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COMPREHENSIVE STUDY OF *IN-VITRO* QUALITY CONTROL AND PHYSICOCHEMICAL EVALUATION OF SELECTIVE BRANDS OF DICLOFENAC SODIUM.

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Abstract:

This study aims to investigate the in-vitro quality control and physicochemical properties of different marketed brands of diclofenac sodium tablet. The research will involve conducting various laboratory tests, including weight variation test, content uniformity test, drug assay, friability test, and the disintegration and dissolution test. Three brands of diclofenac sodium tablets were used in the study, named brand A, brand B & brand C. Quality control (QC) test results for diclofenac sodium tablets shows that brand A, brand B & brand C confirm to the Indian pharmacopeia (IP) standards.

In terms of weight variation, brand A, B & C have an above the mean weight limit variation of 1.288%, 1.222% and 2.538 respectively. The lower mean weight limit variations are 1.377%, 1.052% and 1.522% respectively, which are within the 7.5% standard limits of IP. Friability tests show that brands A, B and C have an average friability of 0.090%, 0.029% and 0.050% mass loss, which are within the1% mass loss limits of IP.

In terms of drug assay, All brands A, B and C fall under the IP parameter of 90%-110%,respectively.The disintegration test shows that brand A, brand B and brand C fall within a 20-minute time interval segment with disintegration time calculated as14min,14.2 min and 15.3 min for brands A,B and C respectively. Brand A, B and C of diclofenac sodium has a drug dissolution percentage of 97.77%, 98.26% and 99.23% respectively within a 45-min sampling time interval.

Keywords: *Diclofenac sodium, quality control testing, weight variation, disintegration, friability, dissolution, drug assay by Non aqueous titration and UV spectrophotometry.*

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INTRODUCTION:

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID), which is used for inflammation, joint stiffness, rheumatic and non-rheumatic conditions. It has a potentially short half-life (approx 2 hours) and the drug can be administered orally, rectally or intramuscularly. It is comparable to other analgesics, has a fast duration of action, and limits potential drug accumulation in the body[2]. The study is intended to analyze certain critical parameters in terms of quality control testing of the diclofenac sodium tablets marketed by various manufactures using an in vitro test. The quality testing involves a wide range of instruments such as friabilator, dissolution test apparatus, disintegration test apparatus, ultraviolet-visible spectrophotometer, digital pH meter, electronic weighing balance, etc. Some of the tests performed are as follows: friability, disintegration test, weight variation test, drug assay, dissolution test, drug content uniformity, etc[1]. The study's aim was to check the quality parameters of the marketed diclofenac tablet by in vitro testing to ensure that all tablets possess the pharmacopeial limits.

We have conducted pre-marketing and post-marketing bioequivalence studies of several drug products. However, increasing emphasis is being placed on in vitro physiochemical quality testing because it does not involve human subjects and have lower cost. In numerous clinical trials the efficacy of diclofenac is equivalent to that of the many newer and established NSAIDs with which it has been compared extensive clinical experience has been gained with diclofenac, clearly establishing its safety profile. It is well tolerated compared with other NSAIDs and rarely produces gastrointestinal ulceration or other serious side effects. Thus, diclofenac can be considered as one of the few NSAIDs of 'first choice' in the treatment of acute and chronic painful and inflammatory conditions.

Quality control (QC) testing ensures drug safety, efficacy, and effectiveness. It involves specific instruments to ensure the quality of drug testing as per set guidelines. Some of the testing procedures are as follows: friability, weight variation test, disintegration test, dissolution test, and drug assay. The equipment used are as follows: friabilator, electronic weighing balance, mixer, ultraviolet (UV)-visible spectrophotometer, digital pH meter, dissolution test apparatus, and disintegration test apparatus[2-5]

1. **ORGANOLEPTIC PROPERTIES:**
   Consumer acceptance, managing lot-to-lot consistency, and tablet-to-tablet uniformity all depend on the overall design, identity, and elegance. The general appearance of the tablet can be controlled by assessing several characteristics such as size, color, shape, presence or absence of taste, and odor, etc.
2. **WEIGHT VARIATION TEST:**
   Weight variation is a checking parameter of tablet in which we check the average variation in weight of tablet, that are these are of same weight or they are variable from the accepted range. Weight variation indicate the over involvement of medicament.
3. **DISINTEGRATION TIME :**
   Disintegration is the process where tablets crushed into tiny particle or granules. From this process, the drug is easily obtained in the form of solution, in disintegration tester the tablet is tested for the disintegration time.
4. **DISSOLUTION TIME TEST :**
   Dissolution is the process in which a substance forms a solution. Dissolution testing measures the extent and rate of solution formation from a dosage form, such as tablet, capsule, ointment, etc. The dissolution of a drug is important for its bioavailability and therapeutic effectiveness.
5. **DIMENSION TEST:**
   The dimension of the tablet is thickness and diameter. Thickness and diameter of a tablet are measured using a vernier calipers or screw gauze.
6. **HARDNESS TEST :**
   The breaking force of tablets is commonly called "hardness". Tablets require a definite amount of hardness to withstand mechanical shocks of handling in manufacture, packaging, and transportation without affecting the disintegration limit.
7. **FRIABILITY TEST :**
   Friability testing is used to test the durability of tablets during packing processes and transit. This involves repeatedly dropping a sample of tablets over a fixed time, using a rotating drum with a baffle. The result is inspected for broken tablets, and the percentage of tablet mass lost through chipping.
8. **NON-AQUEOUS TITRATION:**
   Non-aqueous titration is an acid-base titration involving solvents other than water i.e. there is no involvement of water. Non-aqueous titrations are the titrations in which weakly acidic or basic substances are estimated using non-aqueous solvents to get a sharp end point.
9. **UV SPECTROPHOTOMETRY:**
   Ultraviolet and visible absorption spectrophotometry is the measurement of the absorption of monochromatic radiation by solutions of chemical substances, in the range of

185 nm to 380 nm, and 380 nm to 780 nm of the spectrum, respectively

MATERIAL AND METHODS:

Material:

An analytical pure sample of diclofenac sodium was procured as a gift sample from Aarti Drugs Limited (Mumbai, India). Tablet formulation Reactin 50 (Cipla Ltd.), Divon 50 (Micro Labs Limited) was procured from local pharmacy with labeled amount 50mg per tablet, Diclofenac gastro resistant tablet IP 50mg (Unicure India Limited) was procured from Government Hospital.

Apparatus:

Spectral measurement will be carried out using Spectrophotometer, double beam spectrophotometer colour screen AU-2703 systronics India Limited with "21 CFR compliant software" using 5-100mm cuvettes of all kinds, Ultrasonicator – Lab line USB 1.5L H, Infra Digital electronic balance, Rolex dissolution rate test apparatus, Expo HI-tech tablet disintegration test apparatus, Rolex friability test apparatus.

Chemicals:

All the following chemicals used in the study were of analytical grade:

Distilled water, Glacial acetic acid, Perchloric acid, Acetic anhydride, Potassium hydrogen phthalate, Potassium Chloride (0.2M), Sodium hydroxide (0.2M), Phosphate buffer (7.4 pH), Hydrochloric acid buffer (1.4 pH), Sodium dihydrogen orthophosphate, Crystal Violet.

DIMENSION TEST[6-11]:

The dimension of the tablet is thickness and diameter. Thickness and diameter of a tablet are measured using a vernier calipers or screw guage.

HARDNESS TEST:

The hardness of a tablet is tested using the hardness tester. The tablet is placed across the diameter in between the spindle and the anvil. Adjust the knob to hold the tablet in position. The reading of the pointer is adjusted to 'zero'. The pressure is increased uniformly to break the tablet. "Hardness factor", the average of the several determinations is determined and reported.

FRIABLITY TEST:

Friability testing is a method, which is employed to determine physical strength of uncoated tablets upon exposure to mechanical shock and attrition. In simple words, friability test tells how much mechanical stress tablets are able to withstand during their manufacturing, distribution and handling by the customer. It means Surface Erosion by certain mechanical shock and lost of material from intact tablet.20 randomly-selected units of each formulation were examined. They were weighted, placed in the friabilator (25 revolutions /minute for 4 min), de-dusted and weighted again, and friability was determined as% weight loss.

WEIGHT VARIATION TEST:

This test examines uniformity in accordance with the formulation of each batch of tablets, which illustrates its content. In this study, we selected 20 tablets of diclofenac sodium from Brand A, which were weighed individually and collectively. Weight variation was calculated using the formula - (Initial weight - Average weight)/Average weight X 100. It is meant to compare the IP limits and the data were recorded in table format. The same procedure was repeated for Brand B & C.

CONTENT UNIFORMITY TEST:

10 Tablets are triturated to form fine powder and from this mixture 50 mg equivalent weight powder was weighed and transferred to a volumetric flask. It is then dissolved in phosphate buffer pH 7.4 and was made up to 100 ml to get stock solution A.1ml of this stock solution A is taken in 100ml volumetric flask and diluted with phosphate buffer pH 7.4 and made up to 100 ml to get Stock B. The absorbance of this solution is measured at 276nm using double beam spectrophotometer colour screen AU-2703. The drug content is estimated by obtained absorbance value.

DISITEGRATION TEST:

6 randomly-selected unites of each formulation were examined using 0.1 N HCL for 2 h followed by phosphate buffer (pH 7.4) as disintegration medium. The basket rack was placed in a 1000 ml vessel containing 900 ml disintegration medium maintained at 37 ± 2 °C with the test unit remaining 1.5 cm below the surface of the liquid on their upward movement and above 2.5 cm from the bottom of the beaker in their downward movement. The basket rack moved up and down (5–6 cm) at a frequency of 31 cycles per minute. Range of disintegration time (time to no particle on the basket) was determined.

DISSOLUTION TEST:

In vitro dissolution was performed by using IP pharmacopoeia dissolution type II apparatus at of 37 ± 0.5 °C with the rotation speed 50rpm/min and 900 ml of dissolution medium in per vessel used. 8 randomly-selected units of each formulation were examined using 0.1 N HCL for 2 h followed by phosphate buffer (pH 7.4) as dissolution medium

(900 ml), one unit in each vessel, a stirring rate of 50 ± 1 rpm, and a temperature of 37 ± 0.5 °C. The test ended with a stirring rate of 50 rpm for 15 min (infinity). A sample of 5 ml was withdrawn from a zone midway between the surface of the dissolution medium and the top of the rotating blade (not less than 1 cm from the vessel wall) and was immediately replaced with an identical volume of fresh medium. Samples were withdrawn at 60 and 120 min in 0.1 N HCl and at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 min phosphate buffer.

DRUG ASSAY:

CHEMICAL METHOD:

Weigh accurately about 0.2gm of diclofenac sodium dissolve in 30ml of glacial acetic acid, and titrate with 0.1M perchloric acid; the end point was determined by using crystal violet as indicator. The end point was blue to green. Each ml of 0.1N perchloric acid was equivalent to 0.03181 gm of diclofenac sodium.

ANALYTICAL METHOD:

Preparation of standard solution:

The standard stock solution of Diclofenac sodium was prepared by accurately weighing & transferring, 100 mg of API to 50 ml of volumetric flask. Then take from that 2.5ml and add to 50ml volumetric flask and make up with distilled water to get final standard stock solution (100µg/ml) was further diluted with distilled water to obtain 05-25 µg/ml Diclofenac sodium solutions.

Preparation of calibration curve:

For the preparation of standard calibration curve, concentration of 05-25 µg/ml were prepared by pipetting out 0.5, 1, 1.5, 2, and 2.5ml, from the 100 µg/ml solution in to a 10 ml volumetric flask and made up the volume with distilled water. The absorbance of each solution was measured at 276 nm against distilled water as blank Calibration curve of the diclofenac was plotted by taking the absorbance obtained on y axis and theconcentration of the solution on x-axis (Figure 3). The curve showed linearity in the range of 05-25 µg/ml with correlation coefficient 0.9929.

Sample Preparation:

Twenty tablets each containing 50mg of Diclofenac sodium were weighed crushed to powder and average weight was calculated. Powder equivalent to 100 mg of Diclofenac sodium was transferred in 50 ml of volumetric flask. A 25ml of distilled water was added and sonicated for 15minutes. Then solution was further diluted up to the mark with distilled water. The solution was filtered using Whatmann filter paper, first 5ml of filtrate was discarded. This solution was further diluted to obtain 15µg/mL solution with water, subjected for UV analysis using distilled water as blank.

RESULT AND DISCUSSION:

Three brands of diclofenac sodium 50mg tablet were purchased from local retail pharmacy. All the brands of diclofenac sodium tablet use were within their shelf life during the study period as shown in table (1).

Table 1: Brands of diclofenac sodium used in the study

S. No.	Brand Name	Manufacturer	Mfg date	Exp date
1	Divon 50 (A)	Micro labs ltd.	Dec 2022	Nov 2024
2	Reactin 50 (B)	Cipla ltd.	Sep 2022	Aug 2024
3	Diclofenac gastro resistant tablet IP 50mg (C)	UnicureIndia ltd.	Jan 2023	Dec 2024

The QC tests performed are as follows: organoleptic evaluation, weight variation, drug assay, friability, disintegration, and dissolution tests. All tests performed were within the pharmacopeia limits. It is crucial that commonly prescribed NSAIDs like diclofenac sodium conform as per IP standards in order to maintain drug safety, efficacy, and effectiveness in the human body

ORGANOLEPTIC PROPERTIES:

Table 2 : Organoleptic Properties of various brand of diclofenac sodium.

Brand Name	Colour coating	Taste	Shape	Odour
A	pink	bitter	Rounded bi convex	characteristic
B	Yellow ochre	bitter	Rounded bi convex	characteristic
C	brown	bitter	Rounded bi convex	characteristic

DIMENSION TEST:

Uniformity of thickness and diameter for 20 tablets from each brand was shown in tables (3 and 4). Crown thickness and diameter uniformity of tablets are necessary not only for consumer requirements but also for packaging. According to IP pharmacopeia + 5% variation is permissible. From the tabulated results, it was obvious that the thickness and diameter values of the branded tablets were within limit (mean valve ± SD,n=5).

Table 3: Thickness uniformity for various brand of diclofenac sodium tablet.

Code	Brand name	Mean thickness (cm) (n=5)	% deviation	% thickness variation limit
A	Divon 50	0.342	1.156 ± 0.005477	5
B	Reactin 50	0.396	0.502 ± 0.010954	5
C	Govt. 50	0.298	-0.662 ± 0.004472	5

Table 4: Diameter uniformity for various brand of diclofenac sodium tablet.

Code	Brand name	Mean thickness (cm) (n=5)	% Diameter variation limit
A	Divon 50	1.562 ± 0.015811	3
B	Reactin 50	0.286 ± 0.014832	3
C	Govt. 50	0.334 ± 0.014832	3

HARDNESS TEST:

Hardness is one of the most important physical features for evaluating tablet. It may affect tablet friability, disintegration time and bioavailability. Too hard tablets may result in a decrease in the release of the drug. A digital hardness tester was used to measure the hardness of 3 different brands (Mean values ± SD, n=10).

Table 5: Hardness of various brand of diclofenac sodium tablet.

Code	Brand name	Average hardness (kg/cm^2)	Range allowable
A	Divon 50	4.979 ± 0.38	4.191 - 6.468 kg/cm^2
B	Reactin 50	4.721 ± 0.35	4.191 - 6.468 kg/cm^2
C	Govt. 50	4.191 ± 0.35	4.191 - 6.468 kg/cm^2

The observed results are shown that all different brands of tablets hardness limit 4-9 kg/cm^2 (Table 5). In the study, it was found that all brands of diclofenac sodium tablet passed the test of hardness and had acceptable crushing strength of between 4.191 kg/cm^2 to 6.468 kg/cm^2.

FRIABILITY TEST:

Friability test for 20 tablets from each brand was shown in table (6). According to IP pharmacopeia, conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. From the tabulated data it was obvious that friability values of the branded tablets were within limit.

Table 6: Friability values for branded Diclofenac sodium tablets.

Code	Brand name	% Friability	Limit %
A	Divon 50	0.090	1
B	Reactin 50	0.029	1
C	Govt. 50	0.050	1

The average % friability for the brand A was calculated to be – 0.090
The average % friability for the brand B was calculated to be – 0.029
The average % friability for the brand C was calculated to be – 0.050

WEIGHT VARIATION TEST:

The weight variation test results are meant to maintain drug uniformity and distribution. The test results show that all brands of diclofenac sodium - Brand A, Brand B and Brand C - confirm to IP standards.
The highest percentage variation for Brand A upper % deviation was 1.288% and the lowest % deviation was 1.377%.

The highest percentage variation for Brand B upper % deviation was 1.222% and the lowest % deviation was 1.052%.
The highest percentage variation for Brand C upper % deviation was 2.538% and the lowest % deviation was 1.522%.
There were a total of 20 tablet readings for each brand. Each tablet was weighed three times. The average of all three readings was calculated, rounded off, and the percentage weight variation was calculated as mentioned in the procedure above. A graph with the percentage weight was plotted for Brand A, Brand B and Brand C.
The results are given in Tables 7&8 and Figures 1-3 respectively.

Table 7: percentage weight variation limit for Brand A, B and C

Tablet No.	Brand A % wt. Variation	Brand B % wt. Variation	Brand C % wt. Variation
Highest	1.288	1.222	2.538
Lowest	1.377	1.052	1.522

Fig. (01) Graph of percentage weight variation of Brand A

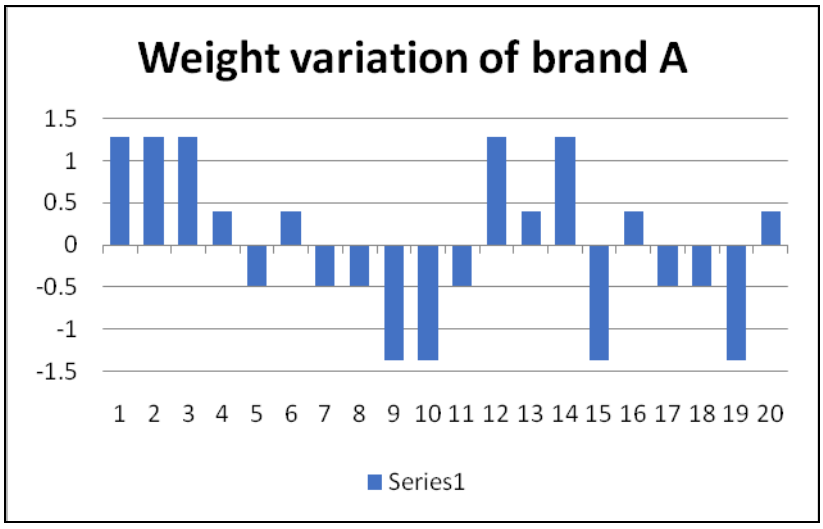


Fig. (02) Graph of percentage weight variation of Brand B

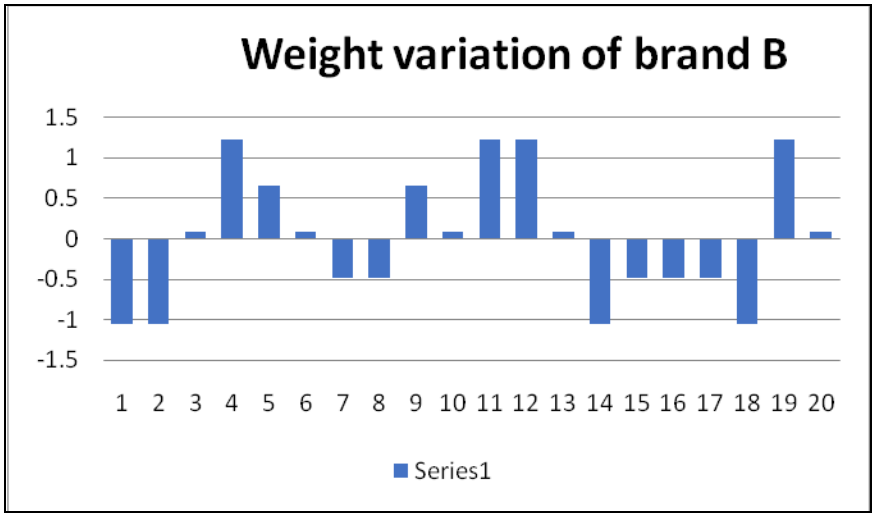
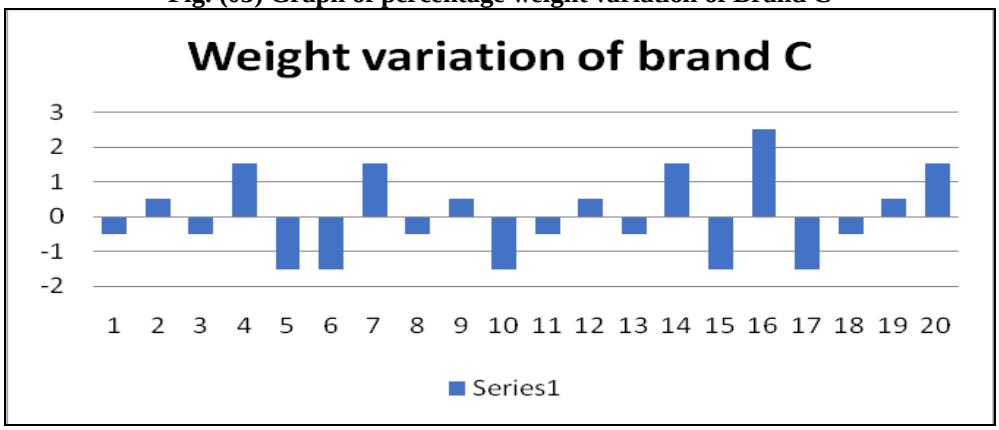


Fig. (03) Graph of percentage weight variation of Brand C



CONTENT UNIFORMITY TEST:

The drug content uniformity result of various brands of diclofenac sodium tablets were within the IP limits (± 10%).The results shown in the table given below

Table No 8: Drug content uniformity of Brand A, B and C

S. No.	Brands	Drug Content %
1	Divon 50	99.7
2	Reactin 50	98.3
3	Govt. 50	99.1

DISINTEGRATION TIME:

As per IP standards, the disintegration time for uncoated tablets is within 1 hour. As per the QC tests performed, the disintegration time for Brand A is 14 minutes, the disintegration time for Brand B is 14 minutes while the disintegration time for Brand C is 15 minutes. As per the results, all brands A, B and C confirms to the IP standards.

Table 9: Disintegration time of Brand A, B and C.

S. No.	Brands	Disintegration time in stimulated gastric fluid (0.1M HCl for 2 hr)	Disintegration time in 7.4 pH Phosphate Buffer (after 2 hour)
1	Divon 50	No disintegration up to 120 min	14 minute
2	Reactin 50	No disintegration up to 120 min	14.2 minute
3	Govt. 50	No disintegration up to 120 min	15.3 minute

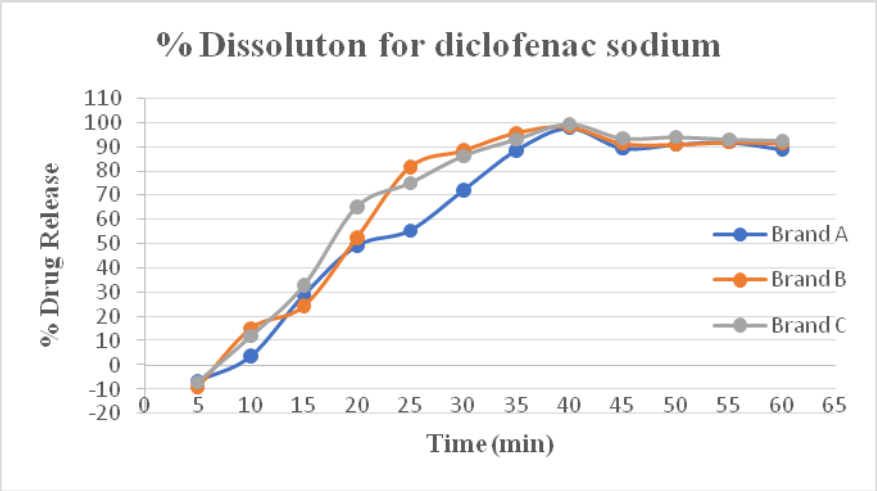
DISSOLUTION TIME:

As per test result Table (11), a Brand A tablet releases 97.77 % drug in 40 minutes, Brand B 98.26 % in 40 minutes while Brand C table releases 99.23 % in 40 minutes. The data provided indicated the all brand of diclofenac sodium were dissolved at fast rate, as shown in the graph (04). The percentage of drug released by all of the brands increased during its peak rate of dissolution, where it continued slowly until almost all the drug was released. All brands exhibited almost similar rate of release of the drug over a period of time.

Table 10 : Drug dissolution of all brands of diclofenac sodium tablet.

Sampling time (minutes)	Brand A % Drug Dissolution	Brand B % Drug Dissolution	Brand C % Drug Dissolution
10	3.49	15.16	11.76
20	49.17	52.58	65.21
30	72.01	88.54	86.11
40	97.77	98.26	99.23

Graph (04) : % Dissolution for diclofenac sodium tablet of all brands (Brands A, Brands B and Brand C)

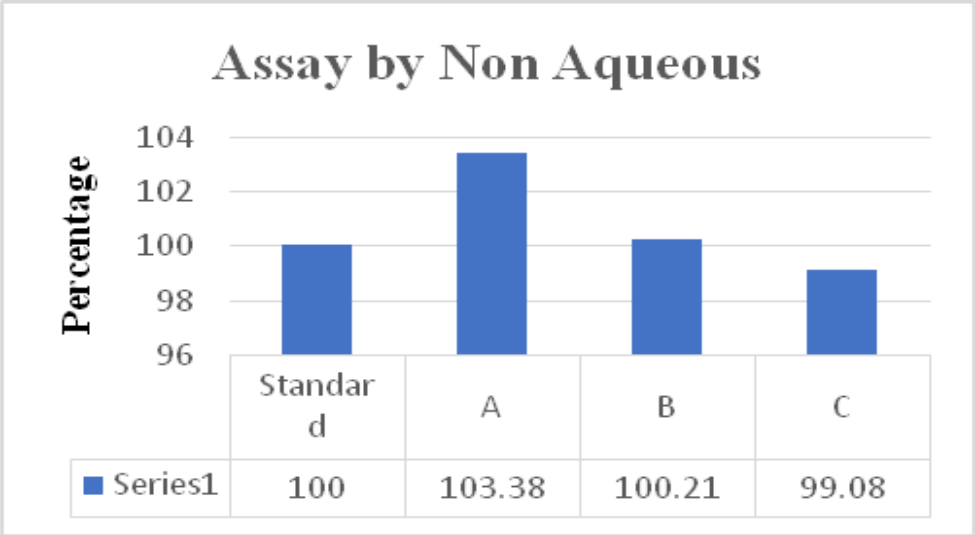


DRUG ASSAY:

1) Chemical Method (Non aqueous titration) :

Twenty tablets were weighed and crushed using motar and pestle. Quantity of powder equivalent to 0.2gm of diclofenac sodium dissolve in 30ml of glacial acetic acid, and titrate with 0.1M perchloric acid, The end point was determined by using crystal violet as an indicator. The end point was blue to green. Each ml of 0.1N perchloric acid was equivalent to 0.03181 gm of diclofenac sodium.

Fig. (05) Assay Graph of Brand A, B, C



2) Analytical Method (UV Spectroscopy) :

Twenty tablets each containing 50mg of Diclofenac sodium were weighed crushed to powder and average weight was calculated. Powder equivalent to 100 mg of Diclofenac sodium was transferred in 50 ml of volumetric flask. A 25ml of distilled water was added and sonicated for 15minutes. Then solution was further diluted up to the mark with distilled water. The solution was filtered using Whatmann filter paper; first 5ml of filtrate was discarded. This solution was further diluted to obtain 15µg/mL solution with water, subjected for UV analysis using distilled water as blank. The absorbance of this solution was measured on UV - spectrophotometer at 276 nm wave length. The assay values for all three brands are given in table (11).

Table 11 : Standard Calibration data of diclofenac sodium in distilled water.

Sr. No.	Concentration (µg/ml)	Absorbance
0	0	0
1	5	0.214
2	10	0.428
3	15	0.606
4	20	0.720
5	25	0.994

Fig. (06) Standard calibration curve of pure diclofenac sodium in distilled water at 276 nm.

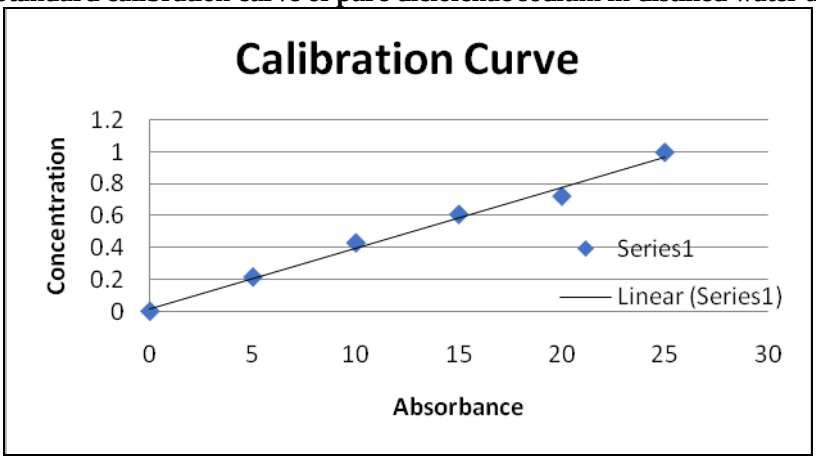
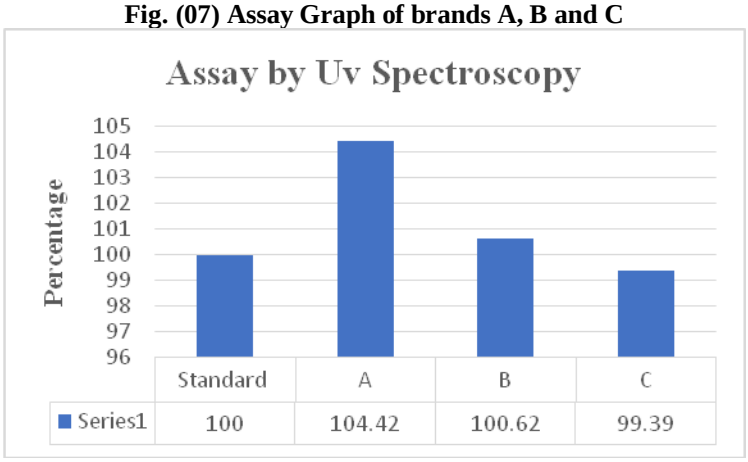


Table 12 : Assay value for all three brands of diclofenac sodium 50mg enteric coated tablet

Brands	A	B	C
% Assay	104.42	100.62	99.39

Fig. (07) Assay Graph of brands A, B and C



CONCLUSION:

The three brands of the Diclofenac sodium enteric coated tablets evaluated in this study namely Divon 50 (Brand A), Reactin 50 (Brand B) and Govt. 50 (Brand C). This work determined the quality parameters of three brands of diclofenac sodium were organoleptic Properties, hardness, dimension, friability, Disintegration time, dissolution, drug content and drug assay.

The study also emphasized the need of constant surveillance on marketed drug product by the government, manufacturer and independent research groups to ensure supply and availability of quality medicines for the patients.

Results related to QC testing of diclofenac sodium tablets show that such tests are necessary to determine the safety, efficacy, and bioavailability of a dosage form. A comprehensive range of analysis helps evaluate drugs qualitatively and quantitatively, and these tests must be performed from time to time in order to validate the drugs as per pharmacopeia standards and maintain drug safety and effectiveness for the human body.

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