



IN-VITRO BIOEQUIVALENCE ASSESSMENT OF FOUR DIFFERENT BRANDS OF LOOP DIURETICS- TORSEMIDE TABLETS

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ABSTRACT

The objective of the current study was to the four distinct Torsemide brands that are sold commercially in the local pharmacy by physiochemical evaluation and UV analysis. Four different brands of Torsemide tablets were compared for their physicochemical equivalency using official standards outlined as per the Indian Pharmacopoeia. These parameters included uniformity in weight, friability, hardness, disintegration, dissolution rate, and drug content. The four evaluated brands were all bioequivalent and met the requirements of the official tests for friability, weight uniformity, disintegration, and dissolution. The results of the friability test fell within the given range. In less than 30 minutes, every formulation begins to crumble. Based on their dissolution examination, the tested brands were formulated a per the required standard. These four different brand tablets had percentage contents of the active component that met the monograph's requirements. From a biological and chemical standpoint, all four of the examined brands may be deemed similar. The rate and absorption of drug that enters the biological system in an active state and can have the desired pharmacological effect, As per the results, patients can change brands the desired brands without risk.

KEYWORDS: Torsemide, bioavailability, bioequivalence, comparison study, physicochemical evaluation.

INTRODUCTION

Bioavailability^[1]

- An oral medication's bioavailability or systemic availability is mostly determined by the degree of hepatic metabolism and absorption.
- When an dosage form is administered orally, Its bioavailability is assessed by comparing, its Area Under Curve (AUC) with the results of an intravenous (IV) dose.

$$\text{Drug bioavailability} = \frac{\text{AUC (oral)}}{\text{AUC (IV)}}$$

$$= \frac{\text{Bioavailable dose}}{\text{Administered dose}}$$

The rate and absorption of drug that enters the biological system in an active state and can have the desired pharmacological effect, including the timing, potency, and duration of its action is referred to as bioavailability.

Need for bioavailability studies

When compared to the bioavailability of a drug, bioavailability studies evaluate the portion of the oral dose that is absorbed into the systemic circulation. For an easily obtainable suspension, solution, or injectable dose form. Bioavailability studies offer further valuable insights into the drug's distribution and elimination properties, which are crucial for formulating dosing regimens and bolstering labeling. Research on bioavailability provides valuable information regarding the efficacy of the formulation.

Bioavailability types^[2]

The percentage of a drug's same dose supplied intravenously that reaches the systemic circulation through an extra vascular route, such as oral administration, is known as absolute bioavailability.

$$\text{Absolute bioavailability} = \frac{(\text{AUC}) \text{ abs}}{(\text{AUC}) \text{ iv}}$$

$$\text{Absolute bioavailability} = \frac{(\text{AUC})_{\text{abs}} \times \text{Div}}{(\text{AUC})_{\text{iv}} \times \text{Dabs}}$$

Where Div is the dosage size given intravenously, and Dabs is the size of the single dose given via the absorption site.

Relative bioavailability: This refers to the percentage of a medication that enters the systemic circulation after being taken at a certain dose as opposed to a standard dose of the medication that has been clinically demonstrated to work.

$$\text{Relative bioavailability} = \frac{(\text{AUC})_{\text{test}}}{(\text{AUC})_{\text{std}}}$$

$$\text{Relative bioavailability} = \frac{(\text{AUC})_{\text{test}} \times \text{D}_{\text{std}}}{(\text{AUC})_{\text{std}} \times \text{D}_{\text{test}}}$$

Bioequivalence Studies^[3]

- Both bioavailability and bioequivalence measuring the absorption of the drug into systemic circulation.
- The phrase "bioequivalence" refers to the relationship between the bioavailability of a drug product and its IV formulation, solution, or suspension, whereas "bioequivalence" refers to the comparison of a medication's bioavailability with predefined bioequivalence parameters.
- Equivalency is a more relative term that is used to compare a medication product to another or to a set of predetermined norms. There are various ways to define equivalency
- Chemical equivalence: When a medication in two or more dosage forms produces the same in vivo effects as determined by a pharmacological response or by controlling a symptom or condition, this is known as clinical equivalency.
- Therapeutic equivalency states that two chemicals with distinct structural makeup's can have the same clinical outcome.
- A medicine is said to be bioequivalent if it enters the general circulation at the same relative rate and extent in two or more dose forms that are comparable.

Need for Bioequivalence

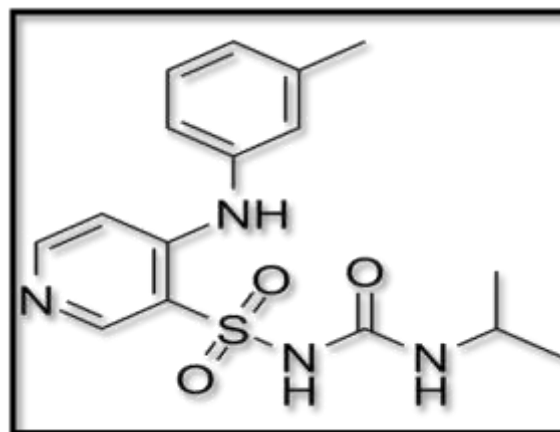
- The pivotal and early clinical trial formulations are linked by bioequivalence investigations.
- Bioequivalence studies are for determination of the therapeutic equivalence between the pharmaceutical equivalence drug product and a corresponding reference listed drug.
- Bioequivalence studies provide information on product and performance when there are changes in components, composition and method of manufacture after approval of the drug product.

Drug Profile^[4]

Torsemide

Torsemide [1-isopropyl-3-([4-(3-methyl-phenylamino)pyridine]-3-sulfonyl)urea] is a diuretic belonging to the pyridyl sulfonylurea class, and it seems that the ascending limb of Henle's loop is where it acts most often. The $\text{Na}^+/\text{2Cl}^-/\text{K}^+$ carrier from the cell's luminal side is mostly inhibited by loop diuretics. Following oral treatment, Torsemide is quickly absorbed, reaching its maximum peak plasma concentration within the first hour. Its bioavailability is about 80% and is not influenced by food. It is highly protein-bound (>99%). The drug is metabolized to a great extent (80%) in the liver. Renal clearance of the parent drug accounts for approximately 20% of total clearance. Torsemide exhibits linear pharmacokinetics and looks to follow a two-compartment open model. Its elimination half-life at the plasma terminal is roughly 3.5 hours. Clinical trials indicate that Torsemide is effective in the treatment of hypertension and edema as well as for other symptoms in patients with chronic renal failure, hepatic dysfunction or congestive heart failure.

Structure



Average Weight: 348.421 g/mol

Monoisotopic Weight: 348.125611216

Chemical Formula: $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$

Melting point: 162-165°C

Solubility: Soluble in DMSO at 18mg /ml and insoluble in water

Colour: White to off white

Synonyms: Torasemida, Torasemide, Torasemidum

Drug interaction: Abacavir - Torsemide may increase the excretion rate of Abacavir which could result in a lower serum level and potentially a reduction in efficacy.

Therapeutic use: Torsemide is used to help treat fluid retention (edema) and swelling that is caused by congestive heart failure, liver failure and kidney disease.

MATERIAL AND METHODS

Materials

Formulations

Following is the list of formulations procured from the local pharmacy of Coimbatore.

Table 1: A lists of the tested commercial tablets of Torsemide 10mg available in the Indian market.

SL NO	FORMULATION NAME	MANUFACTURER	BATCH NUMBER	MANUFACTURING DATE	EXPIRY DATE
1	DYTOR	CIPLA	SN31381	05/2023	07/2026
2	RETORLIX	LUPIN	TOB2200	05/2023	04/2025
3	TORGET	ZYDUS	BEZ1267	05/2023	04/2025
4	TORSENORM	ADHAM PHARMACEUTICALS	BHT2310	10/2023	09/2025

Equipments

Following are the list of instruments used for the study.

Table 2: Instruments which were used in the experiments.

S.NO	NAME OF THE INSTRUMENTS	MODEL
1.	UV-VISIBLE SPECTROSCOPY	OPTIZEN 2021UV
2.	ROCHE FRIABILITOR	FT 1020 S
3.	DISINTEGRATION APPARATUS	DT 1000
4.	DISSOLUTION APPARATUS	DS 8000

Chemical and reagents

Following are the list of chemicals used for the study.

Table 3: Chemicals used in the experiments and respective manufacturer.

S.NO	CHEMICAL/REAGENT NAME	MANUFACTURER
1.	Disodium hydrogen phosphate	Isochem Laboratories, Kochi.
2.	Potassium dihydrogen phosphate	Nice chemicals(P) LTD, Kochi

Preparation of Buffer solutions

Phosphate Buffer pH 6.8

Dissolve 28.80g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate in sufficient water to produce 1000ml.

**Figure 1: Phosphate buffer pH6.8.**

Uniformity of Weights

20 sample tablets from each brand were put on a digital analytical scale and weighed separately. The average weight was determined and the percentage (%) deviation of the individual tablets from mean weight was determined. In order to pass weight variation test, the tablet should be within the limits of the percentage deviation allowed by I.P.

Hardness Test

The hardness of different brand of tablets was determined by Monsanto hardness tester and measured in terms of Kg/cm². Ten sample tablets of each brand were obtained, and each tablet was sandwiched between the hardness tester machine's spindle until it broke. The amount of pressure needed to break the tablet was then noted.

Friability Test

10 tablets of each brand were taken and weight, these tablet subjected to abrasion using a Roche friabilator at 100 revolutions for 4 minutes. The tablets were dedusted carefully and weighed accurately again then percentage of weight loss recorded. The friability of the tablets was calculated using the formula.

% Friability = [(Initial weight – Final weight)/Initial weight] × 100

METHODS

Visual Inspection

The shape, size and color of the different brand of Torsemide tablets were examined visually. The size and thickness of tablets from each brand was examined with the help of Vernier caliper.



Figure 2: Friability apparatus.

Disintegration Test

Tablet disintegration time of randomly selected six tablets of each brand was determined at 37°C using disintegration apparatus employing distilled water as test fluid. The point at which there were no more tablet granules on the mesh was considered to be the disintegration time.



Figure 3: Disintegration Apparatus.

Thickness Test

Thickness is a unofficial test. Thickness of the tablet is inversely proportional to hardness. (increase in hardness decrease in thickness and vice versa). Thickness of tablet is measured by vernier caliper/screw gauge. It is determined for 10 tablets (cm or mm).

RESULT AND DISCUSSIONS**Characteristics of Torsemide Tablets****Visual appearance**

The selected brands of Torsemide were subjected to visual appearance tests which included colour and shape.

Table 4: Physical properties of selected brands of Torsemide.

BRAND NAME	SHAPE	COLOUR
DYTOR	CIRCULAR	WHITE
TORSENNORM	CIRCULAR	WHITE
RETORLIX	CIRCULAR	WHITE
TORGET	CIRCULAR	WHITE

(TABLE CLAIM-10mg)

Table 5: Results of evaluation parameters.

PARAMETERS	DYTOR	TORSENNORM	RETORLIX	TORGET
WEIGHT VARIATION**	0.08	0.22	0.23	0.17
LENGTH(cm)***	0.5	1.2	0.8	0.6
WIDTH(cm)***	0.6	1.8	0.9	0.7
THICKNESS(cm)****	1.2	1.2	1.3	1.3
S%FRIABILITY**	1.25	0.44	0.43	1.19
HARDNESS (kg/cm ²)***	3.5	2.5	3.5	3.5
DISINTEGRATION TIME(mins)****	1.13	0.55	1.14	1.20
DISSOLUTION(% AMOUNT OF DRUG RELEASE) #	95.73	97.35	96.45	95.21

(TABLE CLAIM= 10mg)

** - average measurement of 20 tablets

*** - average measurement of 10 tablets

**** - average measurement of 6 tablets

- measurement of 1 tablet

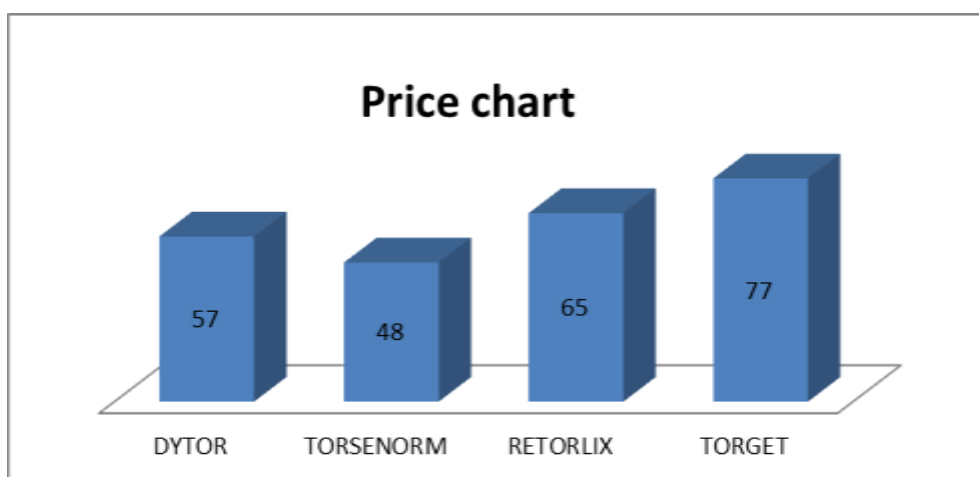


Figure 4: Comparison of price of all the brands.

CONCLUSION

Several generic versions of Torsemide tablets are accessible through India's drug delivery network. Because Torsemide tablets are being used in clinical settings more and more, it is necessary to keep an eye on and verify the quality of the brands that are on the market for drugs in order to do quality control assessments and replace generics. Every product exhibits satisfactory outcomes when it comes to weight variation, hardness, friability, thickness, disintegration, and dissolution profiles. According to USP and IP, every test that was part of the examination of the 10 mg Torsemide tablets IP was successfully completed. The key quality attributes of Torsemide 10 mg tablets IP are precisely specified and regulated. There aren't any unresolved quality issues that could harm the benefit balance. Due to the well-established efficacy of these tablets, patients taking antidiuretics were able to experience the minimal amount of side effects and desired therapeutic results. Everything met the expectations and was in line with the cross reference product. The product's quality was adequate. Thus, this investigation showed that samples of 10 mg of Torsemide that were obtained from Tamilnadu, India was produced in accordance with cGMP as well as other.

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