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Preparation, Evaluation and Optimization of Etodolac Solid Dispersion for Delayed Drug Release.

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ABSTRACT

The present study involved the development and optimization of etodolac solid dispersions for chronotherapeutic drug delivery using response surface methodology on 3^2 factorial design containing Ethyl cellulose , Eudragit S 100 and Polyvinylpyrrolidone K 30 as carriers. The key response variables selected for optimization process were percentage drug release, lag time, entrapment efficiency, which corresponds to the factors like Ethyl cellulose (EC), Eudragit S 100(ER S100) and Polyvinylpyrrolidone K 30 (PVP).The solid dispersions were evaluated for physicochemical properties, interaction studies using DSC, XRD, FT-IR,SEM etc. and *in vitro* dissolution studies were also performed. The results showed absence of interaction between drug and polymers. For significant formulation responses regression models were developed and Derringer's desirability function was used to optimize these responses simultaneously. The optimized model generated showed maximum overall desirability (0.856).This value a high degree of optimization achieved enabling development of delayed release tablets with entrapment efficiency=87.99%,lag time =331.32 min and percentage drug release=96.94%.The prediction efficiency of the model was confirmed by performing the experiment under optimal condition. Good agreements between experimental and predicted responses were observed. Interaction studied revealed that an increase in concentration of ethyl cellulose and Eudragit S 100 demonstrate changes in delaying drug release.
Keywords: Etodolac, Solid dispersions, drug release, entrapment efficiency, lag time, delayed release tablets.

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INTRODUCTION

The oral route of administration is the best considered route for drugs, which is widely used and most acceptable for the patient. About 60% of all dosage forms available are the oral solid dosage forms. The effect of orally administered drugs is largely dependent on the absorption rate from the gastro intestinal tract. A number of technologies are available for the development of modified drug delivery system. The last few decades, modified release oral drug delivery has been focused on marketed drugs as well as for new drug molecules. The unnecessary frequency of administration, untoward side effects, and local irritations can be avoided using the modified release forms.

Experimental designs, involves planning experiments systematically in order to extract the maximum efficient information with the least number of experiments possible. The basic idea is to change all relevant factors simultaneously over a set of planned experiments and then connect and interpret the results using mathematical models. The central composite design applied to optimize the formulation of etodolac loaded solid dispersions .In this work, the important formulation factors were selected and optimized by a central composite design experiment. The selection of factors for optimization was based on preliminary experiments and prior knowledge from literature, as well as certain instrumental limitations. From preliminary experiments the key factors selected for optimization process were the amount of ethyl cellulose (EC) (X_1), eudragit S100 (X_2) and polyvinylpyrrolidone K 30 (PVP) (X_3).

Etodolac, is a drug of choice for rheumatoid arthritis, is a disease state in which the pathological symptoms are at their prime in the mornings. So treatments based on chronotherapy helps to match the rhythms of disease, in order to optimize therapeutic outcomes and minimize the side effects. Etodolac is practically insoluble in water, it comes under the class II of Biopharmaceutics classification system (BCS Class II) and is having short biological half-life. It is difficult to achieve therapeutic activity of drug, if in the form of conventional dosage form. So it is necessary to maintain the drug levels within the therapeutic range for the optimal use of the drug by maintaining the blood level of drug over a long period of time and to improve the patient compliance.

Solid dispersion is one of the effective carrier for developing novel drug delivery system for the preparation of delayed release formulations. Solid dispersion helps to improve the solubility of water insoluble drugs and helps to increase the bioavailability of drugs by using different rate retarding polymers. [16]

The aim of the present work is to prepare solid dispersions containing etodolac using different polymers like like Ethyl cellulose (EC), Eudragit S 100(ER S100) and Polyvinylpyrrolidone K 30 (PVP) as per the experimental design and evaluation of the prepared formulations. The different significant responses are drug entrapment efficiency, delay in drug release (lag time) and percentage drug release were chosen for the optimization of delayed release tablets. The global optimization of these significant responses were performed to develop a quality formulation. The Central composite design and Derringer's desirability function were applied for the global optimization of the responses.

Drug solubility can be enhanced by using solid dispersion technique, by employing a suitable polymer, which can release the maximum amount of drug in the early morning hours, when the formulation is administered at bed time and helps to produce controlled release dosage forms. Also recent market studies indicates that most of patients suffering from rheumatoid arthritis experiences the early morning symptoms like morning stiffness, joint pain and functional disability. This prompted, to develop etodolac delayed release formulations, helps to alleviate symptoms and provides the maximum plasma drug concentration in the early morning hours.

MATERIALS AND METHODS

Materials

Etodolac was obtained as a gift from Ipca Laboratories Ltd. Mumbai India; Eudragit S 100, Ethyl cellulose , Polyvinylpyrrolidone K-30 were obtained from Yarrow Chem Products, Mumbai, India. Magnesium stearate, Microcrystalline Cellulose and all reagents used were of analytical grade.

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Methods

PREPARATION OF SOLID DISPERSIONS

The solid dispersions were prepared by using solvent evaporation method [1, 3, 6, 9]. The carrier used for the preparation of solid dispersions was ethyl cellulose (EC), Eudragit S 100 (ER S100) and polyvinylpyrrolidone K 30 (PVP). The drug was weighed separately. The calculated quantities of polymers like Ethyl cellulose (EC), Eudragit S100(ER S100) and Polyvinylpyrrolidone K 30(PVP) was dissolved in the ethanol and stirred well by using magnetic stirrer (Remi Instruments, India) at 500 rpm for 15 min. Drug was added to the above polymer solution and stirring was continued for 20 minutes to get a uniform drug polymer dispersion. The solvent was evaporated by using a rotary evaporator; and the residue obtained was dried overnight in the oven. The powder was then pulverized and sifted through # 60 to get the final formulation. Each formulation were stored in an air tight container for the performance of further characterization and evaluation studies.

The important formulation factors were selected and optimization of formulations was done by using a central composite design experiment as showed in **Table 1**. The factors were selected based upon preliminary experiments, literature studies as well as certain instrumental limitations. From the above source of information, the key response variables selected for optimization process time were entrapment efficiency, lag time and percentage drug release, which corresponds to the factors like Ethyl cellulose (EC), Eudragit S 100(ER S100) and Polyvinylpyrrolidone K 30 (PVP).

Table 1 Coded central composite rotatable design for three factors in five levels

Formualtion code	X1		X2		X3	
	Coded	Actual	Coded	Actual	Coded	Actual
F 01	-1	210	-1	175	-1	75
F 02	+1	250	-1	175	-1	75
F 03	-1	210	+1	200	-1	75
F 04	+1	250	+1	200	-1	75
F 05	-1	210	-1	175	+1	85
F 06	+1	250	-1	175	+1	85
F 07	-1	210	+1	200	+1	85
F 08	+1	250	+1	200	+1	85
F 09	-1.689	196.36	0	187.5	0	80
F 10	+1.689	263.63	0	187.5	0	80
F 11	0	230	-1.689	166.47	0	80
F 12	0	230	+1.689	208.52	0	80
F 13	0	230	0	187.5	-1.689	71.59
F 14	0	230	0	187.5	+1.689	88.40
F 15	0	230	0	187.5	0	80
F 16	0	230	0	187.5	0	80
F 17	0	230	0	187.5	0	80
F 18	0	230	0	187.5	0	80
F 19	0	230	0	187.5	0	80
F 20	0	230	0	187.5	0	80

Note:

1. *X_1, X_2, and X_3 are represents the amount of formulation variables Ethyl cellulose (EC), Eudragit S 100(ER S100) and Polyvinylpyrrolidone K 30 (PVP).*
2. *Coded values -1.689,-1,0,+1,+1.689 represents–α,low, mild, high and +α respectively*

In the above method, Ethyl cellulose is insoluble carrier, which can retard the dissolution rate of the drug and can prolong the duration of time, when the drug is released [8]. Eudragit S100 can retard the drug release in the upper part of GIT, can extend the lag time for the drug delivery [14]. Polyvinylpyrrolidone K 30

(PVP K-30) can enhance the encapsulation of poorly water soluble drugs, having high degree of biocompatibility, with greater possibility of controlling the release rate of drug and improves the *in vivo* pharmacokinetics. [13]

The prepared solid dispersion were dried and sieved to get free flowing powders. The solid dispersions were prepared at different proportions of polymers by the above mentioned procedure, as per the following **Table 1.**

CHARACTERIZATION STUDIES

Twenty formulation (F01-F20) of etodolac solid dispersions were prepared as per experimental design matrix and the significant responses like entrapment efficiency ,lag time and percentage drug release were evaluated. The characterization studies like physicochemical properties, interaction studies using DSC, XRD, FT-IR [2, 5, 11], SEM [4,12] micrometric properties like angle of repose ,bulk density ,tapped density, compressibility index and Hausner's ratio were performed on pooled batches[15].

Percentage yield of solid dispersions

Percentage yield was determined by weighing the dried solid dispersions and calculated with respect to the weight of equal quantities of drug and polymer used for the formulation. The percentage yield was obtained as the percentage ratio between practical and theoretical yield. The percentage yield were replicated for three times for each of the formulations.

$$\text{Solid dispersion recovery (\%)} = \frac{\text{Recovered weight of Solid dispersion}}{\text{Weight of polymer used + drug}} \times 100$$

Drug entrapment efficiency

100mg of the prepared solid dispersions were powdered and suspended in water and the suspension is sonicated for 20 minutes. The drug was completely extracted from solid dispersions by shaking for further 20 minutes. The above mixture was filtered through a 0.45 µm membrane filter. The drug content was determined by using UV visible spectrophotometer at 274 nm. The entrapment efficiency was calculated by using the formula.

$$\text{Entrapment efficiency} = \frac{\text{Actual weight of drug in sample}}{\text{Microspheres sample weight}} \times 100$$

***In vitro* release studies**

The drug release pattern of all the formulated solid dispersions were studied by using *in vitro* release studies. The following procedures were carried out to study the pattern of the drug release in an *in vitro* environment. Accurately weighed solid dispersions equivalent to 250mg of etodolac was taken and filled in the capsule. The capsules were subjected for dissolution using dissolution test apparatus USP type II (paddle) method. The dissolution studies were conducted by using 900ml at pH 1.2 at the first 4 hours. At the end of 4^{th} hour, half of the medium volume was removed. It is filtered and replaced by the equal amount of buffer having pH 9.3, to achieve an effective pH of 7.4 in medium. The dissolution was continued for further 8 hours at this pH. 5 ml of sample was withdrawn at suitable time intervals and replaced by fresh dissolution medium each sample was passed through 0.45 µm filter, and drug content after suitable dilution was analyzed spectrophotometrically at 274 mm. [1,16]

Lag time

The drug release pattern of all the formulated solid dispersions were studied by using *in vitro* release studies. The lag time is taken as time of <10% drug release [1, 16].

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RESULTS AND DISCUSSIONS

As per the experimental design methodology twenty formulations (F01-F20) containing etodolac loaded solid dispersions were prepared. The significant responses like entrapment efficiency, lag time and percentage drug release were evaluated and investigated.

Drug polymer interaction studies

The individual spectras FTIR of the drug, physical mixture of drug and excipients and the formulation of etodolac loaded solid dispersions were determined. The obtained spectrum of the etodolac is given in **Figure 1**. Drug exhibited characteristic peaks at wave numbers 3344 ,2970 and 1746 cm^{-1} corresponding to C=NH stretching (C=NH stretches at 3300-3500 cm^{-1}), O-H stretching of hydrogen bonded O-H of –COOH (–COOH stretches at 2900-3300 cm^{-1}),C=O stretching of carboxylic acid (C=O stretches at 1650-1750 cm^{-1}) respectively. It was found in accordance to the reference standard from British Pharmacopoeia. In all the above figures it is seen that the characteristic peaks found in the FT-IR spectra of drug were also observed in the spectra's of the physical mixture and the absence of the extra peak confirmed that,there is no degenerative chemical interaction between drug and excipients. **Figure 2 and 3** represents the spectra of physical mixture containing drug and excipients, etodolac loaded solid dispersions respectively.

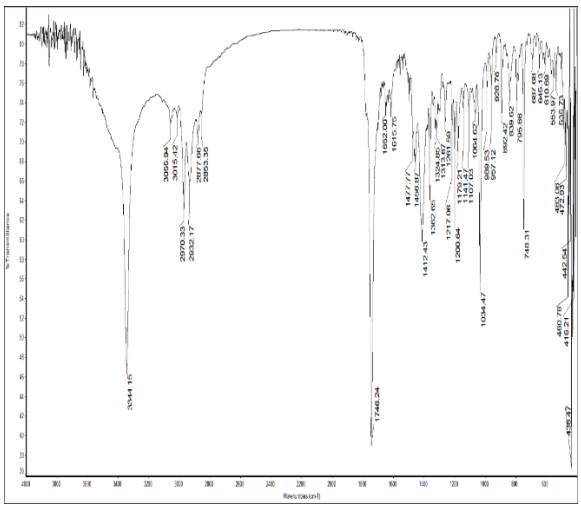

Fig. 1 FTIR spectral data of etodolac

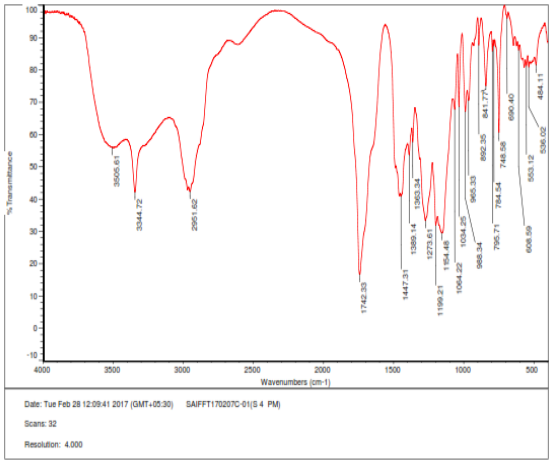

Fig. 2 FT-IR spectra physical mixture

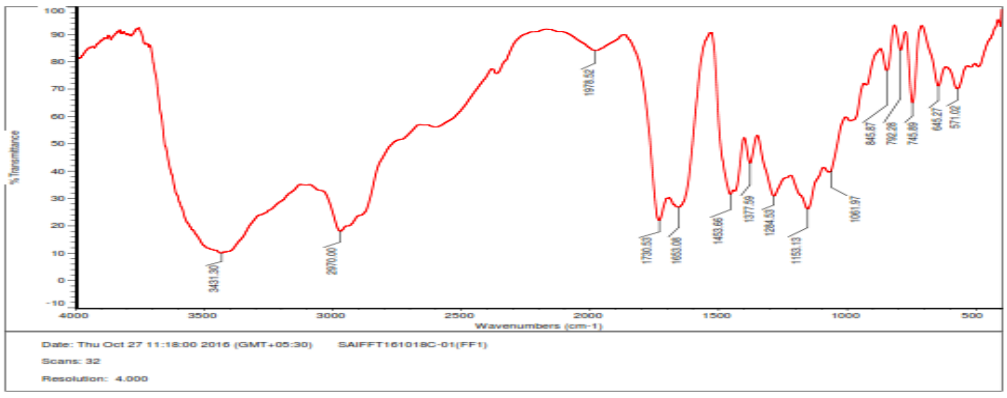

Fig. 3 FTIR spectral data of etodolac loaded solid dispersions

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Percentage yield of solid dispersions

The percentage yield of all the formulations of solid dispersions were found to be 89.73% to 96.37%. The maximum percentage yield was found to be 96.37% in the formulation F08; confirms the uniform distribution of drug and polymers during processing which did not affect the yield of formulations.

Drug entrapment efficiency

The percent of drug entrapment efficiency for the prepared etodolac solid dispersions were determined as mentioned above**.**Triplicate readings were taken for the analysis of all formulation and average was taken for the optimization study and the ANOVA was performed. The entrapment efficiency of all the formulations of solid dispersions were found to be 70.55 % to 86.35%.

Surface Morphology

Figure 4 shows the scanning electron micrographs of formulated solid dispersions. After analysis, it is revealed that pure etodolac has smooth surfaced crystalline shape.From the SEM micrographs of solid dispersions the crystals of etodolac are smallest in size and they have irregular shape, shows the entrapment of drug in the carrier. The particle shape irregularity and smaller particle size increased the specific surface area, and hence enhanced the dissolution rate.

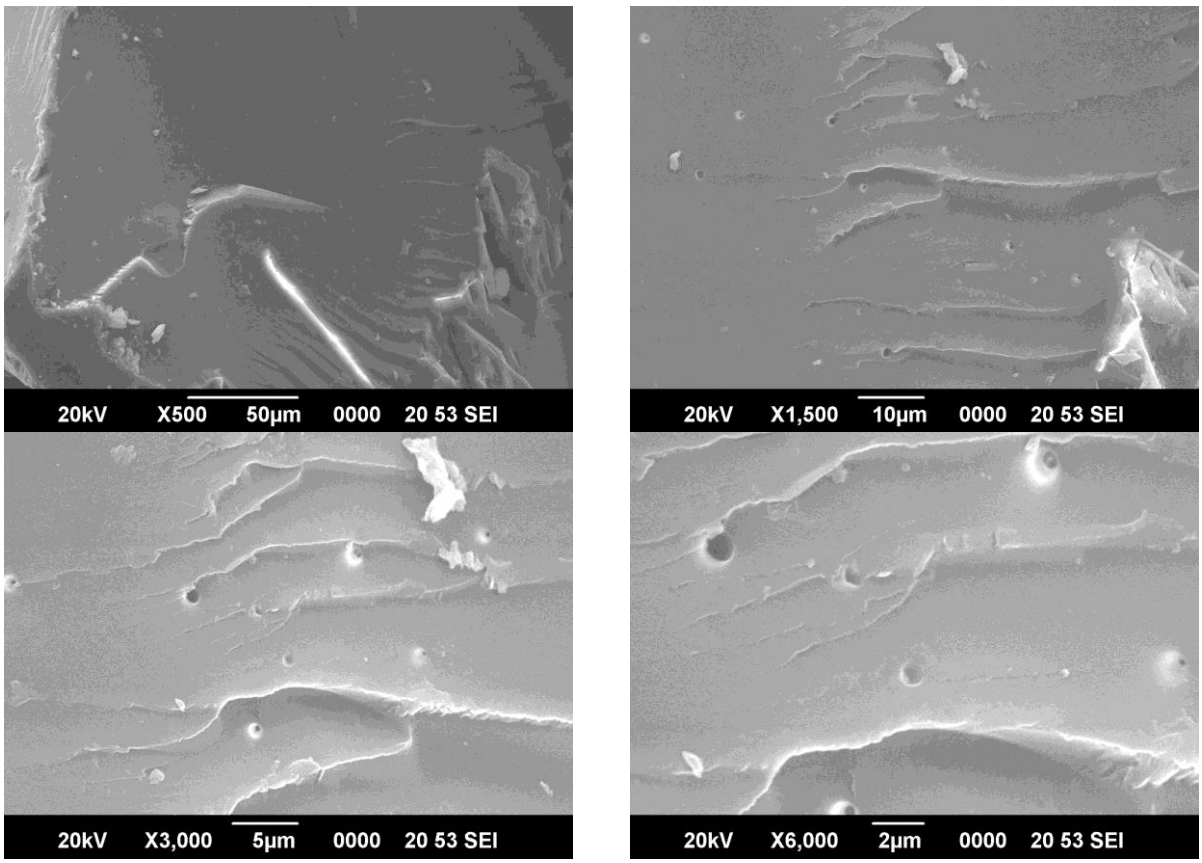

Fig. 4 Scanning electron micrographs of solid dispersion in 50µm, 10µm, 5 µm, 2µm.

Micromeritic properties

The results of evaluation of granules showed that the prepared solid dispersion were found to be porous and free flowing in nature. Angle of repose of all the formulations lies in the range of 23.11-25.66^0. Since the value is less than 25^0 - 30^0, all the formulation blend shows good flow property. The loose bulk density and tapped density for all the formulations varied from 0.554 - 0.598 g/cc and 0.603 - 0.660 g/cc respectively. The values obtained were found to be within the accepted range. There was no large difference seen between loose and tapped bulk density. These values were used in calculating % compressibility of the

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powder blend. Carr's index of the blends was found to be 6.625-9.394, which is considered to be ideal for good compressibility property. This shows that the formulations F01-F20 have good compressibility. Hausner's ratio for all the formulations lies in the range of 1.071 -1.104. Since the value is less than 1.25, the blend has good flow.

Lag time and *in vitro* drug release studies.

The lag time and cumulative percent of drug release were calculated using calibration curve in phosphate buffer pH 7.4 at λ_{max} 274 nm for etodolac. The etodolac solid dispersions were filled in the capsule (size No.0) and dissolution was carried out for a period of 12 hours. For the estimation of lag time, the time taken to release less than 10% of drug from the dosage form was determined. The lag time of all the formulations of solid dispersions were found to be 263 min-352 min.

The *in vitro* drug release was also studied to estimate the cumulative per cent drug release using calibration curve in phosphate buffer pH 7.4 at λ_{max} of 274 nm. The formulated solid dispersions were filled in the hard gelatin capsule (size No.0) and the dissolution was carried out in phosphate buffer at pH of 7.4 at 12 hours. Triplicate readings was taken and its average was taken. The percentage release of all the formulations of solid dispersions were found to be 81.77%-99.3%.Figure 5 and 6 shows the *in vitro* release profiles of controlled release etodolac solid dispersions.

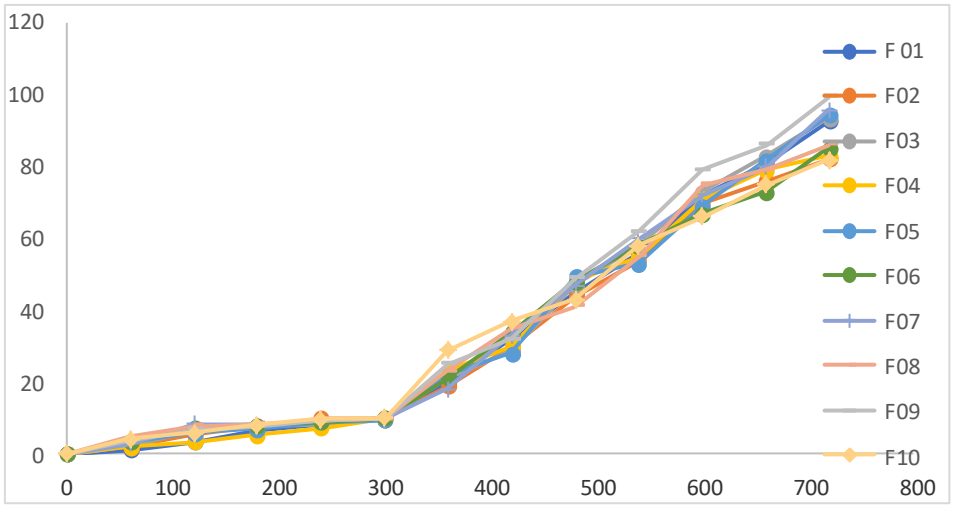

Fig. 5 *In vitro* release profile of etodolac solid dispersions formulations F01-F10

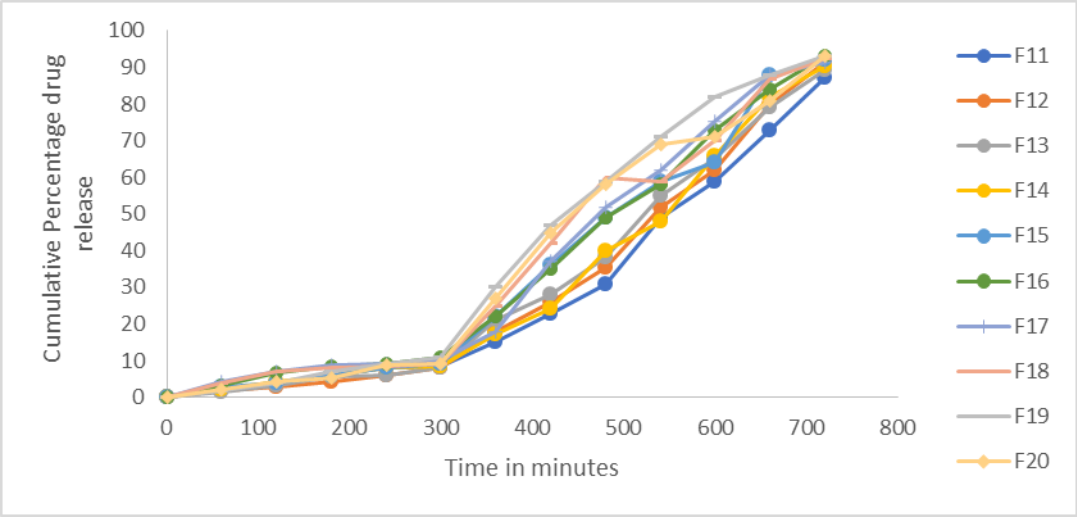

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Fig. 6 *In vitro* release profile of etodolac solid dispersions formulations F11-F20

Differential scanning colorimetry studies (DSC)

Differential scanning colorimetry of etodolac and solid dispersions were conducted in order to investigate crystallinity of drug and possibility of drug carrier interaction. **Figure 7** and **Figure 8** shows the thermograms of etodolac and solid dispersion.From the spectra etodolac shows sharp endothermic peak at temperature of 151.73ºC.The DSC thermogram of the solid dispersion showed endothermic peak at 78.22˚C,which shows that drug is converted to amorphous form after the formulation to solid dispersion **.** The endothermic peak of etodolac is of very high intensity, showing the crystalline form of the drug. The endothermic peaks of solid dispersions loss its sharpness and distinctive appearance. It showed that no possible interactions was found between drug and carrier but the loss of sharpness in the peak may be due to the conversion from crystalline from to amorphous from of the drug.

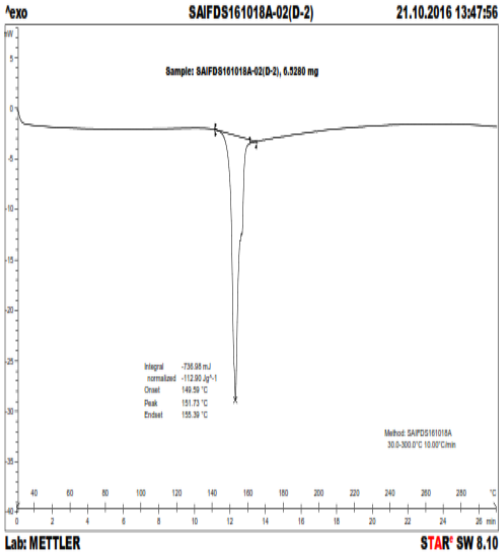

Fig. 7 DSC thermogram of Etodoalc

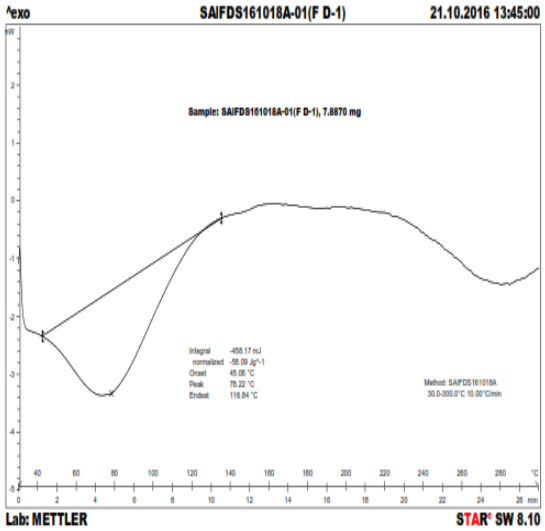

Fig. 8 DSC thermogram of etodolac loaded solid dispersions

X ray diffraction studies (XRD)

The diffractograms of etodolac reveals that, that the drug has crystalline structure. The XRD patterns of the etodolac, and solid dispersions were shown in **Figure 9 and Figure 10** respectively. XRD diffraction patterns of etodolac solid dispersions show the presence of characteristic peak (slight shift) of drug with reduced diffraction intensity, which indicates the changes in crystallinity of drug with the formation of new solid phase, which had an amorphous nature. Prominent peaks of etodolac either disappear or were less intense in the solid dispersions, suggesting a strong interaction between drug and polymers. This decrease in peak intensity and decrease in drug crystallinity was responsible for the increase solubility of the solid dispersions compared to that of pure drug.

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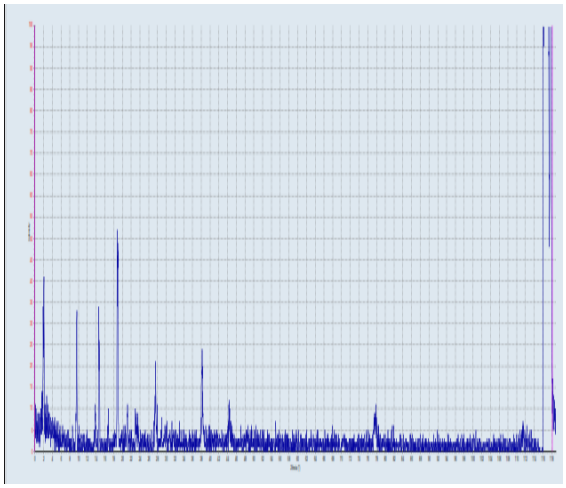

Fig. 9 XRD of etodolac

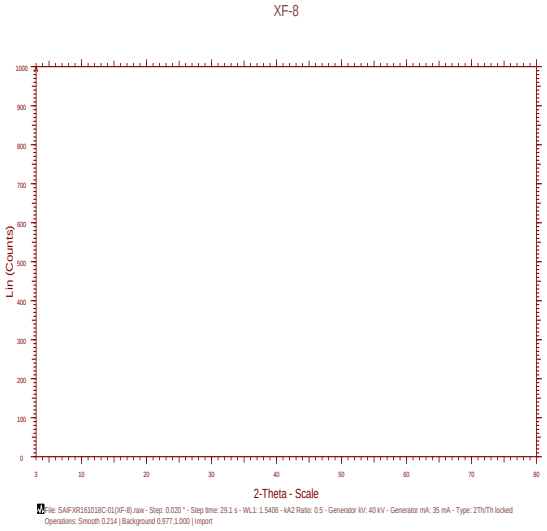

Fig. 10 XRD of etodolac loaded solid dispersion

OPTIMIZATION OF CONTROLLED RELEASE ETODOLAC LOADED SOLID DISPERSIONS FOR DELAYED RELEASE TABLETS

Determination of the response variables Statistical analysis and validation of design

Statistical analysis and validation of model were performed using Design-Expert 7.0 software (Stat-Ease Inc.,USA). The responses were analyzed using one way ANOVA, the individual response parameters were evaluated using F test and polynomial equation was generated for each response using multiple linear regression analysis (MLRA). 3D and contour response plots were constructed using Design-Expert software. By utilizing Design-Expert 7.0 software, one final formulation corresponding to the predicted optimum polymer concentration were prepared to determine the validity of the model generated. Afterward, the observed experimental data of the response properties were quantitatively compared with those of the predicted values. The response variables like drug entrapment efficiency,lag time and percentage drug release were evaluated for optimization studies.

Optimization Design and Analysis

The central composite design applied to optimize the formulation of etodolac loaded solid dispersions .In this work, the important formulation factors were selected and optimized by a central composite design experiment.

From preliminary experiments the key factors selected for optimization process were the amount of ethyl cellulose (EC) (X_1), eudragit S100 (X_2) and polyvinylpyrrolidone K 30 (PVP) (X_3). **Table 2** shows the levels of each factors studied for finding out the optimum values and responses. As can be seen in this table, the ranges of each factors used were: ethyl cellulose (EC) (X_1) (196.36-263.63), eudragit S100 ER S100(X_2) (166.47-208.52) and polyvinylpyrrolidone K 30 (PVP) (X_3) (71.59 – 88.40), as response variables, percentage drug release, lag time and entrapment efficiency. All experiments were performed in randomized order to minimize the effects of uncontrolled variables that may introduce a bias on the measurements. Replicates (n=6) of the central points were performed to estimate the experimental error. For an experimental design with three factors, the model including linear, quadratic, and cross terms can be expressed as

Where Y is the response to be modeled, β is the regression coefficient and X_1, X_2 and X_3 represents factors. To obtain a simple and yet a realistic model, the insignificant terms (P>0.05) are eliminated from the model through 'backward elimination' process. The statistical parameters obtained from the ANOVA for the reduced models are given in **Table 3.**

Since R^2 always decreases when a regressor variable is eliminated from a regression model, in statistical modeling the adjusted R^2 which takes the number of regressor variables into account, is usually

selected [10]. In the present study, the adjusted R^2 were well within the acceptable limits of $R^2 \geq 0.80$ [7] which revealed that the experimental data shows a good fit with the second-order polynomial equations. For all the reduced models, P value of <0.05 are obtained, implying these models are significant. The adequate precision value is a measure of the "signal (response) to noise (deviation) ratio". A ratio greater than 4 is desirable. In this study, the ratio was found to be in the range of 26.57 to 34.83, which indicates an adequate signal and therefore the model is significant for the formulation of solid dispersions.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 + \beta_{33} X_3^2 \quad (1$$

Table 2 Central composite rotatable design[a] arrangement and measured responses for the formulation of etodolac loaded solid dispersions

Formulation code	Factor levels			Responses		
	X_1 EC	X_2 ER S100	X_3 PVP	Entrapment efficiency	Lag time min	% Drug release
F 01	210	175	75	82.5	271	92.8
F 02	250	175	75	72.25	275	82.17
F 03	210	200	75	83.5	303	93.7
F 04	250	200	75	73.56	304	83.12
F 05	210	175	85	84.4	273	94.5
F 06	250	175	85	73.12	279	85.12
F 07	210	200	85	85.6	307	95.7
F 08	250	200	85	76.23	312	86.14
F 09	196.36	187.5	80	85.44	284	99.3
F 10	263.63	187.5	80	70.55	296	81.77
F 11	230	166.47	80	77.22	263	87.22
F 12	230	208.52	80	81.3	319	91.3
F 13	230	187.5	71.59	79.14	283	89.14
F 14	230	187.5	88.40	80.32	290	90.32
F 15	230	187.5	80	85.25	346	92.25
F 16	230	187.5	80	86.24	351	93.24
F 17	230	187.5	80	86.25	352	91.25
F 18	230	187.5	80	86.35	348	92.35
F 19	230	187.5	80	85.25	349	93.25
F 20	230	187.5	80	86.25	350	93.25

Table 3 Reduced response models[a] and statistical parameters obtained from ANOVA (after backward elimination)

Response	Regression model	Adjusted R^2	% CV	Model P-value	Adequate precision
Entrapment Efficiency	$85.92-4.82\ X_1 + 0.98X_2 + 0.69X_3 + 0.27X_1X_2 - 0.05X_1X_3 + 0.25X_2X_3 - 2.73X_1^2 - 2.29X_2^2 - 2.12X_3^2$	0.9827	0.874	<0.0001	32.36
Lag Time	$349.17 + 2.64X_1 + 16.26X_2 + 2.18X_3 - 0.5X_1X_2 + 0.75X_1X_3 + 0.75X_2X_3 - 19.92X_1^2 - 19.57X_2^2 - 21.16X_3^2$	0.9885	1.09	<0.0001	34.83
% Drug Release	$92.61-5.09X_1 + 0.80X_2 + 0.85X_3 - 0.01X_1X_2 + 0.28X_1X_3 + 0.04X_2X_3 - 0.83X_1^2 - 1.28X_2^2 - 1.12X_3^2$	0.9629	1.009	<0.0001	26.57

a Only significant coefficients with P < 0.05 are included. Factors are in coded levels.

Note: X_1, X_2, and X_3 are represents the formulation variables % Drug Release, Lag Time, % Entrapment Efficiency, respectively.

Entrapment efficiency

The capacity of solid dispersions to entrap the drug is the responsible factor for selection of the method of preparation and **Table 2** represents the results of entrapment efficiency. Incorporation of PVP in the formulation increased the entrapment efficiency of the drug. The recorded enhancement in the drug

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loading in presence of PVP can be explained on the basis that PVP is capable of closing the surface pores in the solid dispersions. **Figure 11 and Figure 12** represents the predicted response surface plot and perturbation plot respectively.

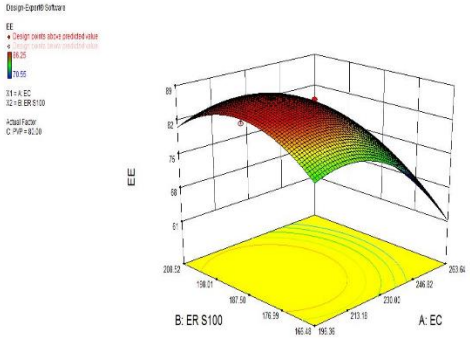

Fig 11 Predicted response surfaces plot – Entrapment efficiency

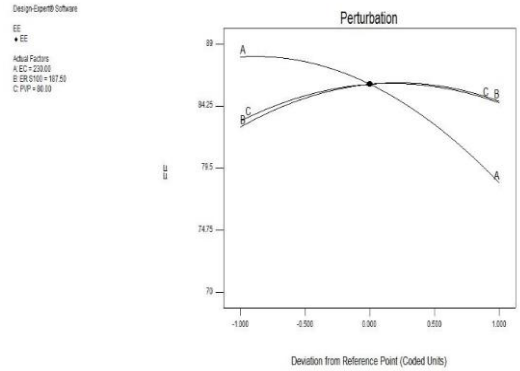

Fig. 12 Perturbation plot –Entrapment efficiency

Lag time

Different formulation variables play a vital role in optimization of the preferred delayed drug release profile to meet the therapeutic condition of the rheumatoid arthritis. Eudragit S100 was chosen as the enteric polymer because of its weak mechanical strength and insolubility throughout the gastrointestinal tract. Though a not very elastic film is desired, it must be strong enough to withstand *in vivo* GIT turbulences and remain intact for the period of lag time. The lag time of formulations was shown in **Table 2** From the *in vitro* release behaviour, it can be resolved that as the viscosity of the polymer increased, stronger and more durable films were formed. The use of ethyl cellulose along with eudragit S100 prolong the lag time because ethyl cellulose significantly retard the erosion of eudragit S100 and decrease in solvent uptake. The results of mathematical model indicate that effect of ethyl cellulose and eudragit S100 shows a curvilinear relationship for cumulative drug release at the end of 12 hour. A significant effect was observed on the lag time of delayed release tablets. From the outcome of the drug release profiles, we can conclude that as the concentration of eudragit S100 is increased, lag time will increase as well. **Figure 13 and Figure 14** represents the predicted response surface plot and perturbation plot respectively.

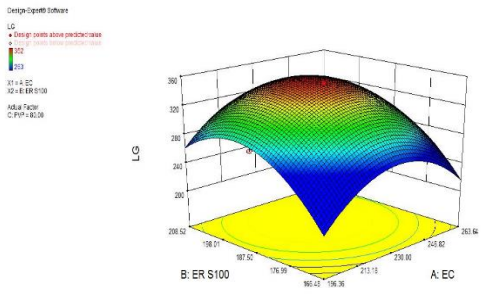

Fig.13 Predicted response surface plot –Lag time

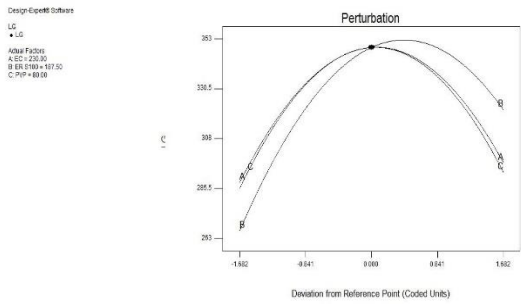

Fig. 14 Perturbation plot –Lag time

Percentage drug release

Optimization of all the constraints plays a crucial role for achieving the desired drug release profile, needed for the chronotherapeutic application of the drug. The tablets released less than 10% in the artificial gastric acid in the initial 4-5 hrs and release 20 -35%, not less than 75%, more than 90% at 6 hrs, 10 hrs and 12 hrs respectively in the simulated intestinal fluid. All the formulation variables were varied to study the effect on *in vitro* release of the drug and to achieve the preferred lag time of 4-5 hours, necessary to meet the therapeutic requirement of delayed release tablets. As the amount of ethyl cellulose increase, there is a decrease in medium uptake, with less pores for the effective drug diffusion leads to the decrease in dissolution rate due to the less porous diffusional path length. The drug release profiles were shown in **Table 2** and **Figure**

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15 and 16 shows predicted response surface plot and perturbation plot. Ethyl cellulose reduces the drug release due to a reduction in the diffusion of the solvent molecules into the system because of the hydrophobic nature of ethylcellulose. As the amount of ethylcellulose increased, the release mechanism of etodolac decreased. The *in vitro* study revealed that with increased concentration of ethyl cellulose the release rate of etodolac is controlled and it was extended up to 12 hours.

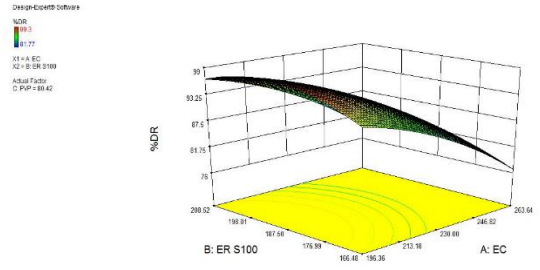

Fig 15 Predicted response surfaces plot – percentage drug release

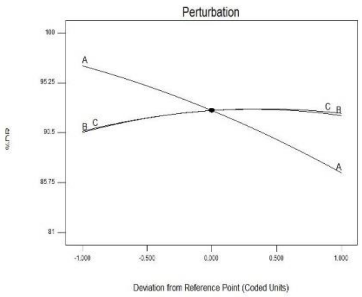

Fig. 16 Perturbation plot –Lag time

Model Fitting

The evaluation results of each formulation in terms of the individual responses calculated. The results of the applied statistical tests indicated that all three response variables measured in this study showed good fitting to the second-order model. The fitting equations that resulted after model simplification are given **Table 3**

The criteria for the optimization of each individual response are shown in **Table 4** Criteria have been proposed for selecting an optimum experimental condition for formulation of etodolac loaded solid dispersions. As can be seen under criteria, three responses of entrapment efficiency, lag time, percentage drug release were maximised, in order to get high yield etodolac loaded solid dispersions, with good entrapment efficiency.

Table 4 Criteria for the optimization of the individual responses

Response	Lower limit	Upper limit	Criteria	
			Goal	Importance
% drug release,	81.77	99.3	Maximise	3
Lag time (min)	263	352	Maximise	3
Entrapment efficiency	70.55	86.25	Maximise	3

Importance can range from 1 (the least important) to 5 (the most important), 4 which gives emphasis to a target value. For instance, high importance value of 3 was assigned the response as to delay the release is usually preferred for chronotherapeutic system. Following the conditions and restrictions above, the optimization procedure was carried out.

The response surface obtained for the global desirability function is presented in **Figure 17**. The co-ordinates producing the maximum desirability value (D= 0.856) were Ethyl Cellulose (EC) of 210, Eudragit S100 (ER S100) of 192, Polyvinylpyrrolidone K30 (PVP) of 80.42. The predicted response values corresponding to the latter value of D were: percentage drug release is 96.94%, Lag time is 331.32min and entrapment efficiency is 87.99 %.The prediction efficiency of the model was confirmed by performing the experiment under the optimal condition.

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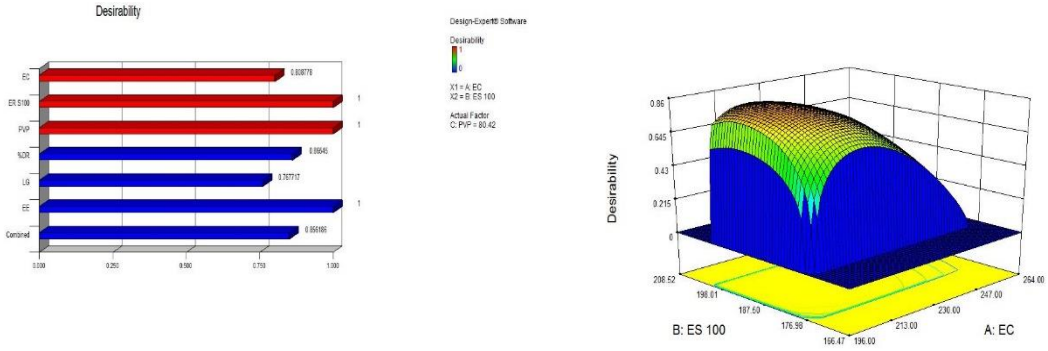

Fig. 17. Graphical representation of the overall desirability function D.

Results and Discussions of the Optimized Formulation

Formulation of etodolac loaded solid dispersions was prepared as per optimum condition provided by experimental design methodology. Evaluation parameters of the prepared etodolac solid dispersions were investigated. The optimized formulation of solid dispersion were prepared by solvent evaporation technique.

Micromeritic properties

The results obtained for precompression parameters for the optimized formulations of etodolac loaded solid dispersions was shown in **Table 5**. All the parameters were evaluated thrice and the average was taken. The prepared microsphere formulation was found to be porous and free flowing in nature.

Table 5 Micromeritic properties of optimized solid dispersions

Sl. No.	Parameter	Observed values
1	Angle of Repose	24.23° ±0.001
2	Bulk density	0.579 ± 0.004 g/cc
3	True density	0.621± 003 g/cc
4	Carr's Index	7.725± 0.002
5	Hausner's Ratio	1.09± 0.003

Drug entrapment efficiency

The percent drug entrapment and percent free drug for the prepared solid dispersions was determined and the optimized etodolac loaded solid dispersions was analysed for the drug entrapment. The results are shown in **Table 6.** All the analysis was carried out in triplicate and the average was taken.

Lag time

The lag time and cumulative percent of drug release were calculated using calibration curve in phosphate buffer pH 7.4 at λ_{max} 274 nm for etodolac. All the analysis were carried out in triplicate and the average was taken. For the estimation of lag time, the time taken to release less than 10% of drug from the dosage form was determined. The results are shown in **Table 6**

Percentage drug release

The cumulative percent of drug release was calculated using calibration curve in phosphate buffer pH 7.4 at λ_{max} 274 nm for etodolac. The etodolac solid dispersions were filled in the capsule (size No.0) and dissolution was carried out for a period of 12 hours. The results are shown in **Table 6.**

Table 6 Entrapment Efficiency,Lag time, % Drug Release of optimized solid dispersion formulation

FORMULATION CODE	FACTOR LEVELS		
	X 1 (EC)	X2 (ER S100)	X3 (PVP)

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Optimized Formulation	210	192	80.42
	Predicted Value		Experimental Value
Entrapment Efficiency	87.99		87.26
Lag Time (min)	331.32		329
% Drug Release	96.94		96.22

The agreements between experimental and predicted responses for the predicted optimum are shown in **Table 7.** The errors for entrapment efficiency, lag time and percentage drug release was found to be 0.82, 0.7, 0.74 % respectively, which were found to be in good agreement with a difference of 1-6%.

Table 7 The comparison of experimental and predictive values of different objective functions under optimal conditions

X_1 EC	X_2 ERS100	X_3 PVP	Entrapment Efficiency	Lag time (min)	% drug release
Desirability value (D) =0.856					
210	192	80.42			
Predictive			87.99	331.32min	96.94
Experimental			87.26	329 min	96.22
Error			0.82	0.7	0.74

SUMMARYAND CONCLUSION

Etodolac loaded controlled release solid dispersions formulation was optimized using response surface methodology by fitting a second-order model to the response data. DSC and XRD were adopted in this investigation to identify the physical state of the drug in solid dispersion and it proved that the crystalline etodoalc transformed into the amorphous state after preparation. The model was found to be satisfactory for describing the relationships between formulation variables and individual responses as well as the relationships between formulation variables and the overall desirability. The optimization method enabled us to predict the values of response variables and overall desirability within the experimental range with good agreement between the predicted and experimental values. An optimum desirability of etodolac loaded controlled release solid dispersions was achieved at high levels of ethylcellulose (EC), eudragit S100 (ERS100) and polyvinylpyrrolidone K-30(PVP).

In conclusion, solid dispersions using ethyl cellulose and eudragit S100 as retardants has successfully delay the release of release of drug from its tablet formulations. In the present case, it is found that the incorporation of ethyl cellulose and eudragit S100 and polyvinylpyrrollidone K30 (PVP) in the matrix not only helped to provide good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time with good entrapment efficiency. The manufacturing method employed is simple and easily adaptable in the conventional tablet-manufacturing units. Moreover, this approach can improve patient compliance, provide rapid onset of action and increase the bioavailability making it an ideal dosage form for administering etodolac in the treatment of rheumatoid arthritis. In this retrospect this method can be efficaciously used for the delayed release tablets.

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