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Original Research Article

Design, Development and Evaluation of Aceclofenac Matrix Tablet Using Eudragit and Carbopol as Matrix Forming Agents

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Abstract:
Aceclofenac is a non-steroidal anti-inflammatory, analgesic and antipyretic agent. It has short biological half-life (4 hours). The present study aims to formulate sustained release Matrix tablet of Aceclofenac for improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity. Total six formulations (F1-F6) were prepared with varying ratios of Eudragit RS100 and Carbopol 934P as matrix forming agents and evaluated for various pre-compression and post compression parameters. Formulation (F3) containing 1:1 ratio of Eudragit RS100 and Carbopol 934P showed promising results in dissolution studies when compared to the rest of the formulations.
Keywords: Aceclofenac, Matrix Tablets, Eudragit, Carbopol, Sustained Release.

Introduction

The most common example of controlled release drug delivery system, is matrix tablet, in which release of drug occur either by diffusion or by dissolution control mechanism. The active content is uniformly dispersed in the rate controlling material i.e. polymers, which may be hydrophilic, plastic, lipid, or mineral etc. The polymeric substance acts as release rate inhibitors. Hence it controls drug blood level with uniform therapeutic level and avoid fluctuation i.e. minimum or toxic concentration, thus prevent local or systemic adverse reactions. Different types of matrices have property to show different release pattern hence the different properties of matrix substance helps to indicate the drug release pattern. (1)

Aceclofenac [[2-(2', 6'-dichlorophenyl) amino] phenylacetoxyacetic acid] is a phenylacetic acid derivative which belongs to the group of non-steroidal anti-inflammatory drug (NSAID).). It is a white crystalline solid, practically insoluble in water, freely soluble in acetone and soluble in ethanol (96%). It is well absorbed orally (60-70

% of bioavailability following oral administration) and undergoes hepatic first pass metabolism. It is 99% bound to plasma protein extensively with albumin. The elimination half life is 4 hrs and volume of distribution is 25 litres.[2] In the present study the acclofenac matrix tablets has been prepared to sustained the drug release to attain better therapeutic outcomes.

Materials and Methods

Aceclofenac was obtained from Nishchem International Pvt. Ltd., Mumbai, Eudragit RS100 was obtained from Evonik Degussa and Carbopol 934P was obtained from Lubrizol. All other chemicals used were of research grade obtained from Merck.

Methodology

Physicochemical Characterization of Drug (Preformulation Studies)

Preformulation studies were performed for following parameters:

Physical Appearance

The physical form and color of the drug (Aceclofenac) was observed visually.

Melting Point

The melting point determination of the drug was done by using the melting point apparatus. A small amount of pure drug of Aceclofenac was taken in a capillary tube and it was kept in the melting point apparatus. The reading of melting point was taken in triplicate and noted.

Calibration Curve of Aceclofenac using UV-Visible Spectroscopy:

Scanning of Aceclofenac in Distilled water, Acid buffer pH 1.2, Phosphate buffer pH 6.8,

50 mg of drug was dissolved in the given solvent in 100 ml volumetric flask, and volume was made to 100 ml. 2 ml of this stock solution was further diluted to 50 ml to get concentration of 20 µg/ml. This solution was scanned in UV-spectrophotometer and characteristic peak (λmax) was observed. The process was performed in triplicate for each solvent. The standard curve was obtained by plotting concentration (µg/ml) on X-axis and absorbance on Y-axis.

Solubility determination

An excess of the drug was added to conical flasks, each containing 50 ml of distilled water, Acid buffer pH 1.2 and Phosphate buffer pH 6.8 respectively. Then conical flasks were shaken manually for some time. After that the conical flasks were kept on rotary shaker for 24 hours. After 24 hours of shaking, the solutions were filtered using a 0.45µ size filter. Then absorbances of the filtered liquids were taken by using a UV-Visible spectrophotometer at respective λmax. Concentrations of dissolved drug was calculated using the standard curve, which is equal to solubility of drug in respective solvent.

Drug-Excipient Compatibility Study (FTIR)

The Drug-Excipient compatibility study is carried out to ensure that the drug does not undergo any change(s) after it has been subjected to various processing steps during the formulation.

The drug-excipient compatibility study was done by using an FTIR spectrophotometer. The FTIR spectrum of pure drug and excipients alone were recorded. Physical mixture of ingredients corresponding to that formulation were also recorded. The range of scanning was 4000 cm^{-1} - 400 cm^{-1}. The characteristic peaks of Aceclofenac were compared in these spectra.

Formulation of Matrix Tablets containing Aceclofenac

In the present study, matrix tablets containing Aceclofenac were prepared using the direct compression process. All of the ingredients were weighed, passed through sieve no. 60 and mixed properly. The powder mixture was again passed through sieve no. 60 and compressed into matrix tablets using tablet punching machine.

Table 1: Formulation of Matrix tablets containing Aceclofenac

Ingredients	F1	F2	F3	F4	F5	F6
Aceclofenac (mg)	200	200	**200**	200	200	200
Eudragit RS100 (mg)	300	200	**150**	100	50	--
Carbopol 934P (mg)	--	100	**150**	200	250	300
Magnesium stearate (mg)	5	5	**5**	5	5	5
Talc (mg)	5	5	**5**	5	5	5

Evaluation of Pre-compression parameters

Powder mixture formulated was evaluated for different pre-compression parameters using standard procedures. The evaluation were done in triplicate (n=3) and mean was calculated.

Angle of repose

Angle of repose is used to determine flow property of the powder. It is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane.

It can be measured by the funnel method. In this method, the funnel is placed above graph paper at distance of 6 cm. The powder is kept in the funnel and allowed to flow. The powder forms a pile. The height and diameter of powder pile is measured. The angle of repose is calculated using following formula:

$$\theta = tan^{-1}\left(\frac{h}{r}\right)$$

Where, "θ" is angle of repose, "h" is height of pile and "r" is radius of the base of pile. [3]

Bulk density

The bulk density and tapped density are evaluated to determine filling of powder in the die. To determine bulk density, weighed amount of powder mixtures is filled in a measuring cylinder, and the bulk volume of powder is noted. The following formula is used to determine the bulk density:

$$Bulk\ density = \frac{Weight\ of\ powder}{Bulk\ volume\ of\ powder}$$

Tapped density

To determine tapped density, weighed amount of powder mixtures is filled in a measuring cylinder, tapped for 50 times and the tapped volume of powder is noted. The following formula is used to determine the tapped density:

$$Tapped\ density = \frac{Weight\ of\ powder}{Tapped\ volume\ of\ powder}$$

Carr's Index

It represents the powder flow properties. It can be computed by the formula:

$$Carr's\ index = \frac{D_t - D_b}{D_t}\ x\ 100$$

Where D_t: tapped density of the powder

D_b: bulk density of the powder

Hausner's ratio

Hausner's ratio is also used to represent flow properties of powder. It is calculated by using following formula and it is expressed in percentage:

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Compression of powders into matrix tablets

Matrix tablets containing Aceclofenac were prepared by direct compression. Drug and excipients were weighed and mixed properly. Lubricant (talc) and glidant (magnesium stearate) were mixed to this prepared powder mixture. This powder blend was used to prepare matrix tablets by direct compression using tablet punching machine.[4,5,6]

Evaluation of Prepared Matrix Tablets

After formulation of tablets, they are evaluated for various parameters. Prepared matrix tablets were evaluated for following parameters:

Appearance, Shape and Size

Appearance of prepared tablets was observed visually. Diameter and thickness of prepared matrix tablets were determined using Vernier callipers. Three tablets from each formulation were taken and average was calculated.

Weight variation

This test is performed to check the uniformity of weight of the prepared tablets, as drug content is directly related to the weight of tablet. In this process, 20 tablets were weighed individually. The average weight of one tablet was calculated by taking average mean.(7)

Hardness

Hardness of tablets is the amount of force needed to split them. Both Monsanto and Pfizer type hardness tester were used to determine the hardness of the formulated tablets. The hardness was calculated as kg/cm^2. Three tablets from each formulation were taken and average was calculated.

Friability

The Roche friabilator was used to measure friability of the formulated tablets. Weight of 20 tablets was measured and placed in the friabilator chamber. The friabilator was rotated at speed of 25 rpm for 4 min. After completion of 100 revolutions, the tablets were weighted again and % weight loss is calculated, which corresponds to friability.(8,9)

$$\%\ Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100$$

Drug content

The drug content was calculated by triturating ten tablets in a mortar with pestle to get fine powder. Powder equivalent to weight of one tablet was taken and was dissolved in distilled water. Measure the absorbance (after dilution, if required) of Aceclofenac at λmax using UV-Visible Spectrophotometer. The drug content was calculated by using standard calibration curve.(10)

In-vitro Dissolution Studies

Dissolution studies of matrix tablets are performed to ensure sustained release of the drug (Aceclofenac) for longer duration.

Dissolution studies of prepared matrix tablets was performed in two steps. Initially, Acid buffer pH 1.2 (corresponding to gastric environment) was used as dissolution media for initial two hours. Then, the dissolution media was replaced with Phosphate buffer pH 6.8 (corresponding to intestinal environment) as dissolution media for next ten hours. Paddle apparatus was used for dissolution studies at 50 RPM and $37^0 \pm 0.5^0$C.(11)

Accelerated Stability Studies

Short term accelerated stability studies of the selected formulation were carried out at 40^0C/75%RH over a period of 3 months. The matrix tablets were wrapped with aluminium foil, and stored in humidity controlled oven for 3 months. Samples were analysed for residual drug contents at time interval of 15 days.(12)

Result and Discussion

Physicochemical Characterization of Drug (Preformulation Studies):

When visually observed Acelofenac was colourless and odorless white solid powder. The melting point of Aceclofenac was found to be 148^0C - 150^0C, which is same as documented (149^0C).

Calibration Curve of Aceclofenac using UV-Visible Spectroscopy:

Calibration curve of Aceclofenac in Distilled water, Acid buffer pH 1.2 and Phosphate buffer pH 6.8

50 mg of Aceclofenac was taken in three different flasks and Distilled water, Acid buffer pH 1.2 and Phosphate buffer pH 6.8 to respective flasks was added and volume was made up to 100 ml by same solvent. This gave

the concentration of 500 µg/ml (stock solution). 1, 2, 3, 4, 5 and 6 ml of this stock solution was further diluted to 100 ml to get different concentrations of 5, 10, 15, 20, 25 and 30 µg/ml. Absorbances were measured at 272 nm, 272 nm and 346 nm respectively for each solvent.

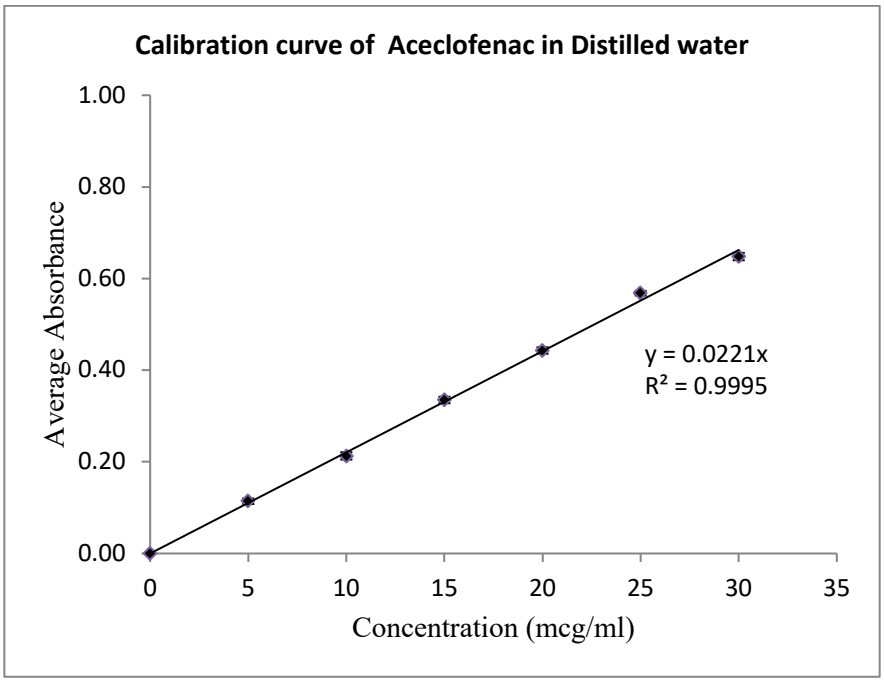

Figure 1: Calibration curve of Aceclofenac in distilled water, n=3

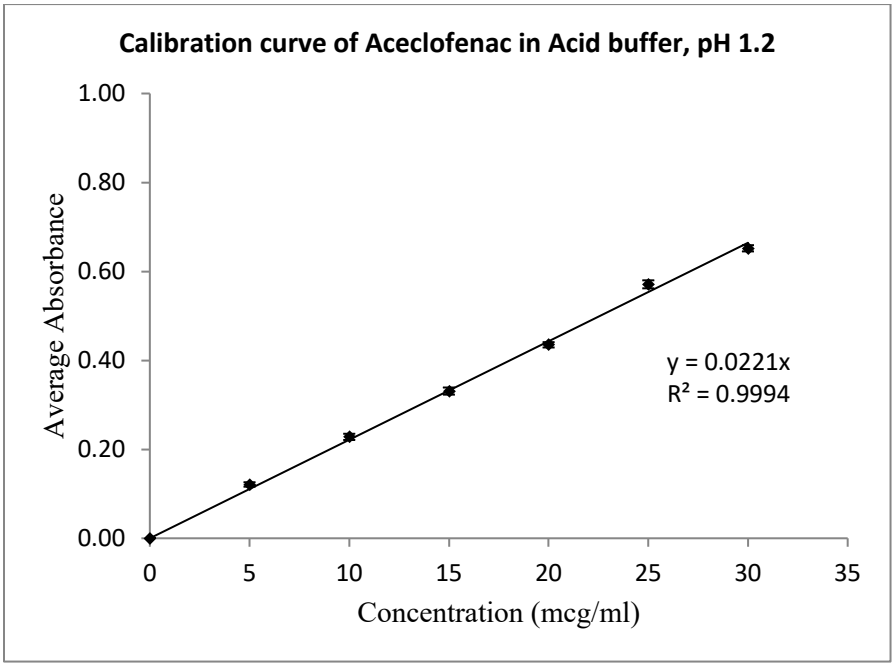

Figure 2: Calibration curve of Aceclofenac in Acid buffer pH 1.2, n=3

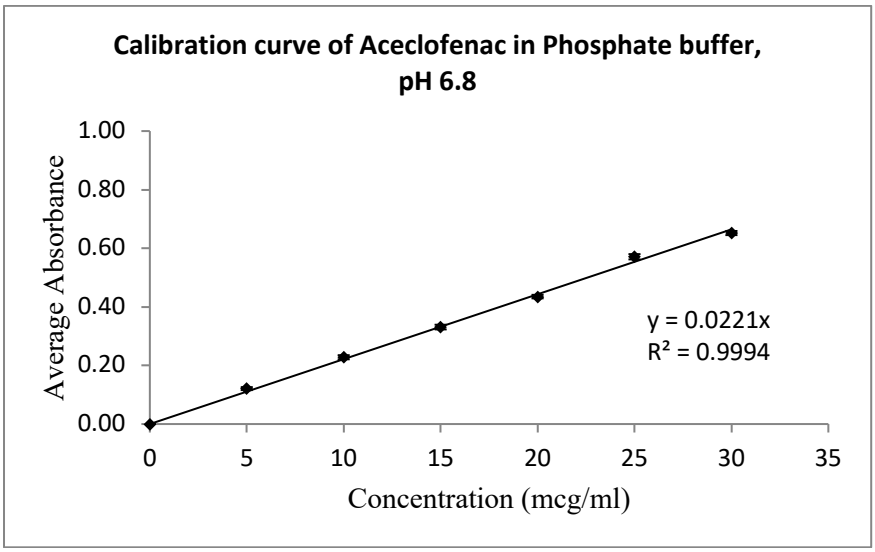

Figure 3: Calibration curve of Aceclofenac in Phosphate buffer pH 6.8, n=3

Solubility determination

It can be observed that the drug Aceclofenac is slightly soluble in distilled water, Acid buffer pH 1.2 and Phosphate buffer pH 6.8.

Table 2: Solubility of Aceclofenac in various solvents

S. No.	Solvent	Solubility of Aceclofenac (µg/ml)
	Distilled water	56.2 µg/ml
	Acid buffer, pH 1.2	16.8 µg/ml
	Phosphate buffer, pH 6.8	12.5 µg/ml

Drug-Excipient Compatibility Study (FTIR)

The drug-excipient compatibility study was done by using an FTIR spectrophotometer. The FTIR spectrum of pure drug and excipients and physical mixture of ingredients corresponding to that formulation (F3) were also recorded. The range of scanning was 4000 cm^{-1} - 400 cm^{-1}. The characteristic peaks of Aceclofenac were compared in these spectra. (Figure 4 and 5)

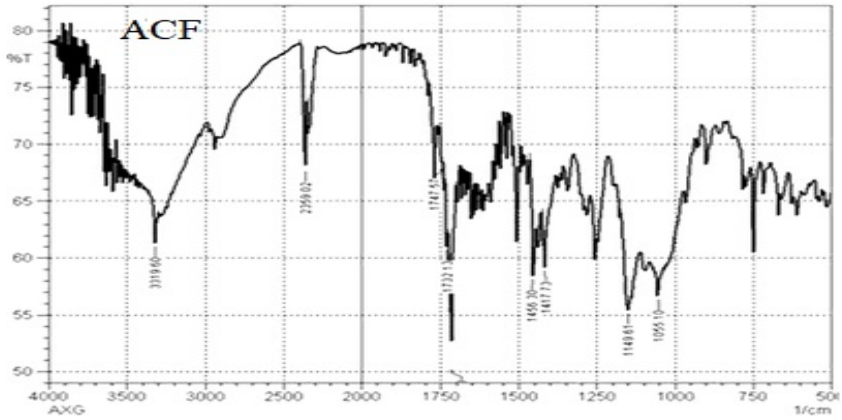

Fig. 4: FTIR spectrum of Aceclofenac

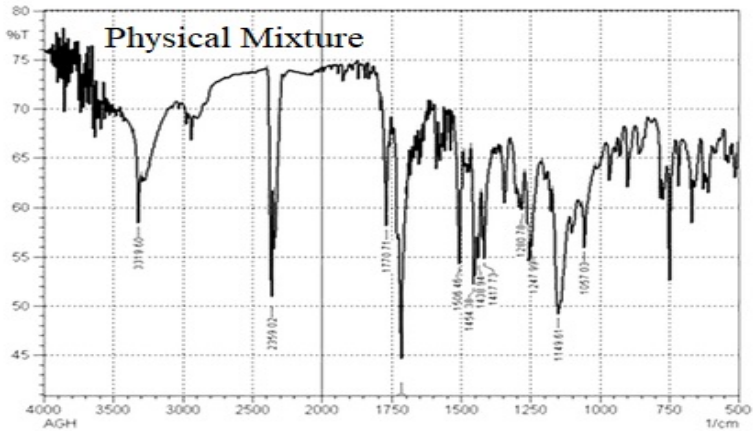

Figure 5: FTIR spectrum of Physical mixture of Aceclofenac and Excipients

The FTIR spectra of pure drug (Aceclofenac) showed all the characteristic peaks, which confirm the identification of drug. FTIR spectra of the physical mixture showed that all the characteristic peaks were intact. It showed that that the drug has not undergone any change(s) after it has been subjected to various processing steps during the formulation. Therefore the method can be used to prepare matrix tablet using the drug and excipients. (9)

Evaluation of Pre-compression parameters

Powder mixture formulated was evaluated for different pre-compression parameters using standard procedures. The evaluation were done in triplicate (n=3) and mean was calculated.

Angle of all the powder mix was determined by the funnel method. Angle of repose was found to be between 28.85^0 - 32.31^0 for all the powder blends which are within the standard limits. It is evident from the results, that the powder blends of all the formulations possess good flow properties. Bulk density and Tapped density were found to be between 0.406 - 0.441 gm/cm^3 and 0.501 - 0.528 gm/cm^3 respectively for all the powder blends. It may be concluded that the powder blends of all the formulations possess good flow properties. Carr's Compressibility Index was found to be between 16.48 - 19.27 for all the powder blends which are within the standard limits. It may be concluded that the powder blends of all the formulations possess good flow properties. Hausner's ratio was found to be between 1.20 - 1.24 for all the powder blends which are within the standard limits. It may be concluded that the powder blends of all the formulations possess good flow properties. Based upon various pre-compression parameters, it was concluded that the powder blends are suitable for compression into tablet. (12)

Compression of powders into matrix tablets

Matrix tablets containing Aceclofenac were prepared by direct compression. Drug and excipients were weighed and mixed properly. Lubricant (talc) and glidant (magnesium stearate) were mixed to this prepared powder mixture. This powder blend was used to prepare matrix tablets by direct compression using tablet punching machine. (13)

Evaluation of Prepared Matrix Tablets

After formulation of tablets, they were evaluated for various parameters. Prepared matrix tablets were evaluated for following parameters:

Shape and Size

All the tablets prepared were round in shape. Diameter was found to be 8 mm and thickness was found to be 4 mm for all the formulations.

Weight variation

This test is performed to check the uniformity of weight of the prepared tablets, as drug content is directly related to the weight of tablet. In this process, 20 tablets were weighed individually. The average weight of one tablet was calculated by taking average mean which ranged around 504.50-516.80 mg and none of the tablet deviated by the limit prescribed (5%). Therefore, the prepared tablets pass the test for weight variation.

Hardness

Both Monsanto and Pfizer type hardness tester were used to determine the hardness of the formulated tablets. The hardness was calculated as kg/cm^2. Three tablets from each formulation were taken and average was calculated. The average hardness of prepared tablets was found to be 5.9 - 7.5 kg/cm^3, which are optimum for matrix tablets.

Friability

The friability of prepared tablets was found to be 0.26 - 0.42%, which are less than the standard limits (1%). It may be concluded that the prepared matrix tablets pass the friability test. (13,14)

Drug content

The percent drug content of prepared tablets was found to be 98.25 - 99.60%, which is within the prescribed limits. Therefore, the prepared matrix tablets pass the test for drug content (content of uniformity). (15)

***In-vitro* Dissolution Studies**

Dissolution studies of matrix tablets are performed to ensure sustained release of the drug (Aceclofenac) for longer duration. Dissolution studies of prepared matrix tablets was performed in two steps. Initially, Acid buffer pH 1.2 (corresponding to gastric environment) was used as dissolution media for initial two hours. Then, the dissolution media was replaced with Phosphate buffer pH 6.8 (corresponding to intestinal environment) as dissolution media for next ten hours. Paddle apparatus was used for dissolution studies at 50 RPM and 37^0±0.5^{0}C.

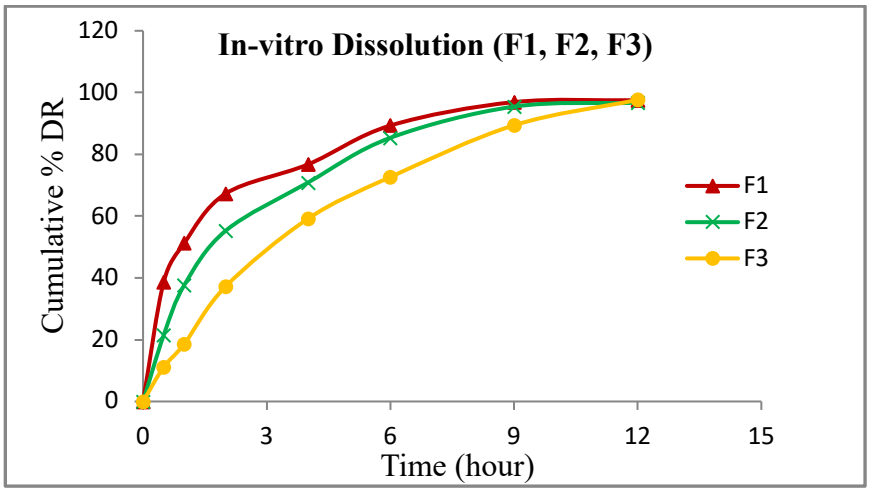

Figure 6 (i): In-vitro dissolution profile of F1, F2 and F3

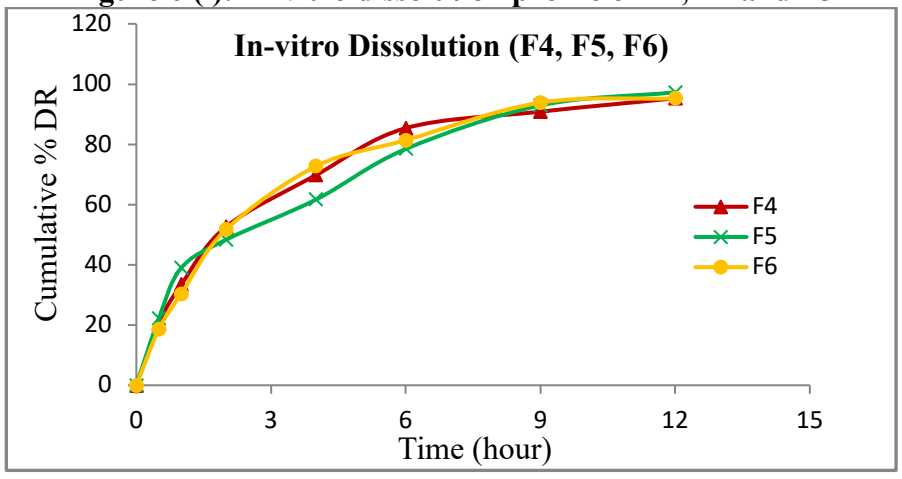

Figure 6 (ii): In-vitro dissolution profile of F4, F5 and F6

All the prepared matrix tablets showed sustained dissolution profile. Dissolution of Aceclofenac was sustained for 12 hours. All the formulations released more than 95% drug.

It can be concluded that matrix tablets can be prepared using above drug, excipients and procedure, that release the drug slowly and continuously for 12 hours. [16,17]

Accelerated Stability Studies

Short term accelerated stability studies of the selected formulation F3) were carried out at 40^0C/75%RH over a period of 3 months. The matrix tablets were wrapped with aluminium foil, and stored in humidity controlled oven for 3 months. Samples were analysed for residual drug contents at time interval of 15 days.

Table 3: Drug content of prepared matrix tablets at accelerated conditions (AST)

S. No.	Formulation Code	% Drug content of films at various time interval (AST) (Mean± S.D.*)						
		Initial	15 days	30 days	45 days	60 days	75 days	90 days
	F1	98.50±1.42	98.35±1.34	98.15±1.28	97.95±1.35	97.85±1.25	97.70±1.45	97.50±1.36
	F2	98.75±1.35	98.45±1.34	98.25±1.62	98.05±1.81	97.85±0.95	97.65±1.29	97.40±1.35
	F3	99.15±1.32	99.05±1.64	98.80±1.74	98.70±1.26	98.55±1.19	98.45±1.46	98.35±1.24
	F4	98.85±1.68	98.65±1.85	98.40±1.61	98.10±1.26	97.80±1.25	97.60±1.43	97.15±1.42
	F5	98.55±1.84	98.25±1.26	98.20±1.55	97.95±1.08	97.75±1.24	97.60±1.65	97.20±1.18
	F6	97.65±1.54	97.55±1.59	97.30±1.34	97.10±1.44	96.90±1.62	96.70±1.18	96.55±1.59

* Standard deviation, n=3

All the formulations showed good stability at accelerated conditions. When content of Aceclofenac were analysed at various time interval, it was found to be more than 96.55% in all the formulations after 3 month. [18]

Summary and Conclusion

Preformulation studies of drug were performed which included Physical appearance, determination of Melting point which confirmed the identity of the drug. Scanning of Aceclofenac was done in distilled water, acid buffer pH 1.2 and phosphate buffer pH 6.8 and peak (λmax) was observed at 272 nm, 272 nm and 346 nm respectively using UV-spectrophotometer. Subsequently, calibration curve of Aceclofenac was prepared in distilled water, acid buffer pH 1.2 and phosphate buffer pH 6.8. Linearity was observed with R^2 values more than 0.998. Solubility of pure drug was also determined in distilled water, acid buffer pH 1.2 and phosphate buffer pH 6.8, which was found to be 56.2µg/ml, 16.8µg/ml and 12.5µg/ml respectively. Drug- excipient compatibility study was performed using FTIR. The FTIR spectrum of pure drug and physical mixture of ingredients was recorded. The range of scanning was 4000 cm^{-1} - 400 cm^{-1}. The characteristic peaks of Aceclofenac were compared in these spectra. The spectra showed that all the characteristic peaks were intact. It showed that no interaction occurred between the drug and excipients during formulation. After preformulation studies, Matrix tablets of Aceclofenac were prepared using varying amount of excipients. Total 6 formulations (F1-F6) were prepared.

Initially the powder blends were evaluated for various pre-compression parameters i.e. angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. All the parameters were found optimum for the suitability of powder blends for compression into tablets.

The prepared matrix tablets were evaluated for various parameters i.e. shape and size, weight variation, hardness, friability, drug content, *In-vitro* dissolution studies, accelerated stability studies etc. The prepared tablet passed all the evaluation tests.

All the prepared tablets were found suitable for various evaluation parameters of matrix tables. They released the drug continuously and in sustained manner upto 12 hours. After comparing the results (particularly dissolution profile), it was concluded that formulation F3 was selected as the best formulation among all.

Finally, it can be concluded that matrix tablet of Aceclofenac can be formulated using above excipients and method that will help in releasing the drug over a prolonged period of time to Minimise dosing frequency, prolong the pharmacological effect and improve patient compliance.

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