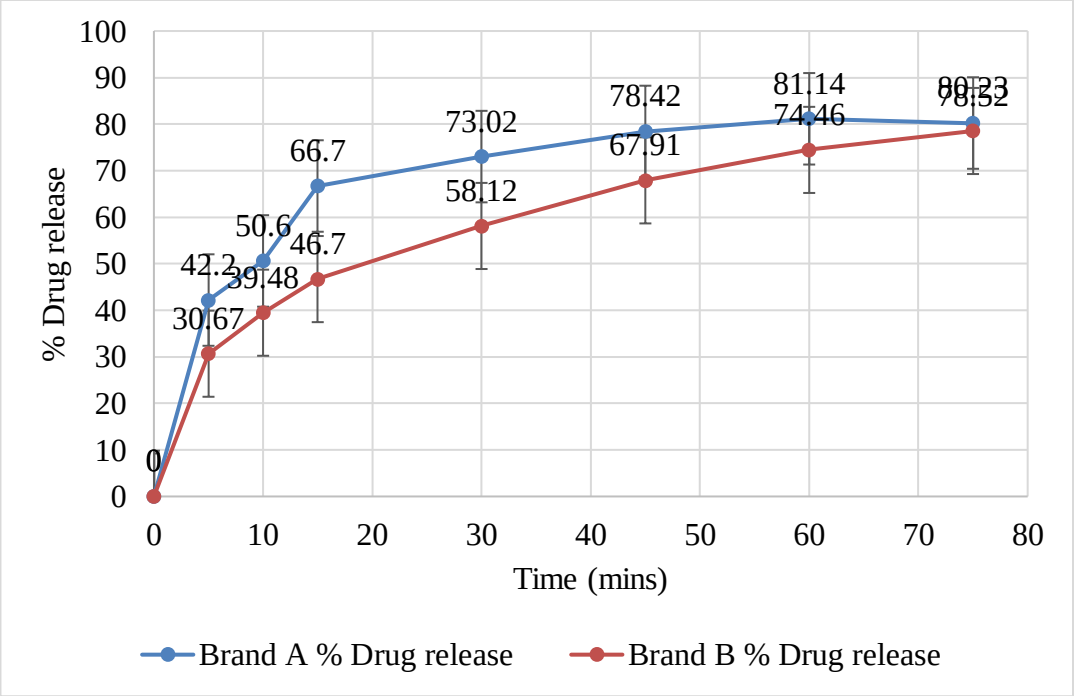

Figure 1.3: Dissolution profile of Diclofenac Sodium tablets

RESULTS AND DISCUSSION

The results of the study indicated that both Brand A and Brand B met the specified criteria for weight variation, hardness, friability and disintegration, demonstrating compliance with the USP/BP standards.

The dissolution test results indicate that Brand A exhibits a faster and more complete drug release profile compared to Brand B. At each sampling time, Brand A consistently shows a higher percentage of drug release, with a notable difference observed within the first 15 minutes where Brand A released 66.70% of the drug while Brand B released only 46.70%. By the end of the 75-minute testing period,

Brand A reaches a peak release of 81.14%, whereas Brand B achieves 78.52%. These results suggest that Brand A tablets have a superior dissolution performance, ensuring a quicker onset of therapeutic action and potentially improved bioavailability.

It is essential to highlight that while weight variation, hardness, and friability are crucial indicators of tablet quality, the disintegration test is particularly significant in assessing the tablet's bioavailability. The disintegration time within the specified limit concerns the potential impact on the drug's therapeutic effectiveness.

CONCLUSION

In conclusion, the pharmaceutical equivalent study conducted on two different brands of Diclofenac sodium tablets (500mg) available in Gujrat, Pakistan, aimed to assess their adherence to quality control parameters specified by the BP/USP. The study focused on weight variation, hardness, friability, disintegration, and dissolution tests, crucial for ensuring the pharmaceutical equivalence of these formulations.

In the broader pharmaceutical landscape, this study underscores the importance of rigorous quality control measures to guarantee the equivalence of generic and reference products. Regulatory agencies, including the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), emphasize the significance of bioequivalence studies in ensuring the safety and efficacy of generic drugs. As such, manufacturers and regulatory bodies should collaborate to address any discrepancies identified in quality control parameters, promoting confidence in the pharmaceutical products available in the market.

In summary, the studied Diclofenac sodium formulations demonstrated adherence to certain quality control parameters, which ensure their bioequivalence and therapeutic effectiveness.

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