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Quality Assessment between Innovator Drug and Generic Drug of Dabigatran Etexilate Mesylate

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ABSTRACT

The purpose of this study was to conduct a comprehensive quality assessment between the innovator drug and generic version of dabigatran etexilate mesylate to ensure patient safety and efficacy. The various parameters such as physicochemical properties of the innovator and generic drugs were analyzed, including weight variation, dissolution test, disintegration test, assay was determined through UV- visible spectrophotometric method. Based on comparison, result was found to be within the pharmacopeial acceptable range. The comparison provides valuable insights into the similarities and differences between the two formulations, ensuring the quality and effectiveness of the generic drug as a viable alternative to the innovator drug. The study results will contribute to enhancing patient confidence and regulatory decision-making, ensuring that generic versions of dabigatran etexilate mesylate are safe and efficacious alternatives to the innovator drug, fostering wider access to essential medications, and promoting overall healthcare quality.

Keywords: *Quality assessment, Innovator drug, Generic Drug, Dabigatran Etexilate Mesylate, Safety and Efficacy, Pharmacopeial Range.*

INTRODUCTION

Dabigatran is an anticoagulant medication used for the prevention and treatment of blood clots. It belongs to the class of direct thrombin inhibitors, which work by inhibiting the activity of thrombin, an enzyme involved in the clotting process[1]. Developing countries like Nepal has received a provision of using a patented medicine without any royalty till July 01, 2034, through the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement as the country belongs to the least developed country list[2]. So, in the scenario of Generic Medicine in Nepal, different pharmaceutical companies are manufacturing the generic drugs without the proper information of the drug on therapeutic range, quality, safety, and efficacy. The country also lacks (Bioavailability and Bioequivalence) BABE analysis of medicines to assure the interchangeability of available brand-named generic medicines manufactured by different pharmaceuticals in Nepal due to the lack of well-equipped facilities, including reference preparations, competency, and economic constraints to perform in-vivo studies. Thus, this will ultimately give poor documentation on the quality of the generic medicines. Multitudes of substandard medicinal products are available in the Nepalese market, and about one-third of these fail to meet the requirements of quality standards. Due to this reason, many drugs have been recalled by the Department of Drug Administration (DDA). Assessing the quality of both innovator and generic versions of dabigatran etexilate mesylate is crucial for

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ensuring patient safety and efficacy. If there are differences in the quality attributes between the two versions, it could potentially lead to variations in drug performance, including differences in bioavailability, therapeutic effect, or adverse events. By conducting a thorough quality assessment, the study aims to identify any potential differences that could have implications for patient care.

MATERIALS

The active ingredients Dabigatran Etexilate Mesylate was received as a gift from National Healthcare Pvt. Ltd. Other materials used like Methanol, Chloroform, Distilled Water, Hydrochloric acid was provided by Karnali College of Health Sciences.

Methodology

Study Design: Descriptive study
Study Method: Quantitative and Qualitative
Study Site: Karnali College of Health Sciences

Criteria for Sample Selection

Inclusion Criteria

Only GMP Certified Nepalese companies registered in Nepal were taken.

Exclusion Criteria

1) Drugs which were not GMP certified and not registered in DDA were rejected.
2) Expired and visibly deteriorated drugs were excluded.

Samples

1) One innovator drug of Dabigatran Etexilate Mesylate capsule 110mg.
2) Two generic drugs of Dabigatran Etexilate Mesylate capsule 110mg.

Sample Size

3 different brands of Dabigatran Etexilate Mesylate dosage forms were brought from pharmaceutical industry and from retail pharmacy in Kathmandu Nepal.

Determination of Solubility

The solubility test of standard Dabigatran Etexilate Mesylate was performed in various organic and inorganic solvent.

Determination of λ_{max}

A solution of Dabigatran etexilate Mesylate with the concentration of 10 µg/ml was prepared in 0.01N HCl. The solution was scanned in UV visible spectrophotometer in the range of 200-400nm.

Preparation of Standard Calibration Curve of Dabigatran Etexilate Mesylate

10mg of Dabigatran etexilate Mesylate was weighed and dissolved in 100ml of 0.01N HCl solution to obtain a standard stock solution of 100µg/ml. From the stock solution a series of dilution were made from the working stock solution by pipetting out 1, 2, 3, 4, and 5ml respectively into separate 10ml VF for each and volume was made up to mark by 0.01N HCl to produce the concentration ranging from10 to 50µg/ml. The standard curve was obtained by plotting absorbance versus concentration (µg/ml)[3].

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Evaluation of Dabigatran Etexilate Mesylate capsules

Label information Dabigatran Etexilate Mesylate Capsule 110mg

The product code, Physical appearance, Batch number, manufactured date, Expiry date of all the drugs was analyzed. The shape, size, color of selected dosage form was examined visually. The height and the diameter of capsules were measured; average and standard deviation were calculated.

Weight Variation

Weight of 20 randomly selected Dabigatran Etexilate Mesylate capsules of same brand was weighed collectively to obtain mean weight. Then, the capsules were weighed, individually, empty capsules were weighed and the percentage deviation was calculated from the mean weight. The procedure was repeated for each brand[4].

$$\text{Deviation (\%)} = \frac{Average\ wight\ of\ capsule - weight\ of\ capsule}{Average\ weight\ of\ capsule} \times 100\%$$

Disintegration Test

The beaker was filled with 900ml of distilled water and the temperature was maintained at 37±2ºC.A standard motor driven device was used to move the basket assembly containing the capsules up and down at a frequency of 28- 32 cycles per minutes. Perforated plastic discs was used to prevent the floating of capsule and the time at which all the Dabigatran capsules passed through the sieve was the disintegration time and the average disintegration time were calculated[4].

In vitro Dissolution Study

900ml of dissolution medium was taken for Dabigatran etexilate 110mg capsules in each of six vessels of the apparatus. It was carried out by using Rotating Basket Apparatus. Temperature was adjusted at 37 ± 0.5ºC with the speed of 100 RPM using 0.01N HCl as a medium for 45min. Then 10ml sample was withdrawn from each of the vessels and filtered 1ml of filtrate solution was taken in 10ml VF and diluted up to mark and mixed. And then absorbance was measured at 326 nm by using UV- visible spectrophotometer[3].

Drug Content

Twenty capsules were weighed accurately and finely powdered. Capsule powder equivalent to110 mg was taken in 100ml volumetric flask. The sample was dissolved in 20 ml 0.01N HCl solution, shaken and diluted up to mark. The solution was filtered using filter paper. From above filtered solution 1ml was taken and transferred into 100ml volumetric flask and diluted upto mark. The assay was determined by using a UV visible spectrophotometer at 326nm[5].

RESULT AND DISCUSSION

Determination of Solubility

Solubility study was carried out under different solvent and its observation is tabulated below:

Table 1: Solubility Profile of Dabigatran Etexilate Mesylate

Solvent	Solubility
Methanol	Soluble
Chloroform	Sparingly soluble

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0.01N HCl	Soluble
Ethanol	Slightly soluble
Distilled water	Soluble
Acetone	Insoluble
Isopropanol	Sparingly soluble

Determination of λ_{max}

Dabigatran etexilate Mesylate showed maximum absorbance at wavelength 326 nm in 0.01N HCl and reported λ_{max} was 326 nm. The result observed is presented below.

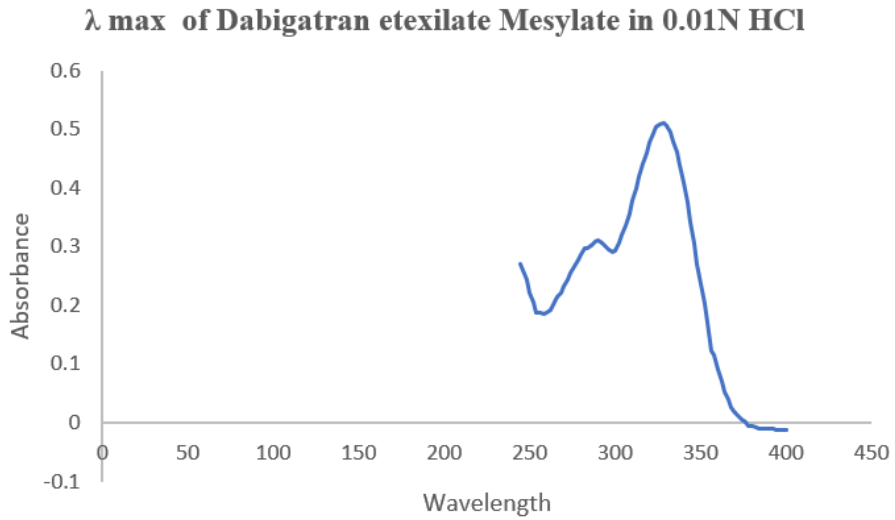

Fig. 1: λ max of Dabigatran etexilate Mesylate in 0.01NHCL

Standard Calibration Curve of Dabigatran Etexilate Mesylate

A linear relationship was obtained in Beer lamberts of Dabigatran Etexilate Mesylate in 0.01N HCl (y = 0.0522x - 0.0527, R^2 = 0.9981). The graph obtained after plotting absorbance(y) vs. concentration(x) is shown in Figure. When absorbance v/s concentration was plotted, a straight line was obtained which suggests that the process used to measure the absorbance of sample is validated.

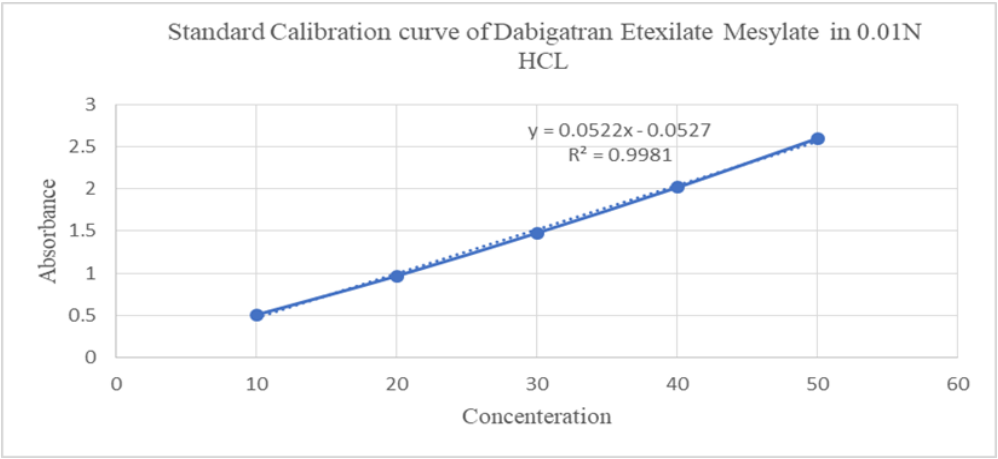

Fig. 2: Standard Calibration Curve of Dabigatran Etexilate Mesylate in 0.01N HCL

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Label information Dabigatran etexilate Mesylate capsule:
It includes Serial number, Product code, Batch number, Manufacture date, Expiry date and price. All the drugs were analyzed within their shelf-life period.

Table 2: Label Information of Dabigatran Etexilate Mesylate Capsules

S.N	Product code	Batch no.	Mfg. Date	Exp. Date	Price
1	Innovator	103433	MAR. 2021	FEB. 2024	Rs. 1149
2	DAB1	DBS-07	OCT. 2022	SEP.2024	Rs. 800
3	DAB2	DBCF 22019	NOV. 2022	APR. 2024	Rs. 700

In below table, all the brands were found to have spherical pellets. Among all the brands diameter of capsules ranges from and height ranges from18.79 mm to 21.14mm.

Table 3: Physical parameters of Dabigatran Etexilate Mesylate capsules

S.N	Product code	Type	Shape	Color	Diameter	Height	Unique identifi-cation code	Packaging type
1	Innovator	Hard gelatin capsule	Spherical pellets	Off white	6.48mm	19.07mm	Present	Blister
2	DAB1	Hard gelatin capsule	Spherical pellets	Off white	6.99mm	18.79mm	Present	Blister
3	DAB2	Hard gelatin capsule	Spherical pellets	Off white	7.53mm	21.13mm	Absent	Strip

Uniformity of Weight
All the samples investigated for uniformity in weight were found within the pharmacopeial limit i.e., within 7% deviation.

Table 4: Uniformity of Weight of Dabigatran Etexilate Mesylate

S.N	Product Code	Uniformity of Weight
1	Innovator	310±3.45
2	DAB1	320±4.73
3	DAB2	318±6.42

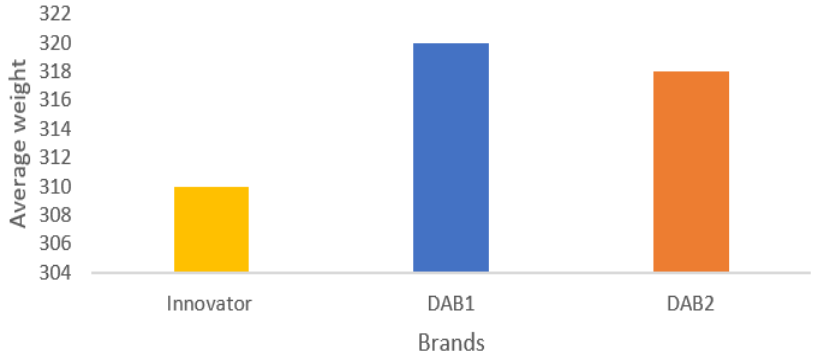

Fig. 3: Comparison of different brands weight variation of different brands of Dabigatran Etexilate Mesylate

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Disintegration Study

The disintegration time for hard gelatin capsule IP specification is not more than the 15min. From below figure disintegration time for Dabigatran etexilate mesylate capsule ranges from10min 8 sec to 15min 5 sec. All the brands comply with IP specifications.

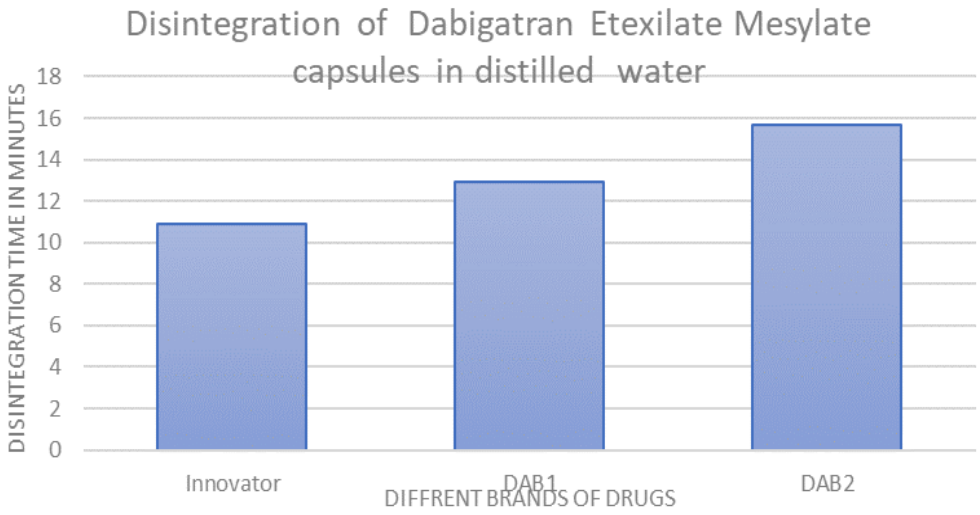

Fig. 4: Disintegration of Dabigatran Etexilate Mesylate capsules in distilled water

In-Vitro Dissolution Study

Table 5: In-Vitro Dissolution Study of different brands of Dabigatran Etexilate Mesylate

TIME(MINUTES)	INNOVATOR	DAB1	DAB2
0 Min	0%	0%	0%
10 Min	39.40%	40.84%	45.38%
20 Min	81.79%	82.61%	72.42%
30 Min	87.79%	88.66%	83.77%
40 Min	95.65%	93.93%	88.11%
45 Min	102.61%	98.45%	91.58%

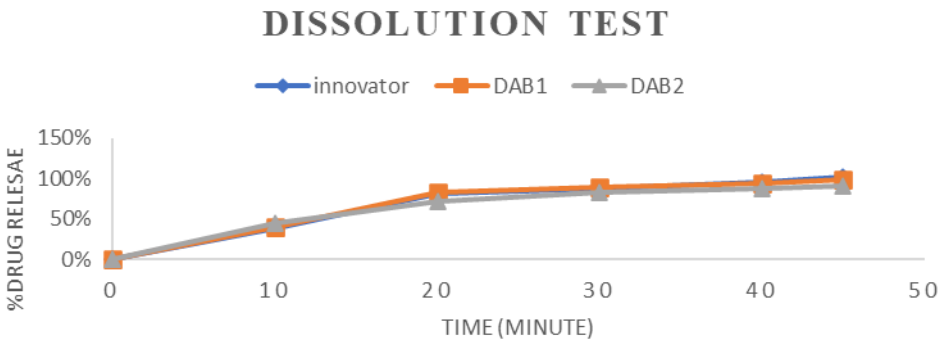

Fig. 5: Graph showing the drug release of different brands of Dabigatran Etexilate Mesylate

The data obtained from the in vitro drug release study performed up to 45minutes. The percent drug released was obtained in the range from 91.58% to 102.61% which gives clear indication that capsules show the immediate release profile. i.e., it complies with IP specifications.

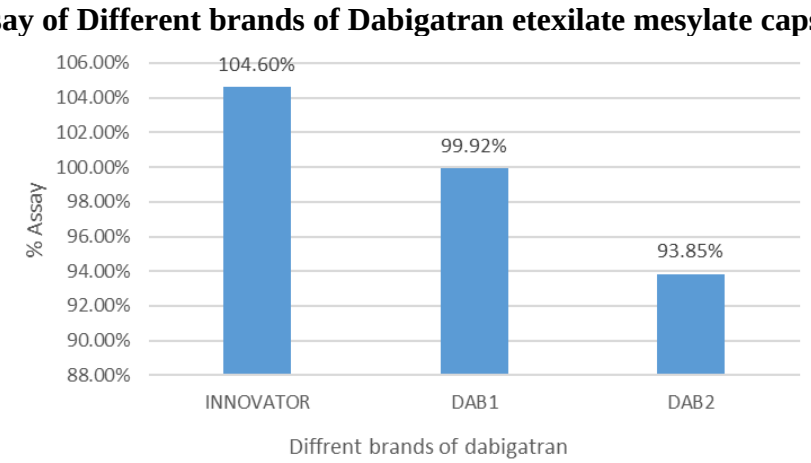

Fig. 6: Comparison of assay content (Percent %) of different brands of Dabigatran etexilate mesylate capsule

The assay was determined by using a UV visible spectrophotometer at 326nm. In the present study the Assay content of different brands of dabigatran capsule was 93.85% to 104.60% which is within the acceptable range i.e. 90% to 110%.

CONCLUSION

The results suggest that all the tested brands satisfied the pharmacopeial requirements i.e., weight variation, disintegration test, dissolution rate and assay. All brands comply with weight variation according to the IP specification. All the brands passed the disintegration test, dissolution test releasing more than 80% of drugs within 45 minutes as per IP specification. All the 3 brands complied with the assay test and were within the acceptable range of 90% to 110%. The findings of present study show that all the generic brands are equivalents to innovator product with respect to the in vitro drug release features and hence these products could be used interchangeably. In general, generic versions of medicines are less costly than innovator product. Hence moving to generic prescriptions will contribute to the noteworthy cost saving for the patients.

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