WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 13, 840-855. Research Article ISSN 2277– 7105

POST COMPRESSION EVALUATION AND *IN-VITRO* DISSOLUTION ASSESSMENT OF VARIOUS MARKETED DICLOFENAC SODIUM TABLETS (50MG) IN INDIA

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Article Received on
01 Sept. 2020,

Revised on 22 Sept. 2020,
Accepted on 12 Oct. 2020

DOI: 10.20959/wjpr202013-18979

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ABSTRACT

The aim of this work was to compare the post compressional data and investigate dissolution behavior of five different marketed brands of enteric coated Diclofenac Sodium tablets(50mg) obtained from local pharmacies, Davanagere. Diclofenac Sodium is moderately water-soluble drug which comes under BCS Class (II). All the formulations contain same amount of drug and different number of excipients. These five different brands of diclofenac sodium are tested by considering different parameters according to standard guidelines. In the present study, these brands were compared in terms of diameter, thickness, weight variation, hardness, friability, drug content, disintegration and dissolution. The marketed product Voveran showed 85.93% in three hours when compared to other marketed products. However, Dicloran showed 75.11 % in three hours which was almost nearer to the drug release of Voveran. Furthermore, based on the release report obtained by the dissolution studies, similarity and dissimilarity factor between marketed products were identified. All the parameters studies of preferred marketed tablets of diclofenac Sodium(50mg) showed varied results. However, these results obtained were within prescribed limits.

KEYWORDS: Diclofenac Sodium, weight variation, friability, disintegration, dissolution.

INTODUCTION

Diclofenac sodium is the anti-inflammatory agent, which is the first phenylacetic acid derivative. Diclofenac sodium is used as an analgesic, antipyretic and anti-inflammatory agent.[1] these are mediated via prostaglandin inhibition. This prostaglandin inhibition itself intercede via the cyclooxygenase (COX) enzyme inhibition. Cyclooxygenase (COX) enzymes are 2 types. COX-1 is intricate in 'housekeeping' activities such as normal functioning of platelet, renal blood flow regulation and protect gastric mucosa by providing cytoprotective action. COX-2 is intricate in the retaliation to damage of tissue, pain and inflammation. The COX-2 inhibitor has been related with greater rate of cardiovascular antipathetic events.[2]

Diclofenac sodium mechanism of action

COX-1 and COX-2 enzymes are impeded by the diclofenac which is NSAID`S. Inhibition 0f synthesis of prostanoids such as prostaglandin [PG]-$E_2$, $PGD_2$, $PGF_2$, prostacyclin [$PGI_2$] and thromboxane [TX]$A_2$ by COX isoenzymes where NSAID`S binds, the presiding prostanoid generated in inflammation is PG-E_2 and analgesic, anti-inflammatory character of diclofenac is hang on the inhibit synthesis of PG-$E_2$by NSAID`S.[3]

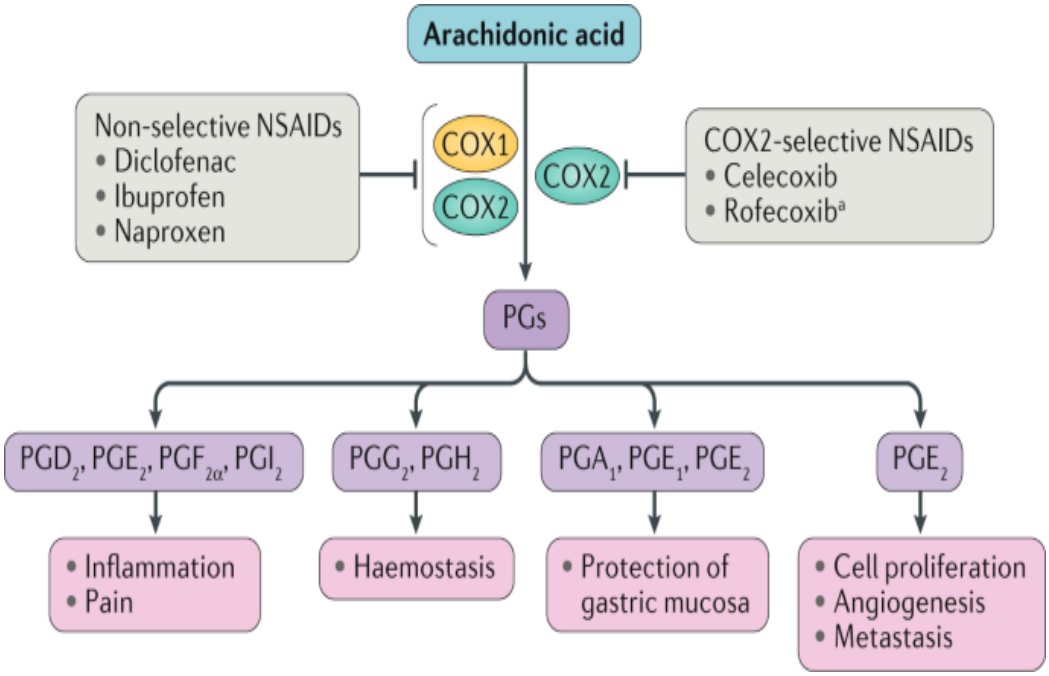

Fig 1: Mechanism of action of Diclofenac sodium.

Diclofenac is an NSAID`s is the first line remedy for chronic and acute pain. Diclofenac was the rational drug design product deploy on the phenylbutazone, indomethacin and mefenamic

acid structure. Two chlorine group added in ortho position of phenyl ring leads to lock of ring in maximal torsion which seems to be increase in potency.[4] Diclofenac sodium is the mono sodium salt which is the delayed release tablet 2 -[(2,6-dicholorophenyl) amino] benzene acetic acid.[5]

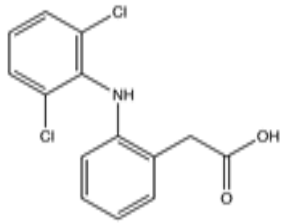

Fig 2: Structure of diclofenac sodium.

Molecular formula: $C_{14}H_{10}Cl_2NNaO_2$

Molecular weight: 318.1g/mol

Diclofenac sodium tablet is an enteric coated which is delivered through oral route which is consider to be one of the safest and most suitable method for taking medication.[6] For the avoid o dissolution or disintegration of tablet in gastric PH (3.5) polymer barrier is apply on the tablet. Which secure drug from stomach acidity and make tablet break quickly in alkaline PH (7-9) in small intestine.

POST COMPRESSION PARAMETERS OF ENTERIC COATED TABLETS)[7]

1. Weight variation
2. Friability
3. Hardness
4. Thickness
5. Drug content uniformity
6. Disintegration
7. Dissolution

a) standard calibration curve of pure drug to know the slope and regression coefficient

b) calculating % cumulative drug release.[7]

1.Weight Variation

Weight variation is considered to be a basic in process quality control test, it has often examined to ensure that each of tablet contains the proper amount of drug or not. By analytical balance 20 tablets which randomly selected are weighed individually then average

weight is calculated, tablet may show any difference in weight of tablet. Weight variation is due to inappropriate flow of granules from hopper into the die and machine performance.[7,8] Enteric coated tablets are usually free from weight variation but to confirm content uniformity of tablet test must be conducted.[9]

2. Friability

The mechanical strength of tablet is checked by using Roche friabilator, it is used to confirm the loss of weight of tablet by chipping, capping during manufacturing and transport time which leads to friability. Pre-weight of the 20 tablets must be noted. All 20 tablet should be placed in friabilator and tested at the speed of 25rpm for 4min. dust is removed and tablets are checked for post weight, percentages weight loss of tablet was calculated.[10]

3. Hardness

To determine the hardness of tablet Pfizer tester, Monsanto hardness tester is used. In this test 6 tablets are used.[11] Crushing strength of tablet is tested by placing the tablet between the anvils where tablet breaks by applying mechanical strength and result is recorded.[12]

4. Thickness

Tablet thickness is checked by using Vernier calliper, by knowing diameter of the tablet thickness is determined. The official standard limit for tablet is ±5%. The tablet is measured in Vernier calliper in centimetre. Factors affecting tablet thickness may be due to uneven size distribution and compression force.[13]

5. Disintegration

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. here gastric fluid 0.1N HCl (acidic pH) is used for first two hour for disintegration test of enteric coated tablet, up to two hours there is no disintegration, soothing or splitting of tablet when there is no disintegration of tablet further, the same tablet is dip in the phosphate buffer 7.2pH which simulates the intestinal fluid condition, Where the tablet starts to disintegrate and shows drug release.

Fig No 3: Disintegration test apparatus.

The Disintegration test apparatus contain 6 glass tubes which are 3 inches in length and at bottom end 10 mesh screen are present and open at the top. To conduct disintegration test in each tube one tablet is placed and basket is positioned in disintegration testing apparatus rack is in 1-L beaker, 37± 2°C maintained with stimulated gastric fluid followed by simulated intestinal fluid. By placing the perforated plastic disc on tablet floating of tablet is blocked. The apparatus is maintained in a such way that the tablet is 2.5cm under the top of liquid on their ascending motion, not adjacent to bottom of the beaker by 2.5cm distance in their descending motion. The tablet containing baskets are move up and down by maintaining space of 5-6cm at a prevalence of 28 to 32 cycles per minute.[14]

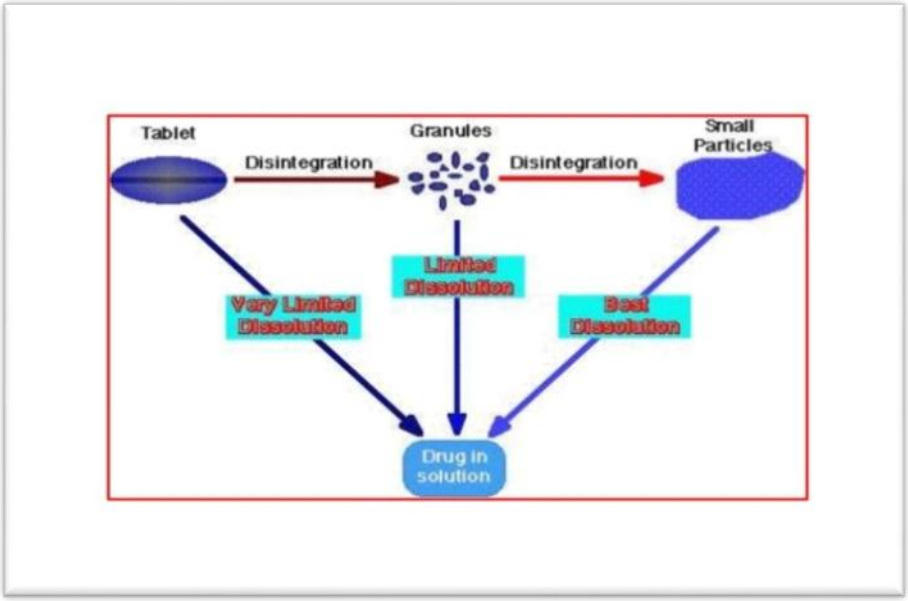

Fig No 4: Disintegration process of tablet.

6. DISSOLUTION

Dissolution, where the solid matter run through a solution. i.e. a mass converts solid surface to liquid phase. Is also defined as, in specific temperature and in solid/ liquid interface under standard condition, the volume of drug medium that run through solution per unit time.[15] Dissolution is the one of major parameter to check quality of tablet which is connected to Bioavailability and absorption of tablet. The examination report better disentangles rate of drug at distinct time intermission.[16] according to USP distinct variety of tablet dissolution apparatus are there,

1. Paddle
2. Basket
3. Reciprocating cylinder
4. Reciprocating disk
5. Paddle over disk
6. Rotating cylinder
7. Flow through cell.[17]

Here dissolution test of diclofenac enteric-coated tablet is performed, Electro lab USP dissolution tester is the apparatus, and paddles are used which rotates at 50 rotation per minute. In the dissolution test of the enteric-coated tablet, for the first 2 hours drug is placed in dissolution media i.e.in 0.1N HCl. drug sample is collected after 2 hours in the intermission of 15 minutes, later drug was shifted to phosphate buffer medium at pH 7.2 for 45 minutes and the drug sample is collected in an interval of 5 minutes. The proportion of bath is kept up to 1000ml and temperature at 37° $\pm$ 0.5°C.[18]

Importance of dissolution

1. Variation in *in-vivo* availability is described by taking out come from *in-vitro* dissolution rate experiment.
2. Standard of pharmaceutical dosage form is assured by dissolution test.
3. Dissolution is highly sensitive and predictor of in-vivo availability,
4. Analytical parameters are evaluated such as enough bioavailability and give the statics for formulator in growth at more effective and medicinal optimal dosage form by dissolution experiment.[19]

MATERIAL AND METHODS

The different marketed diclofenac sodium tablet 50mg was purchased from local pharmacy in Davanagere they are mentioned below with all the description in table no. 1.

Table No 1: Description of Various marketed Diclofenac sodium tablet in India.

SL NO	BRAND	DOSAGE	MANUFACURED BY /FOR	M.R.P RS.
1	Diclofenac sodium (Janaushad)	50mg	Bureace of pharma public sector under takings of India	4.00 per 10 tabs
2	Reactin (Cipla)	50mg	Acme generic LLP India	19.13 per 10 tbs
3	Dicloran	50mg	Lekar pharma ltd India	20.03 per 10 tabs
4	Divon	50mg	Micro lab limited India	20.05 per 10 tbs
5	Voveran (Novartis)	50mg	Geltec private limited India	94.50 per 15 tbs

Weight variation

Weight variation was carried out by analytical balance. It shows that each of the tablets contains the actual amount of drug. 20 tablets were weighed separately, average weight is calculated from the total weight of all tablets then comparing the individual weight of the tablet to the average weight. The percentage deviation is calculated with the help of the formula.[20,21]

%deviation =individual weight-average weight/average weight*100

Friability

10 tablets were weighed and placed in a friabilator. It rotates at a rate of 25rpm and follows 100 rotation (4 min) later tablets were weighed. The loss of tablet less than 0.5to1.0% roughly acceptable Percentage friability is obtained by the following formula.[22]

Friability=(W1-W2)/W2*100

W1=weight of the tablets before the test

W2=weight of the tablets after the test

Hardness

Monsanto hardness tester used to test the hardness of the tablet. The main reason to check hardness to know the resistance to mechanical shocks while handling mechanical shocks while handling.[23]

Thickness

The thickness and diameter of tablets are measured by using a screw gauze. The thickness and diameter of the tablet is accurately calculated using the following formula.

T. R= P.S. R ± [(C.H. R+Z) *L.C]

Where T. R= Total reading

P.S. R=Pitch scale reading

C.H. R=Coinciding head scale reading

L.C=Least count,

Z =Zero correction

L.C=P.D/N.H. D

P.D =Pitch scale division

N.H. D= Number of head scale Content uniformity.[24]

Drug 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 7.2 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 7.2 and made up to 100 ml to get Stock B. The absorbance of this solution is measured at 276.8nm using Shimadzu UV-Visible spectrophotometer. The drug content is estimated by obtained absorbance value.[25]

Disintegration test

The disintegration test apparatus made up of basket -rack construction containing 6 open-ended glass tubes. They are placed vertically, and the bottom of the tube is covered with 10-mesh screen Motor helps the basket increase and decrease in the immersion fluid at frequency of 28 to 32 cycles per minute.37-degree Celsius fluid temperature is maintained throughout the test. The tablets placed in the basket then the plastic weight is placed over each tablet to prevent the tablet from coming outside of the tubes of the basket. The basket can operate at optimum speed and at the end required for the disintegration of all 6 tablets noted down.

DISSOLUTION

Determination of the standard calibration curve of pure diclofenac sodium tablet standard calibration curve of pure drug is performed to know the slope and regression coefficient. 10 mg of Diclofenac sodium was accurately weighed in sensitive balance

(Shimadzu, sensitivity 0.0001g) and weighed diclofenac sodium placed in a100ml volumetric flask. The volume is made up to 100ml with phosphate buffer solution PH 7.2. Seven test tube were collected and named 1,2,3,4,5,6,7, from the above stock solution add 0,0.5,1.0,1.5,2.0,2.5,3.0, respectively. The volume of the solution in all the test tube is made up to 10ml with phosphate buffer solution. The resulting solution have the concentration of 0,5,10,15,20,25,30mcg/ml. The absorbance was measured at 276.8nm in a UV-visible spectrometer. The standard curve was plotted taking concentration on x-axis and absorbance on the y-axis.

Preparation of 7.2 pH buffer solution

Preparation of 0.2M potassium dihydrogen phosphate

Weighed 2.7218g of potassium dihydrogen phosphate placed in 500ml of the beaker. The distilled water is added in little quantities with continuously stirring with a glass rod to make solid completely dissolved, the volume is made up of 100ml with distilled water.

Preparation of 0.2 M sodium hydroxide solution

Weighed quantity (800mg) of sodium hydroxide is dissolved in 100ml of distilled water.

Preparation of phosphate buffer solution PH 7.2

Combining 50ml of 0.2M potassium dihydrogen phosphate solution and 34.7ml of sodium hydroxide solution. The volume is made up of distilled water.[20]

b) calculating % cumulative drug release

USP dissolution apparatus used for the first 2 hours adding 900ml of 0.1N HCl solution followed by the addition of phosphate buffer next 1 hour. The temperature is maintained at 37°C, at a specific time interval 9 samples withdrawn the absorbance is measured using Shimadzu UV visible spectrophotometer at 276.8nm.[26]

Similarity and dissimilarity index

Similarity factor and dissimilarity factor are endorsed by the FDA as acceptable methods for dissolution profile comparison, though the similarity factor is preferred. Values of similarity factor (F_2) between 50 and 100 and values of dissimilarity factor (F_1) between zero and 15 ensure sameness or equivalence'. These calculations are applicable for those dissolution profiles where difference at any dissolution time point between test and reference mean profiles should not exceed 50%.[27,28]

Table No 2: Acceptance criteria for dissolution profile of comparative marketed product.

Stages	Observation	Inference
Stage 1	Within 15 min, 85% of the drug dissolves in both test as well as reference products	Dissolution study complies indicating the two products are equivalent.
	Within 15 min, less than 85% of the drug dissolves in test or reference sample	Dissolution study does not comply, go to Stage 2
Stage 2	Calculate similarity factor by taking minimum 3 samples data in which one sample must represent more than 85% drug dissolution. **AND**	Dissolution study complies if similarity factor lies between 50 and 100 indicating the two products are equivalent. **AND**
	Calculate dissimilarity factor by taking minimum 3 samples data in which one sample must represent more than 85% drug dissolution.	Dissolution study complies if dissimilarity factor lies between zero and 15 indicating the two products are equivalent.

RESULTS AND DISCUSSION

The friability, weight variation, diameter, thickness, hardness of various brands of diclofenac sodium tablet are shown below in table no 3.

Table No 3: Friability, Weight variation, Diameter, Thickness, Hardness of various marketed Diclofenac Sodium tablets.

Sl. no	Brand	Friability %	Weight variation %	Diameter (mm)	Thickness (mm)	Average hardness (kg/cm^2)
1	Janaushad	0.91±0.002	3.18 ±0.003	5.48±0.031	2.32± 0.030	4.52±0.038
2	Reactin 50mg (Cipla)	0.80±0.005	2.38±0.001	6.37±0.022	3.23±0.027	6.98±0.045
3	Dicloran 50mg (Lekar Pharma unit of JB Chemicals)	0.85±0.006	1.74±0.004	7.26±0.036	4.37±0.025	4.6±0.047
4	Divon 50mg (Micro)	0.80±0.008	1.67±0.002	7.01±0.036	4.13±0.033	3.68±0.049
5	Voveran 50mg (Novartis)	0.97±0.008	1.11±0.010	8.10±0.038	3.36±0.035	7.28±0.050

DRUG CONTENT

The Drug content results of various brands of diclofenac sodium is shown in the Table No 4. The results shown that all the marketed tablets were within the IP limits **(±10%).**

Table no 4: Drug content data of studies of marketed diclofenac sodium products.

Sl. no	Brand	Drug content (%)
1	Janaushad	98.2±0.003
2	Reactin 50mg (Cipla)	99.30±0.004
3	Dicloran 50mg (Lekar Pharma unit of JB Chemicals)	99.5±0.006
4	Divon 50mg (Micro)	98.1±0.003
5	Voveran 50mg (Novartis)	99.7±0.007

DISINTEGRATION

The disintegration results of various brands of diclofenac sodium is shown in the Table No 5. The results revealed that Janaushad tablet containing diclofenac sodium delayed disintegration compared to other brands.

Table No 5: Disintegration data of studies of marketed diclofenac sodium products.

Sl.no	Brands	Disintegration time in stimulated gastric fluid	Disintegration time in 7.2 phosphate buffer (after 120min)
1	Diclofenac sodium 50mg (Janaushad)	No disintegration up to 120min	17min 5sec
2	Reactin 50mg (Cipla)	No disintegration up to 120min	6min 59sec
3	Dicloran 50mg	No disintegration up to 120min	5min 4sec
4	Divon 50mg	No disintegration up to 120min	13in 5sec
5	Voveran 50mg (Novartis)	No disintegration up to120min	5min

DISSOLUTION

a) standard calibration curve of pure drug to know the slope and regression coefficient

Absorbance value for the calibration curve and standard calibration graph of diclofenac sodium pure drug in phosphate buffer 7.2 pH are shown in table no. 6 and fig no.5.

Table no 6: standard calibration data of diclofenac sodium in phosphate buffer pH 7.2.

Sr no.	Concentration µg/ml	absorbance
1	0	0
2	5	0.1568±0.0054
3	10	0.3313±0.0015
4	15	0.5153±0.0043
5	20	0.7123±0.0019
6	25	0.8582±0.0011

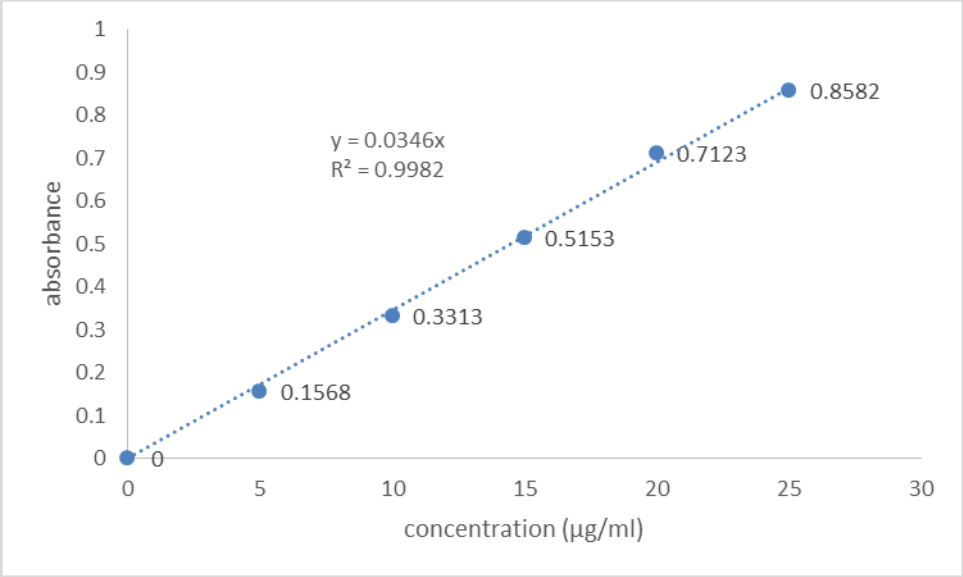

Fig 5: Standard calibration curve of pure drug diclofenac sodium in phosphate buffer pH 7.2 at 276.8nm.

The dissolution profile of marketed tablets like diclofenac sodium(janaushad) 50mg, Reactin 50mg (Cipla), Dicloran 50mg, Divon 50mg, Voveran 50mg (Novartis) are shown in table No 7 and figure No 6. The data showcased maximum dissolution of drug from Voveran of Novartis in 180 minutes compared to other marketed products.

Table No 7: % drug release of various marketed diclofenac sodium tablet.

SL.NO	Time (min)	% drug release of various marketed diclofenac sodium tablet				
		Voveran (F_1)	Reactin (F_2)	Divon (F_3)	Dicloran (F_4)	Janaushad (F_5)
1	0	0.00	0.00	0.00	0.00	0.00
2	30	0.00	0.00	0.00	0.00	0.00
3	60	0.00	0.00	0.00	0.00	0.00
4	90	0.00	0.00	0.00	0.00	0.00
5	120	0.00	0.00	0.00	0.00	0.00
6	135	28.62±0.0014	20.78±0.0021	22.73±0.0019	35.92±0.0021	15.26±0.0018
7	150	47.46±0.0015	33.98±0.0027	27.64±0.0024	48.21±0.0026	33.36±0.0023
8	165	72.15±0.0071	58.64±0.0029	40.96±0.0027	63.21±0.0029	46.40±0.0026
9	180	85.93±0.0022	67.94±0.0031	60.46±0.0030	75.11±0.0032	58.78±0.0030

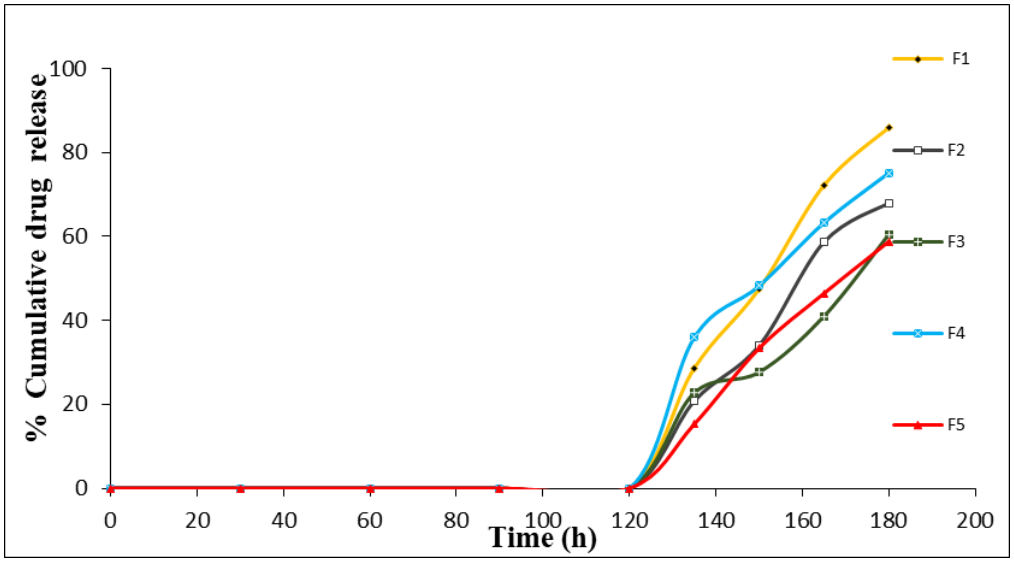

Figure No 6: % Cumulative Drug release of various marketed tablets of Diclofenac sodium. F_1- Voveran, F_2- Reactin, F_3- Divon, F_4- Dicloran, F_5- Janaushad.

Similarity and Dissimilarity factor

Based on the above results Voveran from Novartis marketed product has been taken as standard(reference) and other brands considered as test, similarity and dissimilarity factor is examined. According to the acceptance criteria atleast 1 dissolution value in both the products under comparision should cross above 85%. However, in this current study only one marketed product has shown dissolution of 85% in 3 hours. This study may be used as a tool for selection of best marketed product based on dissolution. From the studies it has been observed that Voveran shows similarity and dissimilarity factor with Dicloran compared to the other products because dicloran was nearer to the acceptance range and this is represented in table No 8.

Table No 8: Similarity dissimilarity index of various marketed diclofenac sodium tablet.

SL.NO	REFERNCE	TEST	SIMMILARIY	DISSIMILARITY
1	Voveran	Reactin	43.12	22.55
2	Voveran	Divon	32.24	35.17
3	Voveran	Dicloran	54.89	11.87
4	Voveran	Janaushad	33.78	34.31

CONCLUSION

From this current work, it can be concluded that all the marketed product of Diclofenac Sodium 50 mg tablets passed the finished product quality control test. Voveran showed 85.93% drug release in 3 hours which is the maximum among all other brands. However, other brands complied with the official quality specifications. This study gives the data

regarding the quality of the marketed tablets in India. The attempt of similarity and dissimilarity studies gives the assurance about the best marketed products among the selected product. Overall, above study ensure that the commercially available Diclofenac Sodium tablet in market confirmed with the pharmacopeial standards.

ACKNOWLEDGEMENT

We the authors heartfully thank Bapuji Pharmacy College, Davanagere for giving us all the necessary facility to conduct the research work.

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