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STUDIES ON FORMULATION AND EVALUATION OF ACECLOFENAC MATRIX DRUG DELIVERY SYSTEM USING A NATURAL GUM FOUND IN SATPUDA REGION OF NORTH MAHARASHTRA

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ABSTRACT

Aceclofenac is an NSAID (Non-Steroidal Anti-Inflammatory class drug) it is an analogue of Diclofenac, many researchers developed Aceclofenac matrix dosage form which are capable of providing a prolonged therapeutic effect. But, in this formulation Aceclofenac is combined with a Natural polymer and also with a Synthetic polymer, for Synthetic polymer HPMC K200M were preferred and for Natural polymer a Natural gum specially from the region of North Maharashtra mountain ranges also known as "Satpuda" ranges a gum were collected known as "Guggul Gum" which has a good binding ability and itself has many therapeutic properties like Anti-Inflammatory, Anti-Bacterial which can increase the therapeutic effect of formulation and which can help in increasing the period of Half-life or storage of the formulation. It has good binding abilities so, can also be used as a Natural Binder. In this study the formulation was developed as a matrix dosage system in an oral tablet form with a dose of 300 mg/Tablet and formulations were made by Factorially designed.

KEYWORDS: - Aceclofenac, Natural Gum, Guggul Gum, Matrix drug delivery system.

INTRODUCTION

Aceclofenac is a NSAID (Non-Steroidal Anti-Inflammatory) class drug used to treat rheumatoid arthritis, ankylosing spondylitis, inflammation and also in the treatment of Osteoarthritis.[1,11] The minimum dose of Aceclofenac is 100 mg a day, and the maximum dose of Aceclofenac is 400 mg a day.

Aceclofenac, as in a tablet form has the frequency of a minimum of three tablets a day and so, to reduce the frequency of dosing, there was a need to develop such type of dosage form which can provide a long therapeutic response in a single or twice a day dosing. So, Aceclofenac matrix tablets by various excipients and polymers are formulated by many researchers.[1,2,3,4,5,8] But, in this study, Aceclofenac is combined with a "Natural Gum" called "Guggul Gum" as a natural polymer, "Guggul Gum" is a natural, resinous, gummy, sticky and pliable (if in contact with heat) substance. It is present on sap of some well-known trees. This "Guggul Gum" was collected from North Maharashtra Mountain ranges, also known as "Satpuda mountain ranges" from there a tribal village known as "Molgi". "Guggul Gum" is a good binder but it has some of the therapeutic properties such as Antibacterial, Antifungal and Anti-inflammatory. It has a vast number of chemical constituents present in it which are capable of giving the product a natural therapeutic boost and so, if added in any formulation can give some effect. So, in the formulation development, the Natural Gum i.e., "Guggul Gum" is used as a natural polymer, HPMC K200M is used as a synthetic polymer, and the excipients such as Lactose, PVP K30, Talc and Magnesium stearate are used. Titanium dioxide is used as a tablet coating material. By the help of a software named Design Expert® developed by State Ease Corp. the factorial design of tablet batches was developed and the in-vitro studies such as Dissolution Studies on formulation were also studied. The Stability Studies of the formulation were studied as per the ICH guidelines on stability studies by the Accelerated Stability Studies at (40^0 C ± 2^0 C, 75% RH) for 0-1 Month and further tested for Accelerated Stability Studies, all of the obtained results were compared with the standard references and were in the standard range, to check their increased therapeutic

response and stability therefore further in-vivo and long-term stability studies are required.

MATERIALS AND METHODS

"Guggul Gum" was collected from "Molgi" a tribal village in the Northern Satpuda mountain ranges of Maharashtra, Aceclofenac (API) were received as gift sample by "Shree Swami Samartha Ayurvedic Pharmacy (Allopathic Division) Jalgaon", (Maharashtra). HPMC K200 M, Lactose, Magnesium Stearate were obtained from "Research Fine Chem Industries, Mumbai", (Maharashtra). PVP K30, Talc and Titanium Dioxide were obtained from "Thermosil Fine Chem Industries, Pune", (Maharashtra).

JIIU's Ali-Allana College of Pharmacy, Akkalkuwa, provided all the excipients, the gift sample were requested by College of Pharmacy, Akkalkuwa and all the chemicals used were of "Analytical Grade".

- Extraction of Natural Gum: - The Raw Gum were washed with distilled water to clean the surface and remove the debris. Then it was extracted with 70% Ethanol in a 40:50 ratio, then the extract was filtered with a Muslin cloth and then further dried in a Hot air oven at 45^0 C (not exceeding 50^0 C) then the dry extract powder was passed through a 60 # Mesh sieve and calculated the % yield.

- Design of Factorial Batches: - All the batches i.e., F1-F9 were designed with the help of Design Expert Software.

Table 1: - Factorial Designed batches.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
ACECLOFENAC	100	100	100	100	100	100	100	100	100
GUGGUL GUM	30	30	30	50	50	50	70	70	70
HPMC K200 M	15	30	45	15	30	45	15	30	45
LACTOSE	123	108	93	103	88	73	83	68	53
PVP K30	20	20	20	20	20	20	20	20	20
TALC	5	5	5	5	5	5	5	5	5
MAGNESIUM STEARATE	7	7	7	7	7	7	7	7	7
TITANIUM DIOXIDE	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
TOTAL WEIGHT	300	300	300	300	300	300	300	300	300

- Preparation of Granules: - The granules of the formulation were made by "Wet Granulation technique" and water were used as a Granulating agent, and after the granulating agent, the granules were passed through a 60 # mesh sieve.
- Compression of Granules: - The compression was performed on a 9-stationed tablet compression machine [Rimek model: DL 09 Stationed Tablet Compression Machine, Karnavati Engineering, (Mehsana, Gujrat, India)] equipped with 9 mm of round shaped punches and further studied for post-Compression parameters.

RESULTS AND DISCUSSION

A) Determination of Melting point: - The Melting point of Aceclofenac API was determined by the Capillary Tube Method. The Melting Point was found within the standard range of 148-150^0 C.

B) Calibration Curve of Aceclofenac in 7.4 pH Phosphate Buffer: - 100 mg of Aceclofenac was dissolved in a 10 ml of pH 7.4 Buffer and the volume was made upto 100 ml using 7.4 pH Phosphate Buffer, from this solution 10 ml was withdrawn and diluted to 100 ml with Phosphate Buffer 7.4 pH (Stock Solution). From this stock solution 20 ml was withdrawn and diluted to 100 ml with Phosphate Buffer 7.4 pH, dilutions were made by withdrawing 0.2, 0.4, 0.6, 0.8, 1.0 ml and diluted to 10 ml with Phosphate Buffer pH 7.4 to obtain the solution in the concentration range of 2, 4, 6, 8, 10 µg/ml. The absorbance was measured at 275 nm using UV Spectrophotometer.

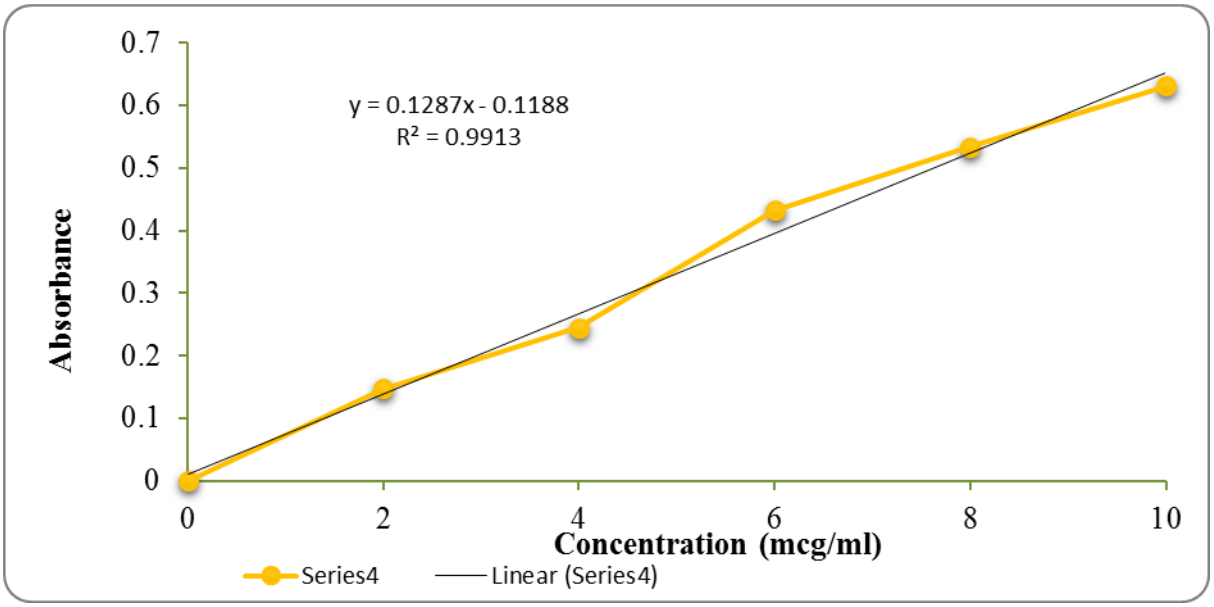

Figure-1: - Standard Calibration Curve of Aceclofenac in 7.4 pH Phosphate Buffer.

Table- 2: - Standard Calibration Curve of Aceclofenac in 7.4 pH Phosphate Buffer.

CONC (mg/ml)	ABSORBANCE
0	0
2	0.147
4	0.245
6	0.432
8	0.534
10	0.631

C) FTIR Studies

1) FTIR of Aceclofenac (Pure Drug)

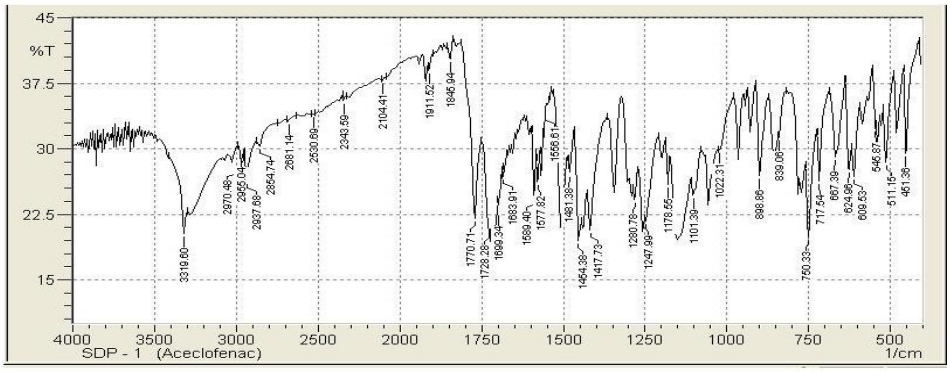

Figure-2: - FTIR of Aceclofenac (Pure Drug).

Table 3: Interpretation of FTIR of Aceclofenac (Pure Drug).

Functional group	Characteristic Peaks cm^{-1}
N-H Stretching	3319.50
C-H Stretching	2937.59
O-H Stretching	3282.84
Aromatic outplane Bending C-H	750.31
C=O Stretching	1714.72

2) FTIR of (Natural Polymer) "Guggul Gum "and (Synthetic Polymer) "HPMC K200 M"

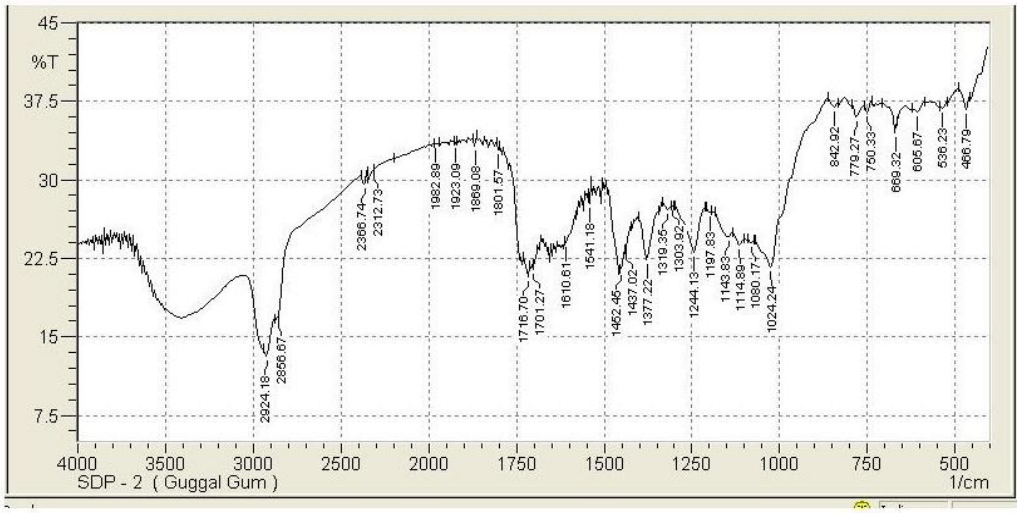

Figure3: - FTIR of (Natural Polymer) "Guggul Gum"

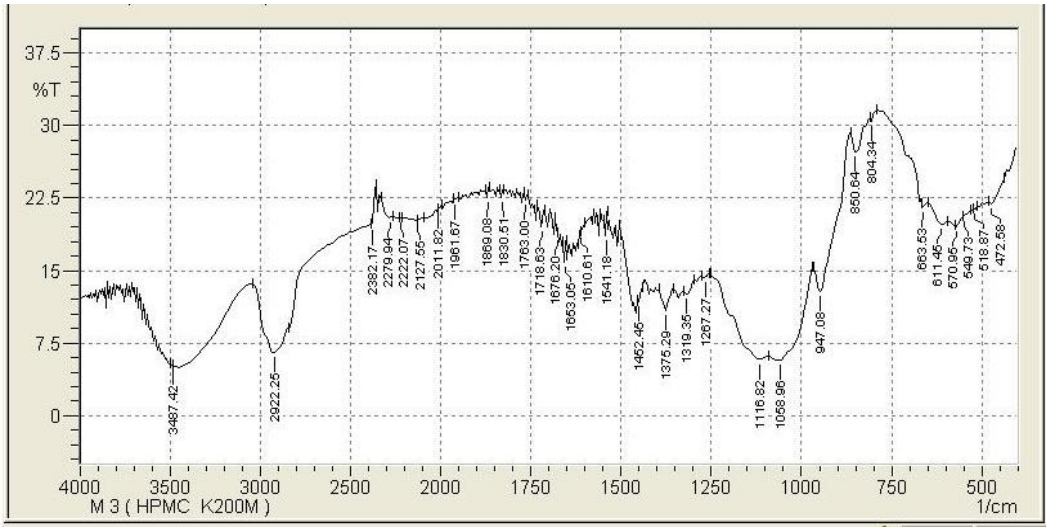

Figure 4: - FTIR of (Synthetic Polymer) "HPMC K200 M".

3) FTIR of Blend (Mixture)

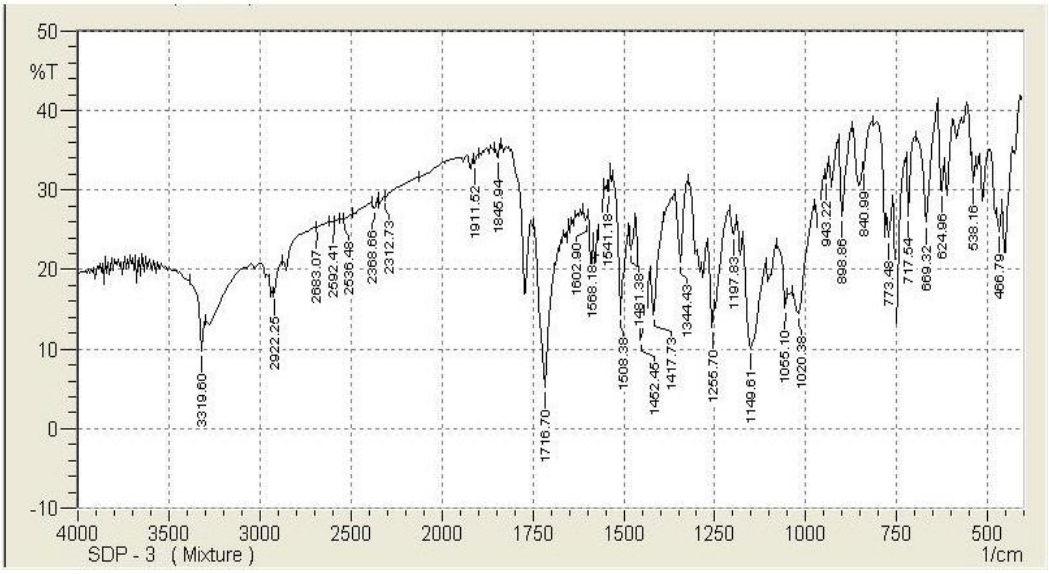

Figure 5: - FTIR of Blend of Factorially designed batches.

D) DSC Studies

1) DSC graph of Aceclofenac (Pure Drug)

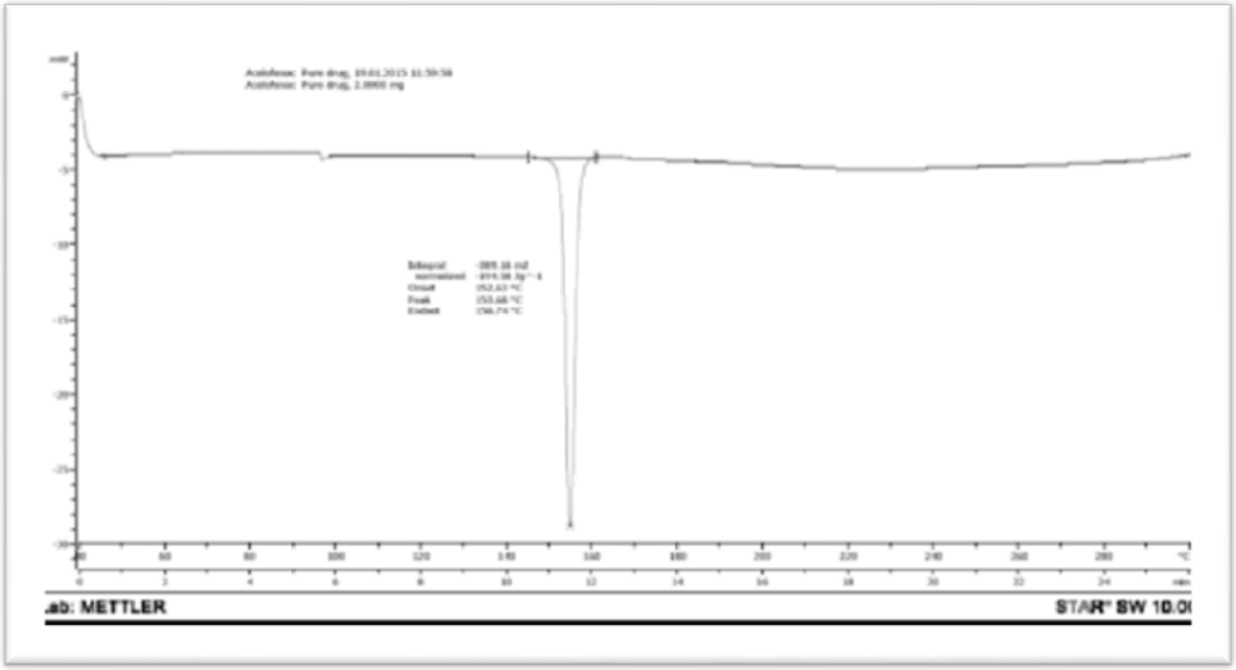

Figure 6: - DSC graph of Aceclofenac (Pure Drug).

2) DSC graph of Blend

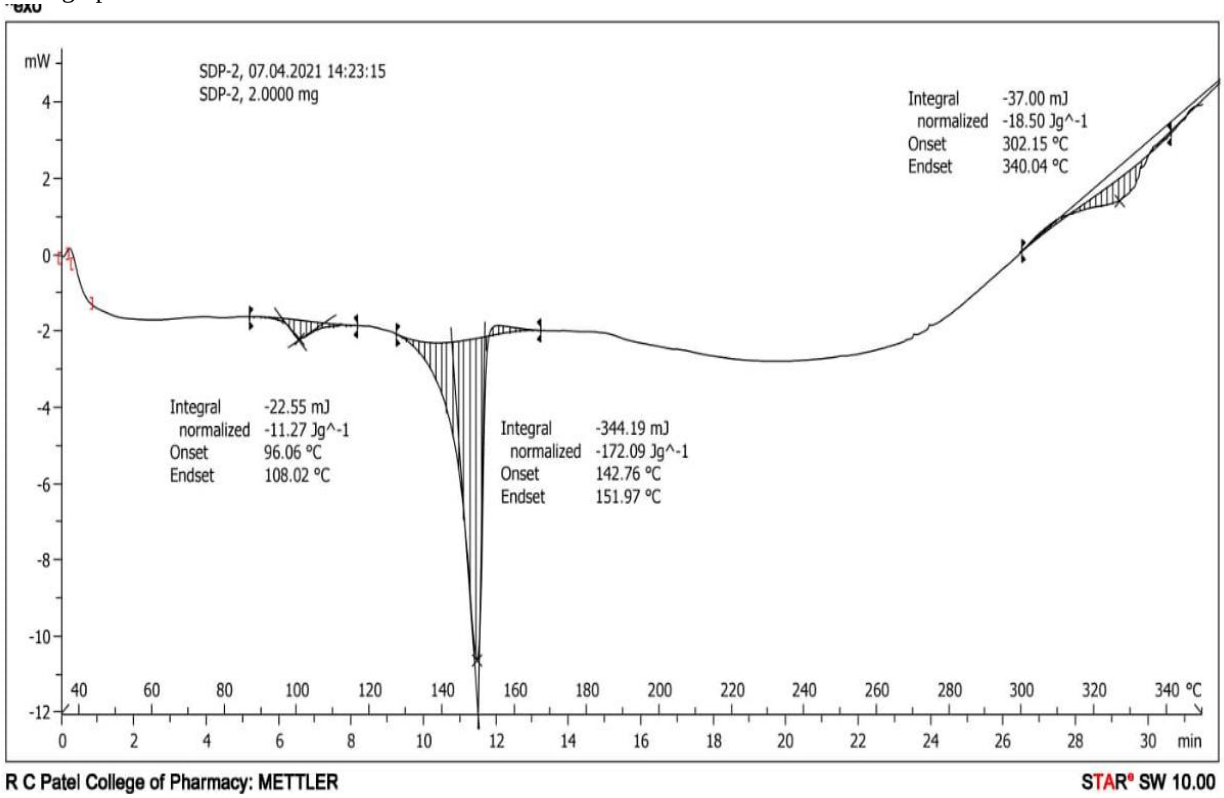

Figure 7: - DSC graph of Blend of factorially designed batches.

E) Evaluation of Sustained release matrix tablets

i. **Appearance: -** The tablets were observed visually and did not show any defects such as Capping, Chipping, lamination and overlapping.

ii. **Dimensions (Thickness):** - The Size/Diameter of the tablets of all formulations was 4.40 ± 0.06 to 5.48 ± 0.02 nm.

iii. **Tablet Hardness: -** The Hardness of tablets was measured by a Monsanto hardness tester, and the

hardness of tablets was found to be in the range of 4.38 ± 0.06 kg/cm^2 to 5.22 ± 0.02 kg/cm^2. This indicates good tablet strength.

iv. **Friability Test:** - Friability test was done in Friability Apparatus [Electro labs, Ltd, EF2 (USP) (Type- II) Apparatus]. The friability test or the Percent Friability of all the formulations was found between 0.47 ± 0.05 % to 0.758 ± 0.02 %. This indicates the good handling property of the prepared Sustained release Tablet.

v. **In-Vitro Drug release study of Optimized Batches: -** The In-Vitro dissolution studies of the Factorially designed tablet batches were studied for 8 Hr., first two hours i.e., 0-2 Hrs. in 0.1 N HCL (pH 1.2) and the rest i.e., 3-8 Hrs. in 7.4 pH Phosphate Buffer and the results obtained were given in the table and the figure given below.

Table-4: - In-Vitro Drug release (0-8 Hr.) of Optimized formulations (F1-F9).

Time (hrs)	Cumulative % Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	2.95	3.23	4.28	4.57	5.27	4.42	3.86	4.14	4.35
2	6.18	6.82	8.99	9.98	10.68	10.61	9.28	8.85	9.77
3	10.54	12.30	14.83	16.38	17.57	17.50	16.17	15.39	16.31
4	20.03	22.57	25.52	27.49	29.17	29.95	26.64	25.10	26.43
5	32.20	35.50	39.09	42.25	45.63	46.12	39.09	37.82	40.35
6	49.50	53.78	58.57	60.75	63.49	64.12	53.08	54.46	54.63
7	70.31	74.95	79.73	81.00	82.26	83.60	73.19	67.64	71.50
8	91.89	95.55	99.21	96.10	97.24	99.10	98.35	98.00	97.42

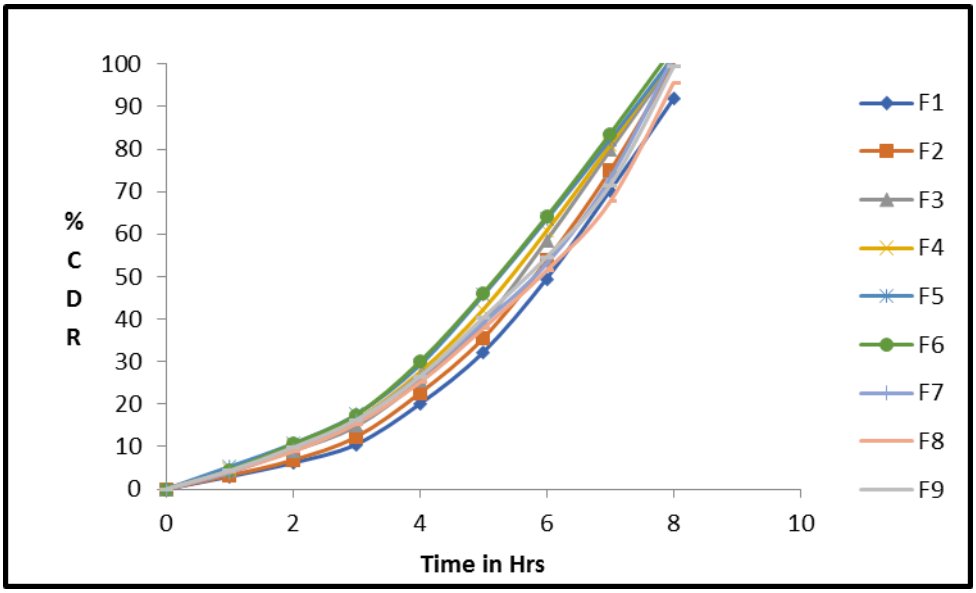

Figure 8: - In-Vitro Drug release (0-8 Hr.) of Optimized formulations (F1-F9).

The release of all formulations was companied and evaluated. The results showed that the formulations give more drug release were considered optimized and further studied for stability studies.

Stability Studies: - Stability Study is carried out on formulation batch (F3) according to ICH Guidelines, the tablet did not show any physical changes during the study period. The drug content was found to be 96.51 ± 1.47 % for Aceclofenac at the end of 1- Month of stability conditions shown in the table of stability study.

Table-5: - Stability Study of Optimized Batch (F3).

Temperature	Time in month	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	% Drug Release
40°C± 2°C 75% RH ± 5% RH	0	5.18 ± 0.06	0.65 ± 0.03	97.77 ± 1.32 %	99.21 %
40°C± 2°C 75% RH ± 5% RH	1	4.28 ± 0.10	0.47 ± 0.05	96.51 ± 1.47 %	98.43 %

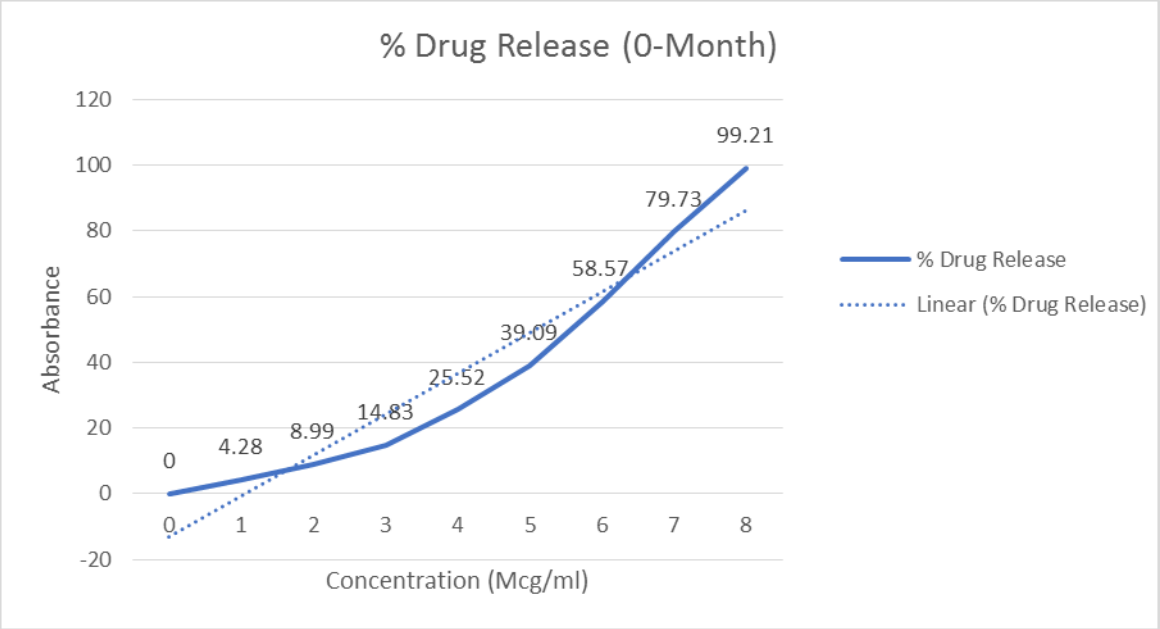

Figure-9: - Dissolution Profile of Optimized batch (F3) after 0-Month under stability period.

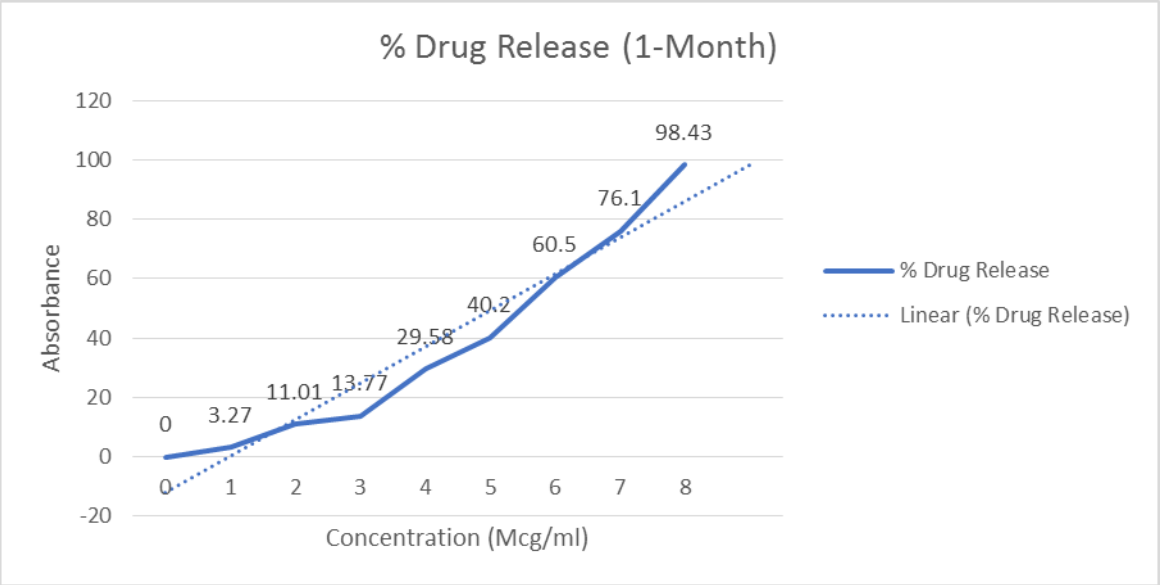

Figure-10: Dissolution Profile of Optimized batch (F3) after 1-Month under stability period.

CONCLUSION

The Aim of this study was to Formulate, Optimize and to Evaluate sustained release matrix tablets of Aceclofenac, Aceclofenac sustained release matrix tablets were formulated by using the Active Pharmaceutical Ingredient i.e., (Drug), the Natural Gum and the Natural Polymer i.e., (Guggul Gum), the Synthetic Polymer (HPMC K200 M) and Excipients. Guggul Gum and HPMC K200 M with their proportions, it can be seen that by increasing the concentration of Guggul Gum and by decreasing the concentration of HPMC K200 M in the formulation, the drug release rate from the tablets was found to be increased in formulation number F3, by using this ratio of drug and polymer it gives optimum release, i.e., Drug, Natural Polymer, Synthetic Polymer, PVP K30, Talc, Magnesium Stearate, lactose.

In this study F3 showed satisfactory results. But when the concentration of HPMC K200 M increased and the concentration of Natural Gum decreased, the drug release rate was found to be 99.21 % from the formulations F1-F9, the formulation batch F3 was selected as an optimized formulation because it showed maximum drug release i.e., 99.21 % in 8-Hrs. and the compatibility of Aceclofenac with Polymers HPMC K200 M and Guggul Gum, the studies of FTIR shows that all of the above characteristic peaks of Aceclofenac were observed near their respective values so, it has been concluded that there is no incompatibility between polymers and pure drug. The preliminary parameters of examination of Aceclofenac like its Melting Point which were obtained in the range of 148-150^0 C by the capillary tube method with the help of Thiele's Tube and in Liquid Paraffin to check the Melting Point.

The calibration curve was taken in 7.4 pH Phosphate Buffer at 275 nm by using a dual beam UV Spectrophotometer (Shimadzu 1800 series). The physical study of formulation like its Friability, Hardness, Weight Variation, Thickness, Surface pH, Drug Content Uniformity, In-Vitro residence time, etc. have been performed, the Hardness result showed that as increase in the polymer concentration will increase the tablet Hardness. The Percentage Friability was good in the range and was below 1 % and in the range by the standards of Indian Pharmacopoeia (IP-1996, 2018) the Thickness and Weight Variation of all the trial as well as factorially designed formulation batches was found and the obtained results indicate that all of tablets of different formulations were within the IP specifications.

The In-Vitro drug dissolution studies were carried out for a period of 0-8 Hrs. on all the formulation batches i.e., F1-F9 and the percentage of drug release was found to be in the range of 97.21 % to 99.21%; the Stability Study was performed according to ICH Guidelines and the tablet showed very minute or little changes on its physical appearance like its Hardness and Percent Friability.

The Formulation number F3 was selected for Stability Studies and were kept under the Accelerated Stability Studies (Guidelines by ICH) for 0-1 Month period under (40^0 C ± 2^0 C; 75 % RH ± 5 % RH) and the % Drug release was found to be 99.21 % and 98.43 % for 0 and 1 month. All of the results were found with the Pharmacopeial limits and passes all of the tests. The main objective of this research was to develop a formulation by adding a natural and a synthetic polymer so, author(s) suggests that in future in-vivo release studies using different models are required to set the in-vitro, in-vivo correlation necessary for the development of a successful formulation and long-term stability studies are necessary for the further future view of research.

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CONFLICTS OF INTEREST

The Author(s) declares "No Conflict of Interest".

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