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Formulation and Evaluation of Fast Dissolving Tablet of Diclofenac Sodium

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HUMAN

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ABSTRACT

The present study was aimed to formulate, evaluate, and optimize a tablet that disintegrates and dissolved rapidly to show a rapid onset action. Diclofenac sodium, non-steroidal-inflammatory, analgesic, and pyretic properties were selected as a model drug. Diclofenac sodium is among the most extensively used Non-steroidal anti-inflammatory drugs, employed in mucosal skeletal complaints, especially arthritis. In the present study, an attempt has been made to prepare fast dissolving tablets of diclofenac sodium using super disintegrants like sodium starch Glycolate, Croscarmellose sodium, Crospovidone and starch by direct compression technique using 3 different concentrations of super disintegrants. The pre-compression parameters of the tablet-like hardness, friability, weight variation, disintegration time, in-vitro dissolution release rate, and drug content. It was concluded that the batch which was prepared by using a combination of crospovidone and sodium starch Glycolate as a superdisintegrants shows excellent disintegration time, enhance dissolution rate, taste-masking and hence lead to improve efficacy and bioavailability of a drug.

INTRODUCTION

Introduction conventional dosage form is very popular because of ease of self-administration, compact in nature, easy to manufacture and it can be delivered inaccurate dose. One important drawback of the conventional dosage form (tablet and capsule) is that it possesses higher disintegration time and pharmacological action is achieved after 30-45 min. of dosage of administration. To overcome this problem tablets that can rapidly disintegrate or dissolve within one minute in the oral cavity have attracted a great deal of attention. A fast-dissolving drug delivery system can be defined as a dosage form for oral administration, which when placed in the mouth, rapidly disintegrates or dissolves and can be swallowed in the form liquid. The conventional dosage form is very popular in pharmaceutical industries because of its low manufacturing cost. FDT disintegrate and/ or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. The target populations for these new fast-dissolving/disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or developmentally disabled patients. Patients with persistent nausea, who are traveling, or who have little or no access to water are also good candidates for FDT. The ease of administration of fast-dissolving/ disintegrating tablet, along with its pleasant taste, may encourage a patient to adhere to a daily medication regimen. Although FDT may not solve all compliance issues, it may be enough of an advance to be of therapeutic significance.[1]

Diclofenac sodium is a synthetic, non-steroidal anti-inflammatory & analgesic compound. The mechanism responsible for its anti-inflammatory, antipyretic, analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). Diclofenac may also be a unique member of the NSAIDs. There is some evidence that diclofenac inhibits the lipoxygenase pathways, thus reducing the formation of the leukotriene's (also pro-inflammatory autacoids). It is well absorbed orally and shows 100% bioavailability, more than 99% protein-bound, metabolized and excreted both in urine and biles, and plasma $t_{1/2}$ 1.2-2hr.[2]

Diclofenac is used for musculoskeletal complaints, especially arthritis (rheumatoid arthritis, osteoarthritis, gout attacks, and pain management in case of kidney stones and gallstones.[2]

DRUG PROFILE

Diclofenac sodium:

Structure:

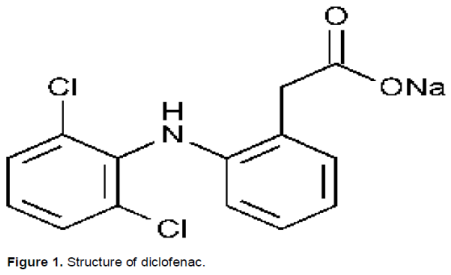


Figure 1. Structure of diclofenac.

Figure No. 1: Structure of Diclofenac

"Diclofenac sodium" derives from its chemical name 2-(2,6dichloranilino) phenylacetic acid.

Chemical Names: Diclofenac sodium salt; Voltaren; Sodium diclofenac

Formula: $C_{14}H_{11}Cl_2NNaO$

Molecular Mass: 296.148 g/mol

Melting point: 284°C (543.2°F)

Dose: The dose of diclofenac sodium is 100 mg given twice daily as a tablet.

Category: Non-steroidal anti-inflammatory drug.

Storage: Storage in a well-closed container, protected from light

Routes of administration: Orel, rectal, intramuscular, intravenous (renal and gallstones), topical

Pharmacology

Diclofenac Sodium is the type of sodium salt derived form of Diclofenac, derived and non-steroidal anti-inflammatory drug (NSAID) with an analgesic, antipyretic and selective reversible and competitive inhibitor of cyclooxygenase (COX), subsequently blocking the conversion of arachidonic acid into prostaglandin precursors. This leads to an inhibition of the formation of prostaglandins that are involved in pain, in inflammation and fever.[4, 5]

EXCIPIENTS PROFILE

Mannitol:

Trade name: Osmitrol

Empirical Formula: $C_6H_{14}O_6$

Mo1ecular Weight: 182.17g/mol

Structural Formula:

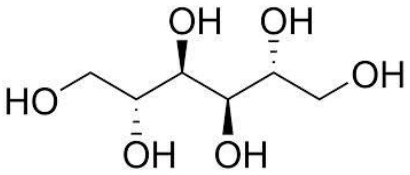


Figure No. 2: Structure of Mannitol

Solubility: It is soluble in alkalis, methanol, and water and practically insoluble in ether.

Melting Point: 166-168ºC

Usage: It used as an excipient in the manufacture of chewable tablets, therapeutically used as an osmotic diuretic.[9]

Lactose

Structure:

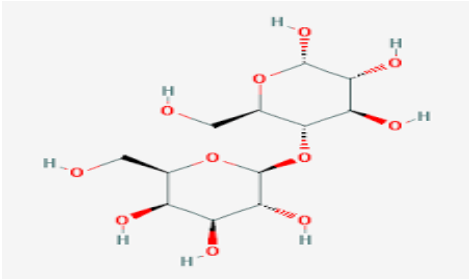


Figure No. 3: Structure of Lactose

Description: A disaccharide of glucose and galactose in human and cow milk. It used in tablets, as a medicine, and as a nutrient.

Chemical formula: $C_{12}H_{22}O_{11}$

Categories: Sweetening Agents

Uses: Lactose is milk sugar. It is a disaccharide composed of one galactose in the formulation of tablets lactose is used to help form tablets because it has excellent compressibility.[7]

Citric acid

Structure:

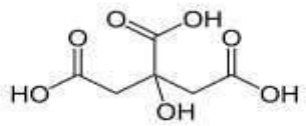


Figure No. 4: Structure of Citric acid

Citric acid is a week of organic tri-carboxylic acid. Citric acid is also a type of food.

Chemical formula: $C_6H_8O_7$

Molecular mass: 192.12g/mol

Appurtenance: Crystalline white solid

Odor: Odorless

Melting point: 156ºC

Boiling point: 310ºC

Solubility: Solubility in water 117.43g/100ml (10ºC).Soluble in alcohol, ether, ethyl acetate insoluble in toluene

Uses: Citric acid is naturally used as a preservative. As a weak organic acid, it is commonly purchased in powder form but is found in all citric fruits in lemons, limes, oranges, and tangerines.[9]

Menthol

Menthol is an organic compound which is obtained from peppermint. It is in the form of crystalline substance, or white, which is solid at room temperature and melts slightly above.[10]

Structure :

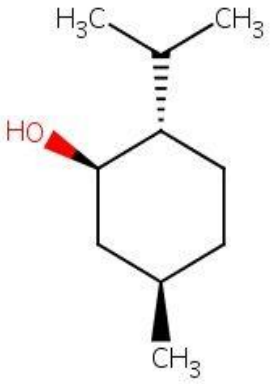


Figure No. 5: Structure of Menthol

Synonyms: 3-p-Menthol, Menthamenthol, Peppermint camphor

Chemical formula: $C_{10}H_{20}O$

Molar mass: 156.27g/mol

Appearance: White or colorless crystalline solid

Density: 0.890g/cm

Melting point: 36 to 38^0C

Boiling point: 212^0C

Solubility: Menthol is slightly soluble in water

Uses: Menthol is used for: minor pain caused by a condition such as arthritis, bursitis, tendonitis, muscle strains or sprains, backache, bruising. It may also be used for other conditions as detracted by your doctor. Menthol also is a topical analgesic.

Magnesium Stearate

Structure:

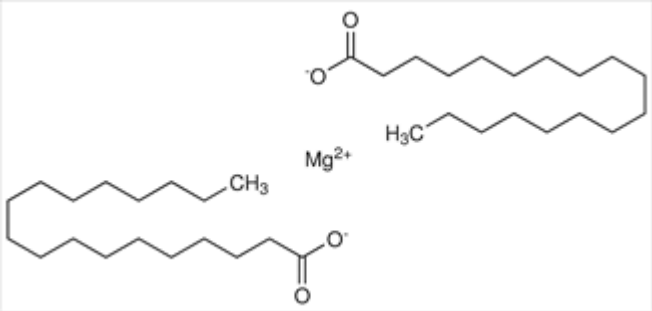


Figure No. 6: Structure of Magnesium Stearate

Magnesium Stearate is the chemical compound it is white in color and insoluble in water.

IUPAC Name: Magnesium octadecanoic

Chemical formula: Mg $(C_{18}H_{35}O_2)_2$

Molar mass: 591.27g/mole

Appearance: Light white powder

Odor: Slight

Density: 1.026g/cm

Melting point: 200^0C

Uses: It is also useful because it has lubricating properties, magnesium stearate is commonly used lubricant for tablets.

Talc

Category: Silicate mineral

Chemical Formula: $Mg_3Si_4O_{10}$ $(OH)_2$

Color: Light to dark green, brown, white, grey

Uses: Talc is used as an ingredient in cosmetics, talcum, and baby powders.

Polyvinylpyrrolidone (PVP)

Chemical structure

Polyvinylpyrrolidone, also commonly called Polyvidone or Povidone is a water-soluble polymer made from the monomer *N-vinylpyrrolidone.*

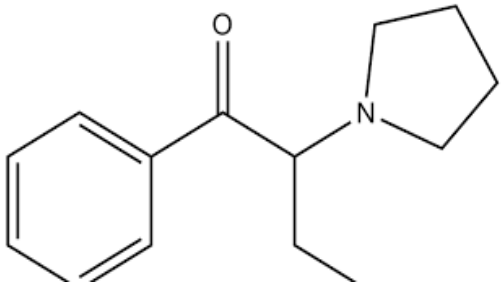


Figure No. 7: Structure of PVP

Chemical name: PVP, Povidone, Crospovidone, Polyvidone

Chemical formula: (C_6H_9NO) n

Molar mass: 2500 - 2500000 $g.mol^{-1}$

Appearance: White to light yellow hygroscopic, amorphous powder

Density: 1.2 g/cm3

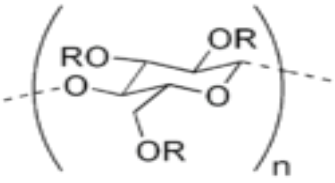
Melting point: 150-180^{0}C

Solubility: PVP is soluble in water and alcohol.

Uses: It is used as a binder in many pharmaceutical tablets.

Hydroxyethylcellulose (HPMC)

Chemical structure



R = H or CH_3 or $CH_2CH(OH)CH_3$

Figure No. 8: Structure of HPMC

Hypromellose in an aqueous solution, unlike methylcellulose, exhibits a thermal gelation property.

Chemical formula: CH_2CH (OH) CH3

Appearance

Hypromellose is a solid, and is a slightly off white to being powder and may be formed into granules.

Uses: Hypromellose, short for hydroxypropyl methylcellulose (HPMC), is used as an ophthalmic lubricant and excipient.

MATERIALS AND METHODS

MATERIALS

All the materials used in this project work were commercial samples. Diclofenac sodium, Menthol, Citric acid, and PVP was received from Fine chemicals, Chennai, Mannitol received from Qualigens Fine Chemicals, Mumbai, Magnesium Stearate received from Hi media Laboratory, HPMC received from Loba Chemical PVT, LTD, Microcrystalline cellulose from Ignite Chemicals, Mumbai, Talc received from SD. Fine Chemical, LTD, Mumbai. All the reagents are used in analytical grade. Purified distilled water was used in the preparation of diclofenac sodium.

METHOD

FDTs of Diclofenac Sodium using direct compression method:

Direct compression is used to define the process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients. Different batches of tablets prepared by direct compression methods. Six different batches of tablets prepared by taking super disintegrate (Sodium starch Glycolate, Croscarmellose sodium, Crospovidone) are used different concentrations of each with HPMC and compare with Six different batches of tablet prepared by taking another polymer (Starch) same as the concentration of HPMC. Thus all batches were prepared (all batch different combination shown in table). Different content was taken accordingly to the need for 20 tablets.

Weight all the ingredients accurately and pass through sieve # 36 and Mix all the ingredients geometrically except Magnesium Stearate. Then lubricate the blend with Magnesium stearate. Tablets were compressed using tooling of 9.0 mm; circular punches with break line on one side and plain on the other side and dies were fixed to the 16 station single rotary tablets compression machine (Cadmach, Ahmadabad, India).

Table No. 1: Formulation design of fast dissolving tablet of Diclofenac Sodium

Sr. No.	Tablet Ingredients (mg)	B_1	B_2	B_3	B_4	B_5	B_6
1.	Diclofenac Sodium	22.5	22.5	22.5	22.5	22.5	22.5
2.	Crospovidone	3	-	-	3	3	-
3.	Croscarmellose Sodium	-	2	-	4	-	5
4.	Sodium Starch Glycolate	-	-	5	-	5	8.2
5.	Manitol	60	61	58	56	55	54.8
6.	Microcrystalline Cellulose	6	6	6	6	6	6
7.	Magnesium stearate	2	2	2	2	2	2
8.	Talc	4	4	4	4	4	4
9.	Aspartame	1.5	1.5	1.5	1.5	1.5	1.5
10.	Peppermint Flavour	1	1	1	1	1	1
11.	Total	100	100	100	100	100	100

EVALUATION

Pre- Compression Parameter

- **Angle of Repose:**

Angle of repose was determined by using funnel methods. The powder was poured through the funnel that can be determined vertically until a maximum cone height (h) was obtained. A funnel was fixed on a stand at a high on the graph paper and powder was placed into the funnel and powder was allowed to flow down on the graph paper power made angle on the graph paper. The angle of repose was calculated with the help of the formula given below.

$$\text{Tan } \theta = 2h/D$$

Table No. 2: Properties of Angle of repose

ANGLE OF REPOSE (ĐEGREES)	TYPE OF FLOW
<25	Excellent
25 TO 30	Good
30 TO 40	Passable
>40	Very poor

- **Bulk density**

The bulk density of a powder is defined as the ratio of the mass of the powder to its bulk volume. It is used to describe the packing of particles. For bulk determination, a weighed volume of powder material was introduced into a graduated measuring cylinder and the amount of powder was determined.

Bulk Density= Mass of the powder/ bulk volume

- **Tapped density**

For the determination of tapped density, a weighed volume of powder was introduced into a graduated cylinder and mechanically either tapped or using a tape device until a constant volume was obtained.

Tapped Density= Mass of the powder/ tapped volume

➢ **Carr's compressibility index**

The simplest method of measurement of the free flow of powder is compressive, an indication of the ease with which a material can be induced to flow. The compressive index is determined by Carr's index, which is calculated using the following formula,

C= 100(1-B/T)

Where B is bulk density, T is tapped density

➢ **Hausner's Ratio**

Hausner's ratio is an index of ease of powder flow. It is calculated by the following formula,

Hausner's Ratio= Tapped density/ Bulk density

Lower Hausner's ratio (< 1.25) indicates better flow properties than higher ones (>1.25)

Table No. 3: Flow Characteristics

Carr's Index	Flow Character	Hausner's Ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Post Compression Parameters

All formulated tablets were subjected to various physical characteristics such as crushing, friability, thickness, diameter, disintegration time, wetting time, weight variation, and drug content.

➢ **Weight Variation**

A weight variation test was performed by weighing 20 tablets individually, using an electronic balance. Calculating average weight and comparing the weight of individual tablets to the average weight.

Table No. 4: Weight Variation According to IP

Average weight of tablets (IP)	Average weight of tablets (USP)	Maximum % Difference allowed
<80 mg	<130 mg	10
80-250 mg	130-324 mg	7.5
>250 mg	>324 mg	5

- **Tablet thickness**

Thickness was measured by placing the tablet between the two arms of the Vernier calipers. 5 tablets were taken and their thickness was measured.

- **Tablet hardness**

The stiffness of a tablet, which is the force required to break a tablet into a diameter. The hardness tester used in the study was the Monsanto hardness tester, which applies force to the pellet with the help of an inbuilt spring.

- **Tablet friability**

The stability of the tablets was measured in a Roach Friabilator (Elite Scientific and Instruments). Tablets of known weight (W_o) or a sample of 20 tablets are cut into drums for a fixed time (100 revolutions) and weighed again (W). Percent stability was calculated from the loss in the weight given in the equation below. Weight loss should not exceed 1%. The determination was made in triplicate.

$$\% \text{ Friability} = 100 (W_o - W) / W_o$$

In vitro characterization of prepared tablets

- **In the wetting time study**

In the wetting time study, a piece of folded tissue paper was placed in a Petri plates (with internal diameter 6.5 cm) with 5 ml of distilled water. The tablet was placed on paper and the time for the tablet to become completely wet was measured in seconds.

- **Disintegration test**

The disintegration time of the fast-dissolving tablets was determined using the Disintegration test apparatus. The operation was performed on 6 tablets.

- **The *in-vitro* dissolution rate study**

In-vitro dissolution rate study was done by using USP Type II apparatus which was rotated at 75 rpm. Phosphate buffer pH 6.8 (900 ml) was taken as a dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5°C. Aliquots of dissolution medium were withdrawn at a specific time interval and it was filtered. The absorbance of filtered solution was determined by Spectrophotometer (SYSTRONICS-UV Double beam spectrophotometer-2101) at 283 nm and drug concentration was determined from the standard calibration curve.

- **Determination of drug content**

20 tablets were taken and powdered accurately. Powdered containing about 50mg of Diclofenac sodium was taken and shake it with 60ml methanol in 200ml volumetric flask and dilute to volume with methanol. 5ml of this solution was taken and diluted up to 100ml with methanol and absorbance was noted at 285 nm[1].

- **Stability Studies**

The best formulation was charged for stability studies at temperature and relative humidity of 40ºC / 75%RH for one month. The parameter used to assess the effect of stress condition on tablets include Weight variation, Avg. Thickness, Friability, Disintegration Time, Avg. Hardness, Wetting time, Drug content and % Drug released.[1]

RESULTS AND DISCUSSION

Diclofenac Sodium FDTs were prepared by the direct compression method. Sodium starch Glycolate and starch were used as super disintegrate which help in rapid and drug dissolution.

Weight Variation:

All tablets from each formulation passed weight variation test, as the % weight variation was within the Pharmacopeia limits.

Friability:

The friability of the formulations was found to be between 0.24-0.66 percent and was within the official requirement (i.e. less than 1%).

Hardness:

The hardness was maintained to be within 4.40-4.91 kp, no variation in the hardness was found which indicates that the blending was uniform.

Disintegration time:

In-vitro disintegration time for all the formulations varied from 35 to 78 seconds. The formulation B5 shows a better disintegration time of 35 seconds.

Table No. 5 Evaluation of Pre-formulation studies

Formulation	Car's Index %	Angle of repose	Hausner's ratio g/ml	Bulk density g/ml	Tapped density g/ml
B1	15.9	30.19	1. 18	0.50	0.61
B2	19.1	25.23	1.28	0.49	0.58
B3	16.3	22.30	1.26	0.51	0.62
B4	20.4	26.06	1.33	0.52	0.60
B5	19.1	26.15	1.29	0.51	0.59
B6	13.01	25.36	1.23	0.42	0.62

Table No. 6: Evaluation of Post-formulation studies

Formulation	%Weight variation	Hardness (kp)	Thickness (mm)	Friability %	Wetting time (sec.)	Disintegration time (sec.)
B1	1.5	4.50	2.73	0.55	75	78
B2	2.1	4.95	2.65	0.24	69	66
B3	1.99	4.58	2.07	0.58	71	73
B4	2.3	4.81	2.72	0.46	50	50
B5	1.7	4.40	2.76	0.63	36	35
B6	2.3	4.51	2.83	0.66	51	49

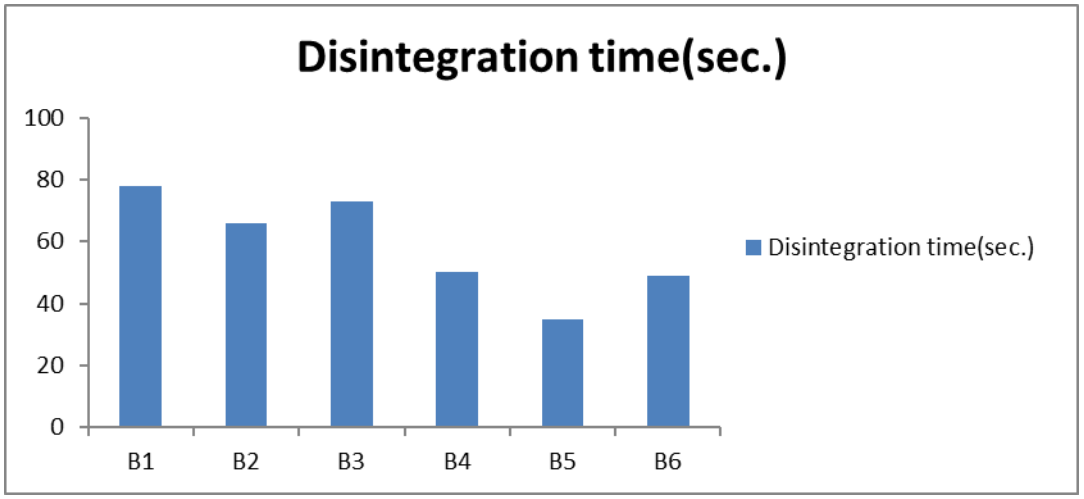


Figure No. 9: Disintegration study

***In-vitro* Dissolution study**

The result of the *in-vitro* dissolution study indicates that process used to prepare the FDTs to enhance the rate and extent of dissolution data it was found that as the super Disintegrants increased, the drug release also increased. Among the different batches of formulation, B_4 shows the highest dissolution rate were around 49.71.

Table No. 7: Comparative study of % drug release of FDT of diclofenac sodium of different batches

Sr. N0.	Time in Min	% Drug Release					
		B1	B2	B3	B4	B5	B6
1	0	0	0	0	0	0	0
2	2	8.65	14.45	15.75	21.78	7.34	12.71
3	4	10.2	20.53	22.11	27.59	11.25	17.09
4	6	14.45	27.5	26.29	32.31	13.5	23.19
5	8	16.15	28.98	32.59	35.52	19.19	27.21
6	10	20.81	33.08	35.51	38.49	23.06	32.81
7	12	21.99	35.19	37.79	41.59	26.85	41.63
8	14	25.5	37.85	42.81	49.71	29.83	43.21

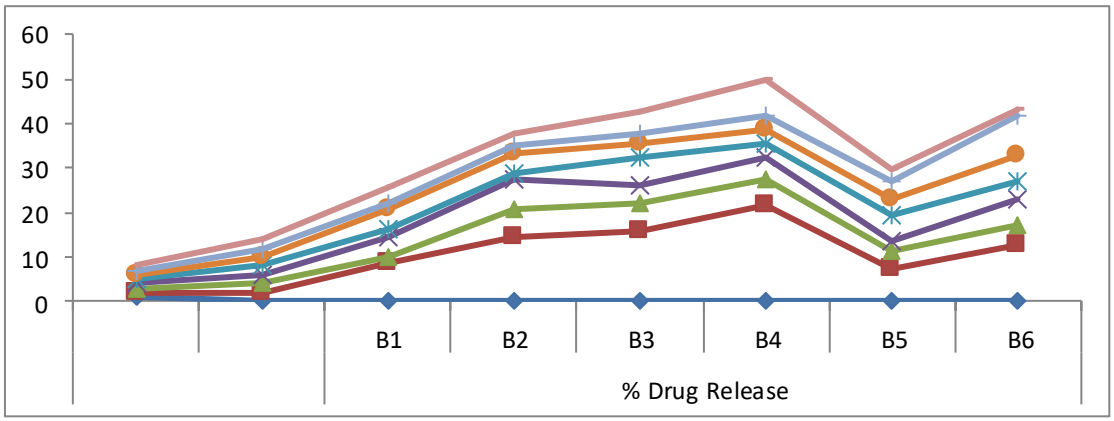


Figure No. 10: *In-vitro* dissolution studies

Table No. 8 Drug content study of FDTs of Diclofenac Sodium

Batch No.	Assay %
B_1	25.5
B_2	37.85
B_3	42.81
B_4	49.71
B_5	29.83
B_6	43.21

Table No. 9: Study of Different Parameter

S. No.	Evaluation Parameter	Evaluation Result
1	% Weight variation	1.70
2	Average thickness (mm)	2.76
3	Friability (%)	0.63
4	Disintegration time	35 sec
5	Average Hardness	4.40
6	Wetting time (sec)	36
7	Drug Content	49.71

CONCLUSION

Diclofenac Sodium is widely used NSAIDs for rheumatoid arthritis, inflammation, and pain relief. Fast dissolving tablets of Diclofenac sodium are a useful approach for pain management and a feasible alternative to the available conventional immediate release dosage form. Form the results, optimized B_5formulation showed improves drug release characteristics.

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