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Fast Dissolving Diclofenac Sodium Tablets: A Novel Approach For Effective Musculoskeletal Pain Management.

[1] Ms. Varsha Gajanan Rane, [2]Mr. Harshad Santosh Dalvi, [3]Mr. Hari Prakash Warang, [4]Mr. Swapnil Uddhav Patil, [5]Mr. Rameshwar Mahaldar Wakde

[1] Asst. Professor,[2]Student,[3]Student, [4] Student,[5]Student

[1-5] V P College of Pharmacy, Sawantwadi- Maharashtra 416510

Abstract: Musculoskeletal (MSK) pain represents a significant global health burden, frequently leading to chronic conditions such as osteoarthritis and rheumatoid arthritis. Although nonsteroidal anti-inflammatory drugs (NSAIDs) like Diclofenac Sodium are commonly prescribed for the management of MSK pain, conventional oral dosage forms are associated with limitations including delayed onset of action, low bioavailability due to first-pass metabolism, and poor patient compliance particularly among geriatric, pediatric, and dysphagic populations. This study aims to develop and evaluate fast dissolving tablets (FDTs) of Diclofenac Sodium, leveraging their potential to offer rapid disintegration in the oral cavity and enhanced systemic absorption via pre-gastric pathways. Tablets were formulated via direct compression using various super disintegrants, including Crospovidone, Croscarmellose Sodium, and Sodium Starch Glycolate. The formulations were subjected to comprehensive physicochemical characterization, including pre-compression (angle of repose, bulk density) and post-compression evaluations (hardness, friability, disintegration time, drug content, and in vitro dissolution studies). The optimized formulation demonstrated superior disintegration (≤30 seconds), improved dissolution rate, and acceptable mechanical integrity. These findings confirm the feasibility of FDTs as an alternative drug delivery system for Diclofenac Sodium, providing enhanced bioavailability, rapid therapeutic onset, and improved patient adherence. In conclusion, the developed FDTs represent a promising strategy for the effective management of musculoskeletal disorders, offering clinical advantages over conventional dosage forms through improved pharmacokinetic and patient-centric profiles.

keywords **– FDT, NSAIDs, Musculoskeletal, Anti- inflammatory**

I. INTRODUCTION

Musculoskeletal pain is a difficult condition to manage for both patients and healthcare providers. Most adults experience at least one episode of musculoskeletal pain at some point in their lives, regardless of their age, gender, or socioeconomic background [1]. Musculoskeletal pain is described as either acute or chronic pain that impacts the bones, muscles, ligaments, joints, tendons, and even nerves. The pain linked to musculoskeletal (MSK) disorders represents a widespread medical and socioeconomic issue across the globe [2]. The most common symptom of musculoskeletal disorders is pain, which can sometimes be severe. Around one-quarter of adult patients report pain intensity at a level of 7 or higher on a 0–10 numeric pain scale [3]. Musculoskeletal pain is often intense and localized. In cases of joint pain, specific postures or movements can either aggravate or ease the discomfort. Individuals with moderate musculoskeletal pain often describe it as resembling the sensation of a strained or overused muscle.

A common manifestation is regional pain affecting a single joint [4]. A subset of individuals with musculoskeletal pain may report muscle aches, twitching, or other unpleasant muscle sensations. In chronic musculoskeletal disorders, there may be a neuropathic component, characterized by burning, shock-like, or "electrical" pain. This type of pain can begin suddenly and often without any clear trigger. Neuropathic pain may also present as numbness or a "pins and needles" sensation. It's important to recognize that the experience of musculoskeletal symptoms can vary greatly from one patient to another [4]. Body aches, malaise, and stiffness are frequently reported by patients with musculoskeletal pain. For many, joint stiffness and discomfort are most pronounced upon waking or after periods of inactivity, but tend to ease as they begin to move. [5]. Additionally, the intensity of symptoms or level of pain does not always reflect the actual severity of the musculoskeletal injury.

Classification of pain:

Musculoskeletal pain poses both diagnostic and therapeutic challenges. Increasing evidence suggests that muscle hyperalgesia, referred pain, and widespread hyperalgesia significantly contribute to chronic musculoskeletal pain. Beyond the sensory impact, this type of pain also affects motor control systems and alters related biomechanical functions [6].

Based on pathophysiological mechanisms, pain can be classified into several categories:

1. **Nociceptive pain:** Nociceptive pain is the most common type of pain following tissue injury and is the primary category associated with musculoskeletal pain. Also referred to as physiological or inflammatory pain, it serves a protective function by alerting the body to potential or actual harm [7],[8]. This type of pain is a normal sensory response triggered by the activation of peripheral pain receptors, which in turn stimulates the relevant spinal cord pathways and their sensory nuclei [9],[10].
2. **Neuropathic pain:** Major types of pain include neuropathic pain, which is caused by a primary lesion or dysfunction of the somatosensory nervous system, often referred to as pathological pain. Unlike nociceptive pain, neuropathic pain does not serve a protective function [11],[12].
3. **Mixed type pain:** Mixed pain arises when both nociceptive and neuropathic components are present simultaneously in the same patient. In such cases, the mechanical low back pain reflects the nociceptive component, while the radicular pain radiating to the lower limbs represents the neuropathic component [10],[11].
4. **Idiopathic pain:** Idiopathic pain refers to pain that is either disproportionate to the nature or extent of tissue injury or occurs without any identifiable cause. Psychological factors may play a role in the development or perception of this type of pain [10],[11].
5. **Nociplastic pain:** It is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors, or evidence of disease or lesion in the somatosensory system causing the pain" [13].

Treatment

Both pharmacological and nonpharmacological treatments are important and can be combined to effectively manage a patient's pain [14]. Pharmacological treatment forms the cornerstone of pain management.[15]. The WHO analgesic ladder emphasizes key principles for effective pain relief: using the simplest route of administration (such as oral), administering medication at regular intervals (by the clock), and tailoring treatment to the type and severity of the pain [16], NSAIDs are a treatment option to consider for patients with chronic non-specific low back pain and musculoskeletal pain [17]. Oral NSAIDs are strongly recommended as the first-line pharmacologic treatment for musculoskeletal pain, including knee, hip, and hand osteoarthritis. They are considered the cornerstone of oral medication due to their proven short-term effectiveness in numerous clinical trials and are preferred over other oral treatment options, regardless of the pain’s anatomical location [18],[19].

Fast Dissolving Tablets:

Conventional dosage forms, such as tablets and capsules, are widely popular due to their ease of self-administration, compact size, simple manufacturing process, and accurate dose delivery. However, a significant drawback of these traditional forms is their longer disintegration time, often leading to a delay of 30–45 minutes before the onset of pharmacological action. To address this limitation, fast-dissolving

tablets (FDTs) have been developed. These tablets rapidly disintegrate or dissolve within one minute when placed in the oral cavity, allowing the medication to be swallowed as a liquid. Fast-dissolving drug delivery systems are specifically designed for quick action without the need for water. Some formulations can dissolve in saliva within just a few seconds, offering an even faster onset of action. Despite these innovations, conventional dosage forms remain popular in the pharmaceutical industry due to their low production costs [20].

Physiological Considerations and the Role of Fast-Dissolving Tablets:

Dysphagia, or difficulty in swallowing, is commonly observed among pediatric and geriatric populations, although it can affect patients across all age groups. Conventional solid dosage forms often present challenges for these individuals, highlighting the need for alternative drug delivery systems. Fast-dissolving tablets (FDTs), which disintegrate, dissolve, or form a suspension in the saliva, offer significant advantages by facilitating easier swallowing without the need for water. These formulations are particularly beneficial for populations with compromised swallowing ability and for patients seeking greater convenience. Upon placement on the tongue, FDTs rapidly disintegrate, releasing the active pharmaceutical ingredient for immediate dissolution or dispersion in the oral cavity [20].

The convenient administration and pleasant taste of fast-dissolving/disintegrating tablets can promote better patient adherence to daily medication regimens. While FDTs may not fully resolve all compliance challenges, they represent a meaningful advancement with potential therapeutic benefits [21]. Diclofenac sodium is one of the most commonly used NSAIDs, primarily for musculoskeletal conditions such as arthritis. However, conventional diclofenac sodium tablets available on the market are not ideal for situations where a rapid onset of action is necessary [22]. Diclofenac sodium is a synthetic, non-steroidal anti-inflammatory and analgesic agent. Its therapeutic effects—anti-inflammatory, antipyretic, and analgesic—are primarily due to the inhibition of prostaglandin synthesis through the blockade of cyclooxygenase (COX). Diclofenac may also have a unique characteristic among NSAIDs, as it has been shown to inhibit the lipoxygenase pathway, thereby reducing the formation of leukotrienes, which are also pro-inflammatory mediators. It is well absorbed orally with 100% bioavailability, over 99% protein-bound, and is metabolized in the liver, with excretion occurring via both urine and bile. Its plasma half-life is between 1.2 and 2 hours. Diclofenac is commonly used for musculoskeletal conditions, particularly arthritis (rheumatoid arthritis, osteoarthritis, gout attacks), as well as pain management in kidney and gallstone conditions [23]. Diclofenac is frequently used to manage mild to moderate pain following surgery or injury, especially when inflammation is involved, and is also effective in relieving menstrual pain [24].

Material:

Diclofenac sodium (Dhamtec Pharma and Consultants. Kamothe, Navi Mumbai), and Crospovidone (PPXL), Sodium Starch Glycolate, Croscarmellose Sodium (Ac-Di-Sol), Mannitol, Microcrystalline cellulose (PH102), Magnesium stearate, Talc, Aspartame, Menthol were obtained from RESEARCH-LAB FINE CHEM INDUSTRIES, MUMBAI. All reagents are of analytical grade.

Methods:

Identification of Drug: The drug was identified using melting point determination and ultraviolet (UV) spectroscopy [25].

Melting point Determination: The melting point of Diclofenac was assessed using the capillary tube method. A finely powdered sample of the drug was introduced into a glass capillary tube, previously sealed at one end. The tube was affixed to a thermometer and subjected to a controlled increase in temperature. The temperature at which the Diclofenac sample exhibited complete melting was recorded [25].

Ultraviolet Spectroscopy: The samples underwent UV spectrophotometric analysis, during which their absorption maxima (λmax) were recorded within the wavelength range of 200–400 nm using a UV-Vis spectrophotometer in a suitable solvent system. The resulting spectral data were then compared with literature-reported reference values [26].

Formulation of tablets by direct compression method:

All ingredients were accurately weighed and passed through a #44 sieve. The sieved components were mixed geometrically, excluding magnesium stearate. Subsequently, the blend was lubricated with magnesium stearate. The tablets were compressed using 6.5 mm circular punches, featuring a break line on one side and a plain surface on the other. Compression was carried out on a 16-station single rotary tablet compression machine (Cadmach, Ahmedabad, India) [41].

Post compression parameters:

1. **Weight Variation: A** weight variation test was conducted by individually weighing 20 tablets using an electronic balance. The average weight was calculated, and the weight of each tablet was compared against this average value [30].

Table No.1: Weight Variation According to IP & USP

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

2. **Tablet thickness:** Tablet thickness was determined by positioning each tablet between the two arms of a Vernier calliper. Measurements were taken for five tablets, expressed in millimetres, and the average thickness was subsequently calculated [31].
3. **Hardness:** Tablet stiffness, defined as the force necessary to fracture a tablet across its diameter, was assessed using a Monsanto hardness tester. This device applies pressure to the tablet through an integrated spring mechanism, and the resulting hardness is expressed in kg/cm² [32].
4. **Friability:** This test assesses the tablet's resistance to abrasion and edge damage during packing, handling, and shipping. Friability is typically an indicator of weak cohesion between the tablet ingredients. The friability was measured using a Roche friabilator. Ten tablets were weighed and placed in a plastic chamber that rotates at 25 rpm for 4 minutes. Afterward, the tablets were re-weighed, following the removal of fines (de-dusting). The acceptable friability range is between 0.5% and 1%. The friability was then calculated using the following formula [33]:

%friability = 100 × initial weight – final weight /initial weight

5. **In vitro dispersion time:** Two tablets were placed in a 100 mL beaker containing a pH 6.8 phosphate buffer solution at 37°C. The time taken for the complete dispersion of the tablets was observed and recorded [34].
6. **Water absorption ratio: A** piece of tissue paper, folded twice, was placed in a small Petri dish containing 6 mL of water, to which Eosin, a water-soluble dye, was added. A tablet was placed on the paper, and the time taken for complete wetting was recorded. After wetting, the tablet was weighed. The water absorption ratio, R, was then calculated using the following equation [35].

R=10 (Wa /Wb)

Where, Wb = is the weight of the tablet before water absorption,
Wa = is the weight of the tablet after water absorption.

7. **Wetting time:** Five circular tissue papers, each with a 10 cm diameter, were placed in a Petri dish of the same diameter. Ten millilitres of water, containing Eosin (a water-soluble dye), were added to the dish. A tablet was then carefully placed on the surface of the tissue paper. The time taken for the water to reach the upper surface of the tablet was recorded as the wetting time [36].

8. **In vitro disintegration time:** The breakdown of a tablet into smaller particles is referred to as disintegration. One tablet was placed in each of the six tubes of the basket. A disc was added to each tube, and the apparatus was operated using a 6.8 pH phosphate buffer, maintained at 37°C, as the immersion liquid. The assembly was raised and lowered at a rate of 30 cycles per minute in the phosphate buffer. The time, in seconds, required for the complete disintegration of the tablet, with no residue remaining in the apparatus, was measured and recorded. The tablet must disintegrate within 60 seconds [37].
9. **In vitro Dissolution study:**
   In-vitro dissolution studies of the tablets were performed using a USP type II dissolution apparatus, employing a paddle stirrer operated at 75 rpm. The dissolution medium consisted of 900 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5 °C. One tablet was used per test. Aliquots of 1 mL were withdrawn at predetermined time intervals (2, 4, 6, 8, and 10 minutes) and replaced with an equal volume of fresh dissolution medium. The collected samples were analysed spectrophotometrically at a wavelength of 273–276 nm to determine the drug content. The concentration of the drug was then calculated and expressed as the cumulative percentage of drug released [38].
10. **Determination of drug content:** Twenty tablets were accurately weighed and powdered. A quantity of powder equivalent to approximately 50 mg of diclofenac sodium was transferred to a 200 mL volumetric flask, shaken with 60 mL of methanol, and then diluted to volume with methanol. From this solution, 5 mL was withdrawn and further diluted to 100 mL with methanol. The absorbance of the resulting solution was measured at 285 nm [39].
11. **Stability Studies:**
    The optimized formulation was subjected to stability studies under accelerated conditions at 40 °C and 75% relative humidity for a duration of one month. The parameters evaluated to determine the impact of these stress conditions on the tablets included: weight variation, average thickness, friability, disintegration time, average hardness, wetting time, drug content, and percentage of drug released [40].

Table No.2: Formulation Code of Fast Dissolving Tablet of Diclofenac Sodium

SR.NO	INGREDIENTS (mg/tablet)	FORMULATION CODE									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Diclofenac sodium	50	50	50	50	50	50	50	50	50	50
2	Crospovidone (PPXL)	-	24	-	-	08	16	18	62	31	72
3	Croscarmellose Sodium (Ac-Di-Sol)	-	-	24	-	08	04	6	-	31	-
4	Sodium Starch Glycolate	-	-	-	24	08	04	-	-	-	-
5	mannitol	82	58	58	58	58	58	58	20	20	10
6	Microcrystalline cellulose (PH102)	9	9	9	9	9	9	9	9	9	9
7	Magnesium stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
8	Sodium saccharine	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
9	Talc	3	3	3	3	3	3	3	3	3	3
10	Menthol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
11	Total weight	150	150	150	150	150	150	150	150	150	150

RESULTS AND DISCUSSION

UV Spectroscopy: The drug sample when subjected to UV spectrophotometric analysis, showed absorption maxima (λ max) at a wavelength of 275nm. The obtained peak was as per the reference values in literature.

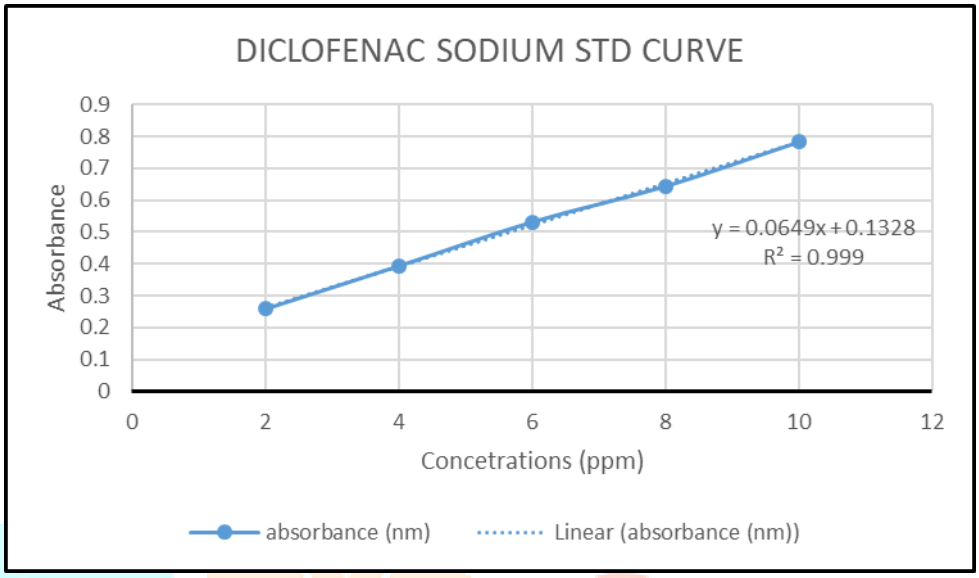

Fig 1: Calibration Curve of Diclofenac Sodium FDT

Micromeritics study: The angle of repose of the formulation blend was in the range of 24.30º-27.61º, which indicates good flow properties of the different blends. The Carr's index, Hausner's ratios were found to be in the range of 13-25 and 1.12-1.34 indicating good compressibility.

Table no. 3: Evaluation of pre-compression parameters

Formulations	Angle of repose (θ) (Mean±SD)	Bulk density (g/cm^3) (Mean±SD)	Tapped density (g/cm^3) (Mean±SD)	Carr's Compressibility index (Mean±SD)	Hausner's ratio (Mean±SD)
F1	25.17±0.38	0.43±0.38	0.50±0.021	25±0.89	1.34±0.028
F2	27.61±0.80	0.41±0.80	0.51±0.012	19±0.81	1.24±0.016
F3	25.75±2.20	0.42±2.20	0.53±0.016	20±0.81	1.26±0.012
F4	27.46±0.73	0.44±0.73	0.51±0.018	13±0.81	1.15±0.028
F5	24.37±0.59	0.43±0.59	0.53±0.009	18±0.82	1.23±0.029
F6	24.30±0.77	0.41±0.16	0.52±0.022	19±0.82	1.22±0.021
F7	25.76±0.23	0.45±0.08	0.51±0.082	17±0.70	1.24±0.024
F8	26.12±0.55	0.44±0.12	0.50±0.012	15±0.89	1.18±0.029
F9	24.58±0.42	0.42±0.81	0.52±0.096	14±0.78	1.34±0.026
F10	26.45±0.14	0.41±0.16	0.53±0.014	15±0.65	1.12±0.027

Post formulations study:

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

Thickness: The thickness was maintained to be within 2.32-2.50, no variation in the thickness was found which clearly indicates that the blending was uniform.

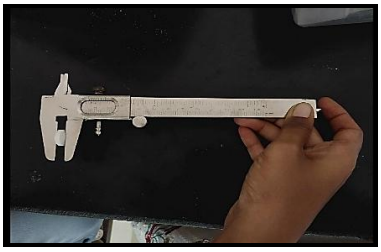

Fig 2: Thickness of FDT Diclofenac sodium

Friability: The friability of the formulations was found to be between 0.14-0.92 % and was within the official requirement (i.e. less than 1%).

Hardness: The hardness was maintained to be within 4.0-4.9 kg/cm^2, no variation in the hardness was found which clearly indicates that the blending was uniform

Table No.4: Evaluation of post compression parameters

Formulation Code	Hardness (Kg/cm^2) (Mean±SD)	Thickness (mm) (Mean±SD)	Friability (%) (Mean±SD)	Weight Variation (mg) (Mean±SD)
F1	4.5±0.25	2.50±0.35	0.70±0.30	144±0.09
F2	4.7±0.17	2.40±0.15	0.52±0.26	152±0.13
F3	4.4±0.16	2.32±0.18	0.33±0.22	149±0.10
F4	4.3±0.08	2.44±0.30	0.92±0.18	152±0.17
F5	4.9±0.19	2.50±0.12	0.64±0.10	149.5±0.16
F6	4.0±0.02	2.33±0.20	0.92±0.28	151±0.89
F7	4.9±0.07	2.37±0.05	0.78±0.39	147±0.23
F8	4.8±0.10	2.39±0.19	0.77±0.31	155.5±0.21
F9	4.7±0.22	2.44±0.35	0.14±0.27	148.7±0.09
F10	4.2±0.03	2.50±0.23	0.66±0.48	150.3±0.07

Water absorption ratio: The water absorption ratio for all formulations within the range of 24- 30. The formulation containing 72 mg of Crospovidone (F10) showed higher absorption ratio i.e. 30 when compared to other formulations.

Wetting time: The wetting time for all formulations within the range of 18- 38 seconds. The formulation containing 72 mg of Crospovidone (F10) showed lesser wetting time of 18 seconds when compared to other formulations.

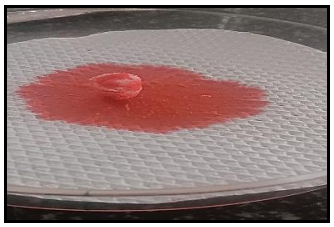

Fig 3: Wetting time of FDT Diclofenac sodium

In vitro dispersion time: The values of the formulations were found to be within the range of 37-58 seconds. The formulation containing 72 mg of Crospovidone (F10) showed a faster dispersion time of 28 seconds when compared with other formulations.

In vitro disintegration time: In vitro disintegration time for all the formulations varied from 25-70 seconds. The formulation F10 showed better disintegration time of 25 seconds.

Table No.5: Evaluation of post compression parameters

Formulation Code	Wetting time (sec)	Water absorption ratio	*In vitro* dispersion time (sec)	*In vitro* disintegration time (sec)
F1	74	18	30	21
F2	26	27	45	58
F3	30	25	40	70
F4	32	24	42	67
F5	33	23	52	62
F6	27	28	58	57
F7	35	23	37	48
F8	38	24	47	47
F9	36	26	35	48
F10	18	30	28	25

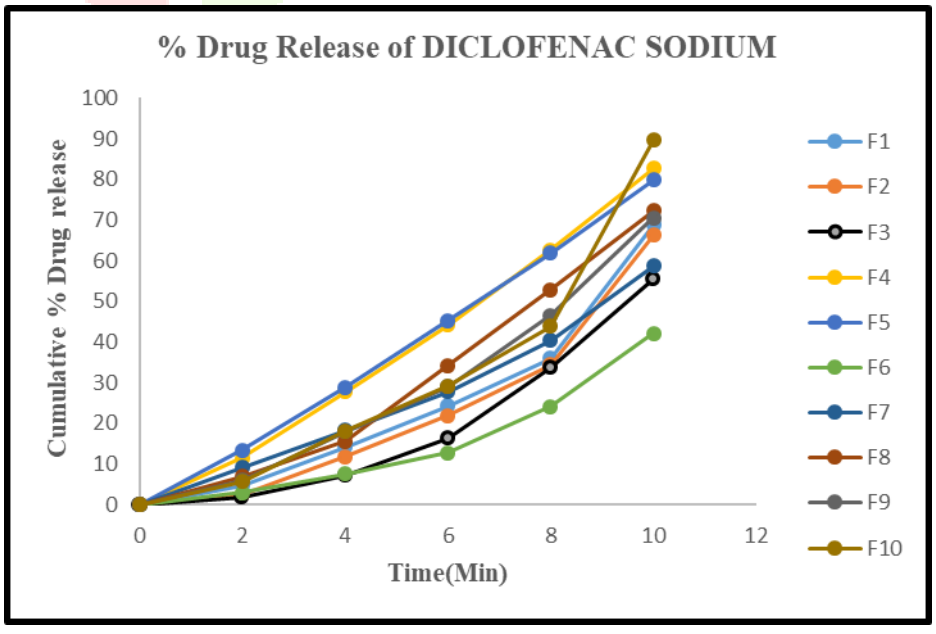

Fig 4: % Drug Release of Diclofenac Sodium FDT

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