Studies on the investigation of preformulation parameters, compatibility studies to design and formulate the etodolac solid dispersions

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ABSTRACT

The present study involves the investigation of certain fundamental physical and chemical properties of Etodolac loaded solid dispersions. Etodolac (+) 1, 8 diethyl -1,3,4,9-tetrahydropyrano-(3,4,-b) indole-1 acetic acid is a member of pyranocarboxylic acid group of non-steroidal anti-inflammatory drugs (NSAIDS).Before the development of any dosage form it is essential to study the compatibility of drug and excipients , the divided properties of powder etc. The results from the studies helps to decide the formulation approaches for the development of solid dispersions. Solid dispersions for delayed release tablets were done by solvent evaporation method by using the polymers like Eudragit S 100, Ethyl cellulose and polyvinyl pyrollidone. The preformulation studies helps for the successful selection of excipients for the formulation of delayed release tablets using solid dispersion as a carrier. On the basis of the results from experiments, it is found the Etodolac is found to compatible with the excipients like Eudragit S 100, Ethyl Cellulose, polyvinyl pyrollidone. The FTIR spectra reveals that there is no major degenerative interations between the drug and excipients.

Keywords: Compatibility; DSC; Etodolac; Excipients; Solid dispersions.

INTRODUCTION

One of the most important parameter to be considered before the development of a dosage from, is to characterise the preformulation parameters and the drug excipient compatibility studies. It helps the manufacturer to select the right excipient, thereby to develop an effective and stable dosage form, which helps to enhance the bioavailability of drugs (Choudry P.K et al., 2012). Nonsteroidal anti-inflammatory drugs commonly called as (NSAIDs) are the drug of choice for inflammation, pain, rheumatoid arthritis etc. These drugs exerts its therapeutic activity by blocking the generation of Prostaglandins (PGs). NSAIDs can inhibit the cyclooxygenase enzymes which includes a part in the production of PGs. Etodolac (+) 1, 8 diethyl -1,3,4,9-tetrahydropyrano-(3,4,-b) indole-1 acetic acid is a member of pyranocarboxylic acid group and it consists of two enantiomers, S- and R-etodolac. (Inoue N et al., 2011) Etodolac is used for the treatment of chronic conditions like arthritis, helps to reduce the plain, swelling and joint stiffness (Rohini Pilli et al., 2014).

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After oral administration, etodolac is metabolised into 6-, 7-, and 8-hydroxylated-Etodolac and Etodolac glucuronide. Etodolac can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, which can be fatal.

Preformulation studies is an important step in product development. To develop an optimum drug delivery system, the preformulation studies helps to study the physical and chemical parameters of the drug (Gopinath., 2011). Preformulation studies helps to generate information for developing the most stable and bioavailable dosage form.

In recent years many analytical methods are available for the drug-excipient compatibility testing. The present study, is to determine the physical and chemical properties of drug, the derived properties of powder, FT-IR methods. The physicochemical characterization includes the solubility, pKa, melting point, assay development. Angle of repose, bulk density, compress ibility index etc includes the derived properties of powder. In addition dissolution studies of the formulations of containing etodolac were performed to evaluate the controlled release of the drug. In FTIR, the spectrum of pure drug was compared with that of the drug-excipient mixture.

MATERIALS AND METHODS

Drug sample were obtained from IPCA Laboratories Mumbai .Excipients like, Ethyl Cellulose, Eudragit S 100, Polyvinyl pyrolidone, were purchased from Yarrow chemicals Mumbai. All the chemicals used were of analytical grade and are used without any further purification.

EXPERIMENTAL STUDY

Solubility determination

As per the British pharmacopoeia specifications the solubility of etodolac was evaluated in aqueous solvents like water and in organic solvents like methanol, acetone, chloroform, ethanol and diethyl ether. (Shengjum et al., 2007, British Pharmacopoeia 2004)

Determination of pH

This was performed by preparing a dispersion of 1% w/v of etodolac and it is shaked for 5 minutes .The pH of the above dispersion was determined by using digital pH meter (model 335, Systronics, India) (Ohwoavworhua F O et al., 2005). Triplicate determinations were taken and average of the data is reported.

Determination of True density

Liquid displacement method was used to determine the true density, (D), is calculated using the formula below. (Lachman et al., 1986).

$$D = \left(\frac{M}{V_p - V_i}\right)$$

The total volume in the pycnometer is Vp; the volume of intrusion fluid in the pycnometer is Vi containing the powder mass (M).

Determination of bulkiness, bulk density and compressibility index

Three tap method is used to determine the Bulk density of the etodolac (Martin *et al.*, 1994).About 50 cc of Etodolac was introduced into a 100 ml graduated measuring cylinder. The measuring cylinder was tapped onto a flat surface three times from a height of one inch in two seconds. Bulk density was calculated from the final volume and the weight of the sample using the formula

$$Bulk\ density, \rho B = \frac{weight\ of\ the\ powder}{bulk\ volume\ of\ the\ powder}$$

The bulkiness of the powder was calculated from the reciprocal of bulk density. The percentage compressibility index (I) (Marshall *et al.*, 1991) of the etodolac was calculated from following formula.

$$I = \left(1 - \frac{V}{V_o}\right)100$$

Angle of repose

The angle of repose was calculated by static method using Funnel. Funnel was kept on triangular stand, which was kept on horizontal plane at a distance of 2cm. The sample was introduced into the funnel. As the pile forms it reaches to the tip of funnel. The diameter of the pile was noted. The angle of repose (θ) was calculated by the following formula

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

Where   h = height of pile of microspheres

r = radius of pile of microspheres

Partition coefficient

About 10 mg of drug was added in a mixture containing 1:1 ratio of n-Octanol (previously done saturation with water) and distilled water (previously done saturation with n- Octanol). The above mixture shaked for 24 hours. Separate the organic phase and aqueous phases after shaking for 24 hour .The absorbance of both phases was taken and concentration in each phases was calculated (Carstensen et al, 1998).

$$Partition\ Coefficient = \left(\frac{Drug\ concentration\ in\ Octanol}{Drug\ concentration\ in\ water}\right)$$

Determination percent of moisture loss

The prepared solid dispersions were subjected to evaluate percent of moisture loss which helps to evaluate the hydrophilicity of the drug. The solid dispersions weighed initially and were placed in desiccator containing calcium chloride at 37 °C for 24 hours. The final weight was noted down until there is no further change in weight of sample was observed . (Shovarani *et al.*, 1994; Ghosh *et al.*, 2007).

$$\%\ of\ moisture\ loss = \left(\frac{Initial\ weight - Final\ weight}{Initial\ weight}\right) \times 100$$

Determination of distribution in particle size

A dispersion of 1% w/v Etodolac in glycerin was prepared. The smear of the sample was closely viewed under microscope. By using calibrated eyepiece micrometer size of the particles was taken. (Conner *et al.*, 1995; Paronen *et al.*, 1983). The particle size distribution of the Etodolac was estimated.

Preparation of Calibration Curve of etodolac in Distilled Water

10mg etodolac was accurately weighted and dissolved in 100 ml of Methanol to produce a solution 0.1 mg/ml. 20ml of the solution was transferred in a volumetric flask and volume was made up to 100ml with distilled water. 2,4,6,8 ml of this solution was taken in 10ml volumetric flasks and distilled water was added to adjust the volume up to the mark to prepare standard solutions. These serial dilutions were carried out to get

different etodolac concentrations. Standard solutions were then analyzed by UV spectrophotometer (UV-mini-1240, Shimadzu Corp., Kyoto, Japan) at 274 nm and absorbance was noted. Then the absorbance values were plotted against drug concentration and standard curve of etodolac was prepared.

Preparation of solid dispersion

Solid dispersions was prepared by using solvent evaporation method, which is a widely accepted process. Drug (Etodolac) and carrier (Eudragit S 100, ethyl cellulose and polyvinyl pyrollidone) were dissolved in a common solvent (Methanol) and solvent was evaporated to form the solid mass. Basically, this solvent evaporation method involves two steps and these are: (i) preparation of a solution containing both matrix material or carrier and drug and (ii) the removal of the solvent resulting in the formation of the solid mass. The prepared solid dispersions were sifted in sieve #80 and stored in a desicator.

Percentage yield

Percentage yield was determined by weighing the dried solid dispersion and calculated with respect to the weight of the initial components according to the following formula;

$$Percentage\ yield\ (\%) = \frac{Recovered\ weight\ of\ solid\ dispersions}{Weight\ of\ polymer\ used\ +\ drug} \times 100$$

Fourier transform infrared spectroscopy (FTIR)

FT-IR spectra of Etodolac were recorded on a FT-IR spectrophotometer by using KBr pellet method .The drug–excipient sample mixture were recorded to perform the compatibility studies. The spectrum of each sample was recorded over $400cm^{-1}$ to $4000cm^{-1}$ spectral region with resolution of $4\ cm^{-1}$

Entrapment efficiency

The entrapment efficiency was determined by dispersing accurately weighed 10 mg of formulation in 10 mL of ethanol followed by agitation with a magnetic stirrer for 24 h to dissolve the polymer and extract the drug. The solution was then filtered through Whatmann filter paper and the filtrate was assayed for content by an UV spectrophotometer at 274 nm.

$$Encapsulation\ efficiency = \frac{Calculated\ drug\ concentration}{Theoretical\ drug\ concentration} \times 100$$

Invitro drug release Studies

The solid dispersions were evaluated for their integrity in the physiological environment to simulate the conditions of gastrointestinal tract. The dissolution was carried for first 3hour at pH 1.2 .At the end of 3 hour half volume of the medium was filtered and removed. Then it is replaced by equal amount of buffer of pH 9.3.This helps to achieve the pH of the dissolution medium to

7.4 and the dissolution was carried at this pH for 9 hours. (Amarnath K et al., 2012)

Dissolution studies of solid dispersions were carried out in triplicate using USP XIII dissolution rate test Apparatus .Weighed quantities of solid dispersions were loaded into the basket of dissolution apparatus containing the medium. The temperature of the dissolution medium was maintained at $37\pm0.5°C$ with a stirring speed of 100 rpm.5ml samples were withdrawn at predetermined time intervals and dissolution medium was replaced with fresh dissolution medium .All the samples were filtered through Whatmann filter paper, diluted and analyzed spectrophotometrically for drug release till the end of the test i.e. for 12hours. The dissolution rate of pure drug etodolac were also studied. At various time intervals the percentage of drug r elease was calculated and plotted against time

Stability studies

Stability studies of the prepared solid dispersions were performed by taking the formulations in a crucible and placed at 45^0C and 75% RH for 45 days, the solid dispersions were analysed for their drug content and dissolution studies

RESULTS AND DISCUSSIONS

This work aims to design a new delayed release tablet for the chronotherapeutic delivery of etodolac for the management of rheumatoid arthritis. The formulation process involves two steps .In the first step solid dispersions was prepared using different polymers like Eudrgit S 100, Ethyl cellulose and polyvinyl pyrollidone containing the drug etodolac. In the second step this prepared solid dispersions were subjected to direct compression using the tablet excipients to formulate the tablets.

The derived properties of powders has got a greater influence in the preparation of various dosage form. The powder blend was evaluated for different parameters like true density, bulk density, compressibility index, angle of repose and hausners ratio. So it is essential to study the particle size distribution before manufacturing a dosage form. The physicochemical characterisation were also studied as preformulation procedure, the results was shown in table 1

The particle size is determined by using optical microscopy, which gives direct measurement of the individual particle. Table 2 and figure 1 shows the particle size distribution of etodolac powder.

λ_{max} of the drug was determined using UV-Visible spectrophotometer by scanning the stock solution at a concentration of 0.1mg/ml in the range 200-400nm.The drug shows maximum absorption at 274 nm. Figure 2 shows the calibration curve of etodolac, which shows linearity .The correlation was found to be 0.997.

Figure 3 shows the FT-IR spectrum of etodolac powder gives characteristic peak at wave numbers like 3344 ,

Table 1: Physicochemical characterisation of Etodolac for Solid dispersions

Parameters	Results
Description	Etodolac occurs as white crystalline powder
Solubility	Insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.
pH	7.4 ± 0.29
True density (g/cm^3) ±SD	1.23 ± 0.57
Bulk density(g/cm^3) ± SD	0.362 ± 0.037
Compressibility index (%) ± SD	13.92± 0.40
Angle of repose (º) ±SD	25.33º ± 0.72
Hausner ratio ±SD	1.67 ± 0.16
Moisture content (%)± SD	7.92 ± 0.50
Partition Coefficient	11.4 at pH 7.4
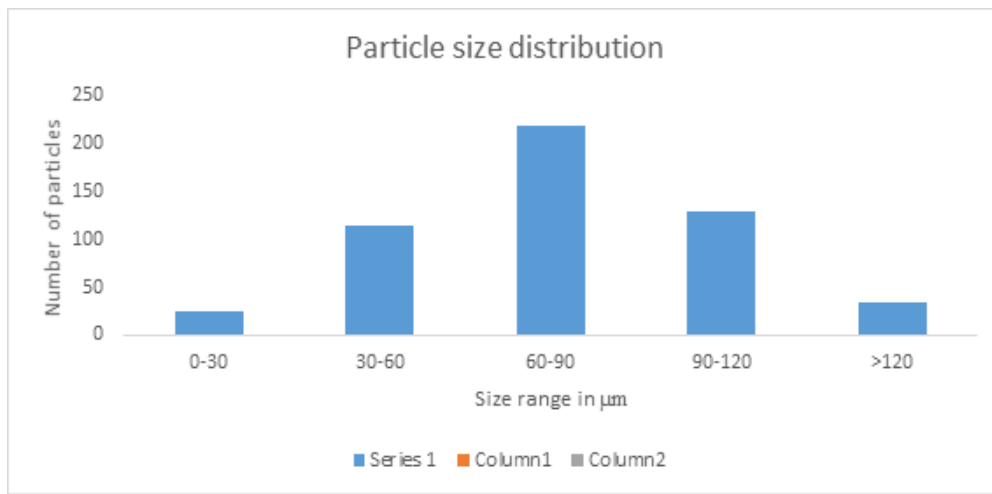
Figure 1: Particle size distribution of etodolac

Table 2: Particle size distribution of Etodolac Powder

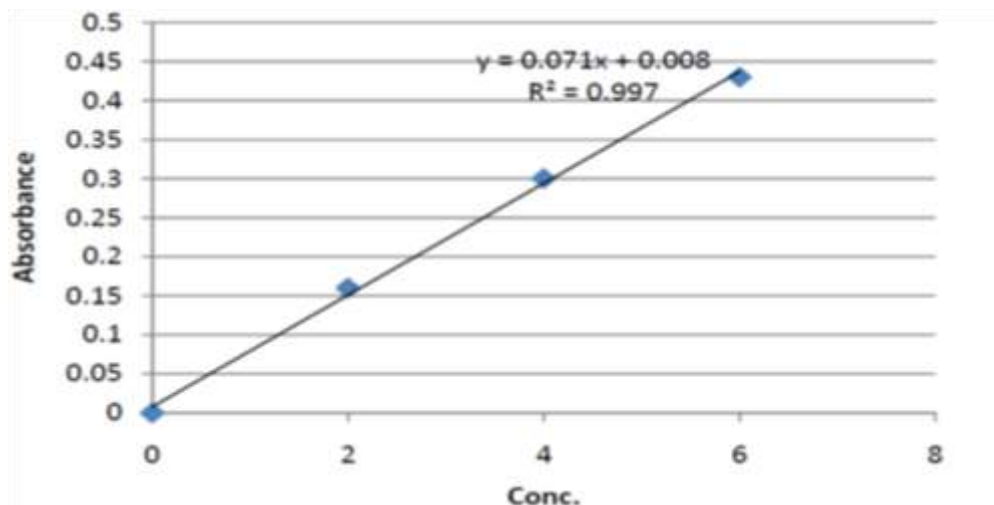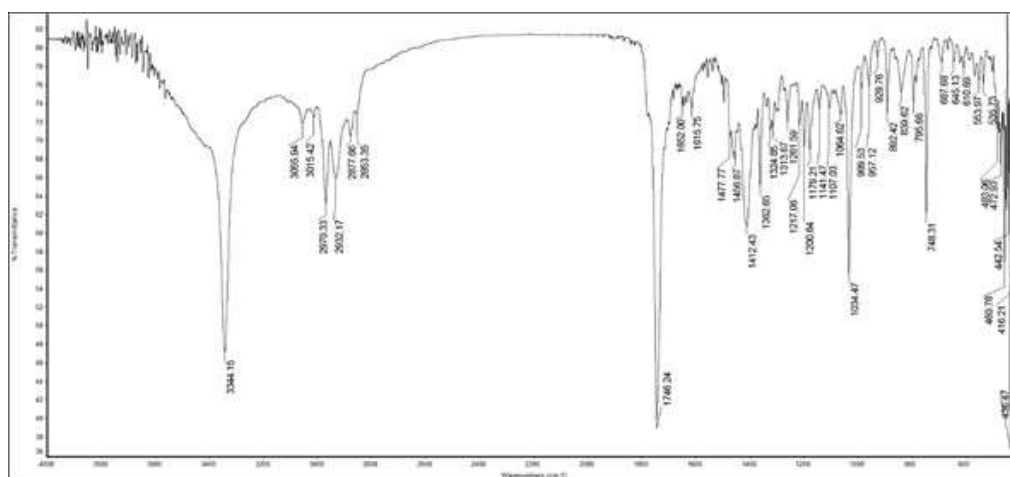| Size range in µm	Number of particles
0-30	25
30-60	115
60-90	220
90-120	130
>120	35

Figure 2: Calibration curve of Etodolac
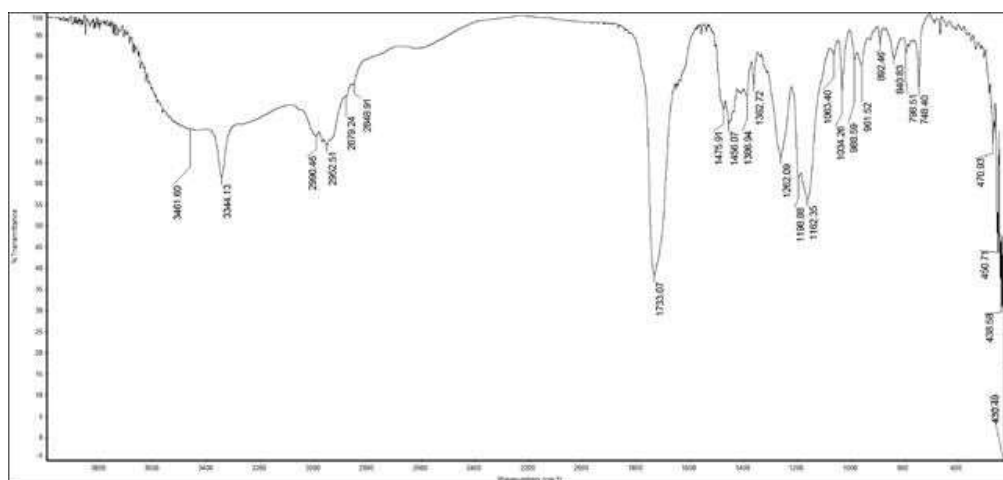
Figure 3: FT-IR spectrum of Etodolac
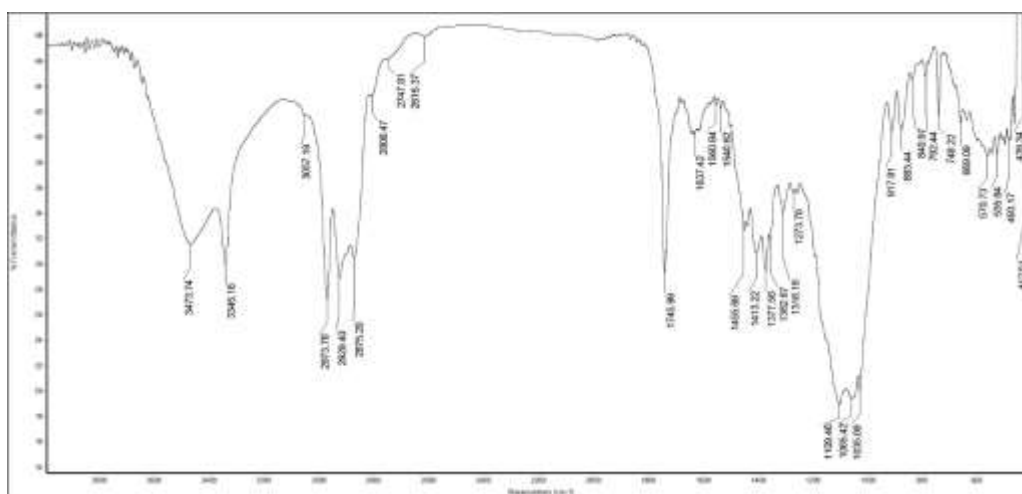

Figure 4: FT-IR of Etodolac and Eudragit S 100

Figure 5: FT-IR spectrum of Etodolac and Ethyl Cellulose

Table 3: Evaluation of etodolac solid dispersions

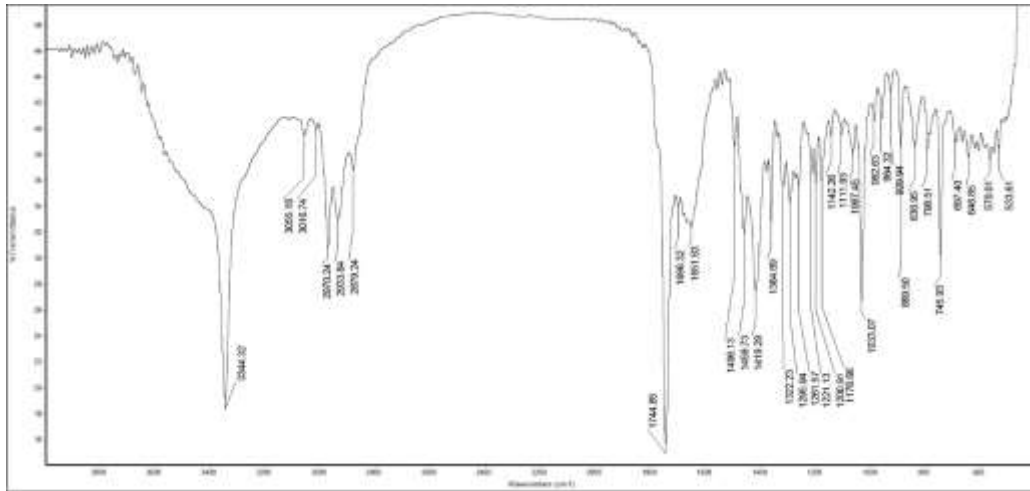| Evaluation studies	Results
Entrapment efficiency	86.23
Percentage yield	84%
Percentage release	93.1%

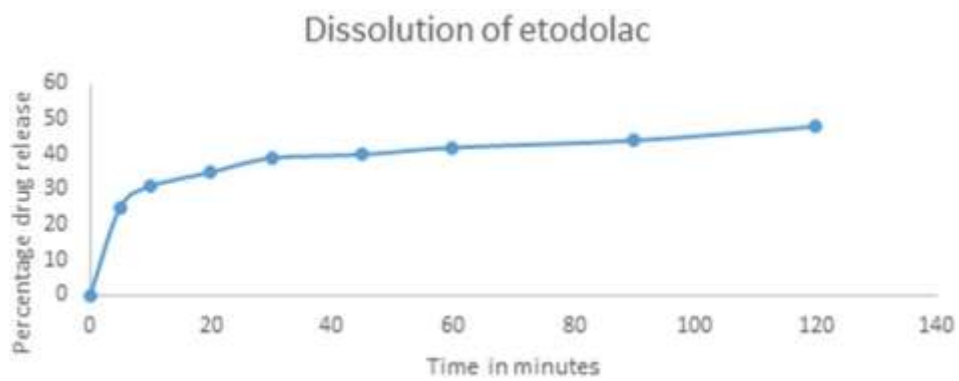**Figure 6: FT-IR spectrum of Etodolac and Polyvinylpyrollidone (PVP)**

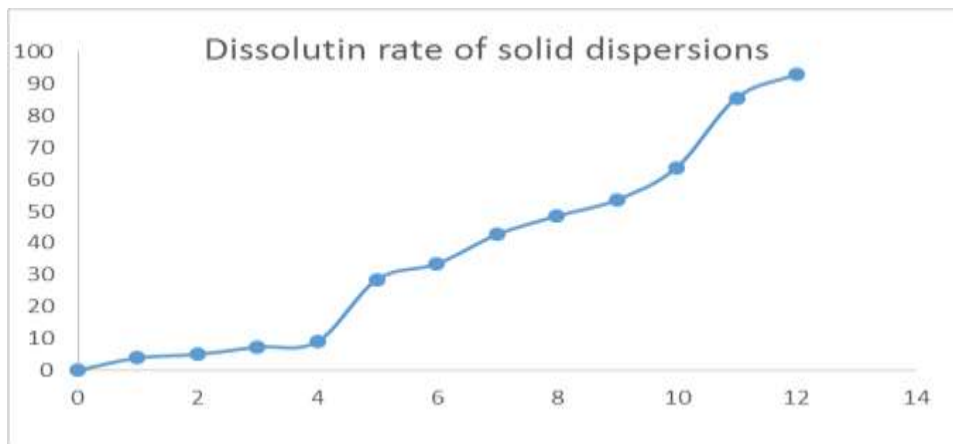**Figure 7: Dissolution rate of Etodolac**

Figure 8: Drug release profile of formulated solid dispersions

Table 4: Stability data of formulations

Sl.No	No of day	Changes observed	% of drug content
1	0	------------	87.33
2	15th day	No transition	87.40
3	30th day	No transition	87.30
4	45th day	No transition	87.35

2877, 1745, 1362, 1034 and 748 cm^{-1}.at a resolution of 4 cm^{-1} .The physical mixture of drug and excipients were shown in figure 4, 5 and 6.The characteristic peak found in the physical mixture was found to be super-imposable to that of the drug. The absence of extra peaks gives clear evidence that the drug is intact in solid dispersions .Moreover there is no shift of peaks or disappearance or modification of the principal peaks. So it can be concluded that there is no interaction be-tween drug and excipients.

The results of entrapment efficiency, percentage yield and % release were shown in Table 3, which shows that the prepared solid dispersions has got uniform distribution of drug and the polymer

The prepared solid dispersions for controlled release were subjected to invitro dissolution studies, entrapment efficiency, percentage yield. Figure 7 and 8 shows the invitro dissolution profile of etodolac powder and the solid dispersions of etodolac respectively. In the dissolution studies of solid dispersions containing the drug etodolac, it is seen that all the solid dispersions were dissolved and only less than 10% of drug is released in the dissolution media at pH1.2 in first 3 hours. From the dissolution graph it is seen that formulations shows a lag time of 4-5 hours which is desirable for chronotherapeutic application and the system could control release of Etodolac at pH 7.4 till the end of 12 hours.

Stability data of formulations containing solid dispersions were shown in table 4, confirms that there is no physical change for the solid dispersions and percentage of drug content.

CONCLUSION

One of the critical phase in the development of a dosage form is the preformulation phase which includes the physicochemical characterisation and compatibility studies. The present study showed the formulations of solid dispersions of etodolac for the delayed release tablets. The studies of physicochemical parameters gives useful information in developing delayed release tablets for the controlled delivery of the drug. The data confirms the absence of any possible interaction between drug and polymer in the solid state. The dissolution rate of solid dispersions provided a better lag-time up to 4-5 hours, helps to solve the issue when formulating a chronotherapeutic delivery for the management of rheumatoid arthritis .The solid dispersions using the polymers like eudragit S 100,ethyl cellulose and polyvinyl pyrollidone helps to achieve the controlled drug release up to 12 hours .Thus chronotherapeutic system of etodoalc solid dispersions helps to improve solubility of drug, can achieve a defined lag time of drug release and can overcome the gastrointestinal effects of drug such as gastric irritation, ulceration etc. Thus by targeting the drug release at a specifies time of a day, helps to manifest the clinical conditions of rheumatoid arthritis after a tablet is taken by a patient.

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