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DESIGN AND CHARACTERIZATION OF PRESS COATED TABLETS OF ACECLOFENAC FOR PULSATILE DELIVERY

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Keywords:

Aceclofenac, 3^2 full factorial design, press-coated tablet, lag time, direct compression, time-controlled.

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ABSTRACT: An oral press-coated tablet was developed by means of direct compression to achieve the time-controlled disintegrating or rupturing function with a distinct predetermined lag time. The aim of the present study is to develop time depended drug delivery systems for Aceclofenac by using HPMC K100M and ethylcellulose (EC) as coating material. By applying 3^2 full factorial design, compression coated tablets of Aceclofenac containing different proportions of EC and HPMC K100M was prepared. All the formulations were evaluated for the hardness, friability, thickness, weight variation, drug content uniformity, and in-vitro drug release studies for 8 hr. Press coated tablets of Aceclofenac released different amount of the Aceclofenac, within the 8hr dissolution study, in the physiological environment of the stomach and small intestine, depending on the proportion of EC: HPMC K100M used in the formulation. The compression coated formulations have been formulated to release minimum amount of Aceclofenac within 6 hr dissolution study in the physiological environment of the stomach and small intestine. The results of the dissolution study showed that compression coated tablet Fp4 with EC: HPMC K100M is most likely to provide time-controlled disintegrating or rupturing function with a distinct predetermined lag time.

INTRODUCTION: Oral route is considered the most effective route for the drug delivery. Most of immediate and delayed release systems are delivered by this route only because of its high level of patient compliance [1]. Even though, this type of delivery system fails to prevent some disease or symptom of disease [2]. The reason for the failure is that some diseases show significant variation in their level during 24 hr which is known as circadian rhythm.

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Conventional preparations are not able to deliver the drug according to the circadian rhythm. It is well documented that some diseases like heart rate, blood pressure, rheumatoid arthritis stroke volume, blood pressure, blood flow, body temperature, gastric-pH, cholesterol level, asthma etc. shows time dependency in their symptoms and effect [3].

Time controlled preparation has been developed to control these types of conditions. Pulsatile drug delivery system has been developed to give time dependent release with lag time to control diseases[4]. Pulsatile delivery system can be formulated by different formulations. Capsule formulation includes OROS soft cap, port, pulsing cap etc. and tablet formulation includes coating by erodible or soluble polymer. Press coated tablet are also known as double compression, compression

coating or dry coating tablet. Press coating is advantageous because it does not involve use of volatile solvent, requires short manufacturing time, physical separation of two incompatible material is also possible, mask the bitter of drug, protection of volatile ingredients and colon targeted can also be achieved if sufficient amount of barrier layer is provided.

Press coated tablet is also one of the approach for colon targeting. Colon drug delivery refers to as a targeted delivery of many drugs into the lower gastrointestinal tract, which occurs mainly in the large intestine [5]. This site delivery is advantageous to delivery of peptide drugs which requires protection from the gastric environment, prevent first pass metabolism, local and systemic delivery can be done, protection of mucosa from irritation caused by drugs, effective treatment of colorectal cancer, reduce dose frequency and improve patient compliance [6].

Generally a rheumatoid arthritis symptom is high in early morning. Aceclofenac has higher anti-inflammatory action than other NSAIDs Aceclofenac is blocking the action of a cyclo-oxygenase in body[7]. Cox is involved in the formation of prostaglandins which cause pain, inflammation. Aceclofenac is chemically synthetic. It is BCS class II drug and is probably metabolized by CYP2C9 to the metabolite form is 4-hydroxyaceclofenac and bioavailability is near to 100%. Peak plasma concentrations levels are reached approximately 1.26 to 3 hours following ingestion. Aceclofenac is highly protein-bound (> 99.7%).

The volume of distribution is approximately 30L. The plasma elimination half-life is 4- 4.3 hours. Aceclofenac has the disadvantage of low solubility due to not being soluble in gastric p^H and its intestinal metabolism by CYP2C9 enzyme. Aceclofenac colon targeting is promising due to the low level of this enzyme in the colon than in the small intestine. By formulating the press coated tablet and targeting it to the colon, first pass metabolism of aceclofenac can be avoided. Delivery of drug in the early morning is possible when it is actually required by formulating its press coating tablet using Ethylcellulose (EC) and Hydroxypropylemethyl celluloseK100M (HPMC K100M). HPMC K100M act as hydrophilic layer which swell with time and EC act as a hydrophobic polymer which protects the core tablet so that it remains intact until they reach to the targeted site i.e. colon. Here amount of both polymers must be sufficient so that it gives sufficient lag time to deliver the drug in the targeted area [8-11].

MATERIALS AND METHODS:

TABLE 1: LIST OF MATERIALS USED

Sl.no	Materials	Source
1	Aceclofenac	Hetero drugs Pvt Ltd, Hyderabad.
2	HPMC K100M	Yarrow chem. products, Mumbai.
3	Ethyl cellulose	Molychem, Mumbai.
4	Sodium starch glycolate	Yarrow chem. products, Mumbai.
5	Microcrystalline cellulose	Molychem, Mumbai.
6	Dicalcium phosphate	S.D. Fine chemicals, Mumbai.
7	Magnesium stearate	S.D. Fine chemicals, Mumbai.

Determination of λ_{max} for Aceclofenac:

Determination of analytical wavelength of Aceclofenac in pH 6.8 phosphate buffers can be done by taking 1 ml from 100 µg/ml standard stock solutions in 10 ml volumetric flask. The volume was made up to 10 ml with pH 6.8 phosphate buffer solution. The resulting solution containing 10µg/ml was scanned between 200 to 400 nm shown in **Fig. 1.**

Preparation of calibration curve:

A stock solution of pure drug (1000µg/ml) was prepared by accurately weighing 100 mg drug and dissolving it in 100 ml of buffer solution. Different dilutions were made with concentration of 1, 2, 4, 6, 8, 10 µg/ml from stock solution and their absorbances were measured at 273 nm using UV-Visible spectrophotometer shown in **Fig. 2.**

Formulation of Rapid Release Core Tablets:

The core was made of the suitable mixture of powder blends of optimized Aceclofenac, Microcrystalline Cellulose (MCC, Avicel PH-101) and Sodium starch glycolate. All above ingredients were dry blended for 20 minutes followed by addition of Magnesium Stearate. The mixture was

then further blended for 10 minutes. The 200 mg of the resultant mixture was then directly compressed using 8 mm punch and die.

TABLE 2: FORMULATIONS TABLE OF RAPID RELEASE CORE TABLETS

Ingredients	Quantity (mg)			
	Fc1	Fc2	Fc3	Fc4
Aceclofenac	100	100	100	100
Sodium starch glycolate	4	8	16	-
Microcrystalline cellulose	47	45	41	49
Dicalcium phosphate	47	45	41	49
Magnesium stearate	2	2	2	2
Total	200	200	200	200

TABLE 3: SELECTED FORMULA FOR CORE

Ingredients	Quantity (mg)
Aceclofenac	100
Dicalcium phosphate	45
Sodium starch glycolate	8
Microcrystalline cellulose	45
Magnesium stearate	2
Total	200

Formulation of Powder Blend for Press Coated Tablet by Using 3^2 Full Factorial Design: [12]

Powder blend for press-coated tablet was prepared by dry blending together different composition of the EC and HPMC K100M. These excipients were dry blended in different weight compositions in order to get suitable polymer composition shown in table no 4. A 3^2 full factorial design was applied to examine the combined effect of two formulation variables, each at 3 levels, and the possible nine combinations of Aceclofenac press coated tablets were prepared. The amount of EC (X1) and the amount of HPMC K100M (X2) were taken as independent variables.

The % drug release 8 hr and % drug release before 6 hr were taken as dependent variables. This composition is dry blended until uniformly blended mixture is obtained. This mixture is then used for the preparation of press–coated tablet using direct compression method.

TABLE 4: EXPERIMENTAL DESIGN BY USING 3^2 FULL FACTORIAL DESIGNS

Run	Factor 1 A:Ec (mg)	Factor 2 B: HPMC K100M (mg)
1	175	175
2	175	200
3	175	225
4	200	175
5	200	200
6	200	225
7	225	175
8	225	200
9	225	225

TABLE 5: COMPOSITION OF THE ALL FORMULATIONS

S.No	Ingredients	Quantity (mg)								
		Fp1	Fp2	Fp3	Fp4	Fp5	Fp6	Fp7	Fp8	Fp9
1	Aceclofenac	100	100	100	100	100	100	100	100	100
2	DCP	45	45	45	45	45	45	45	45	45
3	Sodium starch glycolate	8	8	8	8	8	8	8	8	8
4	Microcrystalline cellulose	45	45	45	45	45	45	45	45	45
5	Magnesium stearate	2	2	2	2	2	2	2	2	2
6	EC	175	175	175	200	200	200	225	225	225
7	HPMC K100M	175	200	225	175	200	225	175	200	225
	Total Weight Of Tablets	550	575	600	575	600	625	600	625	650

Preparation of Press Coated Tablets:

Press Coated Tablets were prepared by direct compression method. The composition of the core tablet is shown in the Table 2 and as per that formulation; core tablets were prepared using the punch of 8 mm diameter using the rotary tablet processing machine. After the preparation of the core tablet, for coating of those tablets, various proportions of EC and HPMC K100M were taken. Half amount of the coating material was filled in the die cavity of 12 mm diameter. Then the core tablet was kept in the center of die cavity, then the remaining quantity was filled in the die cavity and it was punched using the rotary tablet processing machine.

Evaluation studies – Pre - compression parameters: [13, 14]

Angle of repose:

The angle of repose of powder blend was determined by use the funnel method. The accurately weighed powder blend was taken in the funnel. The funnel height was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through on the funnel freely on to the surface. The diameter of the powder cone was measured & angle of repose was calculated using the following formula.

$$\tan\theta = \frac{h}{r}$$

Where, h and r are the height and radius of the powder cone.

Apparent bulk density:-

Apparent bulk density is determined by placing pre-sieved drug excipient blend in to a graduated cylinder & measuring the volume and weight as it is. Bulk density was determined by using following formula.

$$\text{Apparent Bulk Density} = \frac{\text{Weight of the powder blend}}{\text{Untapped Volume of thepacking}}$$

Tapped density:

Weighed sample of powder mixture was transferred to a graduated cylinder and was tapped for a fixed time or for a fixed number of taps (100). The tapped density was determined by using the following formula.

$$\text{Tapped Density} = \frac{\text{Weight of the powder blend}}{\text{TappedVolume of the packing}}$$

Hausner's Ratio:

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

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

Compressibility index (Carr's Index):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$C_I = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped Density}} \times 100$$

Post compression Parameter:

a. Core Tablet:

The tablets were evaluated in process & finished product quality control tests i.e. appearance, dimensions, weight variation, hardness, & friability, assay and drug content.

Weight variation: [15]

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

Tablet hardness: [16]

The resistance of tablets to shipping / breakage under conditions of storage, transportation & handling before usage depends on its hardness. The hardness of each batch of tablets was checked by using Monsanto hardness tester, the hardness of tablets was measured in terms of kg/cm^2. 3 tablets were chosen randomly & tested for hardness. The average hardness of 3 determinations was recorded.

Friability: [17]

Friability generally refers to loss in weight of tablets in the containers to removal of fines from the tablet surface. Friability generally reflects low cohesion of tablet ingredients.

Method: 10 tablets were weighed & the initial weight of tablets was recorded & placed in Roche friabilator & rotated at the speed of 25 rpm for mentis and total 100 revolutions. The tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\text{Friability} = \frac{(w_1 - w_2)}{w_1} \times 100$$

Where: W_1= weight of the tablet before test.

W_2 = weight of the tablet after test.

***In-vitro* Disintegration Time:**
In-vitro disintegration time of three tablets was determined by using digital tablet disintegration apparatus. In-vitro disintegration test was carried out at 37±2°C in 900 ml phosphate buffer pH 6.8.

Content Uniformity: [17]
The tablets were tested for their drug content uniformity. To take 20 tablets were weighed & powdered. The powder equivalent to 100 mg of accurately drug weighed and dissolved in 100ml of phosphate buffer of pH 6.8. The undissolved matter is removed by filtration through Whatman No.1 filter paper. Then transfer 1ml of above solution into 100ml volumetric flask & make up to the volume with phosphate buffer of pH 6.8. The absorbance of the diluted sol^{s} was measured at 273nm. The concentration of the drug was determined from the standard curve of the Aceclofenac in phosphate buffer of pH 6.8.

***In-vitro* Drug Release Study:** [19]
In-vitro dissolution study of optimized core tablet was performed using Paddle type dissolution apparatus at speed of 50 RPM. 900 ml of phosphate buffer pH 6.8 was utilized as dissolution medium. The temperature of the medium was maintained at 37±0.5°C. Aliquot of dissolution medium (5 ml) were withdrawn at specific time intervals (5, 10, 15, 20, 30, 45, 60 min) and filtered each with whatman filter paper. Equal amount of fresh dissolution medium was replaced immediately after each withdrawal. The amount of drug present in each sample was determined by UV-Visible spectrophotometer at 273 nm.

B. Press Coated Tablet:
Weight variation:
The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

Tablet hardness: The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability:
Friability generally refers to loss in weight of tablets in the containers to removal of fines from the tablet surface. Friability generally reflects low cohesion of tablet ingredients.

Method: 10 tablets were weighed & the initial weight of tablets was recorded & placed in Roche friabilator & rotated at the speed of 25 rpm for minits and total 100 revolutions. The tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

$$\text{friability} = \frac{(w_1 - w_2)}{w_1} \times 100$$

Where: W_1= weight of the tablet before test.
W_2 = weight of the tablet after test

Lag Time:
The time for which the tablet does not show any release of the drug is known as its lag time. The lag time can be estimated through the dissolution profile of the tablet

Position of Core Tablet:
Compression coated tablet is cut vertically and cross sectional photographs were taken to evaluate the position of core tablet in the compression coated tablet.

***In-vitro* Drug Release Study:**
The *in-vitro* drug release study was carried out in USP Type II dissolution apparatus (paddle type) at a speed of 50 RPM (Labindia, Mumbai.). The temperature of the medium was maintained at 37±0.5°C. The drug was kept in 0.1 N HCl buffer (pH 1.2) for 2 h then in phosphate buffer (pH 6.8) for 6 h. Aliquot of dissolution medium (5 ml) was withdrawn at specific time intervals and 1 h interval up to 8 h and filter with whatman filter paper and samples were analyzed in UV-Visible spectrophotometer at 273 nm.

RESULTS AND DISCUSSION:

Spectrometric Scanning of Aceclofenac and Calibration Curve of Aceclofenac in pH 6.8 Phosphate Buffer

The solution containing 10 µg/mL of Aceclofenac in pH 6.8 Phosphate Buffer was scanned between 200 and 400 nm using double beam UV-Visible spectrometer. λmax was found to be 273 nm. So, this was selected as analytical wavelength of Aceclofenac in pH 6.8 Phosphate Buffer is shown **Fig.1.** Calibration curve of Aceclofenac in pH 6.8 Phosphate Buffer is shown **Fig.2.**

Determination of λ_{max} for Aceclofenac in pH 6.8:-

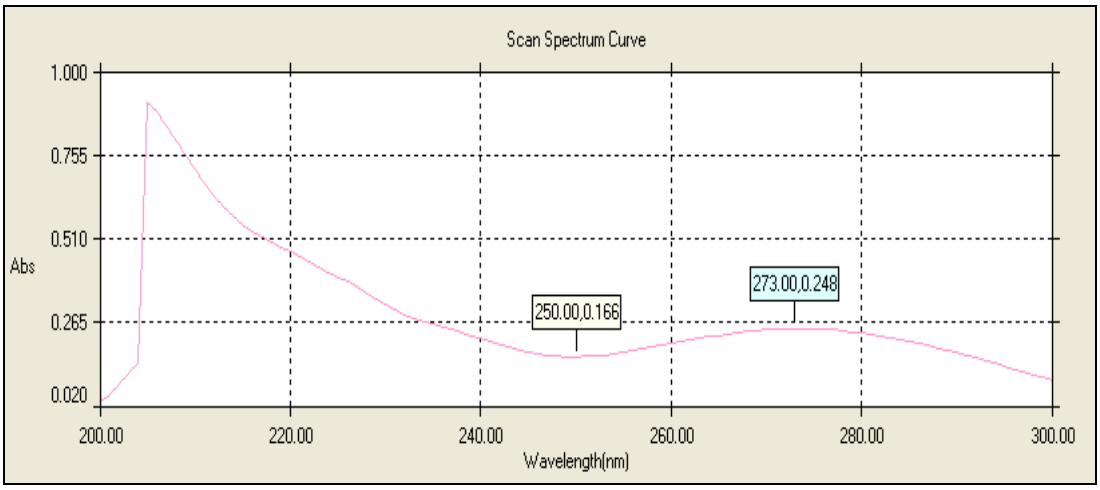

FIG.1: DETERMINATION OF λ_{MAX} FOR ACECLOFENAC IN pH 6.8

Construction of Calibration curve:

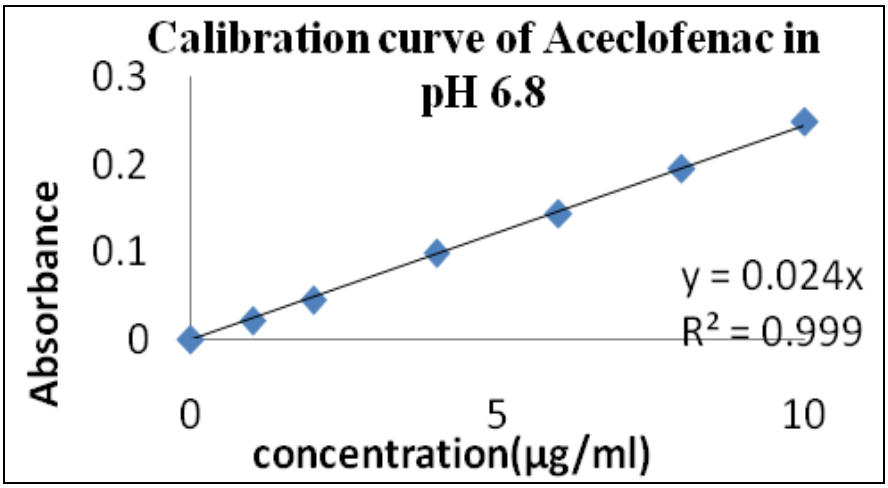

FIG .2: CALIBRATION CURVE OF ACECLOFENAC IN pH 6.8

Pre-Compression Parameters: Prepared core powder blend and coating blend was showing good micromeritic property and flowability (**Table 6** and **7**).

TABLE 6: PRE-COMPRESSION EVALUATION PARAMETERS FOR CORE

Form. Code	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility Index (%)	Hausner's Ratio	Angle of repose
Fc1	0.34	0.38	10.52	1.11	26.29
Fc2	0.33	0.38	13.15	1.15	27.29
Fc3	0.334	0.38	13.14	1.14	28.29
Fc4	0.34	0.39	12.80	1.14	21.29

TABLE 7: PRE-COMPRESSION EVALUATION PARAMETERS FOR PRESS COATED TABLETS

Form. Code	Bulk Density (g/cc)	Tapped Density (g/cc)	Compressibility Index (%)	Hausner's Ratio	Angle of repose
Fp1	0.318	0.38	16.31	1.19	17.10
Fp2	0.342	0.4	15.0	1.176	28.97
Fp3	0.34	0.43	20.93	1.26	18.19
Fp4	0.36	0.42	14.28	1.16	22.61
Fp5	0.33	0.41	19.06	1.24	26.56
Fp6	0.33	0.42	22.35	1.28	23.10
Fp7	0.33	0.41	19.51	1.24	19.85
Fp8	0.32	0.42	24.70	1.32	21.80
Fp9	0.33	0.4	17.5	1.21	17.74

Post-compression parameters:

1. Core Tablet: The weight variation, thickness, hardness, friability and drug content of core tablet were found to be good and in the range as shown in following Table 8. *In-vitro* drug release study in phosphate buffer pH 6.8 was performed and as shown in **Fig.5.** From *in-vitro* drug release profile it was found that nearer 100% of drug release was occur within 30 min. This makes it suitable as a fast dissolving tablet.

TABLE 8: POST-COMPRESSION EVALUATION PARAMETERS FOR CORE TABLETS

Form. code	Weight variation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Disintegration time(sec)	Drug content
Fc1	201	5.8	0.49	3.6	38	99.43
Fc2	200	5.8	0.50	3.6	5	98.63
Fc3	200	5.7	0.48	3.6	3	98.65
Fc4	199.5	5.8	0.49	3.6	186	97.3

2. Press Coated Tablet:

a. Physiochemical Parameters: All formulation shows low weight variation, friability of tablets was found below 1% indicating good mechanical resistance. The drug content thickness and hardness of all the formulation was found within the acceptable limit. Various physiochemical parameters for press coated tablet are shown in **Table 9**.

TABLE 9: POST-COMPRESSION EVALUATION PARAMETERS FOR PRESS COATED TABLETS

Form. code	Weight variation	Hardness (Kg/cm^2)	Friability (%)	Thickness	Lag time (hr)
Fp1	550	6.06	0.18	5.1	4
Fp2	575.5	6.06	0.17	5.2	4
Fp3	600.2	6.09	0.83	5.4	5
Fp4	575.5	6.07	0.17	5.2	6
Fp5	599	6.03	0.16	5.2	6
Fp6	624.5	6.06	0.32	5.5	7
Fp7	600	6.05	0.66	5.4	7
Fp8	624.2	6.06	0.031	5.6	7
Fp9	649.25	6.04	0.30	6.1	8

b. Position of Core Tablet:

Compression coated tablet is cut vertically and cross sectional photographs were taken to evaluate the position of core tablet in the compression coated tablet. Core tablet was found in the center of coating (**Fig. 3**).

TABLE10: *IN-VITRO* RELEASE STUDIES OF CORE TABLET

Time(min)	%CDR			
	Fc1	Fc2	Fc3	Fc4
5	22.08	35.48	38.37	10.14
10	37.41	55.58	59.94	36.98
15	67.66	82.31	85.97	58.90
30	91.20	96.88	98.03	92.53

45	94.60	98.86	98.93	96.66
60	96.92	99.76	100.19	98.27

Cross sectional view of compression coated tablet:

FIG.3: CROSS SECTIONAL VIEW OF COMPRESSION COATED TABLET

c. In-*vitro* Dissolution Study of Compression Coated Tablets: Formulation Fp1 to Fp3 are not able to carry core tablet to the colon region as it has not that much coating integrity. This is indicated by release of drug within 6 h. Formulation Fp6 to Fp9 has higher amount of coating material that not release the core tablet even after 7 h. This is indicated by 0.18 -1.41 % releases at the end of 6 h. Formulation Fp4 has optimum time for release of core tablet. This is indicated by giving the pulse at after 6 h and release 99% out of 99.6. %. At that time the probability of presence of tablet is in the colon. If patient takes formulation Fp4 at bed time, after 6 h drug release occurs and effect of Aceclofenac will obtained at early morning.

TABLE 11: *IN-VITRO* DRUG RELEASE DATA FORMULATION FP1-FP9

Time (hr)	%CDR								
	Fp1	Fp2	Fp3	Fp4	Fp5	Fp6	Fp7	Fp8	Fp9
	pH 1.2 acetate buffer								
1	0.2	0.15	0.07	0.01	0.01	0.001	0.02	0.01	0.007
2	0.45	0.37	0.13	0.05	0.04	0.016	0.09	0.03	0.02
	pH 6.8 phosphate buffer								
3	1.09	0.60	0.41	0.40	0.08	0.17	0.14	0.07	0.04
4	2.2	1.31	0.90	1.33	0.31	0.25	0.25	0.16	0.092
5	98.28	70.57	1.24	1.95	0.7	0.44	0.89	0.23	0.13
6	98.28	97.94	97.64	2.11	1.08	0.615	1.2	1.41	0.18
7	98.28	97.94	99.56	99.10	64.4	20.62	2.44	52.9	2.61
8	98.28	97.95	99.56	99.60	99.1	98.30	98.3	97.1	27.85

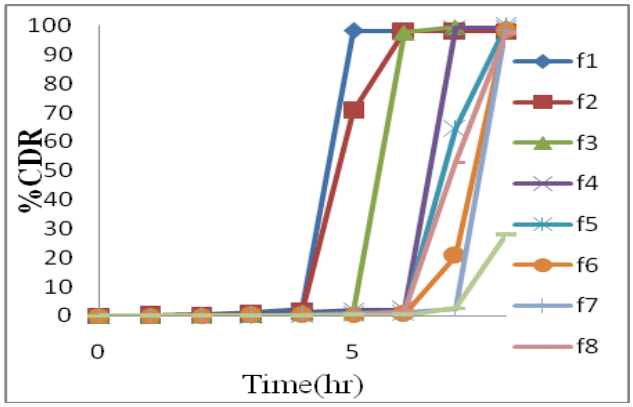

FIG.4: *IN-VITRO* DISSOLUTION PROFILES OF Fp1-Fp9

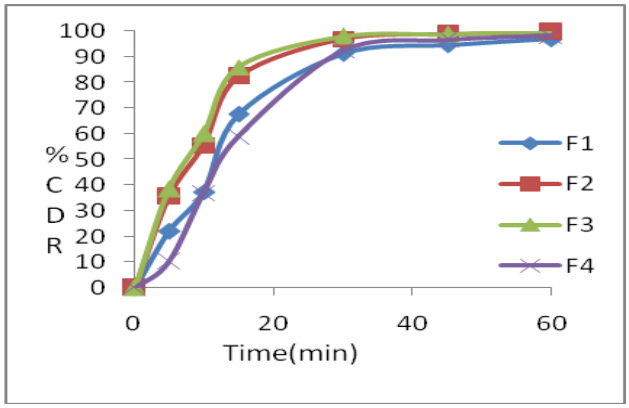

FIG.5: *IN-VITRO* DISSOLUTION PROFILES OF Fc1-Fc4

d. Factorial Design:

The amounts of the polymers (EC, and HPMC K100M,) were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. The % drug release after 6 h and lag time for the nine batches (Fp1 to Fp9) showed a wide variation. The data clearly showed that % drug release before 6 h and lag time are strongly dependent on the selected independent variables.

The fitted equations relating the responses % drug release before 6 h and lag time to the transformed factor are shown in **Fig.7, 8.** The polynomial equations can be used to draw conclusions after considering the magnitude of co-efficient and the mathematical sign it carries (i.e., positive or negative). The high values of correlation coefficient for % drug release before 6 h and lag time indicate a good fit. The equations may be used to get estimates of the response as a small error of variance was noticed in the replicates. The significance test for regression coefficients was performed by applying the Percentage prediction error test. A co-efficient is significant if the calculated value is within limits.

Degrees of Freedom for Evaluation:

Model	4
Residuals	4
Lack Of Fit	3
Pure Error	4
Corr Total	9

A recommendation is a minimum of 3 lack of fit df and 4 df for pure error. This ensures a valid lack of fit test. Fewer df will lead to a test that may not detect lack of fit.

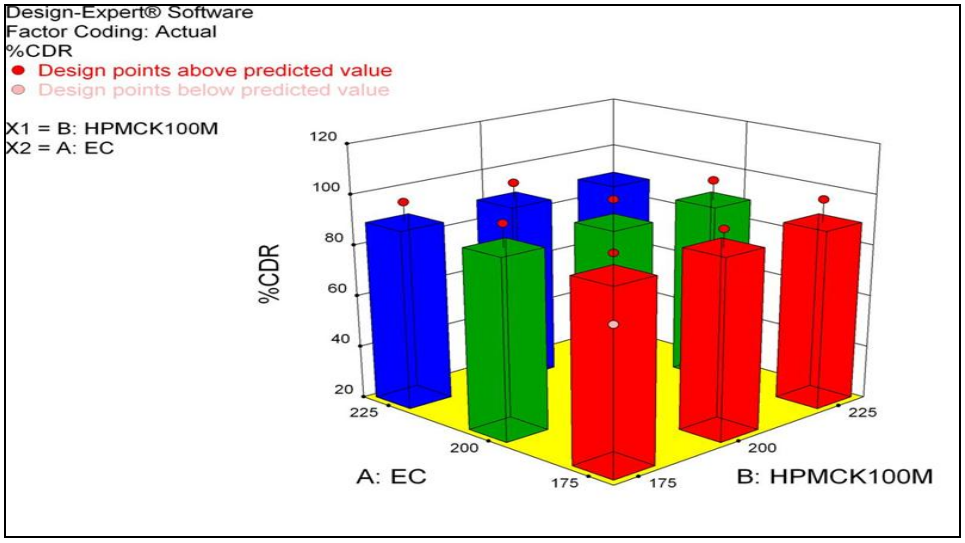

FIG.6:%CDR OF FORMULATIONS

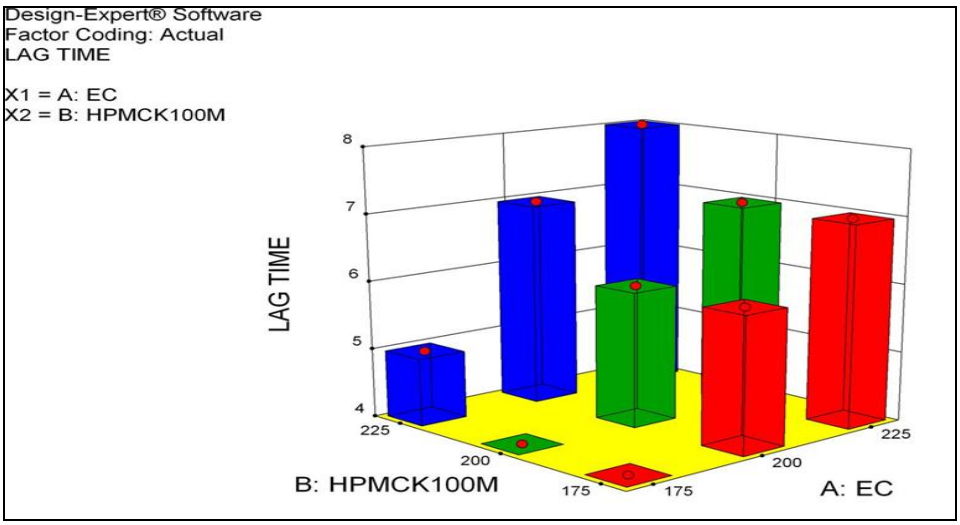

FIG.7: LAG TIME OF FORMULATIONS

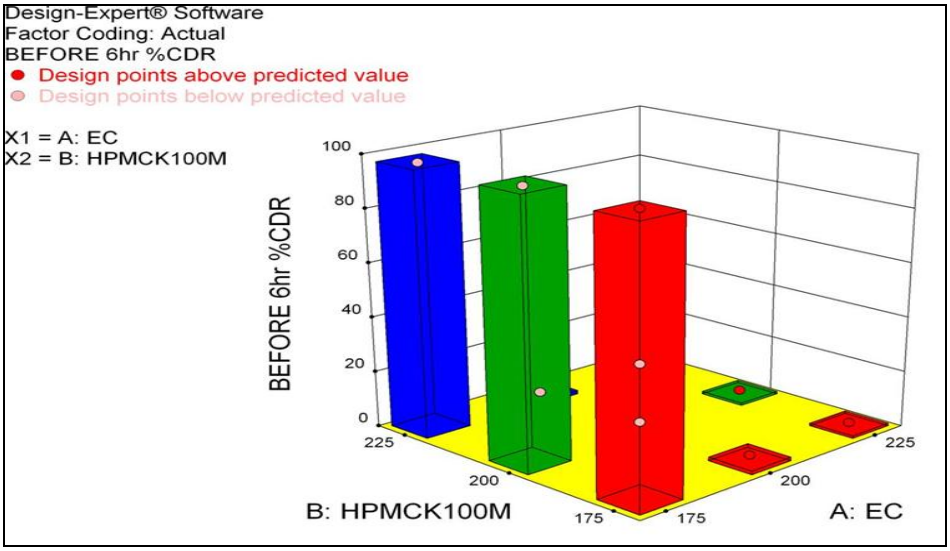

FIG.8: BEFORE 6 hr % CDR OF FORMULATIONS

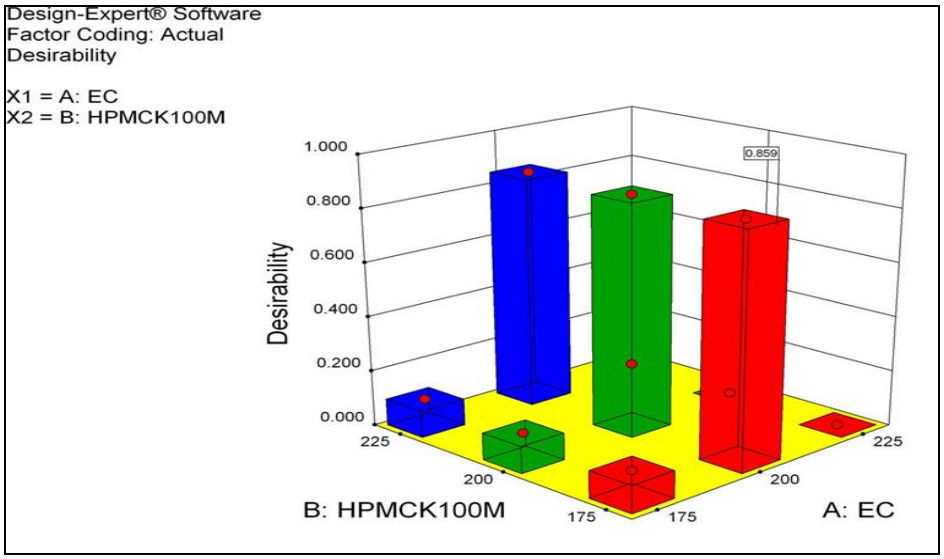

FIG.9: DESIRABILITY OF FORMULATIONS

Constraints:

TABLE 12: CONSTRAINTS

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
%Cdr	maximize	27	99	1	1	3
Lag Time	Target=6	4	7	1	2	2
Before 6hr %Cdr	minimum	0.18	98	1	3	1

Solutions:

TABLE 13: SOLUTIONS

Number	EC	HPMCK100M	%Cdr	Lag Time	Before 6hr %Cdr	Desirability	Selected
1	200	175	97.38	6	2	0.859	

TABLE14: PERCENTAGE PREDICTION ERROR OF THE OPTIMIZED FORMULATION

Response	Predicted Value	Experimental Value	Percentage Prediction Error
% cdr in 6 hr before	2	2.1	4.7
%cdr in 12 hr	97.38	99	1.6

Percentage prediction error can be calculated by using below formula.

$$\text{Percentage prediction error} = \frac{(\text{Experimental Value} - \text{Predicted Value})}{\text{Experimental Value}} \times 100$$

CONCLUSION: The present investigation was aimed to develop time depended press coated tablet of Aceclofenac for lowering of Rheumatoid arthritis and morning stiffness. Rheumatoid arthritis and morning stiffness diseases occurs in according to the circadian rhythms, disease symptoms serve best, which releases drug abruptly after a predetermined lag time. A press coated tablet, taken at bedtime with delayed, start of drug release in the early mornings, i.e. at the time of symptoms. The results from this study clearly conclude that combination of HPMC K100M and EC in the form of compression coat is suitable for time depended drug delivery. Formulation Fp4 is the best formulation which produce pulsatile release pattern with initial 6hr lag time and then burst release.

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