WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 10, 1112-1132. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF PRESS COATED TABLET OF ACELOFENAC SOLID DISPERSION PREPARED USING MICROWAVE INDUCED FUSION METHOD

***Kazi M. S., Chishti N., Shaikh N.,**

Assistant Professor Y.B. Chavan College of Pharmacy Aurangabad Maharashtra India.

Article Received on
1 Aug 2015,

Revised on 21 Aug 2015,
Accepted on 10 Sep 2015

***Correspondence for Author**
Prof. Kazi M. S.
Assistant Professor Y.B. Chavan College of Pharmacy Aurangabad Maharashtra India.

ABSTRACT

The aim of present investigation was to develop press coated tablet of Aceclofenac solid dispersion (SD) for obtaining pulsatile drug release. The drug delivery system was designed to deliver the drug at such a time when it could be most needful to patient of rheumatoid arthritis. Solid Dispersion of Aceclofenac using PVP K-30 as a carrier was prepared by kneading method, solvent evaporation method and microwave fusion technique. Solid dispersions prepared using microwave fusion technique was further selected to prepare press coated tablets, containing Aceclofenac SD in the inner core and different amounts of HPMC K4M as the outer coating material. The release profile of press coated tablet exhibited a lag time depending upon the amount of HPMC K4M in compression coating, followed by burst release. Optimization was done using 3^2 factorial design considering two independent factors at three levels. Data was evaluated statistically by Stat Ease Design Expert 7.1.4 software. The optimized batch F6 gave a lag time of 6 hr and drug release of 98.58% which consisted of 4% crosspovidone and 36% HPMC K4M. The Chronodelivery of Aceclofenac SD was achieved by formulating the tablet by compression coating technique.

KEYWORDS: Press Coated Tablet, Chronotherapy, Solid Dispersion, Microwave Fusion Method, Aceclofenac.

INTRODUCTION

Poorly water soluble drugs are generally associated with slow drug absorption leading eventually to inadequate and variable bioavailability.[1] BCS class II drug possess low

solubility but high penetration and the bioavailability of them can be greatly improved by accelerating the dissolution process of pharmaceutical ingredient in gastrointestinal tract.

Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers.[2] SD can be prepared by using various methods like kneading method, solvent evaporation, and microwave fusion method. In the present investigation microwave induced fusion method was preferred as it offers several advantages such as rapid volumetric heating, no overheating at surface, low operating cost, energy saving, conversion from crystalline to amorphous form and in addition the main advantage of not using organic solvents is the absence of any risk originating from residual solvent.[3]

Aceclofenac (AC), a phenylacetic acid derivative, [(2 {2, 6 dichlorophenyl) amino} phenyl acetooxyacetic acid] is a NSAID. Aceclofenac is practically insoluble in water with good permeability and belongs to BCS class II. Therefore, AC shows dissolution rate limited absorption (57%), which gives rise to difficulties in pharmaceutical formulations for oral delivery, which may lead to variable bioavailability.[4] It is used in the treatment of rheumatoid arthritis, which is characterized by diurnal variation in circulating levels of proinflammatory cytokines, interleukin-6 and tumor necrosis factor-α due to diurnal variation, many symptoms and signs of active rheumatoid arthritis are manifested in the morning.

To coincide with the release of these inflammatory cytokines and peak plasma Aceclofenac levels, in the present investigation an attempt was made to develop a press-coated tablet (PCT) using Aceclofenac SD as the active pharmaceutical ingredient. The press coating technique is a simple and unique technology used to provide tablets with a programmable lag phase, followed by a fast, or rate-controlled, drug release after administration. The technique offers many advantages, and no special coating solvent or coating equipment is required for manufacturing this type of tablet.[5]

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as a gift sample from Flamingo Pharma Pvt Ltd. (Mumbai, India.) PVP K-30, HPMC K4M and Microcrystalline cellulose were obtained as gift samples from

Wockhardt Ltd. (Aurangabad, India.) Crosspovidone was obtained from Atra Pharmaceuticals (Aurangabad, India.) as a gift sample.

METHODS

Drug solubility study

The drug solubility study was carried in water and buffer solutions with pH 7.4 at room temperature. An excess amount of ACE was added to the vials containing the 10ml of solvent and content was stirred for 24 Hrs. the mixture was then filtered through whatman filter paper no.41. The solubility of ACE in the samples was determined spectrophotometrically (Shimadzu Japan UV 1800) at 275 nm.

Drug- Excipients Compatibility Study

To study the drug- excipient's compatibility, DSC (Shimadzu DSC TA60 WS) thermograph of Aceclofenac with the excipients, PVP K-30, Physical mixture, optimized solid dispersion, HPMC4M, Crosspovidone and MCC was recorded on differential scanning calorimeter to check for compatibility, the thermograms of pure ACE and ACE with excipients were matched for appearance or disappearance of any peak and enthalpy height.

Preparation of Solid Dispersion of Aceclofenac[4]

The Solid Dispersions were prepared by Kneading, Solvent Evaporation and Microwave Fusion techniques. Ratio optimization was done and ratio (1:1) giving high solubility was selected.

1. Kneading method (KM)

ACE with PVP K-30 in required was taken. First PVP K-30 is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25^0C for 24 hours, pulverized and passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

2. Solvent Evaporation method (SE)

The required molar quantities of ACE and PVP K-30 were weighed accurately and dissolved in minimum amount of ethanol and water respectively. The solution of ACE was added drop wise into the PVP K-30 solution. The contents were continuously stirred on hot plate till complete evaporation of solvent. Finally, the mass was dried at 45^0C for approximately 6

hours. The dried mass was pulverized and passed through sieve No. 80 and stored in desiccators over fused calcium chloride.

3. Microwave Fusion method (MW)

In this method the Microwave activated solid dispersion of drug to polymer were obtained by microwave irradiation. A fixed amount of physical mixture (i.e. 1g) was taken into a glass beaker and subjected to microwaves for 5 min at the chosen power of 600 W in a domestic microwave oven. Solid dispersions were then grounded in glass mortar and then passed through 100 mesh sieve to obtain uniform particle size.[2, 6]

Evaluation of solid dispersion

The solid dispersion prepared by various techniques was evaluated for FTIR spectroscopy, DSC thermogram, solubility study and XRPD analysis. Based on the above parameters a specific solid dispersion technique was selected for further formulation of press coated tablet.

Characterization of Blend of API and Excipients[7]

The drug (Aceclofenac SD), Directly Compressible Diluent (MCC), Polymer (HPMC) and superdisintegrant (Crosspovidone) were thoroughly blended for 20 min. Later on magnesium stearate was added and again blended for 2 min. The blend was evaluated for Angle of repose, Bulk density, Tapped density, Carr's index, Hausner's ratio and similar evaluation was done for the blend of outer coating material.

Formulation of IRCTs

IRCTs were prepared by direct compression method as per the formula given in Table 1. The ingredients (Aceclofenac SD, MCC and Crosspovidone) were accurately weighed and mixed in geometric proportion. The mixture was blended for 20 min in a sealable polythene bag. Then magnesium stearate was weighed and added to the mixture and again blended for 2 min. The resulting uniform blend was compressed to form the tablets using 8 mm, circular, flat faced punch on 8 station Karnavati compression machine. The total weight of tablets was kept constant at 250 mg. The tablet press setting was kept constant across all formulations.

Evaluation of IRCTs

Physical characterization

The prepared IRCTs were evaluated for the physical characteristics such as thickness, diameter, hardness and weight variation test according to the Indian Pharmacopoeia (IP) 2007.

Drug content

Twenty tablets were taken and powdered. Tablet powder equivalent to 25 mg of aceclofenac was weighed, sufficient volume of phosphate buffer was added and volume was made upto 100 ml with phosphate buffer pH 7.4. Then the solution was sonicated for 30 min. and filtered. The filtrate (4 ml) was further diluted with phosphate buffer pH 7.4 upto 100 ml to get required concentration. The absorbance of resulting solution was measured UV spectrophotometer at 275 nm.

***In-vitro* disintegration time[9]**

In-vitro disintegration time of six tablets from was determined by using disintegration test apparatus. To test for disintegration time 1 tablet was dropped in each glass tube, and the basket rack assembly was set in a 1L beaker of water at 37±2°C.

***In-vitro* dissolution studies[9]**

The *in-vitro* dissolution studies were carried out in pH 7.4 (900 ml) at 37 ± 0.5^{o}C using USP dissolution apparatus type II. The speed of rotation was maintained at 50 rpm. 5 ml samples were withdrawn at predetermined time interval and content of Aceclofenac was determined by using UV spectrophotometer at 275 nm.

Formulation of PCTs

PCTs were prepared by compression coating of prepared 8 mm diameter IRCTs into 13 mm diameter tablets by using different HPMC K4M concentrations as given in Table 1. The polymer concentrations were 32%, 28% and 36% for Factorial batches F1-F3, F4-F6 and F7-F9 respectively.

Compression or press coating of the tablets was done by placing half amount of the compression coat blend into the die cavity, then manually placing the IRCT on the powder bed centrally. Further remaining half quantity of the compression coating material was added in the die cavity from above. Then finally the tablet was compressed by the tablet compression machine.[7]

Evaluation of PCTs[9, 10]

The weight variation test is carried out as per USP XXXII. The hardness or crushing strength of a tablet was measured with the Monsanto hardness tester. The friability was calculated by the following formula:

$$\% F = \left(\frac{W_0 - W}{W}\right) \times 100$$

W_0 is the weight of tablets before test. W is weight of tablets after test.

***In-vitro* dissolution study**

In-vitro dissolution study of press coated tablets was performed by using 0.1 N HCl pH 1.2 (acid stage) as dissolution medium for first two hours and then remaining time in phosphate buffer pH 7.4 (buffer stage) in a USP Type II Paddle Apparatus containing 900 ml of dissolution medium maintained at 37±2°C with a speed of 50 rpm.

Lag time

Lag time is the time before the drug release has started or the time in which less than 10% of the drug has released. The lag time (t_{10}) and release time (t_{80-10}) were defined as the times in hr of 10% and 80–10% drug release respectively. The lag time (hr) for different formulations was obtained from the *In vitro* dissolution study of PCTs.

Water uptake study (% Swelling)[11]

In this study tablet of each batch was separately placed in the basket of dissolution apparatus by using water as immersion medium at 37±2°C. Tablets were withdrawn after a time period of 3 hr and blotted with tissue paper to remove the excess water. The weight of tablet after swelling was measured on an analytical balance. The initial and final weights of the tablet were used to calculate % swelling or water uptake of the tablet as follows:

$$\% \, Water \; uptake = \left(\frac{W_t - W_0}{W_0}\right) \times 100$$

Where, W_t and W_0 are the final weight after swelling and initial dry weight of the tablet respectively.

Longitudinal section view of press coated tablet[12]

To demonstrate the central positioning of the core tablet within the press coated tablet, the core tablet blend was mixed uniformly with Erythrosine, a red dye or amaranth. This blend was then compressed to produce red coloured tablet cores which were then compression coated by the outer coating material.

Longitudinal sections of press coated tablets were made using surgical blade in order to verify the position of position of core tablet.

Kinetics of Drug Release

The dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software. In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of n i.e. release exponent was calculated.

Optimization by 3^2 Factorial Design[13]

A 3^2 full factorial design was used in the present study. In this design 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of superdisintegrant, Crosspovidone (X1) and amount of release retarding polymer HPMC K4M (X2) were selected as independent variables and each factor being studied at -1, 0, +1 level. The %DR (drug release) and lag time were considered as the dependant variables.

Analysis of Data by Design Expert Software

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The statistical treatment and interpretation of data was done by Stat Ease Design Expert 7.1.4 software. The Analysis Of Variance (ANOVA) was determined. The data were also subjected to 3-D response surface methodology to study the interaction of independent variables.

RESULTS AND DISCUSSION

Drug solubility study

Aceclofenac was found to be practically insoluble in water, freely soluble in acetone, soluble in alcohol. The solubility of Aceclofenac in pH 7.4 buffer was found to be 476.16ug/ml.

Drug- Excipients Compatibility Study

The possible interaction between Ketoprofen with excipients and polymers was studied. There was no considerable change in DSC endothermic values, comparing pure Aceclofenac and with the excipients (HPMC K4M, Crosspovidone, MCC) which indicated the absence of any interaction between drug and excipient used in the preparation. Peak value was obtained at 182.46 ℃ which were very much nearer to pure drug. DSC thermogram is shown in Fig.1.

Evaluation of solid dispersion

The solubility data of solid dispersion of ACE-PVP K-30 prepared by Kneading, Solvent Evaporation and Microwave induced fusion methods is shown in Table 2. The solubility study suggested that solubility of Aceclofenac increased significantly after ACE-PVP K-30 Solid dispersion using Microwave Induced Fusion method compared to ACE-PVP K-30 Solid dispersion prepared by other methods. So ACE-PVP K-30 Solid dispersion (1:1) by Microwave induce fusion method were selected for the preparation of press coated tablets. The FT-IR spectra (Table 3 and Fig. 2) of pure drug, pure PVP K-30 and drug: PVP K-30 SD was taken. FT-IR spectra of complexes were found to be result of combination of peaks of the individual ingredient of the system and there is no new peak found indicative of any other functional group only broadening of peaks observed as a result of physical complexation. DSC curves obtained for pure drug, and solid dispersion were displayed in Fig.3. Pure ACE powder had an endothermic peak at 158.47^{0}C with onset at 150.67^{0}C and endset at 163.9^{0}C indicates aceclofenac is crystalline in nature.

In the DSC thermogram of ACE and PVP K-30 Physical mixture a broad endothermic peak at 156.30^{0}C which is in range according to literature, hence there is no chemical interaction of drug with PVP K-30.

In the DSC thermogram of KM formulation, showed endothermic peak at 156.37^{0}C as compared with the corresponding DSC thermogram of ACE indicate the drug is present in crystalline form. In the DSC thermogram of SE & MW, it is observed that there is no peak corresponding to melting point of drug, suggesting a reduction in crystallinity, this indicated that ACE was no longer present as crystalline material, but was converted into amorphous state.

PXRD analysis of the drug was performed to confirm its crystalline structure. The diffraction pattern of Aceclofenac showed maximum intensity peak at [2θ] value equal to 26.214, other sharp peaks at [2θ] values 22.636, 18.899, 19.78, were noticeable (Fig.4) Aceclofenac is crystalline in nature as indicated by numerous sharp peaks. The diffraction pattern of SD (Kneading method) was also slightly crystalline in nature as indicated by broad peaks. Sharp peaks at [2θ] value equal to 25.996, 22.313, 18.544, 24.524 were observed. The diffraction pattern of SD (Solvent evaporation) was very less crystalline in nature as indicated by some broad peaks. Sharp peaks at [2θ] value equal to 21.56, 14.1, and 19.23 were observed. The diffraction pattern of complexes of SD (Microwave method) reduction in sharp peaks only

one peak appear at [2θ] value equal to 21.51, this indicate that almost all part of drug is converted into amorphous form due to microwave induced solid dispersion.

Characterization of Blend of API and Excipients

The blend of API and excipients was evaluated for parameters like Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio. The results obtained were as shown in Table 4.

Evaluation of IRCTs

The IRCTs were evaluated for weight variation test, hardness, thickness, % friability and drug content. The results obtained were as shown in Table 5. The weight of all the tablets was found to be within the range, hardness was constant and % friability and *In-vitro* disintegration time of the tablets was also within the acceptable limits.

Evaluation of PCTs

The press coated tablets were evaluated for weight variation test, hardness, thickness, % friability and drug content (Table 6). All the parameters evaluated were within the acceptable limits.

Lag time

The lag time of the PCTs was measured by determining the time for which there is no release or less than 10% release of the drug from the dosage form. It was done by *in-vitro* dissolution testing of the dosage form.

From the dissolution profile of PCTs (Table 7 and Figure 5), it was evident that the PCTs exhibited a specific lag time which depended on the polymer concentration in that batch. The lag time increases as the polymer concentration was increased, it was 4 hr for 28%, 6 hr for 32% and 8hr for 36% HPMC K4M concentration respectively. The lag time showed a direct relationship with the amount of HPMC K4M in the outer coating.

Water uptake study (% Swelling)

A direct correlation between swelling index and lag time was observed from the obtained results. The lag time was found to increase with increasing swelling index. Higher Swelling Indices were observed in formulation batches containing higher amount of HPMC K4M. This may be due to uptake of water and swelling of the polymer which is hydrophilic and forms a gel upon hydration. The result obtained is as shown in Table 8.

Drug release studies of IRCTs and PCTs

The *in-vitro* dissolution of IRCTs showed more than 80% drug release within 10 min. The maximum drug release was obtained from batches having highest amount of Crosspovidone. The amount of drug released exhibited a direct relationship with the amount of Crosspovidone present in the core tablet. The graphical representation of the dissolution profile of IRCTs is shown in Fig. 6 and Table 9. It was evident that core tablets of all the batches showed an immediate release before it was compression coated with an outer layer consisting of HPMC K4M and MCC. The mechanism of action of Crosspovidone involves rapid and extensive swelling which causes burst release of the drug.

The PCTs of different batches showed a variable lag time depending on the concentration of HPMC K4M in the outer coating layer. The PCTs showed a lag time before the drug release because the IRCTs were completely surrounded by the polymer layer which prevented the release of drug from the IRCTs. Burst release after a specific lag time occurred due swelling and erosion of the outer hydrophilic polymer layer. When the polymer layer swelled adequately, it allowed sufficient dissolution medium to enter into it and reach the core tablet. The superdisintegrant in the core swelled extensively which exerts a pressure on the outer layer resulting in burst release of the drug. The result obtained was as shown in Table 7.

Longitudinal section view of press coated tablet

Longitudinal sections of press coated tablets were made using surgical blade in order to verify the position of position of core tablet. From Fig.7, it was evident that the core tablet was placed centrally within the press coated tablet and was equally surrounded by the outer coating material.

Kinetics of Drug Release

In present study the dissolution results were analyzed by PCP Disso Version 2.08 software to study the kinetics of drug release mechanism. The results showed that all of the factorial design formulations followed zero order dissolution kinetics. The R^2 value of all dissolution models was shown in Table 10. The value of n i.e. release exponent was found in the range of 0.66 to 0.98 ($0.5 < n < 1$) which shows release of drug from system by non-fickian diffusion or anomalous transport.

Optimization and Analysis of Data by Design Expert Software

The 3^2 full factorial design was selected to study the effect of independent variables, amount of HPMC K4M (A) and amount of Crosspovidone (B) on dependent variables lag time and %DR. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses.

The regression coefficient values are the estimates of the model fitting. The R^2 was high indicating the adequate fitting of linear model. The polynomial equations can also be used to draw conclusions considering the magnitude of co-efficient and the mathematical sign it carries; i.e. positive or negative. The first variable i.e. HPMC K4M showed positive coefficient in case of response R1 (Fig.8) i.e. lag time. This indicated that with an increase in amount of polymer i.e. HPMC K4M in the formulation, the lag time increases. The second variable i.e. Crosspovidone showed positive coefficient in case of response R2 (Fig.9) i.e. % DR (Drug Release). This indicated that with an increase in amount of super disintegrant i.e. Crosspovidone in the formulation, the % DR increases.

Evaluation and interpretation of research findings are important and the p-value serves a valuable purpose in these findings. ANOVA for the dependent variables, lag time and % DR, is as shown in Table 11. The coefficients of A_1 and A_2 were found to be significant at $p<0.05$, hence confirmed the significant effect of both the variables on the selected responses. ANOVA and Multiple regression analysis were done using Stat-Ease Design Expert 7.1.4 software.

The Model F-value of 63660000.00 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob> F" less than 0.0500 indicate model terms are significant. In this case A, B is significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Table 1: Formulation composition for factorial batches.

Tablet Ingredient (mg)	Factorial batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet									
ACE SD	200	200	200	200	200	200	200	200	200
Crosspovidone	5	10	15	5	10	15	5	10	15
MCC	43	38	33	43	38	33	43	38	33
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	250	250	250	250	250	250	250	250	250
Coat									
HPMC K4M	70	70	70	80	80	80	90	90	90
MCC	158	158	158	148	148	148	138	138	138
Starch Maize	20	20	20	20	20	20	20	20	20
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200
Total weight of PCT									
	450	450	450	450	450	450	450	450	450

Table 2- Solubility of ACE-PVP K-30 Solid dispersion by different methods complexes.

Complexes	Solubility (µg/ml)
KM	737.8
SE	1021.17
MW	1260.16

Table 3-Interpretaion of IR spectra.

Drug/Carriers	Functional group	Frequency(cm^{-1})
Aceclofenac	O-H stretching	3481
	C-H stretching	2970
	C=O	1636
	-N-H-	3419
	C-Cl	670
KM	O-H	3193
	C-H stretching	2946
	C=O stretching	1643
	-N-H-	3475
	C-Cl	698
SE	O-H	3482
	C-H	2927
	C=O stretching	1731
	-N-H-	3343
	C-Cl	663
MW	O-H	3286
	C-H	3054
	C=O stretching	617
	N-H	3409
	C-Cl	1716

Table 4- Evaluation of precompression parameters.

Batch code	Evaluation of parameters					
	Angle of repose (°)	Bulkdensity (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (%)	Hausner's ratio	Flow
F1	26.92±0.01	0.275±0.03	0.321±0.13	15.5±0.06	1.12±0.05	Good
F2	26.43±0.2	0.265±0.09	0.336±0.27	13.6±0.08	1.15±0.09	Good
F2	26.35±0.56	0.351±0.04	0.251±0.35	15.4±0.03	1.18±0.03	Good
F4	28.45±0.43	0.274±0.08	0.244±0.19	12.53±0.07	1.13±0.08	Good
F5	27.25±0.74	0.257±0.09	0.312±0.63	14.83±0.05	1.17±0.07	Good
F6	27.68±1.03	0.325±0.123	0.274±0.58	13.15±0.09	1.15±0.09	Good
F7	26.65±0.79	0.218±0.90	0.297±0.21	15.41±0.11	1.18±0.06	Good
F8	26.11±0.62	0.2647±0.87	0.312±0.41	15.18±0.16	1.18±0.03	Good
F9	28.54±0.74	0.2756±0.05	0.321±0.34	14.14±0.08	1.16±0.09	Good

Values are mean ± S.D. (n=3).

Table 5- Evaluation of IRCTs.

Batch code	Evaluation parameters					
	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Drug content (%)	*In-vitro* DT (Sec.)	Friability (%)
F1	250.75±1.2	3	2.57±0.06	99.72±0.015	163±3.5	0.398±0.1
F2	250.11±0.82	3	2.54±0.07	99.81±0.023	141±4.50	0.381±0.17
F3	250.77±0.94	3.2	2.58±0.08	100.79±0.019	114±4.04	0.409±0.12
F4	250.8 ± 0.78	3.5	2.54±0.09	100.91±0.013	171±4.04	0.369±0.19
F5	249.55±0.9	2.9	2.58±0.09	99.97±0.021	139±3.51	0.388±0.28
F6	250.87±1.2	3.2	2.56±0.09	100.63±0.035	109±3.51	0.351±0.15
F7	250.45±1.2	3.5	2.56±0.10	99.93±0.067	165±3.60	0.452±0.32
F8	248.66±1.2	3.4	2.54±0.10	100.68±0.05	143±5.29	0.301±0.26
F9	250.08±1.0	3.4	2.53±0.12	100.94±0.04	116±4.3	0.352±0.3

Table-6-Evaluation of PCTs.

Batch code	Evaluation parameters				
	Weight variation (mg±S.D)	Hardness (kg/cm^2)	Thickness (mm±S.D)	Drug content (%)	Friability (%)
F1	500.61±1.18	5.5	4.13±0.31	99.45±0.18	0.468±0.23
F2	500.32±1.26	5.4	4.14±0.48	99.76±0.21	0.448±0.15
F3	501.76±0.94	5	4.16±0.052	99.34±0.10	0.472±0.36
F4	500.76±0.78	5.4	4.15±0.114	100.91±0.19	0.455±0.18
F5	499.65±1.14	5.2	4.12±0.047	99.67±0.23	0.446±0.22
F6	500.15±1.24	5.6	4.17±0.068	100.03±0.19	0.452±0.27
F7	500.43±1.27	5.2	4.18±0.070	99.56±0.24	0.351±0.37
F8	500.34±1.29	5.5	4.10±0.085	100.45±0.11	0.237±0.28
F9	499.18±1.08	5.8	4.12±0.091	100.95±0.35	0.404±0.41

Table 7- Drug release PCTs.

Time (hr)	% DR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0.09± 0.002	0.43± 0.002	0.74± 0.003	0.09± 0.0	0.09± 0.002	0.09± .001	0.001± 0.001	0.09± 0.002	0.09± 0.002
2	0.42± 0.003	0.74± 0.002	0.75± 0.005	0.09± 0.002	0.10± 0.003	0.42± 0.003	0.09± 0.003	0.10± 0.002	0.09± .003
3	4.45± 0.02	5.20±0. 05	6.42±0. 97	1.45±0. 15	1.90±0. 49	2.35±0. 38	1.15±0. 23	1.00±0. 13	1.90±0 .17
4	7.61± 1.2	8.95±0. 93	9.73±1. 26	4.15±0. 82	3.70±0. 69	4.60± 0.76	3.70±0. 19	3.10±0. 28	3.85±0 .29
5	77.22 ±2.9	81.42± 3.61	83.17± 1.93	5.36±1. 37	5.51±0. 52	6.41±0. 93	4.45±0. 24	4.31±0. 57	5.95±0 .46
6	84.65 ±3.1	89.10± 2.83	95.18± 2.37	7.36±1. 96	7.61±0. 76	8.80±0. 99	6.11±0. 62	7.04±0. 76	7.61±0 .83
7	85.01 ±1.9	89.25± 3.72	96.62± 3.08	66.49± 1.39	68.36± 1.25	72.72± 1.16	7.16±0. 47	7.04±0. 88	9.10±0 .78
8				84.12± 1.28	93.59± 1.68	97.60± 1.28	12.58± 0.59	8.82±0. 94	11.20± 0.86
9				86.54± 2.06	94.79± 2.73	98.27± 1.46	57.80± 1.35	61.13± 1.62	68.95± 1.38
10				84.82± 2.13	95.49 ±3.07	98.58± 1.68	81.64± 1.56	92.60± 1.58	97.86± 1.46
11							83.98± 1.99	94.50± 1.67	98.27± 1.99
12							85.05± 2.03	95.35± 1.92	98.37 ±2.08

Table 8- Swelling Indices of PCTs.

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Swelling Index (%)	43.45	41.32	42.28	57.14	56.44	55.85	68.14	69.34	70.04

Table 9- Drug release from IRCTs.

Time (min)	% DR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	29.89 ±1.17	34.17 ±1.09	31.96 ±1.37	47.06 ±1.49	45.03 ±1.56	44.58 ±1.91	53.85 ±1.08	51.23 ±1.36	50.87 ±1.22
5	54.06 ±1.48	56.87 ±1.62	59.26 ±1.57	63.94 ±1.58	69.13 ±1.76	66.72 ±2.06	72.46 ±2.38	74.17 ±2.34	78.56 ±2.35
10	83.64 ±1.59	90.43 ±2.13	91.47 ±1.72	85.72 ±1.93	86.91 ±1.94	87.23 ±2.16	86.19 ±2.71	92.34 ±2.98	95.78 ±3.01
15	89.97 ±1.83	93.63 ±2.09	97.25 ±2.39	90.56 ±2.08	96.74 ±2.13	98.69 ±2.35	90.83 ±2.86	97.19 ±2.86	98.53 ±3.26

Table 10- Kinetics of drug release.

Formulation code	R^2					n	K
	Zero order	1st order	Matrix	Peppas	Hixon Crowell		
F1	0.8148	0.8011	0.6646	0.7745	0.8113	0.7833	4.9392
F2	0.8287	0.7798	0.6567	0.7832	0.7877	0.6840	4.9653
F3	0.8346	0.7920	0.6455	0.7891	0.7993	0.7234	5.6258
F4	0.8149	0.7942	0.6765	0.7796	0.8067	0.8484	7.8653
F5	0.8261	0.7843	0.6809	0.7813	0.8019	0.8575	6.7756
F6	0.8344	0.7822	0.6809	0.7468	0.8010	0.6621	6.7866
F7	0.8319	0.7423	0.6160	0.6897	0.7543	0.7254	7.5335
F8	0.7568	0.7382	0.6164	0.6943	0.7532	0.9753	7.4568
F9	0.7617	0.7471	0.6255	0.7125	0.7604	0.9413	4.6644

Table 11a- Analysis of Variance for R1 (lag time).

Source	Sum of Squares	Degrees of Freedom (df)	Mean Square	F Value	p- value Prob> F	Model
Model	24.00	2	12.00	6.366E+007	< 0.0001	Significant
A	24.00	1	24.00	6.366E+007	< 0.0001	
B	0.000	1	0.000	6.366E+007	< 0.0001	
Residual	0.000	6	0.000	-	-	
Core Total	24.00	8	-	-	-	

Table 11b- Analysis of Variance for R2 (% DR).

Source	Sum of Squares	Degrees of Freedom (df)	Mean Square	F Value	p- value Prob> F	Model
Model	234.73	2	117.37	28.48	0.0009	Significant
A	10.38	1	10.38	2.52	0.1637	
B	224.36	1	224.36	54.44	0.0003	
Residual	24.73	6	4.12	-	-	
Core Total	269.46	8	-	-	-	

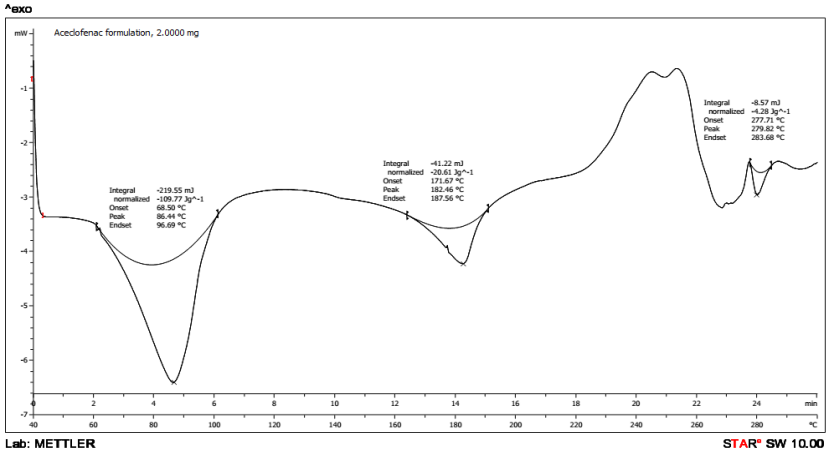
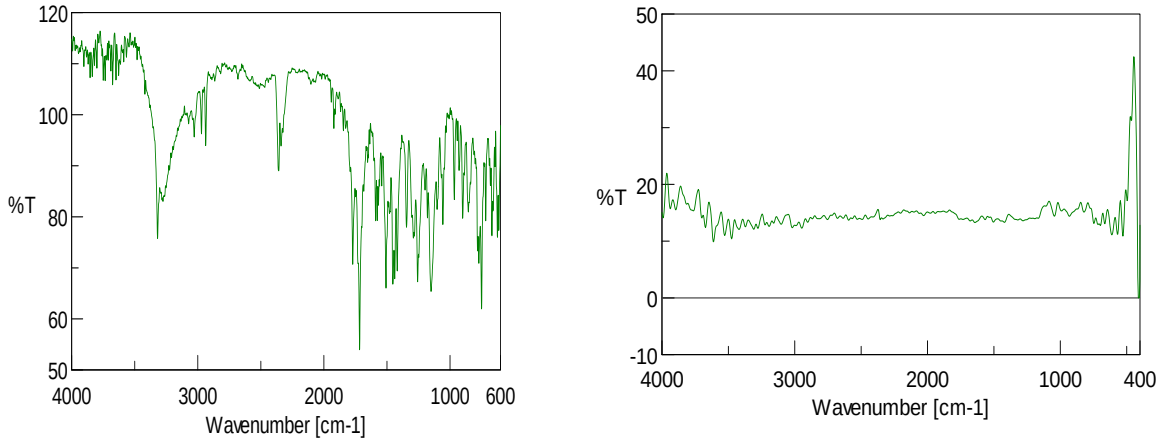
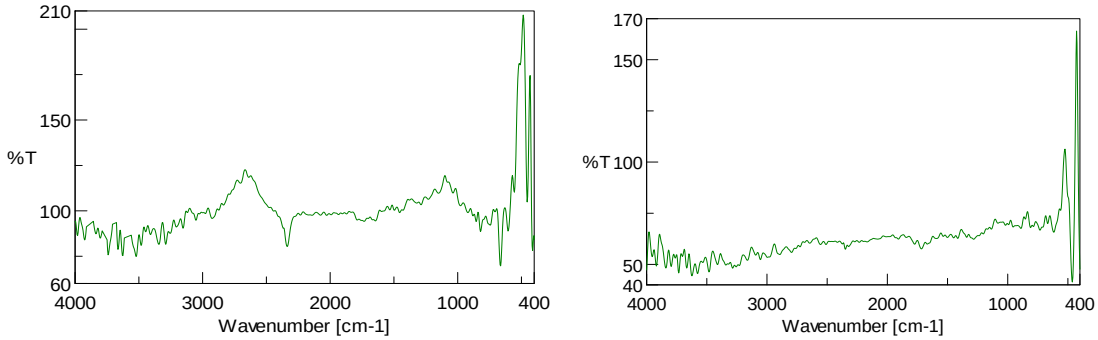


Fig.1- DSC thermogram of Aceclofenac with excipients.



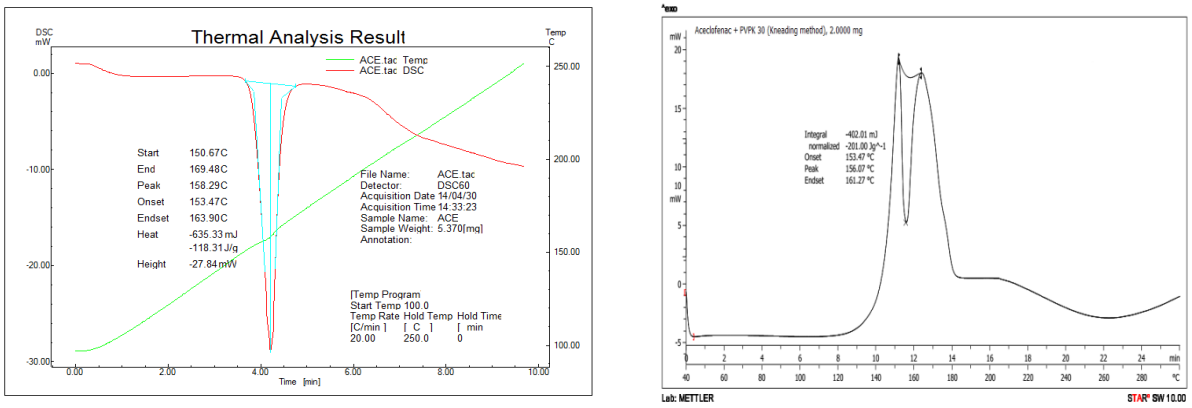
2a-Acelofenac. **2b-Solid dispersion by KM.**

Fig.2-FTIR Spectra of solid dispersions.

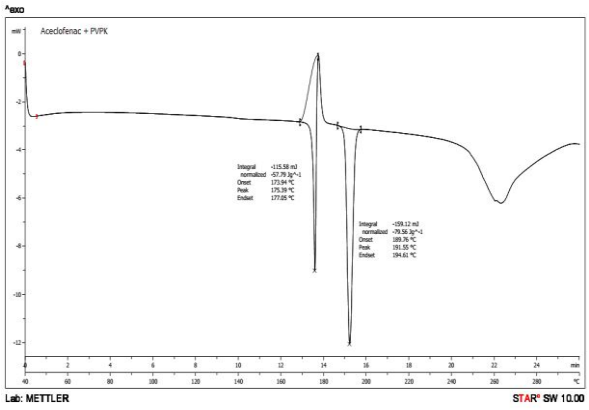


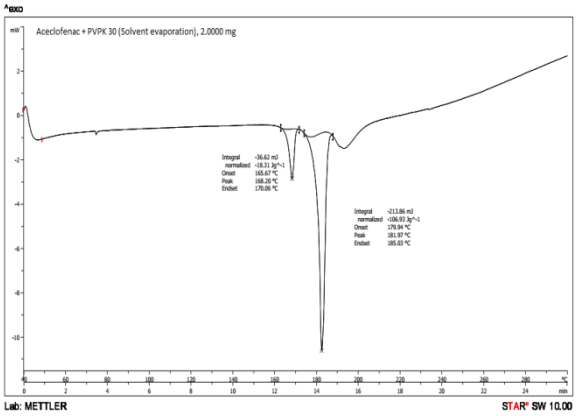
3c- Solid dispersion by SE. **4d-Solid dispersion by MW.**

Fig.3-DSC analysis for solid dispersions.



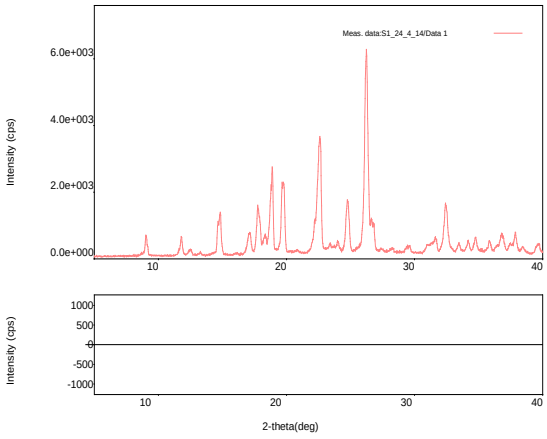
3a- Acelofenac. **3b-Solid dispersion by KM.**

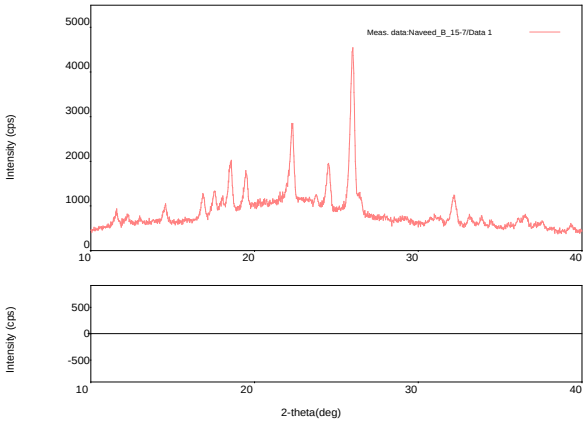




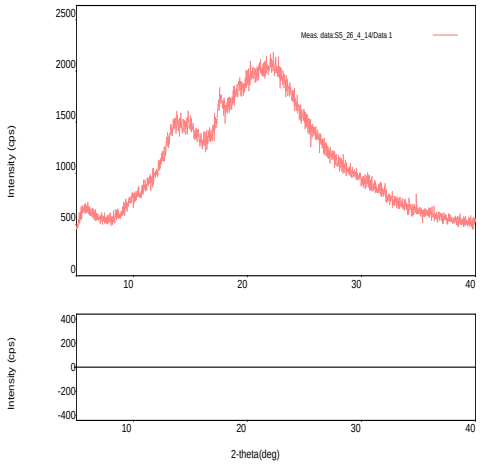
4c- Solid dispersion by SE. **4d-Solid dispersion by MW.**

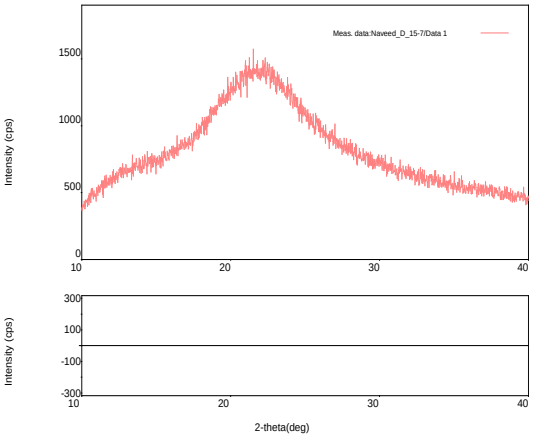
Fig.4-XRPD analysis for solid dispersions.





4a- Acelofenac. **4b-Solid dispersion by KM.**





4c-Solid dispersion by SE. **4d-Solid dispersion by MW.**

Fig.5-Drug release PCTs.

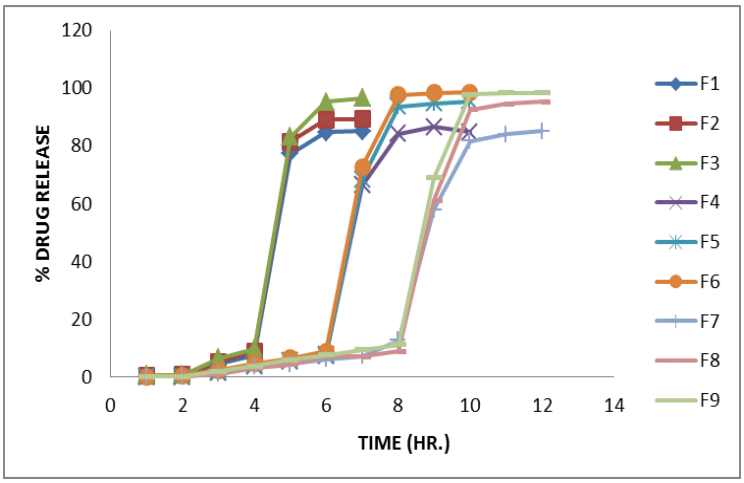


Fig.6-Drug release IRCTs.

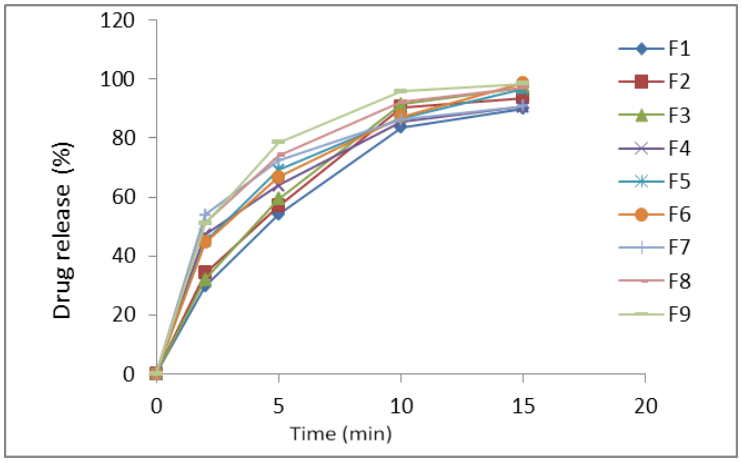


Fig.7-Longitudinal section of press coated tablet.

Fig.8-Surface response for lag time.

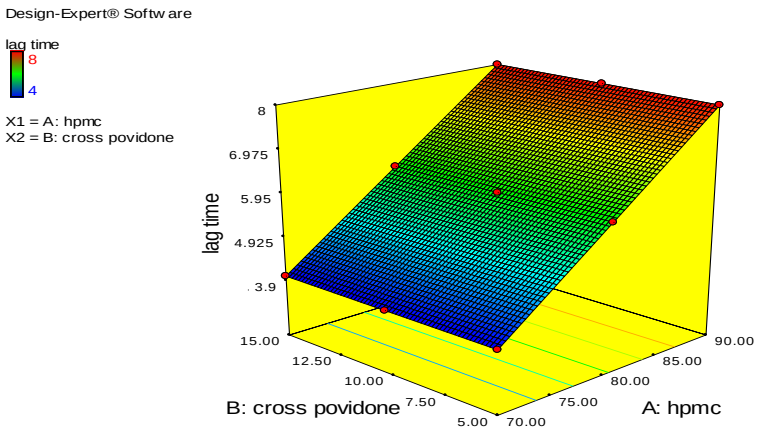
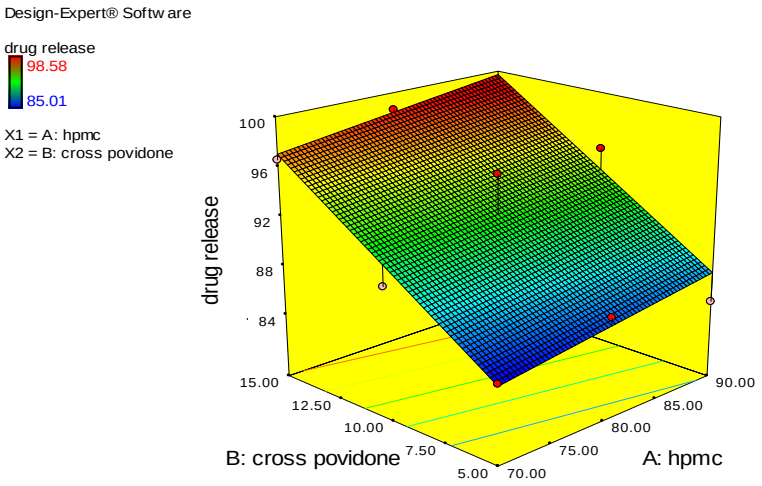


Fig.9-Surface response for % Drug release.



CONCLUSION

From the investigations following can be concluded:

Solubility data suggest 1:1 ratio for solid dispersion of ACE-PVP K30. Solubility of ACE was found to be more by SD prepared by microwave induced fusion method. DSC and PXRD study gives the confirmation about the formation of solid dispersion with PVP K-30.The lag time and time-controlled release behavior of Acelofenac from press-coated tablets could be modulated by varying the concentration of polymer in outer coating layer. Formulation batches F5-F7 compression coated tablets achieve a burst release after 6 hr lag time. The dosages should be timed to ensure that the highest blood levels of the drug coincide with peak pain. For rheumatoid arthritis the optimal time for an NSAID to be taken is after the evening meal. Considering this the preferable lag time would be of 6 hr. Batch F6 was selected as optimized batch which gave lag time of 6 hr and maximum drug release of 98.58% after the

lag time. In-vitro kinetic release profile of formulation batch F6 showed zero order release. The value of n i.e. release exponent was found in the range of 0.65 to 0.97 (0.5 <n <1) which shows release of drug from system by non-fickian diffusion or anomalous transport.

Finally it is concluded that press coated tablet has a potential to be used for release of Aceclofenac for pulsatile drug delivery, thus it may prove to be of help in achieving chronotherapeutic approach for the treatment of rheumatoid arthritis.

ACKNOWLEDGEMENTS

The authors are grateful to Flamingo Pharma Pvt Ltd. (Mumbai, India.) for kindly providing gift sample of Aceclofenac. We are thankful to Wockhardt Ltd. (Aurangabad, India.) for providing PVP K-30, HPMC K4M and Microcrystalline cellulose as gift sample. We extend our thanks to Atra Pharmaceuticals (Aurangabad, India.) for providing us with gift samples of Crosspovidone. We sincerely thank Padmashree Mrs. Fatma Rafiq Zakaria, Chairman, Maulana Azad Educational Trust for providing all the necessary facilities and stimulating environment for carrying out the research.

REFERENCES

1. D. N. Venkatesh, S. Karthick, M. Umesh, R.M. Valliappan, G. Vivek, M. K. Samanta and K. Elango, studies on the preparation and characterisation of β-cyclodextrin-aceclofenac inclusion complexes, Malay. J. Pharm. Sci., 2009; 7(2): 153–168.
2. Mariarosa M., Barbara B., Pietro B., Microwave generated solid dispersion containing ibuprofen, International Journal of Pharmaceutics, 2008; 361: 125-130.
3. Merck. (2001) Merck Index, 13th edition, pp. 22 (New Jersey, USA: Merck and Co. Inc).
4. Serajuddin A., Solid dispersion of poorly water soluble drugs: early promises, subsequent problems and recent breakthroughs, Journal of Pharmaceutical Sciences, 1999; 88(10): 1058-1066.
5. Bose, S., Bogner, R.H., Solventless pharmaceutical coating processes: a review. Pharm. Dev. Technol., 2007; 12: 115–131.
6. Luxmikant Z., Sanjay B., Microwave induced solid dispersion as a novel technique for enhancing dissolution rate of repaglinide, Advances in Pharmacology and Pharmacy, 2013; 1(2): 95-101.
7. Lachman, L., Lieberman, H.A., Kanig, J. L. The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese Publishing House, Bombay, 1987; 171-197.

8. Abhijeet M., Formulation and evaluation of press coated tablets for pulsatile drug delivery system, Journal of Pharmacy Research, 2011; 4(3): 564-567.
9. Indian pharmacopoeia Indian Pharmacopoeial Commision, Ministry of Health and Science Welfare, Government of India, Ghaziabad, 2007; 2: 356-357, 773-774, 59-59.
10. United State Pharmacopoeia 27/ National Formulary 22, The Official Compendia of Standards, Asian edition, United States Pharmacopoeia Convention Inc, 2004; 197U: 2724-2726.
11. Rujivipat S., Bodmeier R., Modified release from hydroxypropyl methylcellulose compression-coated tablets, Int. J. Pharma, 2010; 402: 72–77.
12. Masaki Y.O., Watanabe Y., Danjo K., Evaluation of novel one-step dry-coated tablets as a platform for delayed-release tablets, J. Control. Release, 2004; 95: 51–60.
13. Schwartz J., Conner B., Schnnare R., Optimization techniques in pharmaceutical education and research, in: G.S. Banker, C.T. Rhodes (Eds.), Modern pharmaceutics, Marcel Dekker, USA, 2002; 223-235.
14. Khadabadi S.S., Nahid H. C., Farhan M. K., Akeel A. T., Formulation and evaluation of press coated tablet of ketoprofen –a chronotherapeutic approach, int j pharm pharm sci, 2013; 5(3): 733-740.
15. Dharmarajsinh C., Shrenik S., Formulation and Evaluation of Pulsatile Drug Delivery System of Aceclofenac for treatment of rheumatoid arthritis. Int. J. Pharm. Sci., 2012; 4(3): 507-512.
16. Sable P. N, Shinde S. R., Desai M. B., An approach to enhance solubility of etodolac by microwave induced solid dispersion, Journal of Medical and Pharmaceutical Innovation, 2014; 1(3): 1-8.
17. Patil S., Pund S., Joshi A., Sheesho C., hronomodulated press coated pulsatile therapeutic system for aceclofenac: optimization of factor influencing drug release and lag time, Dove Press Journal, 2011; 1: 1-10.
18. Waterman K.C., Fergione M.B., Press-coating of immediate release powders onto coated controlled release tablets with adhesives. J. Control. Release, 2003; 89: 387–395.