Formulation and *invitro* evaluation of the aceclofenac sustained release matrix tablet

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***Abstract*- Aceclofenac, a potent non-steroidal anti-inflammatory drug (NSAID), has garnered attention for its remarkable analgesic and anti-inflammatory properties. However, its short half-life necessitates frequent dosing, prompting the exploration of sustained-release formulations to extend therapeutic efficacy. This study focuses on the formulation of sustained-release matrix tablets for Aceclofenac via the direct compression technique. Key excipients, including hydroxypropyl methylcellulose (HPMC) variants (K4M, K15M, K100M), were selected to modulate drug release profiles. Formulation techniques encompassing direct compression were employed, followed by rigorous characterization involving drug content uniformity assessment, dissolution studies, release kinetics. The results obtained from these evaluations offer valuable insights into the effectiveness of the developed matrix tablet. The release kinetics of the formulated tablets exhibited a Higuchi model with a non-Fickian diffusion mechanism, indicating controlled and sustained drug release. This research presents a promising approach to enhance the therapeutic potential of Aceclofenac through sustained-release formulations, potentially reducing the frequency of administration and improving patient compliance.**

***Index Terms*- Aceclofenac, sustained release tablet, HPMC, Direct compression.**

INTRODUCTIONS

This explains the critical need for an optimal Drug Delivery System (DDS) to ensure precise medication delivery in terms of timing and dosage for varying therapeutic requirements and drug properties. Conventional oral DDS lacks consideration for site-specific absorption rates in the gastrointestinal tract, necessitating the development of a more tailored DDS. Sustained release DDS is explored, aiming to maintain the necessary drug concentration in the body over a specific duration, enhancing patient compliance and ensuring consistent therapeutic effects. Sustained release tablets and capsules administered once or twice daily prove more effective in sustaining therapeutic effects compared to immediate release forms requiring more frequent dosing. Mechanisms underlying sustained release systems involve dissolution, diffusion, and erosion processes to control drug release, offering advantages like reduced dosing frequency, improved compliance, and lowered likelihood of adverse effects from high drug concentrations. Pharmacopoeias and regulatory bodies, including the US FDA, widely employ terms like "sustained release" and "controlled release" when referring to modified release dosage forms. Advantages of sustained release DDS encompass reduced dosing frequency, enhanced patient convenience, and improved drug utilization, while disadvantages include potential incomplete release, decreased systemic availability, and challenges in predicting efficacy and safety. Criteria for successful integration of drugs into sustained release forms encompass factors like solubility, stability, absorption mechanism, half-life, molecular weight, partition coefficient, biocompatibility, and suitability for the manufacturing process.

MATARIALS AND INSTRUMENTS:

The ingredients include **Aceclofenac** from ***Dr. REDDY'S Laboratories***, various types of Hydroxypropyl Methylcellulose (HPMC K4M, K15M, K100M) from **Marksans Pharma Ltd.,** Microcrystalline cellulose from Nickon laboratories Pvt. Ltd., and additional components like Magnesium stearate, Mannitol, Talc, and Aerosil sourced from **Loba chemie Pvt.Ltd., Mumbai**.

The instruments utilized in this context encompass an Electronic balance (Wensar Pgb 200 Precision Balance), Bulk density apparatus (Indolabs VTAP/MATIC-II, Chennai), Hot air oven (Unicon Pvt Ltd, India), Sixteen punch tablet compression Machine (Cadmach, Ahmadabad, India), Friability apparatus (Veego scientific VFT-DV, Mumbai), Hardness tester (Monsanto), Vernier caliper (Indolabs, Mitutoyo), Humidity chamber (Labtech, Ambala), USP dissolution test apparatus Type I (Secor India), UV spectrophotometer (Agilent Technologies, Cary Series), and FTIR spectrophotometer (Combined JESCO-4100).

METHOD:

The matrix tablet formulation was achieved through direct compression, employing precise measurements of all ingredients except magnesium stearate and talc. These were thoroughly blended for 5 minutes in a mortar. Subsequently, magnesium stearate and talc were integrated into the mixture with great care for even distribution and phase uniformity. Accurate portions of the blend were then weighed for each tablet. The mixture was then placed into a Perkin-Elmer Hydraulic press, employing a 12 mm diameter flat-faced punch and die set, which had been pre-lubricated with a 1% magnesium stearate dispersion in ethanol. Applying 5 tons of pressure, the mixture was compacted and left in this state for 5 minutes. Afterward, the upper punch was withdrawn, and the tablet was released. This process yielded tablets with a diameter of 12 mm.

FORMULATION:

Table 1- Formulation

Formulation	Ingradients									Total
	Aceclofenac	Hpmc K4m	Hpmc K15m	Hpmc K100m	Mcc	Mannitol	Mg. Stearate	Arosil	Talc	
F1	200mg	60mg	-	-	175mg	50mg	5mg	5mg	5mg	500mg
F2	200mg	75mg	-	-	160mg	50mg	5mg	5mg	5mg	500mg
F3	200mg	100mg	-	-	135mg	50mg	5mg	5mg	5mg	500mg
F4	200mg	-	60mg	-	175mg	50mg	5mg	5mg	5mg	500mg
F5	200mg	-	75mg	-	160mg	50mg	5mg	5mg	5mg	500mg
F6	200mg	-	100mg	-	135mg	50mg	5mg	5mg	5mg	500mg
F7	200mg	-	-	60mg	175mg	50mg	5mg	5mg	5mg	500mg
F8	200mg	-	-	75mg	160mg	50mg	5mg	5mg	5mg	500mg
F9	200mg	-	-	100mg	135mg	50mg	5mg	5mg	5mg	500mg

RESULTS

Preformulation Studies

Preformulation studies involve crucial assessments of a drug's physical and chemical properties before formulation. For Aceclofenac, key parameters were evaluated. True density was 1.72 ± 0.42 gm/cc, while bulk density measured 0.674 ± 0.57 gm/cc. Bulkiness was 1.484 ± 0.57, and compressibility index stood at 13.85 ± 0.35%. The angle of repose was 30.16 ± 1.15 degrees. Additionally, the partition coefficient was 1.30 ± 0.35. Solubility tests revealed Aceclofenac's varying degrees of solubility in different solvents. Melting point analysis yielded values consistent with the reported average of 152.3°C, validating the accuracy of experimental results

Evaluation of blended granules

Table-2 Results of blended granules evaluation

Formulation code	Angle of repose (o)*	Loose bulk density	Tapped bulk density	Hausner's ratio*	Carr's index (%) *
F1	21.52±1.03	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F2	22.34±0.49	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F3	24.72±0.51	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
F4	24.92±0.78	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F5	22.27±2.30	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F6	24.04±1.62	0.476±0.00	0.556±0.00	1.17±0.00	14.286±0.00
F7	24.72±0.51	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00
F8	24.04±1.62	0.455±0.00	0.526±0.00	1.16±0.00	13.636±0.00
F9	22.42±2.40	0.500±0.00	0.588±0.00	1.18±0.00	15.000±0.00

FTIR STUDIES-

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Aceclofenac was determined on Fourier transform Infrared Spectrophotometer using KBr dispersion method.

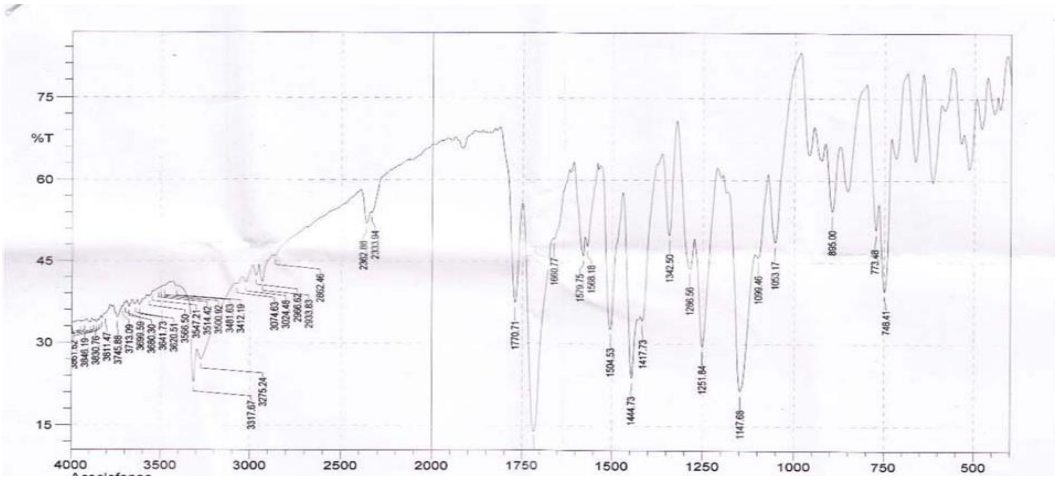

TABLE 3: FTIR Characteristic Bands of Aceclofenac Sample

S.NO	Literature value(cm^{-1})	Observed value(cm^{-1})	Assignments of bands
1	3400-3250	3317	N-H str.
2	2963-2669	2862.19	C-H str.
3	1850-1650	1770.71	C=O str.
4	1500-1400	1444.73	C-C str.
5	852-550	773.48	C-Cl str.

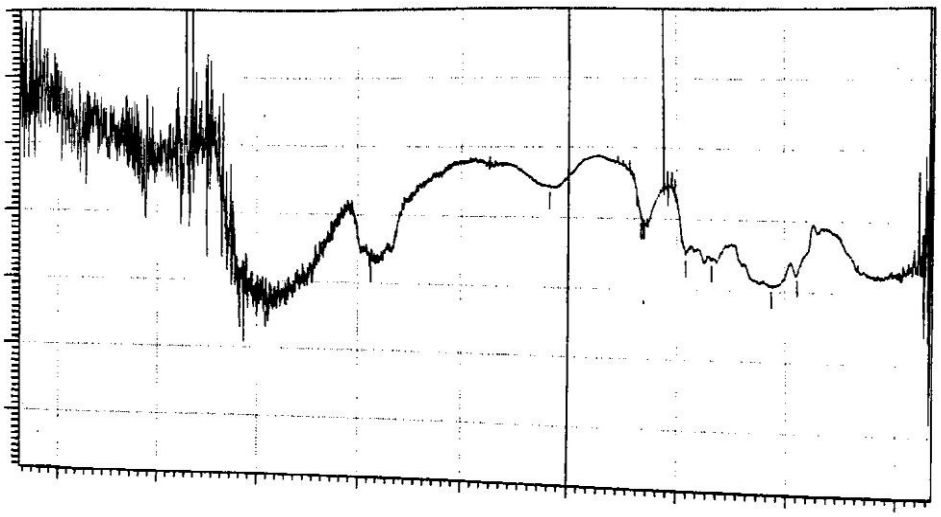

Fig. 2 FTIR of HPMCk100m

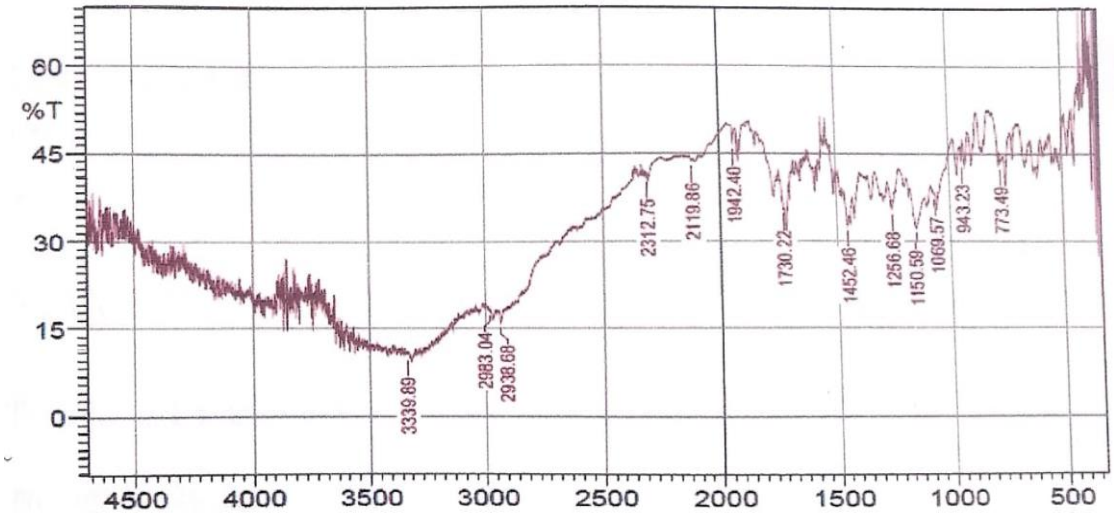

Figure 4- FTIR of aceclofenac & HPMC K100M

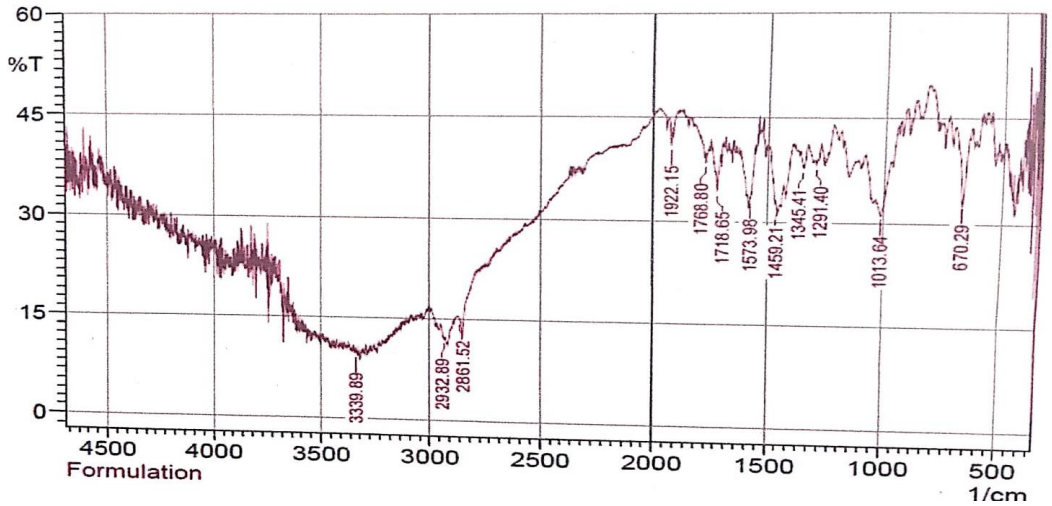

Figure 5- FTIR of f9

***INVITRO*EVALUATION PARAMETER**

Table 4- *invitro* evaluation

F. Code	Drug content (%w/w) **	Weight variation (mg)	Hardness (kg/cm^2) *	Thickness (mm)*
F1	99.48±0.45	501.40±2.26	7.80±0.59	4.42±0.06
F2	99.22±0.56	502.15±2.92	7.75±0.63	4.41±0.04
F3	99.61±0.69	500.10±2.77	7.70±0.54	4.42±0.07
F4	100.21±1.09	502.05±2.39	8.05±0.50	4.48±0.08
F5	99.78±1.05	503.05±2.84	7.85±0.34	4.39±0.06
F6	99.83±1.41	501.55±3.02	7.65±0.58	4.41±0.02
F7	100.61±0.35	502.60±2.39	7.80±0.48	4.44±0.08
F8	99.88±0.87	502.75±2.92	7.95±0.55	4.43±0.07
F9	98.90±0.65	501.75±2.95	7.85±0.41	4.46±0.02

RELEASE KINETICS –

Table 5- Cumulative %DR at Different Time Point of The Formulation of Sustained Release Tablet

TIME (MIN.)	*%DR*									
	PURE DRUG	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0	0
30	30.08	20.1	17.93	15.76	18.47	14.13	14.13	15.21	11.95	9.78
60	37.12	33.69	28.26	26.08	32.6	26.08	24.45	30.43	23.91	21.73
120	42.11	44.02	38.04	36.95	42.93	35.86	35.32	40.21	32.06	31.52
240	48.12	57.06	52.17	48.36	56.52	48.91	46.73	53.26	46.73	44.56
360	54.23	69.02	63.04	59.78	67.93	58.69	57.6	65.21	57.06	55.43
480	**58.08**	80.97	74.45	72.28	74.45	72.82	69.56	73.36	71.73	**68.47**

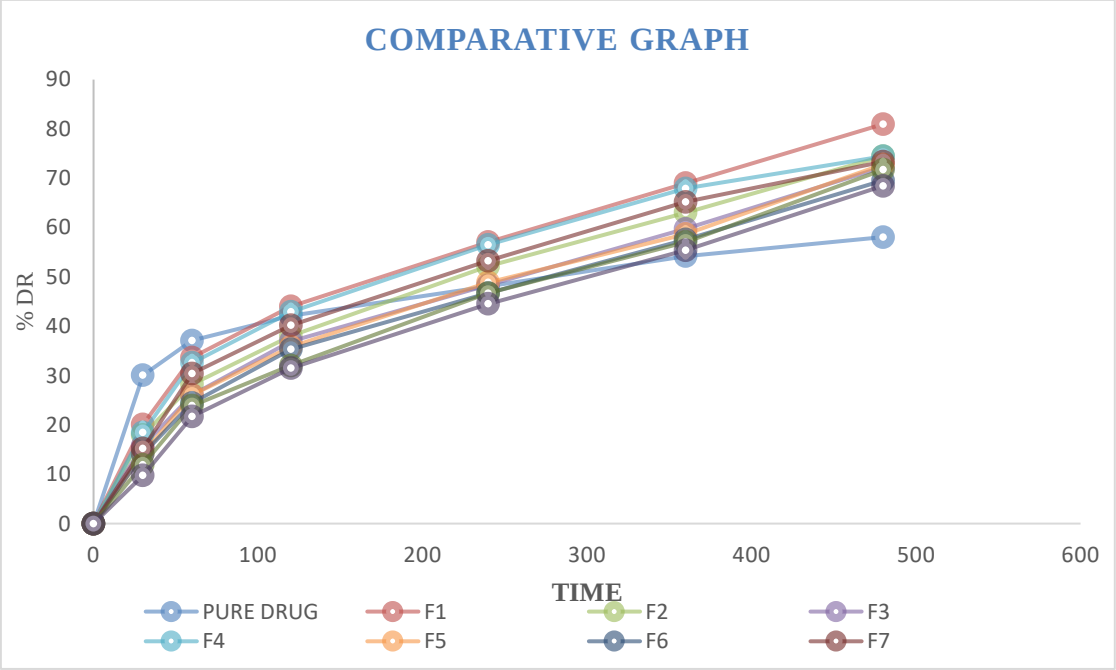

Figure 6- comparative graph of pure drug with different formulation

Table 6 - R^2 Value of All Formulations

Formulation	**Zero-Order Release**	**First-Order Release**	**Higuchi Release**	**Hixon-Crowel Release**
F1	0.8941	0.9798	0.9938	0.5256
F2	0.9153	0.9836	0.9984	0.5464
F3	0.9236	0.9811	0.9962	0.5603
F4	0.8722	0.9692	0.9911	0.5212
F5	0.9279	0.9795	0.9939	0.5729
F6	0.9270	0.9818	0.9959	0.5707
F7	0.8933	0.9766	0.9912	0.5452
F8	0.9456	0.9834	0.9912	0.6020
F9	**0.9480**	**0.9872**	**0.9895**	**0.6189**

Disscussion-

The organoleptic characteristics of the pure Aceclofenac drug were observed. It was found to be yellow in color, bitter in taste, and had a crystalline nature. In spectroscopic analysis using a UV-Visible spectrophotometer with a medium of pH 6.8 buffer, the

maximum wavelength was determined to be 275nm. Carr's Index and Angle of Repose tests were conducted to assess the flow properties of the pure drug. The results indicated that the drug exhibited poor flow characteristics. The solubility of the pure Aceclofenac drug was determined to be 6.921 mg/ml in a pH 6.8 phosphate buffer. In-vitro dissolution studies of the pure drug were conducted using a paddle apparatus at 100 RPM in a pH 6.8 phosphate buffer. It was observed that 58.80% of the drug was released in 480 minutes (8 hours). A sustained release formulation of Aceclofenac was prepared using a direct compression technique, employing various polymers like HPMCK4M, HPMCK15M, and HPMCK100M. Compatibility studies between Aceclofenac and different polymers were conducted in a 1:1 ratio. The results indicated that there was no interaction between the drug and the polymers. The formulated products were evaluated for various physical parameters, along with the percentage of drug release rate through dissolution studies. Formulation F1, F2, and F3 exhibited drug release percentages of 80.97%, 74.43%, and 72.28% respectively over an 8-hour period. Formulation F4, F5, and F6 showed drug release percentages of 74.45%, 72.82%, and 69.56% respectively in 8 hours. Formulation F7, F8, and F9 demonstrated drug release percentages of 73.36%, 71.73%, and 68.47% respectively over 8 hours. All formulations followed a Higuchi order release pattern with non-Fickian diffusion mechanics.

Summary & Conclusion-

The study aimed to develop sustained-release tablets of Aceclofenac, a commonly used muscle relaxant, utilizing various grades of hydroxypropyl methylcellulose (HPMC) as release-retarding polymers. The ideal formulation should exhibit a sustained release profile over a reasonable duration, preferably following Higuchi kinetic.The physical characteristics, analytical profiles, and compatibility between Aceclofenac and the polymers were assessed. Granules were prepared through direct compression and evaluated for properties like angle of repose, bulk density, tapped density, and Carr's index, all of which met specified standards. Post-compression parameters including thickness, hardness, weight variation, friability, content uniformity, and *in vitro* release were assessed. Results showed that hydrophilic polymers were effective in formulating sustained-release tablets of Aceclofenac, maintaining constant plasma concentration for up to 8 hours. This extended-release profile could potentially reduce administration frequency and dose-dependent side effects, enhancing patient compliance. The study highlighted the influence of polymer type and concentration on *in vitro* drug release, indicating that higher polymer concentrations led to extended drug release over 8 hours. Specifically, a formulation with 20% HPMC K100M achieved a release of approximately 68.47% within this time frame. Stability studies revealed no significant changes in hardness, drug content, or in-vitro dissolution for the optimized formulation (F9).

Future prospects for this research include conducting in-vivo studies to validate the sustained release behavior observed *in vitro*, and establishing an *in vitro in vivo* correlation to further support the formulation's effectiveness in clinical settings.

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