PREPARATION AND EVALUATION OF DICLOFENAC SODIUM SUSTAINED REALEASE TABLETS USING SYNTHETIC POLYMER

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ABSTRACT

Oral drug administration is a popular and convenient method due to its ease of swallowing, self-medication, and economic benefits. Tablets are the most popular oral formulation due to their ease of manufacturing, stability, and tamper-proof nature. Drug release is the process of a drug leaving a product and being subjected to absorption, distribution, metabolism, and excretion. Controlled release dosage forms, such as sustained release (SR) dosage forms, are increasingly popular in modern therapeutics. SR dosage forms provide better control of plasma drug levels, less dosage frequency, less side effects, increased efficacy, and constant delivery. Diclofenac sodium, a non-steroidal drug with potent anti-inflammatory, analgesic, and antipyretic effects, is used for pain relief in conditions like rheumatoid arthritis, osteoarthritis, and acute gout. The study aims to formulate a matrix tablet of diclofenac sodium using wet granulation techniques with different concentrations of HPMC and EC.

Keywords: *Diclofenac sodium, Polymer, sustain Release, HPMC, EC.*

INTRODUCTION

Due to its affordability, self-medication capabilities, ease of swallowing, and significance, the oral route of drug administration is the most appealing, useful, significant, and popular method of drug delivery. Tablets are the most popular and preferred oral formulation available in the market because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids and because it is more tamperproof than capsules.[1] Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism and excretion, eventually to becoming available for pharmacological action. Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics.[2] Sustained release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ 1-3. Sustained release dosage forms provide better control of plasma drug levels, less dosage

frequency, less side effect, increased efficacy and constant delivery.[3]
Diclofenac sodium (DS) is a non-steroidal drug having a potent anti-inflammatory, analgesic, and antipyretic effect. It is an inhibitor of prostaglandin synthetase. It is used for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, and following some surgical procedures.[4] The most frequent side effects of Diclofenac sodium on long-term administration are gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding. Diclofenac sodium is poorly soluble in water and has acidic pH (1-3) but is rapidly soluble in alkaline pH (5-8). Hence an attempt was made to formulate a sustained release formulation with increased patient compliance and decreased signs of adverse effects. Pharmacokinetic profile of Diclofenac sodium is after oral administration, diclofenac is rapidly and almost completely absorbed. Absorption is delayed by food. It is highly protein bound. Diclofenac undergoes first-pass metabolism, with 60% of unchanged drug reaching systemic circulation. About 40% to 60% is excreted in the urine; the balance is excreted in the bile.[5] The principal goal of SR dosage forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of SR(sustained release) systems. HPMC is a non-digestible matrix used to control drug release through water penetration, drug diffusion through the swollen hydrated matrix. The release depends on polymer selection and drug-polymer ratio.[6] Ethyl cellulose, an inert hydrophobic polymer, is suitable for designing sustained release matrices due to its toxicity, stability, and compressibility. It is widely used to control drug dissolution rates and solid dispersion techniques.[7] The present invastigation is aimed to formulate the matrix tablet of diclofenac sodium by wet granulation technique with different concentration HPMC (hydroxypropylmethylcellulose) and EC (ethyl cellulose)using no other varying parameter.

LITERATURE REVIEW

Kumar, *et.al*. 2020, The study demonstrates the preparation of sustained release tablets of Diclofenac Sodium using HPMC and Ethyl cellulose, with evaluations including preformulation studies and in-vitro release in a pH 7.2 Phosphate Buffer System. The polymer ratio affects drug release. The Evaluation of tablets is involved the Preformulation studies such as compressibility index, bulk density, angle of repose, and physical characteristics like hardness, weight variation friability,drug- excipient compatibility and drug content.
Savale S.K., *et.al.*2015,Diclofenac is a non-steroidal anti-inflammatory drug (NSAIDS) with anti-inflammatory, antipyretic, and analgesic properties. It is crucial for inhibiting Cyclooxygenase (COX I, COX II) enzyme, which is responsible for inhibiting Prostaglandins Synthesis. Authentication and preparation studies are conducted to maintain the standard and stability of the pure drug. A sustained release tablet is developed to provide prolonged drug release for long-term therapeutic activity. The tablet is prepared using suitable ingredients like HPMC K 100, ethylcellulose, talc, and magnesium stearate. The optimized batch has satisfactory results with good free- flowing properties, within the pharmacopeia limit.
G.N.K.Ganesh,*et.al.*2010, A study on sustained release tablets of Diclofenac Sodium was conducted using cashew nut tree gum, HPMC, and Carbopol. The tablets were evaluated for preformulation, compressibility index, and physical characteristics. In-vitro release was performed in PBS pH 7.2 for twelve hours. The tablets with HPMC and Carbopol showed higher drug content. A better sustained drug release was achieved with a matrix tablet made of carbopol. The dissolution profile indicated that increasing the polymer ratio retarded drug release.

MATERIALS AND METHODS

Table 1: List of materials used

Sr. No.	Name of Ingredient	Name of supplier
1	Diclofenac sodium	RESEARCH-LAB FINE CHEM INDUSTRIES, Mumbai
2	HPMC(K100M)	RESEARCH-LAB FINE CHEM INDUSTRIES, Mumbai
3	Ethyl Cellulose	RESEARCH-LAB FINE CHEM INDUSTRIES, Mumbai
4	Lactose	Pallav Chemicals & Solvent Pvt. Ltd.
5	Polyvinyl Pyrrolidine	RESEARCH-LAB FINE CHEM INDUSTRIES
6	Iso Propyl Alcohol	Pallav Chemicals & Solvent Pvt. Ltd.
7	Magnesium Stearate	RESEARCH-LAB FINE CHEM INDUSTRIES, Mumbai
8	Talc	RESEARCH-LAB FINE CHEM INDUSTRIES, Mumbai

Table 2: List of equipments used

Sr. No.	Equipment	Model/ Make
1	Electronic Balance	CONTECH, India

2	**Bulk density apparatus**	**Lab Hosp Ltd.**
4	**Hot air oven**	**MVTEX Ltd.**
5	**Single station tablet compression machine**	**Cadmach, Ahmadabad, India.**
6	**Friability apparatus**	**LABIINDIA Aalytical Instruments Pvt. Ltd.**
7	**Hardness tester**	**Monsanto, Pfizer**
8	**Vernier caliper**	**Mitutoyo Ltd.**
9	**USP dissolution apparatus Type 2**	**LABINDIA Aalytical Instruments Pvt. Ltd.**
10	**UV spectrophotometer**	**Jasco**

METHOD

The parameters of Authentication and Preformulation are carried out by pure drug Diclofenac for Maintaining their Quality and Standard.

AUTHENTICATION PARAMETERS[8]

Solubility Studies

The Term Solubility is defined as maximum amount of solute that can be dissolved in a given amount of solvent to form a homogenous system at specified temperature and Specific Pressure to from Saturated Solution.

Procedure

- To Prepare PH 6.8 Phosphate Buffer
- The drug material is added in to above solutions till Supersaturated Solution is from.

Calibration Curve

Calibration Curve of Diclofenac Calibration Curve is determined by using UV Spectrophotometric methods. In which 10 mg drug is added in 100 ml of Phosphate Buffer pH 6.8 (100 µg/ml Solution). To Prepared different Dilutions (0, 2, 4, 6, 8, 10, 12) of above solution (100 µg/ml Solution). Take Absorbance in respective λmax 282 nm.

Method of preparation of diclofenac sustained release tablets

Diclofenac sodium matrix tablets were formulated using the formula in Table 1. Granules were prepared using the non aqueous wet granulation technique. Diclofenac sodium (100 mg) was weighed and transferred into a mortar. This was mixed uniformly with 50 mg of HPMC and 310 mg of lactose using a pestle. Polyvinyl pyrollidone (25 mg) was dissolved with sufficient quantity of isopropyl alcohol, added to the powder, mixed and blended uniformly to form a damp mass. The wet mass was passed through a 1.18 mm sieve to form granules. The wet granules were dried in an oven at 40 oC for 1 h., after which the dried granules were sieved with a 710 µm sieve . Magnesium stearate and talc were added to the granules and then compressed into tablets with a predetermined force using a Rotary tablet compression machine. This procedure was repeated following the formula on Table 3 to prepare formulations F1 to F6 tablets.[9]

Table 3: Formulation Batches details of Diclofrnac sodium sustained release tabltes

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Diclofenac Sodium	100	100	100	100	100	100
HPMC	50	100	150	-	-	-
Ethyl Cellulose	-	-	-	50	100	150
Lactose	310	260	210	310	260	210
Polyvinyl pyrollidone	25	25	25	25	25	25
Isoprpyl alcohol	Qs	Qs	Qs	Qs	Qs	Qs
Talc	10	10	10	10	10	10
Magnesium Stearate	5	5	5	5	5	5

PREFORMULATION STUDIES

Bulk density

Bulk density (Db) was determined by measuring the volume (Vb) of known weighed quantity (W) of granules using bulk

density apparatus and can be calculated by using the formula:[10]
Db = W/ Vb

Tapped density

Tapped Density: Tapped density (Dt) was determined by measuring the volume (Vt) of known weighed quantity (W) of granules using bulk density apparatus and can be calculated by using the formula:[10]
Dt = W/ Vt

Hausner's Index:

The Hausner's index was calculated by dividing the tapped density by the bulk density of the granules.

Hausner's index = Dt/Db

Where, **Dt** is the tapped density and **Db** is the bulk density.

Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weight granules were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The granules were allowed to flow through the funnel freely on to the surface13. The diameter of the granules cone was measured and angle of repose was calculated using the following equation.[11]

Tan θ = h/r

Where, **h** = height of the powder cone. **r** = radius of the powder cone.

Sr. no.	Flowability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable	30-40
4	Poor	37-45
5	Very poor	>45

Carr's index

It is also known as compressibility index, int is simple method to measure the compressibility index, indicating easiness of material free flowing, it is calculated by.[12]

Carr's Index%	Flowability
5-15	Excellent
12-16	Good
18-21	Fairly acceptable
23-35	Poor
33-38	Very poor
<40	Very very poor

I= (Vo-Vt/Vo) ×100

Where, **Vo** is the bulk volume **Vt**= tapped volume.

Evaluation of Sustained Release Tablet of Diclofenac

Thickness and diameter of tablet was estimated utilizing calibrated vernier calipers. Ten tablets of every formulation were selected randomly and evaluated for thickness and diameter. The tablets were assessed for appearance, thickness, weight variation, hardness and friability.

Dimensions

Thickness of tablets was measured by using calibrated vernier Calipers. Tablet was Placed in between two jaws vertically and thickness was measured. Thickness was measured in mm.[12]

Hardness

Monsanto hardness tester was used for determination of hardness. Hardness of tablet was measured by fitting of tablet lengthwise between plungers and applied the force. The pressure at which tablets was crushed was noted, Called hardness of Tablet. It is measured in Kg/cm2. This study requires 6 tablets were used for this study.[12]

Percent friability[13]

Friability is defined as Loss of Tablets during transportation and Storage. Roche friabilator is used for calculation of friability.

i. 20 tablets are randomly selected from each formulation; tablets are weighed, not down the initial weight.
ii. Place into drum friabilator, and tested for 4 min. by rotating at 25 RPM.
iii. After 4 min. the tablets was withdrawn from drum and dust was removed.
iv. Tablets were re-weighed for calculation of % Friability and friability percentage was calculated using the following equation. C It is expressed in percentage (%) and calculated by the following formula: **Friability (%) = Initial weight-Final weight \Initial weight×100**

0.5-1.0% for compressed tablets that lose less than of their weight was generally considered acceptable.[13]

Weight variation

Weight of 20 tablets from each formulation was taken individually, Avreage weight of tablets was calculated and the weight of individual tablet was compared with the average weight of tablets.

USP States that the tablets meet the USP test if close to two tablet are outside the percentage limit if no tablet vary by two times of percentage limit. The weight variation resistances for uncoated tablets vary contingent by and large weight. Weight variation of tablets was determined by comparing the of weight of individual tablet average weight.[14]

Acceptance criteria for % Deviation.

Sr. No.	Average Weight of tablet	% Deviation
1	80 mg or less	10
2	More than 80 but less than 250 mg	7.5
3	250 mg or more	5

Drug Release Study

The tablet tests were exposed to in-vitro dissolution studies using USP Type II dissolution apparatus at 37±2°C and 50 rpm speed. According to the official proposal of USFDA, 900 ml of 7.4 Phosphate Buffer was utilized as dissolution medium. Aliquot equal to 10 ml was pulled back at explicit time intervals and, the dissolution media volume was complimented with fresh and equal volume of 7.4 Phosphate Buffer. The aliquots were filtered and checked with suitable weakening and amount of Diclofenac sodium discharged from the tablet tests was determined spectrophotometrically at a wavelength of 276 nm by comparing with the standard calibration curve.[15]

RESULT AND DISCUSSION

Solubility studies

Table 4: Solubility Profile of Diclofenac sodium

Sr. No.	Medium	Inference
1	Water	Insoluble
2	pH 6.8 Phosphate Buffer	Soluble
Result	**Class of Drug**	**BCS Class II**

Determination of Wavelength of Diclofenac Sodium

The weight amount of 100 mg of Diclofenac sodium drug was methanol in a 100 ml volumetric flask to frame a stock arrangement of 100 µg/ml. The stock arrangement was then pipetted into a 10 ml volumetric flask, and the volume was raised of 10 µg/ml. The subsequent solution was then examined in the range of 200 and 400 nm with an UV -spectrophotometer (Model-1700, JASCO, India). The UV range was recorded and the most elevated worth acquired was contrasted with the

authority monograph's UV range.

Table 5: Wavelength maximum (λ max) of Diclofenac sodium

Drug	**λ max**	
	Actual λ max	**Observed λ max**
Diclofenac sodium	282	284

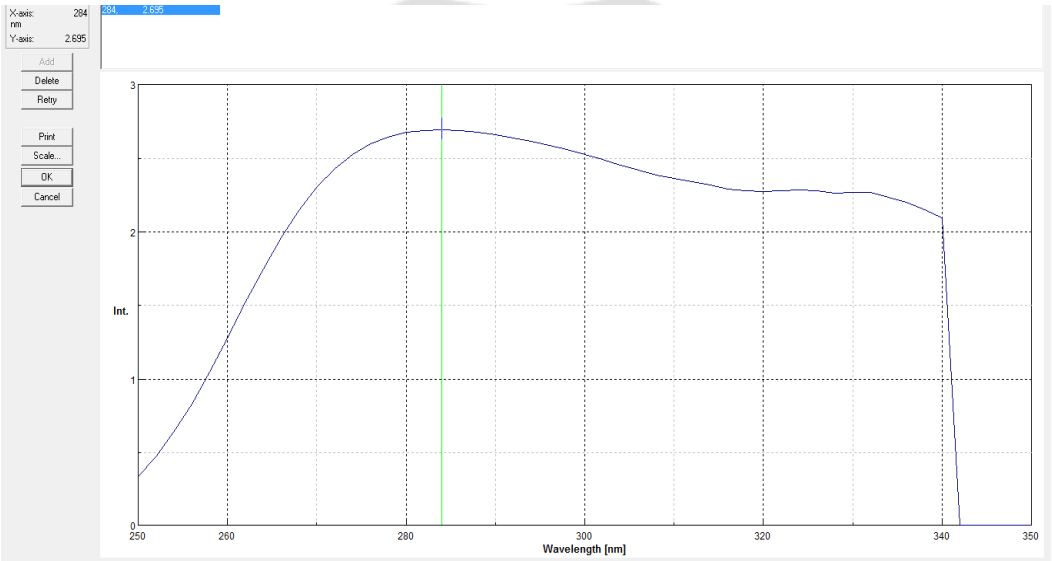

Fig. 1: Uv Spectrum of Diclofenac Sodium Calibration Curve of Diclofenac Sodium in Phosphate Buffer (pH 6.8)

The absorbance versus concentration graph represents the Diclofenac sodium standard calibration curve. Diclofenac sodium maximum concentration was reported to be at 282 nm in phosphate buffer at pH 6.8. According to Figure no.1 Diclofenac sodium standard calibration curve was plotted between 2.0 and 10 g/ml.

Table 6 : Test absorbance of different concentration

Concentration (µg/ml)	**Absorbance**
0	0
2	0.0123
4	0.0225
6	0.0311
8	0.0395
10	0.05

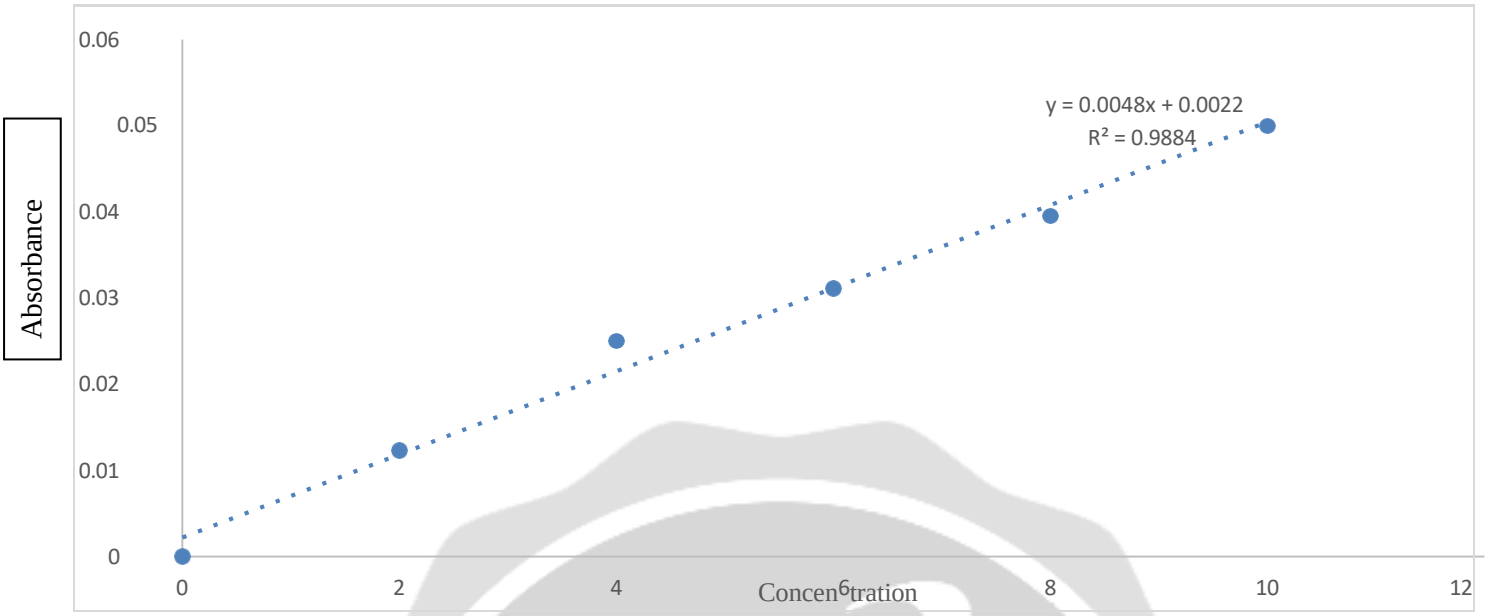

Fig. 2 Calibration curve of Diclofenac Sodium

Drug- Excipient Compatibality Studies[5,8,12]

Drug is an active part of dosages form and it is mainly responsible for therapeutic value and Excipient substances which are included along with drugs being formulated in a dosage form so as to impart specific qualities to them.Ethyl cellulose and Hydroxypropyl Methylcellulose (HPMC) are both biocompatible polymers commonly used in pharmaceutical formulations. When combined with other excipients, such as plasticizers or stabilizers, they maintain their biocompatibility profiles. This compatibility extends to various drug delivery systems, ensuring safe interactions with biological systems and minimal risk of toxicity. As key components in pharmaceutical formulations, ethyl cellulose and HPMC contribute to the efficacy and safety of medicinal products, making them essential choices for biomedical applications.

PRE FORMULATION STUDY

Table 7: Characterisation of powder Blend

Formulation code	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index	Angle of Repose
F1	0.714	0.769	1.07	7.14%	34.25
F2	0.666	0.760	1.15	17.14%	28.23
F3	0.681	0.833	1.22	13.63%	32.40
F4	0.746	0.835	1.11	10.66%	34.16
F5	0.625	0.714	1.14	12.50%	28.45
F6	0.588	0.641	1.08	8.23%	24.25

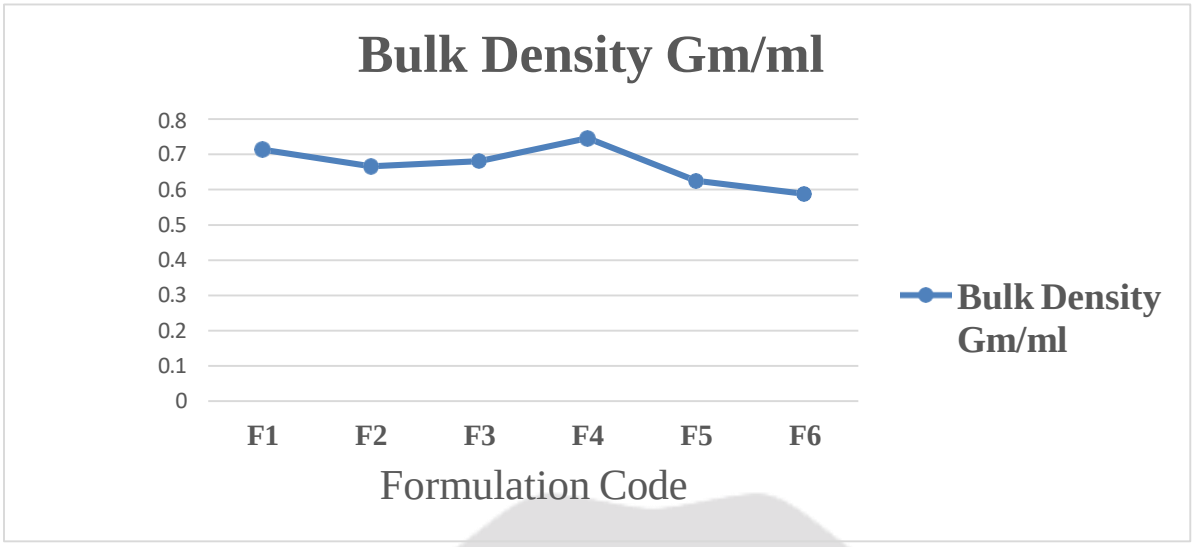

Fig.3 : Bulk Density

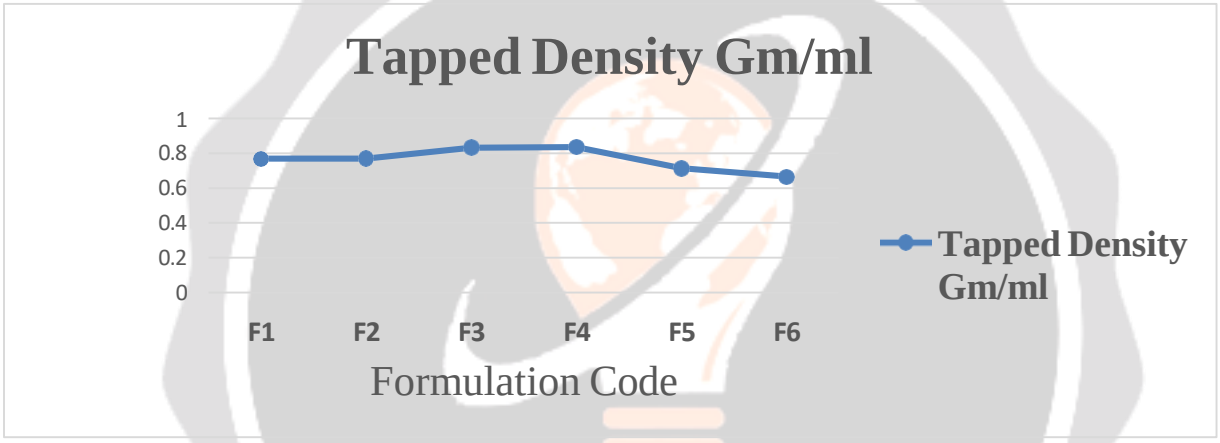

Fig. 4 : Tapped Density

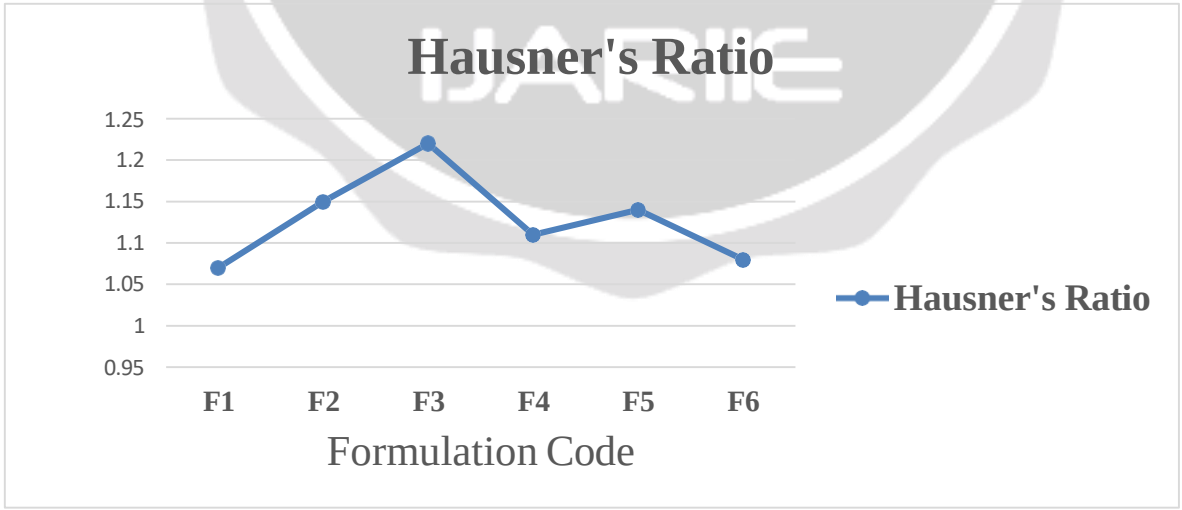

Fig. 5 Hausner's Ratio

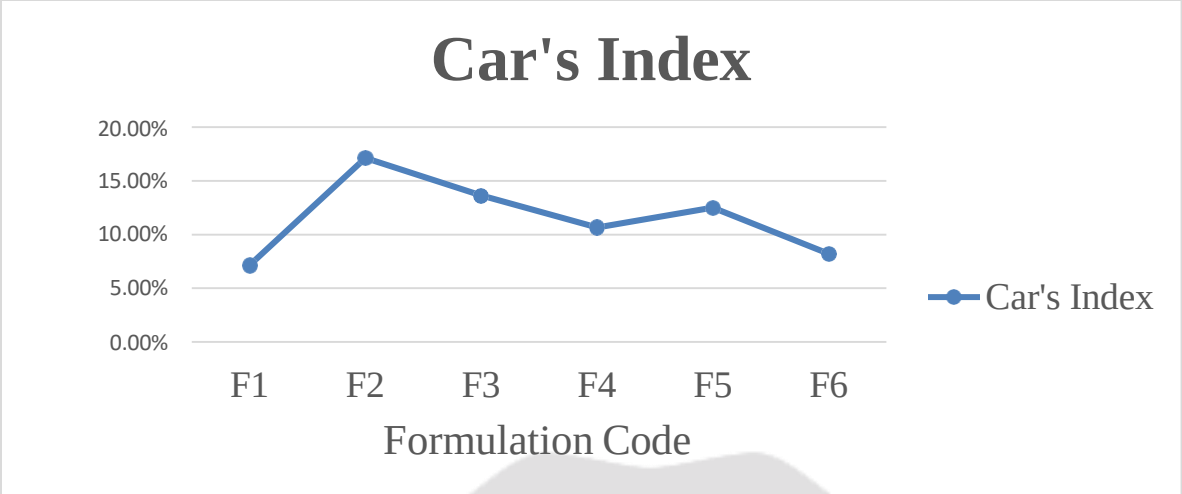

Fig. 6: Car's Index

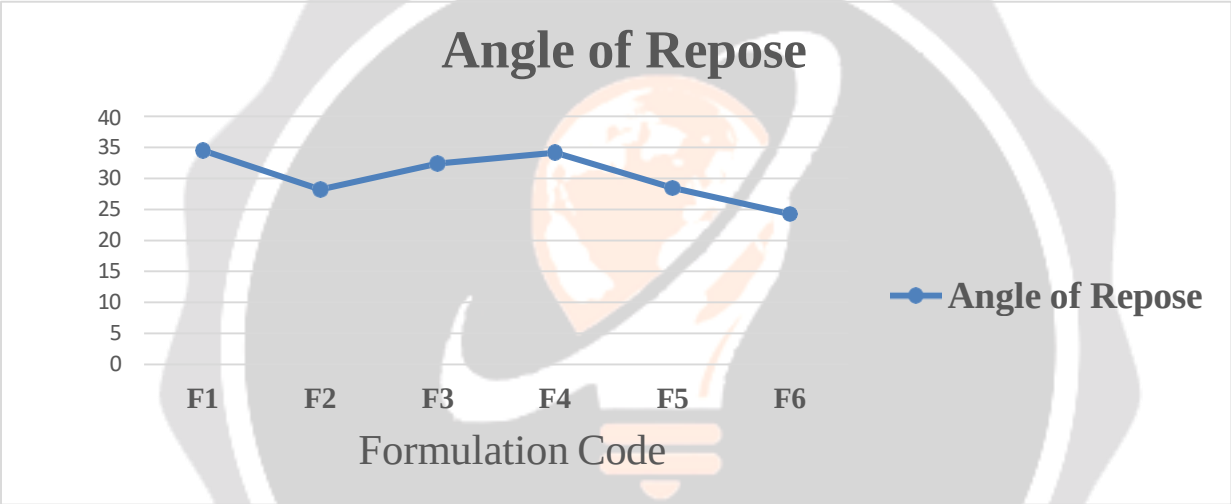

Fig. 7: Angle of Repose

POST-COMPRESSIONAL EVALUATION:

Table 8: Post-compressional studies of Diclofenac sustained release tablets

Formulation code	Weight Variation	Hardness(kg/cm)	Thickness(mm)	% Friability
F1	0.492 ± 0.003	5.7 ± 0.2	3.06 ± 0.06	0.49 ± 0.001
F2	0.497 ± 0.004	6.5 ± 0.2	3.00 ± 0.09	0.72 ± 0.09
F3	0.498 ± 0.005	7.2 ± 0.3	3.20 ± 0.17	1.00 ± 0.012
F4	0.492 ± 0.004	6.5 ± 0.2	3.13 ± 0.13	0.31 ± 0.03
F5	0.495 ± 0.002	6.8 ± 0.4	3.35 ± 0.19	0.9 ± 0.021
F6	0.496 ± 0.002	7.0 ± 0.3	3.47 ± 0.04	0.9 ± 0.01

Table 9: Drug Release of Diclofenac sustained release Tablets

Time (hrs)	% Cumulative Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	19.2	18.5	15.4	16.7	17.4	15.2
2	33.5	28.2	22.5	25.3	25.6	25.6
3	46.2	37.4	35.2	34.2	35.3	35.3
4	55.7	45.4	41.1	42.5	43.6	43.6
5	66.3	57.4	54.3	55.4	56.4	56.4
6	78.2	68.3	65.3	75.2	66.4	66.4
7	87.5	80.6	75.2	82.7	78.11	78.1
8	-	87.2	88.6	-	87.67	88.3

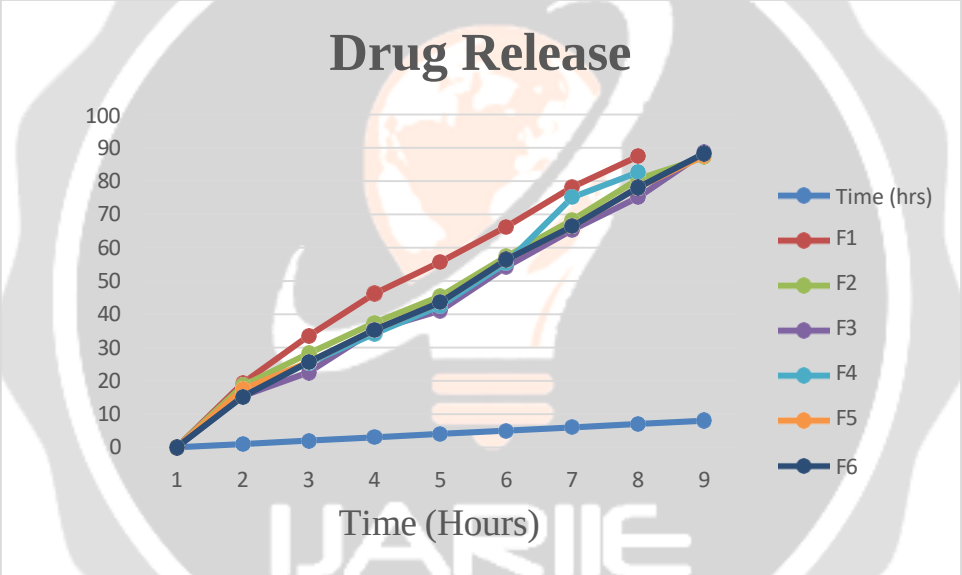

Fig.8: % Drug release of Diclofenac Sustained release tablets

CONCLUSION

Using HPMC K100M and ethyl cellulose as release-delaying polymers, an attempt was made for the development of Diclofenac Sodium sustained release tablets based on the estimate from the previously mentioned research that the synthetic polymer exhibits release over an extended period of time.The wet granulation process was used to create the granules. The prepared granules were assessed for bulk density, Hausner's Ratio, tapped density, Car's index, and angle of repose. The results obtained were found to be satisfactory and within the specified limits. Evaluations were conducted on post-compression characteristics such as thickness, hardness, weight fluctuation, friability, and in vitro release experiments.The impact of polymer kinds and concentrations on in vitro drug release was investigated in the current work. It shows that increase in concentration of polymer results in the sustained drug release for 8 hours. The research findings indicate that the release rate of the drug from hydrophilic matrix tablets is dependent on the kind and concentration of polymer, as the drug release rate was shown to be slowed with increasing polymer concentration.

REFERENCE

[1]. Joshi Y, Chaudhary RK, Teotia UV. Formulation and evaluation of diclofenac sodium sustained release matrix tablets using Aegle marmelos gum. Int J Curr Trends Pharm Res. 2013;1(3):174-80.

[2]. Mali RR, Goel V, Gupta S. Novel study in sustained release drug delivery system: A Review. Int. J. Pharm. Med. Res. 2015 Apr 10;3(2):204-15.
[3]. Ratnaparkhi MP, Gupta Jyoti P. Sustained release oral drug delivery system-an overview. Terminology. 2013;3(4):10-22270.
[4]. Savaşer A, Özkan Y, Işımer A. Preparation and in vitro evaluation of sustained release tablet formulations of diclofenac sodium. Il Farmaco. 2005 Feb 1;60(2):171-7.
[5]. Ganesh, G.N.K., Sureshkumar, R., Jawahar, N., Senthil, V., Venkatesh, D.N. and Srinivas, M.S., 2010. Preparation and evaluation of sustained release matrix tablet of diclofenac sodium using natural polymer. *Journal of pharmaceutical sciences and research*, *2*(6), p.360.
[6]. Khar RK. Lachman/liebermans: the theory and practice of industrial pharmacy. Cbs Publishers & Distribu; 2013.
[7]. Quadir MA, Chanda E, Haider SS, Reza MD, Datta BK. Evaluation of ethylcellulose as matrices for controlled release drug delivery. Pak J Pharm Sci. 2005 Apr 1;18:29-34.
[8]. Savale SK. Formulation and Evolution of Diclofenac Sustained Released Tablet. Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry. 2015;3(4)
[9]. Tabasum et al., formulation and evaluation of diclofenac sodium matrix Tablets using abelmoschus esculentus mucilage as a polymer, international journal of pharmaceutical, chemical and biological sciences, 2013; 418..
[10]. Joshi Y, Chaudhary RK, Teotia UV. Formulation and evaluation of diclofenac sodium sustained release matrix tablets using Aegle marmelos gum. Int J Curr Trends Pharm Res. 2013;1(3):174-80.
[11]. Pawan P, Nitin N. Formulation, evaluation and comparison of sustained release matrix tablet of diclofenac sodium using natural polymer. Int J Res Pharm Biomed Sci. 2013 Jan;4(1):367-79.
[12]. Kumar R, Bhatt PK, Sharma S. Formulation and Evaluation of Diclofenac Sustained Release Tablets. August). doi. 2020 Jan 1;10
[13]. Tabasum et al., formulation and evaluation of diclofenac sodium matrix Tablets using abelmoschus esculentus mucilage as a polymer, international journal of pharmaceutical, chemical and biological sciences, 2013; 418.
[14]. Asija Rajesh et al., Fromulation and Evaluation of Diclofenac sodium Sustained Released Tablets using melt granulation technique, International Research Journal in Pharmacy and Science, 2012; 3(5): 217.