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FORMULATION AND *INVITRO* EVALUATION OF ACECLOFENAC CONTRLLED RELEASE TABLETS BY USING SODIUM CARBOXY METHYL CELLULOSE

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ABSTRACT

The present study was carried out to develop controlled release Aceclofenac matrix tablets by a hydrophilic polymer such as sodium carboxy-methyl-cellulose (Na-CMC). The formulation was prepared by using Aceclofenacand Na-CMC at different ratios (1:05, 1:1, and 1:15) and the prepared drug polymers mixtures were granulated by wet granulation technique (F1, F2&F3). The prepared granules were found to have good flow properties (compressibility index, Hausner's ratio and angle of repose). These granules are used to prepare tablets by using tablet compression maching. The prepared tablets were evaluated for post compression parameters as specified in pharmacopoeias (thickness, diameter, hardness, friability, weight variation, content uniformity, disintegration and dissolution). From the results it is observed that F2 formulation has superior quality than others and hence F2 is considered as optimesed formulation. FTIR spectra indicates there were no intractions between drug and polymer. The reproducibility of method of preparation of F2 was further confirmed by ANOVA. The results indicated that the method of preparation of controlled release tablets of Aceclofenac and Na- CMC at 1:1 ratio is reproducible and it fulfills as the parameters as per pharmacopoeias.

Keywords: Aceclofenac, Na-CMC, pre and post compression parameters, FTIR, ANOVA

INTRODUCTION

Ideal drug delivery systems enable the release of the active pharmaceutical ingredient in such a way to achieve a desired therapeutic response. Moreover, the drug has to be delivered at a specified controlled rate and at the target site as precisely as possible to achieve maximum efficacy and safety. Controlled drug delivery systems are developed to combat the problems associated with conventional drug delivery. Controlled drug delivery is a system that is designed to deliver the drug for a specified period either locally or systemically at a predetermined rate. An Oral Controlled Drug Delivery System employ drug-encapsulating devices from which therapeutic agents may be released at controlled rates for long periods of time, ranging from days to months **[1-4]**.

In present study Aceclofenac is considered a model drug. It belongs to the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) class and is considered to be the first-line drug in the treatment of rheumatoid arthritis, osteoarthritis, and spondylitis. It is a modified form of diclofenac with low gastrointestinal complications. The drug belongs to BCS classII with a short biological half life ($t_{1/2}$) of 3-4 hours and dosing frequency of more than one per day making Aceclofenac an ideal candidate for controlled release to reduce the frequency of administration and to improve patient compliance **[5, 6]**.

A matrix tablet is formed when an active drug is homogeneously dispersed (embedded) in an inert material. Matrix materials are often swellable hydrophilic or non-swellable (hydrophobic polymers. They contain drug and polymer as release retarding material which offers the simplest approach to designing a controlled release system **[7]**.

Polymers became important in field of the drug delivery. Hydrophillic polymers are ideal matrix materials that can control the rate of diffusion, which is important in the drug delivery field. A polymer's pH also plays an important role in DDS. Controlled drug delivery occurs when a natural/ synthetic/ semi synthetic polymer is wisely combined with a drug or other chemically active agent in such a way that the drug is released from the material in a pre designed manner. The main objective behind control drug delivery is to achieve safer and effective therapies while decreasing the potential for both under and overdosing issues **[8, 9]**.

Sodium Cfarboxy Methyl Cellulose (Na- CMC) is the sodium salt of carboxymethyl cellulose, an anionic derivative. It is highly soluble in water at all temperatures, forming clear solutions. Its solubility depends on its degree of substitution. When it used as a binder it

yields softer granules that have good compressibility forming tough tablets of moderate strength. Na-CMC being highly hygroscopic can absorb a large quantity of water (> 50%) at elevated relative humidity conditions **[10]**.

1. MATERIALS

Aceclofenac, Sodium Carboxy Methyl Cellulose (Na-CMC), Lactose, Starch and Magnesium stearate and Microcrystalline cellulose were supplied by UV Scientific, Hyderabad. All the chemicals and glassware used in the study were of analytical grade. **METHODOLOGY**

1.1. Physical appearance [11]

Aceclofenac powder was poured on light and dark backgrounds, and its physical appearance was observed. The results were compared with standard references.

1.2. Determination of melting point [12]

The melting point of the Aceclofenac was determined by the capillary fusion method. A one-sided closed capillary was filled with drug and placed into the Remi's melting point apparatus. The temperature at which solid drug converted into liquid was recorded and compared with standard reference

1.3. Solubility study [13]:

The solubility of Aceclofenac was tested in different solvents. The drug (50 mg) was dissolved in 10 ml of solvent in a solubility bottle. The bottle was adequately covered with a lid and placed in the water bath shaker maintained at 37 ^{0}C for 24 hours. Samples were taken manually and filter through 0.45 µm filter paper. The UV absorbance of the solution was recorded using a UV spectrophotometer after suitable dilutions at 275 nm.

1.4. Preformulation studies [14]:

The preformulation studies such as organoleptic properties, loss on drying and pH were performed for the drug sample. Loss on drying was determined by weighing about 1.0 g of sample, drying at 105 ^{0}C for 3-4 hours and cooling it for 30± 5 minutes. pH was determined for 1% w/v of the sample in solvent by using a digital pH meter.

1.5. Estimation of Lambda max [15]:

50 mg of Aceclofenac was accurately weighed and transferred to a 50 ml volumetric flask. It was dissolved in minimal amount of ethanol and volume was made up to 50 ml with solvent to get 1mg/ ml solution. Exactly 1 ml of the this solution was pipette out and was diluted to 100 ml with solvent to get 10µg/ ml. The spectrum was recorded in the range of 200-300 nm.

1.6. Calibration curve of drug in 0.1 N HCl and 6.8 phosphate buffer [16] :

Accurately weighed amount (100 mg) of the drug was dissolved in minimal amount of ethanol in a 500 ml volumetric flask and the volume was made up with pH 0.1N HCl [Hydrochloric acid] buffer. From this stock

solution 10 ml of solution was transferred into a 100 ml volumetric flask and the volume was made up with 0.1N HCl buffer {Primary dilution}. From this secondary dilution was prepared by taking 10 ml from the primary dilution into a 100 ml volumetric flask and again the volume was made up with 0.1N HCl buffer, different concentrations of 2, 4, 6, 8 and 10 µg/ml were prepared and same was repeated with 6.8 phosphate buffer, their corresponding absorbance values were measured at 275 nm in a UV- Visible Spectrophotometer.

1.7. Preparation of drug-polymer mixtures/ formulation:

All the ingredients used in the preparation of drug -polymer mixtures were passed through 100 sieves. Quantities of drugand polymer at various ratios were weighed as specified in **Table 1** and mixed in a mortar by using geometric dilution technique. After thorough mixing of drug and the respective polymer, specified quantity of spray dried lactose (diluents) was weighed and added to this mixture and triturated to form homogenous mixture.

Table 1: Composition of Aceclofenac controlled release matrix tablets

Formulation	F1 (mg)	F2 (mg)	F3 (mg)
Aceclofenac	200	200	200
Sodium-CMC	50	100	150
Magnesium stearate	40	40	40
Microcrystalline cellulose	40	40	40
Starch	40	40	40
Spray Dried Lactose	130	80	30
Total weight	500	500	500

1.8.Preparation of granules [17] :

Granules will be having good flow properties than powder which will be most widely used in the preparation of tablets. Hence the prepared drug- polymer mixtures were converted to granular form by using wet granulation technique. All the prepared drug- polymer mixtures were passed through sieve No.80 and they were mixed with microcrystalline cellulose which will be used as disintegrating agent, then sufficient volume of granulating agent was added slowly with continuous mixing. After enough cohesiveness was obtained, the wet mass was sieved through sieve No. 60. The obtained granules were dried at 60°C for 30 minutes and then the dried granules were passed through sieve No.20. Finally specified quantities of starch and magnesium stearate were added as a glidant and lubricant respectively.

1.9. Evaluation of the prepared granules for micrometric properties

The prepared granuleswere evaluated for micrometric properties like Bulk density, Carr's (compressibility) Index, Hausner's ratio, and Angle of repose.

1.9.1. Bulk density:

Bulk density was defined as the mass of the powder divided by the bulk volume and expressed as g/cm^3. It depends upon particle size distribution, particle shape, and particle adhere. Apparent bulk density was determined by pouring the blend into a 10 mL graduated cylinder and calculated based on the equation. Each experiment was performed in triplicate and average values were recorded.

Bulk density = Mass of granules/Bulk volume of granules

1.9.2. Tapped density:

The measuring cylinder containing a known mass of powder blend was tapped 100 times using density apparatus. The minimum volume occupied by the powder in the cylinder was measured. The tapped density was calculated based on the equation. Each experiment was performed in triplicate and average values were recorded.

Tapped density = Total weight of granules/ Tapped volume of granules

1.9.3. Carr's (compressibility) Index (CI) :

Carr's Index of the powder was found by using the following equation:

CI = [(Tapped density-Bulk density)/Tapped density]×100

Determination of compressibility index was the simplest way to measure the flow property of powder to determine its compressibility. Compressibility index indicates the ease with which a material could induce flow, which was calculated using above equation. Compressibility index (CI) values up to 15% exhibits excellent flow properties where as compressibility index >15% and <25% indicates good flow properties and more than 25% indicates poor flow properties.

1.9.4. Hausner's ratio (HR):

Hausner's ratio was an indirect index of ease of powder flow. Density determinations were used to calculate the Hausner's ratio using below mentioned equation. Hausner's ratio value of less than 1.25 indicates a good flow property and more than 1.25 indicates poor flow property.

Hausner's ratio = (Tapped density ÷ Bulk Density)

1.9.5. Angle of repose (AR) :

The angle of repose (θ) was determined using the funnel method. Briefly, the powder blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured, and the angle of repose was calculated based on the equation mentioned below. Angle of repose values ≤30° indicates a free flowing material and the values ≥40° suggests a poorly flowing material.

$$\theta = \tan^{-1}(h/r)$$

1.10. Preparation of Tablets:

The prepared granules were compressed

into tablets on rotary tablet compression machine using 11 mm round biconcave punches. The prepared tablets were placed in self sealed cover and stored in dicicator till further use.

1.11. Evaluation of prepared tablet [18]:

All the prepared matrix tablets were evaluated for thickness, diameter, hardness, friability, weight variation, drug content uniformity, disintigratiion and dissolution as per I.P.

1.11.1. Thickness & Diameter:

Tablet thickness was an essential parameter in reproducing appearance and also in counting and filling. Many tablet filling/packaging equipment utilizes the uniform thickness of the tablets as a counting mechanism. The thickness and diameter of the tablets was determined using a vernier caliper. Ten tablets from each type of formulation were used to measure the thickness and diameter and average values were calculated.

1.11.2. Hardness:

The hardness of the tablet was defined as the force applied across the diameter of the tablet to break it. The resistance of a tablet to chipping, abrasion, or breakage under the condition of storage, transportation, and handling before use depends on its hardness or strength. For the determination of tablet hardness, 10 tablets from each batch were randomly selected, and hardness was determined using Monsanto tablet hardness tester.

1.11.3. Friability:

The friability of the prepared tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at the height of 6 inches in each revolution. Previously weighed, 20 tablets were placed in the friabilator and subjected to 100 rpm. Tablets were de-dusted using a soft muslin cloth and re-weighed. The percentage friability was determined using the equation as follows:

$$\textbf{Friability} = \{(W_1 - W_2)/W_1\} \times 100$$

Where W_1= Initial weight of tablets

W_2= Final weight of tablets after friability

1.11.4. Content uniformity:

Twenty tablets from each batch were weighed and finely powdered using a clean and dry mortar and pestle. Powder equivalent to the weight of one tablet was transferred to a 100 mL volumetric flask and shaken with minimal quantity of ethanol for 10 minutes. The volume of the resulting solution was made to 100 ml and kept for 24 hours. After 24 hours, the content was filtered. An aliquot of 1 ml from the filtrate was diluted to 100 ml with phosphate buffer in a volumetric flask, and then further 1 mL from this solution was diluted up to 10 mL phosphate buffer in a 10 ml volumetric flask. The sample was analyzed by a UV spectrophotometer at

275.nm.

1.11.5. Weight variation test:

According to IP, 20 tablets were taken and weighed individually and collectively using a digital analytical balance. The average weight of one tablet was determined from the collective weight. The allowed weight variation limits were 10%, 7.5%, and 5% for tablets having weight 130 mg or less, 130-324 mg, and >324 mg, respectively.

1.11.6. *Invitro* dissolution studies [19]:

The *in-vitro* dissolution studies were performed by using a USP type II dissolution apparatus at 50 rpm at a temperature of 37± 0.5 ^{0} C. The dissolution test was carried out for a total period of 2 hours using 900 ml of 0.1N HCl. Then the contents were shifted to 900 ml of pH 6.8 phosphate buffer solution and the procedure is continued for the rest of the period An aliquot (5ml) of samples were withdrawn at specific time. Complete sink condition was maintained by replacing the same volume of fresh dissolution medium after each sampling. The collected samples were suitably diluted and their absorbances were determined by U.V. spectrophotometer at 275 nm.

1.12. Drug release kinetic studies [20] :

The analysis of kinetics and mechanism of drug release from a pharmaceutical dosage form is an important process. This can be confirmed by fitting the dissolution data of the optimized formulation to different mathematical models. In the model dependent approach, the dissolution data of all three formulations (F1, F2, and F3) were fitted to five popular release models as shown below.

1.12.1. Zero order release kinetics [21]:

It defines the linear relationship between fractions of drug released vs. time.

$$Q=K_0t$$

Where "Q" is fraction of drug released at time t and "K_0" is the zero order release rate constant. A plot of the % drug dissolved vs. time will be linear if the release obeys zero order kinetics.

1.12.2. First order release kinetics [22, 23]:

The drug release from most slow release formulations could be described adequately by apparent first order kinetics. The equation used to describe the first order release kinetics is

$$\ln (1-Q) = -K_1t$$

Where "Q" is % drug released at time t and "K_1" is the first order release rate constant. A plot of the logarithm of the % drug remained against time will be linear if the release obeys first order kinetics.

1.12.3. Higuchi equation [24]:

It defines a linear dependence of the active fraction of drug released per unit of surface on the square root of time.

$$Q=K_2t^{1/2}$$

Where "K_2" is release rate constant. A plot of the % drug released against the square

root of time will be linear if the release obeys Higuchi equation.

1.12.4. Erosion equation [25]:

This equation defines the drug release based on erosion alone.

$$Q=1-(1-K_3t)^3$$

Where "Q" is fraction of drug released at time t and "K_3" is the release rate constant.Thus a plot between $[1-(1-Q)^{1/3}]$ against time will be linear if the release obeys erosion equation.

1.12.5. Power law (Peppas) [26, 27]

In order to define a model which represents a better fit for the formulation, dissolution data was further analyzed by power law (Peppas and Korsmeyer equation).

$$M_t/M_0 = Kt^n$$

Where "M_t" is amount of drug released at time t, "M0" is initial amount of drug, "M_t/M_0" is fraction of drug released at time t, "K" is release rate constant and "n" is release exponent. According to Korsmeyer-Peppas equation, the release exponent "n" value is used to characterize different release mechanism for a dosage form. A value of n= 0.5 indicates case-1 (Fickian) diffusion, 0.5<n<1 (Non-Fickian) diffusion.

1.13. Fourier Transform Infraded Spectroscopy (FTIR) studies [28]:

FTIR spectrum of pure drug, polymer and the optimized formulation were obtained by using an infrared spectrometer (Shimadzu IR-470, Japan). Samples were grounded, mixed thoroughly with potassium bromide and compressed in a hydraulic press to form a pellet. Then the samples were analyzed in IR spectrophotometer in the region between 4000-500 cm^{-1}.

1.14. Reproducibility of method of preparation [27]:

The optimized formulation from above studies was taken to check the reproducibility of method of preparation. Three different batches of these formulations were prepared separately under similar conditions to assess the reproducibility of the method of preparation. From each batch, the prepared tablets were evaluated for drug content. The results of the drug content estimation were subjected to statistical analysis to test whether the drug was uniformly distributed in the core-polymer mixture. ANOVA test was used to find out whether there was any significant difference between % drug content of different batches of tablets prepared by the above method.

2. RESULTS AND DISCUSSIONS:

2.1. Physical appearance [30]

Pure aceclofenac was observed as faded white crystalline powder which was identical to the reference standard. These results confirm the identity of aceclofenac.

2.2. Determination of melting point [28]

The melting point value observed was 149ºC which was found to be in the range of standard references (149-153ºC), confirming that the drugs used in this study

was in it's pure form.

2.3. Solubility study:

The solubility studies were performed as discussed in **Sec. 2.3**. The drug was found to be insoluble in distilled water, 0.1N HCl and pH 6.8 phosphatebuffer where as it was soluble in methanol. The results of solubility studies were shown in **Table 2**. Hence in further studies the drug will be first dissolved in methanol and then diluted with 0.1N HCl/ pH 6.8 phosphate buffer whenever it is required.

2.4.Preformulation studies:

Aceclofeac was identified to be odorless, powder. The percentage of loss on drying of the drug was found to be 0.03% of its original weight. The pH of 1% drug solution was observed and tabulated in **Table 3**.

2.5.Table 3: pH determination of Aceclofenac

2.6.Lambda max(*λmax*) determination:

The estimation of Lambda max was performed as mentioned in **Sec.2.5.** and the results were obtained as shown in **Figure 1**. From the figure the absorption maxima (*λmax)* of Aceclofenac in both 0.1N HCl and pH 6.8 phosphate buffer the buffers were found to be at 275 nm. And hence in further studies the same wave length was used to identify the Aceclofenac by using U.V. Visible spectrophotometer.

2.7. Calibration curve of Aceclofenac by using 0.1N HCl and 6.8 phosphate buffer:

The calibration curve of Aceclofenac by using 0.1N HCl and 6.8 phosphate buffer were performed as mentioned in the **Sec.2. 6** and the results obtained for absorbance of various concentrations are shown in **Table 4 (a) and (b) and Figure 2& 3.**

The method obeyed Beer's law in the studied range of 0-10 µg/ml in both the media. Good linear relationship was observed between the concentration and absorbance values with correlation coefficient (r^2) value of 0.996 for both 0.1N HCl and pH 6.8 phosphate buffer. The mathematical form of linear relationship between the two variables (concentration and absorbance) under consideration were Y= 0.035X+0.010 and Y=0.022X- 0.002 for 0.1N HCl and pH 6.8 phosphate buffer respectively. The standard deviation (s.d.) of the estimated values were found to be very low indicating the reproducibility of the method (n=3). The calibration curves obtained so were used directly for the estimation of Aceclofenac in the prepared formulations and in the dissolution studies.

2.8. Preparation of drug-polymer mixtures: The drug polymer mixtures were formulated as mentioned in the **Sec. 2. 7** at a concentration of 1:0.5, 1:1 and 1:1.5. They were mixed in a mortar by using geometric dilution technique. After thorough mixing of drug and polymer, specified quantity of spray dried lactose

was weighed and added to this mixture and triturated to form homogenous mixture.

2.9. Preparation of granules: The formulated drug polymer mixtures were granulated as mentioned in the **Sec. 2.8** and was stored in disicator till further use.

2.10. Evaluation of the prepared granules for micrometric properties:

The micromeritic properties such as bulk density, compressibility index, Hausner's ratio and angle of repose of powders depend mainly on particle size distribution, particle shape and tendency of the particles to adhere together. These micromeritic properties are often referred as the derived properties of powders. They play an important role in preparation of tablet since the flow characteristics of the powder mass are very important physical properties such as bulk density, tapped density, Carr's compressibility Index and the angle of repose was performed as mentioned in the **Sec. 2.9**, and the results obtained are shown in the **Table 5**.

Bulk density, Hausner's ratio, compressibility index and angle of repose values for the prepared tablets were observed to be in the range of 1.14±0.02 to 1.16±0.01, 12.72±0.12 to 14.04±0.13 and 25.38±1.51 to 27.40±1.7 respectively. The results indicated that all the prepared core-polymer mixtures were having good flow properties.

2.11. Preparation of compressed tablets:

The matrix tablets were compressed as mentioned in the **Sec.2.10.**

2.12. Evaluation of prepared tablets:

The Aceclofenac controlled release tablets were evaluated for thickness, hardness, and friability micrometric properties as mentioned in the above **Sec.3.11** and the results were shown in following **Table 6.**

The tablets of different formulations were found to be uniform with respect to thickness and diameter 4.2 ± 0.5 to 4.7 ± 0.3 mm and 11.2 ± 0.2 to 12.5 ± 0.4 mm. The hardness of the formulated tablets was found to be in the range of 6.70 ± 0.54 kg/cm^2 to 6.80 ± 0.59 kg/cm^2. The Percentage friability of all the formulations was found between 0.057 to 0.285%. This indicates that the prepared tablets have uniform thickness, diameter and good tablet strength. The content uniformity of prepared tablets was measured as discussed in **Sec. 2.11.4** and results are shown in **Table 8** and the results indicated that the drug content of all the prepared tablets was almost near to 100%.

The weight variation of the prepared tablets was measured as discussed in **Sec. 2.11.5** and results are shown in **Table 8**. The weight variations of all the prepared tablets were within the limits. These results indicated that the method of filling of granules form hopper to die cavity was uniform.

The *in- vitro* dissolution studies of the

formulated tablets were performed as mentioned in the **Sec.2.11.6** and the results were shown in following **Table 9 and Figure 4**.

From the dissolution studies it is clearly seen that the Na-CMC is able to control the drug release for 12 hours at a ratio of 1:1 (F2 formulation) and as the concentration of Na- CMC increases (i.e. for F3) the drug release was decreased. The results clearly indicated that as the concentration of polymer increased, the drug release was retarded, which may be due to the high swellability of Na- CMC such that it absorbs the fluid and might form a complex network like structures from which the drug release was retarded[31]. Around 25% of the drug was released within 1 hour (Loading dose) and the remaining drug was released till 12 hours (Maintenance dose), so it clearly indicates in the case of F1 formulation drug release (100%) is showing both loading dose and maintenance dose, which is a drug release pattern of control drug delivery systems and it can be further confirmed by kinetic studies.

2.13. Drug release kinetic studies:

The dissolution data of the optimized tablet (F2) was fitted to zero order and first order release kinetics for the evaluation of kinetics of drug release and to Higuchi, erosion and Peppas models for the establishment of mechanism of drug release to obtain respective correlation coefficient (r^2) values. The results of drug release kinetics of optimized tablet are shown in **Table 10 & Figure 5**. The drug release from optimized tablet followed zero order kinetics proved by correlation coefficient (r^2) values (**0.996**) which were slightly higher when compared with those of first order release (0.946). When % drug released was plotted against time, straight lines were obtained for optimized tablet which indicated that the release pattern followed zero order kinetics. The relative contributions of drug diffusion and matrix erosion to drug release were further confirmed by subjecting the dissolution data to Higuchi model and erosion model. The r^2 values of diffusion model were found to be higher compared to erosion model indicating the mechanism of drug release followed diffusion. To further confirm the diffusion mechanism the data was fitted to Korsmeyer-Peppas model. The plot of log % drug released vs. log time of optimized formulation was found to be linear. From the results it was found that diffusion exponent (n) values of optimized tablet was 0.692, which indicated non-Fickian diffusion mechanism of drug release. The results of the study indicated that the release of drug from the optimized tablet followed zero order kinetics via anomalous (non-Fickian) diffusion.

2.14. FTIR spectrophotometer:

Drug excipient compatibility studies were carried out by an FTIR spectrophotometer. The results obtained were shown as given **Figure 6 and Figure 7**. The IR spectra of pure Aceclofenac and its polymer showed there was no interaction between drug and polymer. In both the cases the spectras has shown characteristic peaks of Aceclofenac such as 1447.57, 1708.45, 2879.27 and 3330.04 which were due to the presence of functional groups like C=C stretching, C=O streaching, NH, aeromatic streaching and OH hydrogen bonding respectively. It clearly indicates there were no interactions between drug and polymer.

2.15. Reproducibility of method of preparation [32]

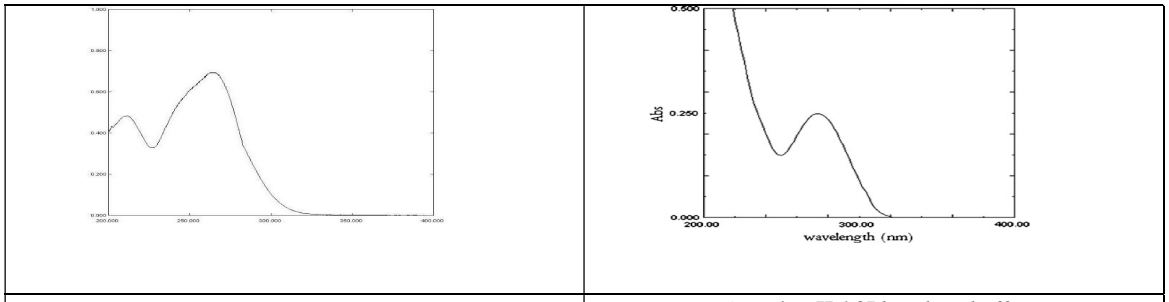
The optimised tablet (F2) was further evaluated for its reproducibility of method of preparation. Here three different batches of optimised tablet was prepared to test the method of preparation. The drug contents in each case were estimated and they were subjected to analysis for variance test (ANOVA) to test the reproducibility of the method of preparation. The results are given in the **Table 11**. The ANOVA test proved the % drug content of optimised tablet was not significantly different among the prepared batches. Hence it can be concluded that the preparation optimised tablets was reproducible.

Table 2: Solubility of Aceclofenac in different solvents

S. No.	Solvent used	Inference
1.	Distilled water	Insoluble
2.	0.1N HCl	Insoluble
3.	pH 6.8 phosphatebuffer	Insoluble
4.	Methanol	Soluble

Table 3: Preformulation studies

S. No	pH	Mean± SD (n=3)
1	7.3	7.13± 0.16
2	7.2	
3	6.9	



λmax in 0.1N HCl | *λmax in pH 6.8Phosphate buffer*

Figure 1: λmax in 0.1N HCl and in pH 6.8 phosphate buffer

Table 4(a): Calibration Curve of Aceclofenac by using 0.1N HCl

S.No	Concentration (µg/ml)	Average ± s.d. (n=3)
1	0	0
2	2	0.091±0.346
3	4	0.159±0.051
4	6	0.218±0.025
5	8	0.29±0.031
6	10	0.361±0.020

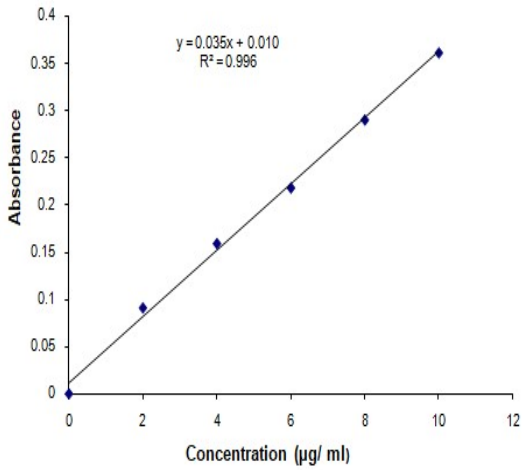


Figure-2: Calibration Curve of Aceclofenac by using 0.1N

Table 4 (b): Calibration Curve of Aceclofenac of Aceclofenac by using 6.8 Phosphate buffer

S.No	Concentration (µg/ml)	Average ± s.d. (n=3)
1	0	0
2	2	0.048±0.001
3	4	0.080±0.008
4	6	0.130±0.005
5	8	0.184±0.018
6	10	0.219±0.004

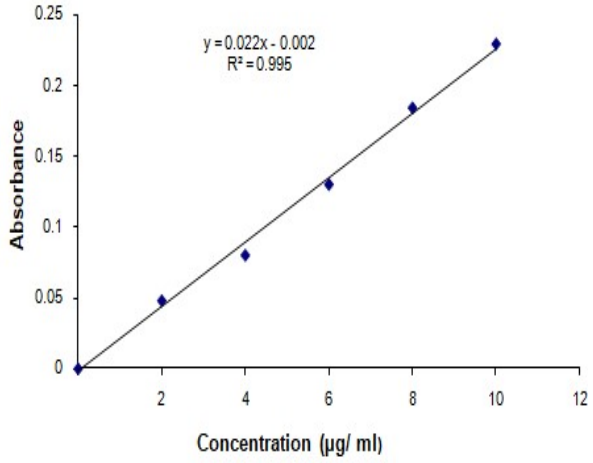


Figure-3: Calibration Curve of Aceclofenac of Aceclofenac by using 6.8 phosphate buffer

Table 5: Results obtained for micrometric properties of prepared granules

Formulation	Bulk density (g/cc)	Tappeddensity (g/cc)	Angle ofrepose (^{0})	Carr's Index	Hausner's ratio
F1	0.46±0.02	0.53±0.01	25.38±1.51	13.20±0.13	1.15±0.01
F2	0.48±0.01	0.55±0.01	26.06±0.62	12.72±0.12	1.14±0.02
F3	0.49±0.01	0.57±0.02	27.40±1.71	14.04±0.13	1.16±0.01

Table 6: Thickness, diameter, hardness and friability of prepared Aceclofenac controlled release matrisx tablets (n=3)

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability
F1	4.2±0.5	11.2±0.2	6.80±0.59	0.057±0.03
F2	4.7±0.3	12.5±0.4	6.75±0.63	0.071±0.02
F3	4.7±0.3	11.6±0.2	6.70±0.54	0.085±0.01

Table 8: Content uniformity data of formulated tablets (n=20).

Formulation code	Content uniformity	Weight variation
F1	99.48±0.45	1.48± 0.22
F2	99.22±0.56	1.75± 0.14
F3	99.61±0.69	1.68±0.09

Table 9: Dissolution data profile of various formulations F1-F3

Time period (hrs)	Amount of drug released (mg)		
	F1	F2	F3
0	0	0	0
0.25	7.32± 0.12	9.92± 0.55	7.32± 0.56
0.5	15.2± 0.45	33.67±0.15	22.38± 0.98
0.75	29.3± 0.56	64.85± 0.41	33.3± 0.91
1	47.7± 0.22	78.08± 0.87	48.89± 0.83
1.5	58.1 0.35	87.088± 0.55	57.14± 0.84
2	77.16± 0.48	105.48± 0.68	78.86± 0.18
3	81.58± 0.98	138.23± 0.95	86.5± 0.59
4	97.39± 0.26	144.11± 0.29	94.59± 0.72
5	108.9± 0.58	147.35± 0.76	99.5± 0.53
6	129.2± 0.77	153.63± 0.56	108.51±0.46
8	142.39± 1.21	162.96± 0.57	115.4± 0.77
10	149.6± 0.89	169.24± 0.39	130.7± 0.71
12	173.6± 0.28	201.68± 0.44	146.7± 0.29

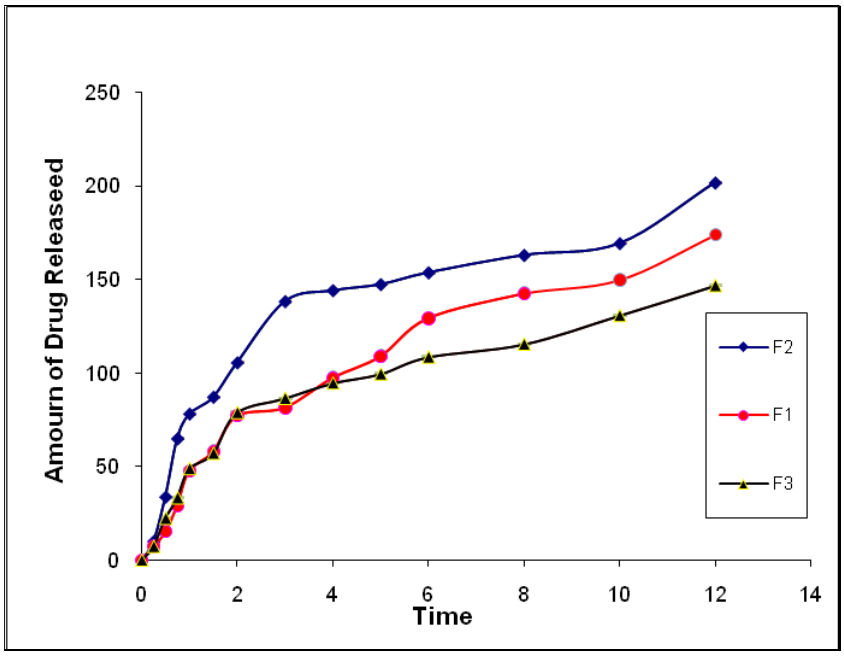


Figure 4: Dissolution data profile of various formulations F1-F3

Table 10: Kinetic data of optimised tablets

Formulation	Zero Order		First Order		Higuchi	Erosion	Peppas
	K_0	r^2	K_1	r^2	r^2	r^2	n
F2	26.01	0.996	0.470	0.946	0.975	0.938	0.692

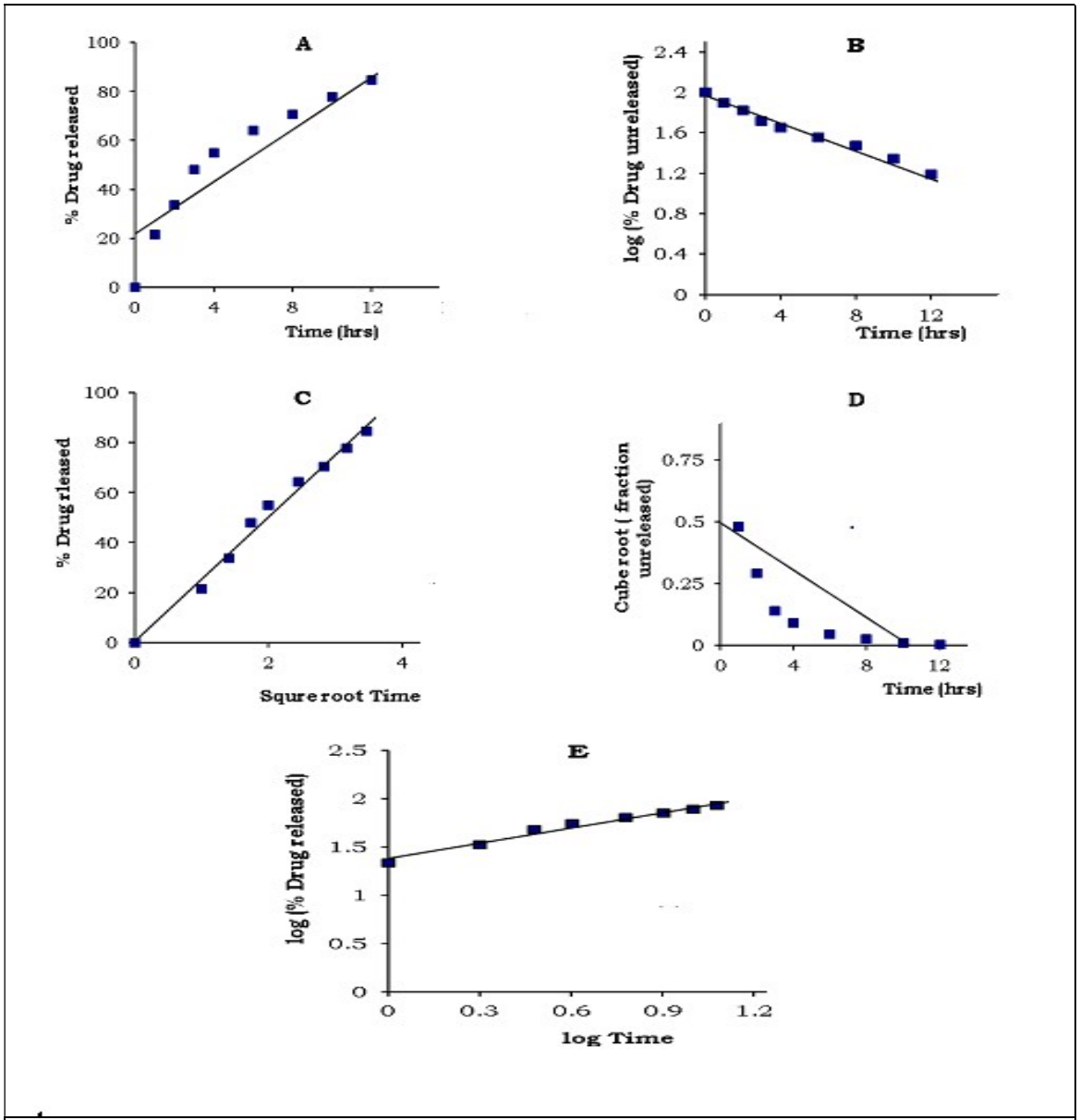


Figure 5: Kinetic plots of Optimised formulation
(A) Zero order plot (B) First order plot (C) Higuchi plot(D) Erosion plot (E) Peppas plot

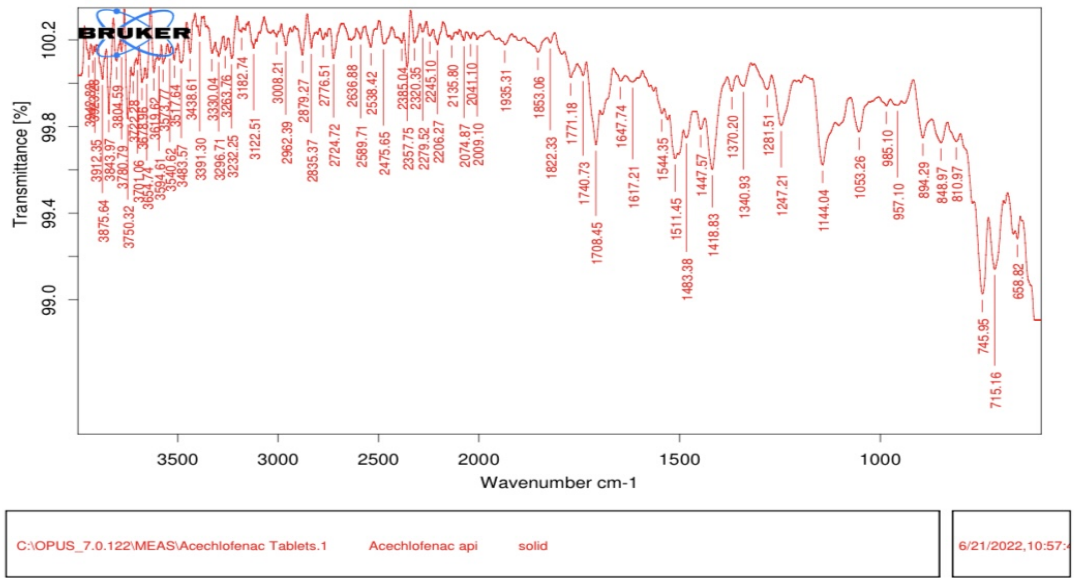


Figure 6: FTIR graph of pure drug (Aceclofenac)

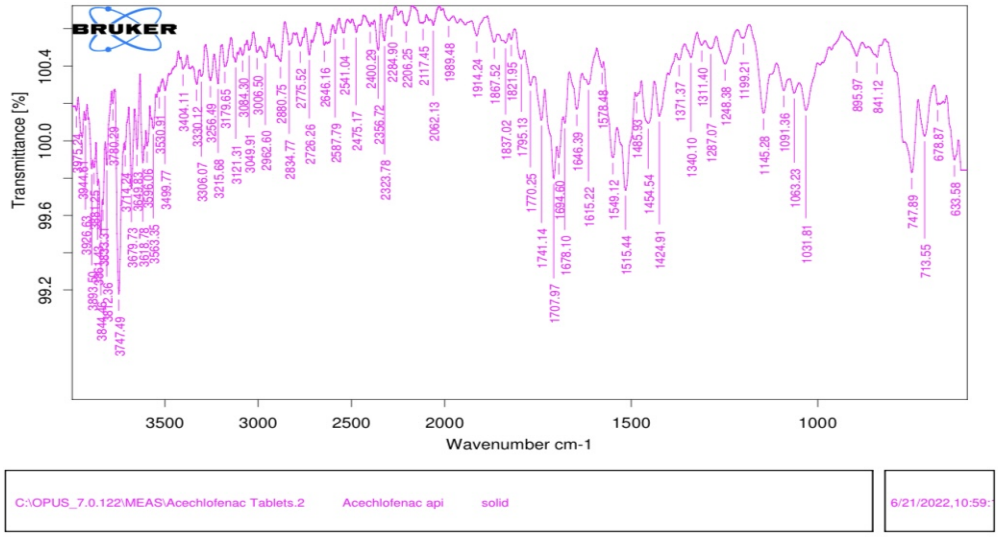


Figure 7: FTIR graph of optimised formulation (F2)

Table 11: ANOVA for test for different batches of optimised tablet prepared under similar conditions

Null hypothesis (H_0): There is no significant difference between % drug content in different batches of optimised formulation (Table value $F_{(2, 9)}$=4.26)					
Batch No.	**Sample 1**	**Sample 2**	**Sample 3**	**Sample 4**	**Mean±s.d**
I	**100.24**	**100.91**	**99.13**	**98.12**	**99.60±1.23**
II	**99.77**	**98.19**	**101.06**	**100.19**	**99.80±1.20**
III	**98.99**	**99.98**	**100.88**	**98.11**	**99.49±1.20**
Average mean % Aceclofenac from three batches					**99.63±0.16**
% C.V. of Aceclofenac from three batches					**0.16**
F ratio					**0.06854**
Result: H_0 is accepted as the calculated F ratio was less than the table value (F) at 5% level of significance. Therefore it was indicated that there was no significant difference between the % Aceclofenac contents of different batches of optimised formulation.					

CONCLUSION:

In the present study, the formulation and production technology of aceclofenac matrix tablets have been developed by using sodium carboxy methyl cellulose, which produced controlled release tablets with acceptable ranges of pre and post compression parameters. Low standard deviation values in all the cases indicate the obtained results were reproducible. This study demonstrated that sodium carboxy methyl cellulose at 1:1 ratio with Aceclofenac provides a reliable controlled release matrix formulation. This study shown F2 formulation can retard the drug release for 12 hr in a controlled manner and study encourages further clinical trials and long term stability study on this formulation.

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