RESEARCH ARTICLE

Enhancement of Solubility of Anti-Inflammatory Drug by Using Different Solubility Enhancement Techniques

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ABSTRACT: Using a range of pure solvents and solvent mixes, this study investigated the solubility enhancement of four cox-2 inhibitors: celecoxib, rofecoxib, meloxicam, and nimesulide. The solvents included water, alcohols, glycols, glycerol, and polyethylene glycol 400 (PEG 400). The combined solvent systems included water-ethanol, glycerol-ethanol, and polyethylene glycol-ethanol. Using 0.05M glycine-sodium hydroxide buffer solutions, a pH-solubility profile of the medications was acquired in the pH range of 7.0 to 19.9. It was discovered that PEG 400, higher glycols, and lower alcohols made effective solvents for these medications. Using ethanol as the second solvent could greatly increase the water solubility of celecoxib, rofecoxib, and nimesulide. The PEG 400-ethanol system had the highest potential for solubilisation among the mixed solvent systems. Meloxicam and nimesulide showed a considerable increase in solubility when the pH value rose. Drug dissolution by pure solvents was shown to be primarily influenced by the solvent's physico-chemical characteristics, including polarity, intermolecular interactions, and the solvent's capacity to establish a hydrogen bond with the drug molecules. The solubilisation power increased with the degree of polarity difference between the two solvents in a particular mixed solution. Nevertheless, the solubilisation power in a particular mixed solvent solution could not be connected to the medicines' polarity. This study has also addressed the significance of the solubility data with regard to formulation development.

Key Words: Solubility Enhancement, Cox-2 Inhibitors, Solvent Systems.

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INTRODUCTION

The most often prescribed pharmaceuticals worldwide are nonsteroidal anti-inflammatory drugs, or NSAIDs. NSAIDs are a class of medications that have antipyretic, analgesic, anti-inflammatory, and platelet-inhibitory effects. However, because these medications block the formation of prostaglandins, they can cause major side effects include gastric mucosal ulcers, gastrointestinal (GI) toxicity, and bleeding(1). The capacity of NSAIDs to inhibit the cyclooxygenase enzyme (cox) has been identified as its mechanism of action. Cox-1, one of the two cyclooxygenase isoforms, mediates prostaglandin synthesis, whereas Cox-2 is mostly linked to fever, pain, and inflammation.Nonselective cox inhibitors make up the conventional NSAIDs. Because they spare cox-1 activity, cox-2 selective NSAIDs are therefore the best anti-inflammatory medications with the fewest possible adverse effects(2).

However, cox-2 inhibitors' extremely low wettability and aqueous solubility make it difficult to create pharmaceutical formulations and result in inconsistent oral bioavailability. Several researchers have used cosolvents to increase the solubility of medications that are not very soluble. Other methods besides the use of cosolvents have been tried to improve the solubility of nimesulide and meloxicam(3). There hasn't been much focus on improving the solubility of celecoxib and rofecoxib thus far. Using a range of solvents and solvent-cosolvent mixtures, the current work aims to improve the solubility of four cox-2 inhibitors: celecoxib, rofecoxib, meloxicam, and nimesulide. The work is pertinent to the creation of parenteral and liquid forms of these medications(4).

MATERIAL AND METHOD

We received gift samples of celecoxib from Ajanta Pharmaceuticals, Mumbai, India. Additionally, every solvent that was bought was of analytical grade.

PREFORMULATION STUDIES

Confirmation of drug was done by melting point determination, UV spectroscopy, infrared spectroscopic study (FTIR) and differential scanning calorimetry (DSC)(5).

A standard solution of 100 mcg/mL was prepared by dissolving 10 mg of RG in 100 mL USP phosphate buffer pH 5.0 and scanned over a range of 400 nm to 200 nm. The obtained spectrum was compared with reported UV spectra of RG(6).

Melting point of drug was determined using capillary tube method. celecoxib was filled into a glass capillary tube, which was sealed at one end and tied to the thermometer, placed in thiels tube containing paraffin oil. The temperature was recorded till complete melting of drug(7). The FTIR spectrum of celecoxib was obtained on a FTIR

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Table 1. Values of exponent Λ and the corresponding release mechanism

Exponent λ			Release Mechanism
Thin film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
0.5 < Λ < 1.0	0.45 < Λ <0.89	0.43< Λ <0.85	Anamolous transport
1.0	0.89	0.85	Zero-order

Table no: 6 In vitro drug release specifications

Sampling Time (min)	Drug release Specification (%)
10	10-20%
30	40-60
40	70-80
50	> 80%

using diffuse reflectance scan sampling method (1 mg sample in 100 mg KBr). The scanning range was of 4000 - 400 cm^{-1} with resolution of 1 cm^{-1}.

DSC thermogram of celecoxib was obtained by a DSC. Samples weighing between 20 and 25 mg were loaded in aluminium pans and placed into DSC cell. Thermal analysis of samples was carried out at a scanning rate of 10^{o} C/minute, over a temperature range of 30 - 300^{o} C(8).

SOLUBILITY DETERMINATION

Celecoxib's apparent solubility was assessed at 37°C in distilled water and buffers with pH values of 1.2, 3.3, 5.0, 7.0, and 9.0.

Each of the eighteen vials contained 10 mg of celecoxib. Each drug-containing vial received a 10 mL aliquot of each type of solvent. The vials were then stored for 24 hours at 37 ± 0.5o C in a shaker incubator. The vials were shaken and then incubated for 12 hours at 37 ± 0.5o C to achieve equilibrium. The filtrate was then subjected to spectrophotometric analysis at 270 nm after the solution was passed through a 0.45 µm millipore filter (9,10).

Preparation of solid mixtures

Using three distinct methods—physical mixing, kneading, and solvent evaporation—solid mixes of the chosen medications, celecoxib with polyvinyl pyrrolidone (PVP), K-30 PEG-6000, and mannitol as carriers, were made for the current study. For celecoxib, solid mixes were made with PVP-K-30, PEG-6000, and mannitol in drug to carrier weight ratios of 1:1, 1:3, and 1:6, respectively. All three of the approaches employed in this inquiry used the same ratios.

Physical mixture preparation

Simple mixing of precisely weighed amounts of medication and the carriers sorted through sieve #100 in a closed glass bottle produced physical combinations. After that, the powders were kept in a desiccator. Five grammes of the physical combination were made in each instance (11).

Table 2: In vitro drug release specifications

Sampling Time (min)	Drug release Specification (%)
10	10-20%
30	40-60
40	70-80
50	> 80%

Preparation of solid dispersions using solvent evaporation technique

Solvent evaporation was used to create solid dispersions of the chosen medication, celecoxib. To get a transparent solution, the right amounts of medication and polymer were dissolved in about 60 millilitres of solvent blend. The solvent blend for PVP-K-30, PEG-6000, and mannitol was a 2:1 mixture of dichloromethane and methanol. Next, the solvent mixture was eliminated by evaporation in a water bath at 45° C with lowered pressure. After that, the residue was moved to a glass desiccator and vacuum-dried to a consistent weight.

Before being used, the dry product was ground into a powder, sieved through sieve #100, and kept in a desiccator. Five grammes of dispersion were made for each instance (3,12).

EVALUATION OF SOLID DISPERSIONS

Drug content uniformity

100 mg samples were obtained from each batch of the solid combinations that were made, and their drug concentration was examined. To make it easier to extract the medication from the solid combination into solvent, 100 mg of the mixture was weighed into a 50 ml volumetric flask, diluted with methanol, and thoroughly mixed before being set aside for four hours with periodic shaking. After being brought to volume, the solution was passed through a 0.45 p membrane filter (Millipore nylon discs). Celecoxib's drug concentration was determined by spectrophotometrically evaluating the absorbencies of the solutions after they had been appropriately diluted further. Celecoxib's mean drug content and coefficient of variation (13).

Drug release studies

Using the paddle method with a rotation speed of 50 rpm, three separate dissolution tests of pure drugs and solid mixes were conducted using the USP XXIV Dissolution Rate Test Apparatus (Labindia Disso 2000). In the case of celecoxib, preparation samples equal to 60 mg of the drug were placed in hard gelatin capsules and added to the dissolution medium; in the case of celecoxib, the drug equivalent of 100 mg was spread out on the dissolution medium. Five millilitres of the sample were taken out at regular intervals and filtered using a 0.45 p membrane filter (Millipore nylon discs). Five millilitres of the dissolving media were added to maintain the starting volume. After being appropriately diluted, the filtered solutions were spectrophotometrically tested for drug concentration by comparing their absorbencies to a blank. The standard deviation and mean percentage of medication dissolved were computed (14).

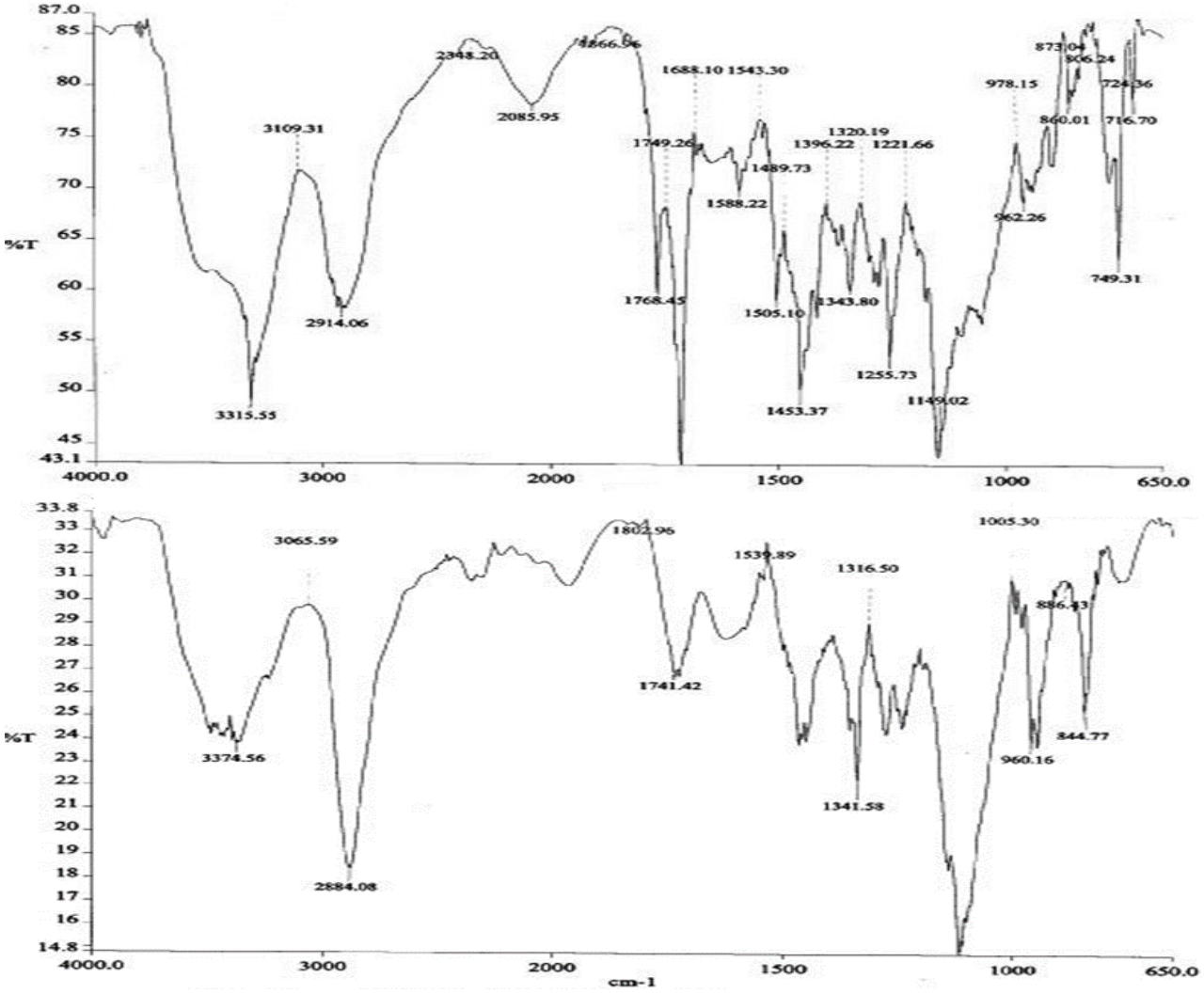

Figure 1.: FTIR Spectra of Physical Mixture Celecoxib + Mannitol, FTIR Spectra of Solid Dispersion of Celecoxib + PEG-6000

Comparison of dissolution profiles and drug release mechanisms and kinetics of dissolution rate

Several methods, including analysis of variance (ANOVA) based, model-independent, and model-dependent approaches, can be used to mathematically compare dissolution data in order to quantify observed changes in the rate and extent of drug release as impacted by formulation and process variables. Statistically significant variations in dissolution profiles can be found using ANOVA procedures, which are frequently employed to identify significant changes between groups. The mean dissolution time or the ratio of the area under the dissolution curve (dissolution efficiency) are the foundations of model-independent methods. In the model-dependent approaches, the release kinetics and release mechanism are evaluated by fitting the individual dissolution data with mathematical models. Despite the difficulties and restrictions associated with each of these approaches, the numerical figures they produce can be used as quantitative measurements to compare the complete dissolution profiles and to describe the kinetics and mechanisms of drug release.

Model-independent approaches

Comparing the time it took for the specified percentage of the active drug to dissolve in the dissolution medium with figures like T5o and T90—which were determined by taking the time points of 50% and 90% of the drug dissolved—as well as another parameter called Dissolution Efficiency (DE), which was proposed by Khan31, was done as a model-independent method. As a percentage of the size of the rectangle described by 100% dissolution at the same time, DE is the area under the dissolution curve up to time t.

$$DE_8\% = \frac{\int_0^t y\,dt}{y_{100}\,t} \times 100$$

Depending on the time period selected, the dissolving efficiency can have a variety of values. In any event, consistent time periods must to be selected for comparison. For instance, the drug's dissolution from a certain formulation after 30 minutes is indicated by the index DE30, which can only be compared to DE30 of other formulations. A single figure DE that summarises the drug dissolving data makes it easy to compare a wide range of formulations. From each formulation's dissolving data, the DE10 and DE2ovalues were computed and

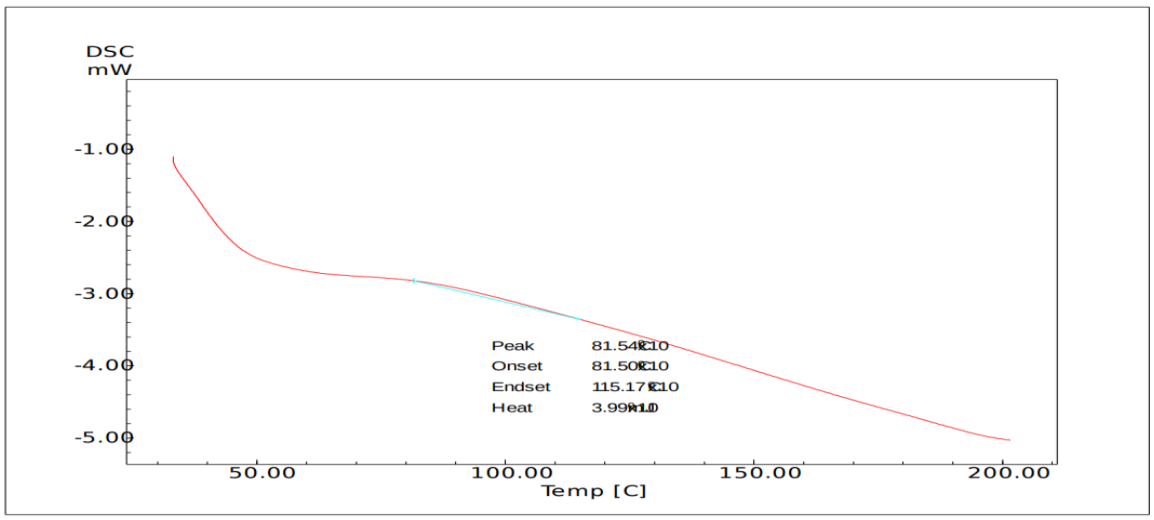

Figure 2: DS Thermogram of Celecoxib Solid dispersion

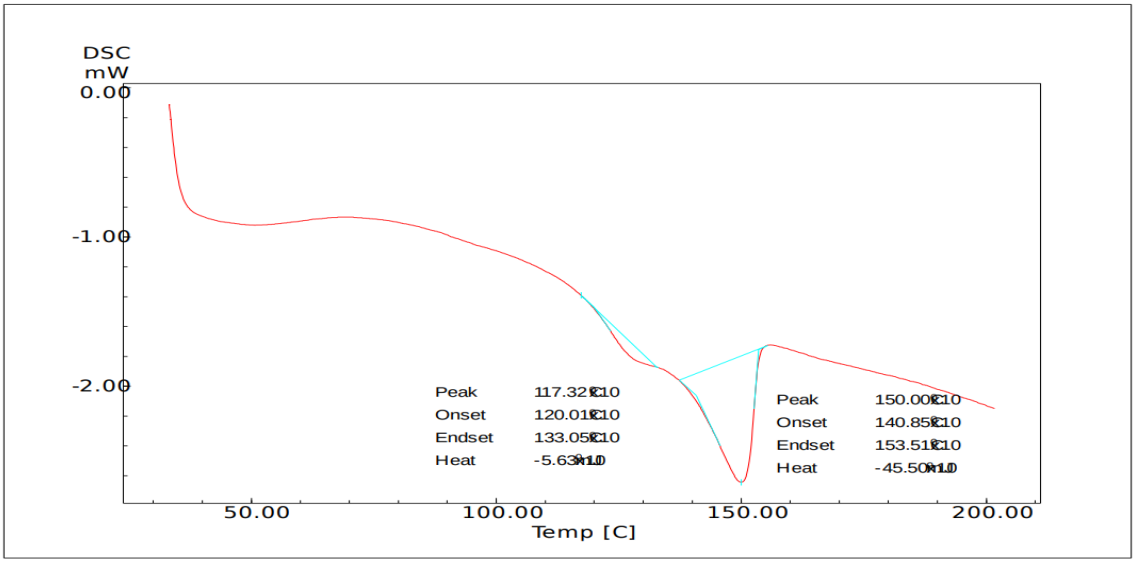

Figure 3: DSC Thermogram of Celecoxib Physical mixture

utilised for comparison. T50, T90, DE10, and DE2o are the dissolution parameters for all solid celecoxib combinations.

Model dependent approaches

Zero order release kinetics

$Qt = Q_0 + K_0t$

where (Ko) denotes the dissolution rate constant for zero order release and Q (t) represents the percentage of medication dissolved as a function of time (t) in minutes. If the drug release follows zero order release kinetics, the plot of the release against time will be linear. The slope of the % drug released against time graphs was used to calculate the release rate (Ko) in each example.

First order release kinetics

$\ln (100-Q) = \ln Q_0 - K_1t$

Where, Q = Amount of drug release at time t,

K_1= First order release constant

A regression coefficient (R2) number that is closer to 1 suggests a first order release, which means that the release is concentration-dependent. This value is derived from the log% ARR (Amount Remaining to Release) vs time.

Higuchi Square Root of Time Model

$Q= K_ht^{1/2}$

Where, Q= Amount of drug release at time t,

K_h= Higuchi square root of time release constant

Higuchi's drug release model suggests Fickian diffusional release, as indicated by the regression coefficient of percentage drug release vs square root of time that is closer to 1.

Hixon-Crowell Cube Root Model

$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = K_HC.t$

Where, Q_0 = initial concentration of drug present

Qt = amount of drug release at time t

R^2 values nearer to 1 for the plot of amount of drug released versus cube root time indicate Hixon – Crowell model.

Korsmeyer And Peppas Model

$Q_t / Q_\infty = K \times t^{\lambda}$

$\text{Log} (Q_t/Q_\infty) = \text{Log } K + \Lambda \text{ Log } t$

Where,

Q_∞ = Total drug released after infinite time.

Q_t/Q_∞ = Fractional drug released at time t

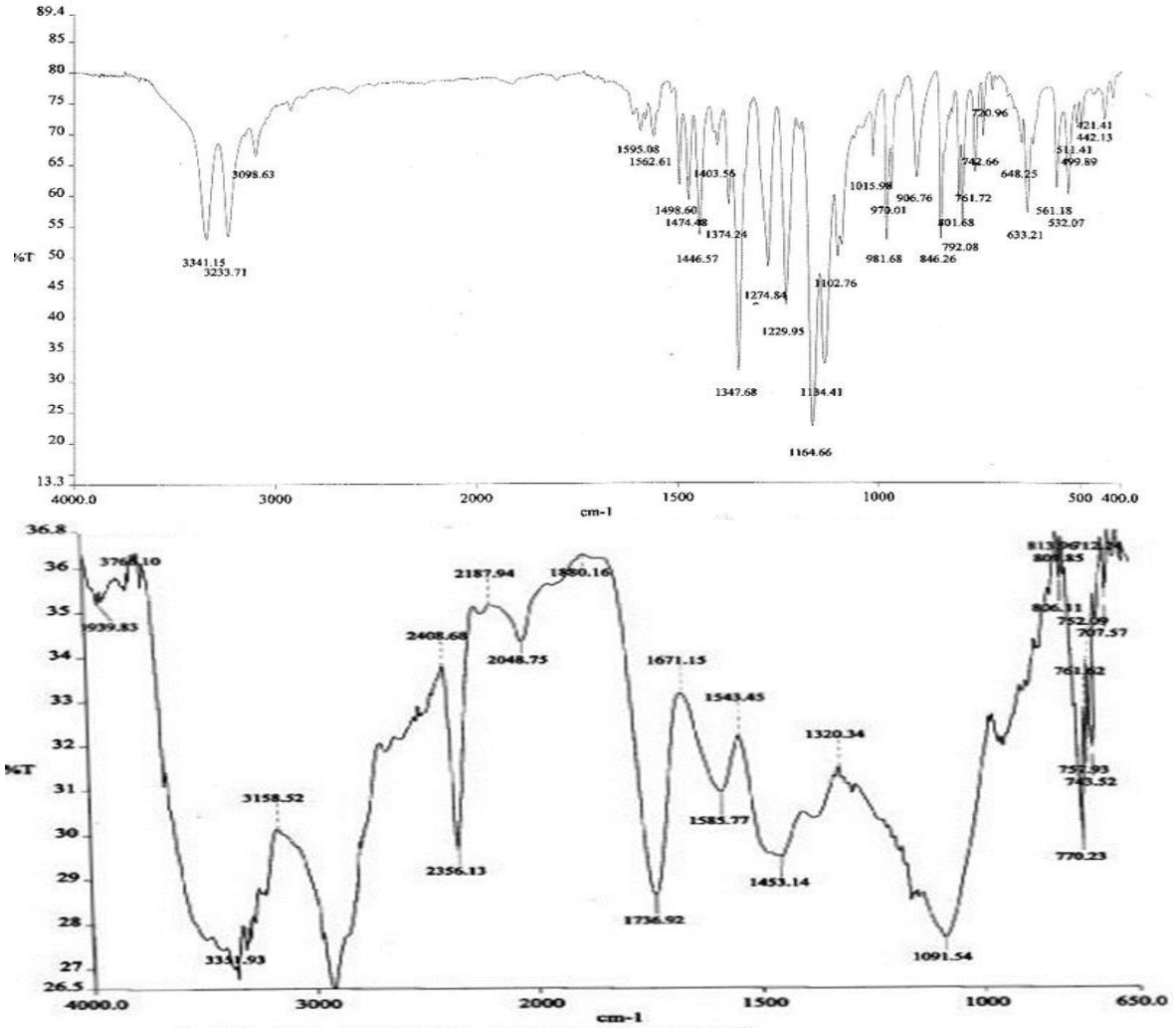

Figure 4: FTIR Spectra of Celecoxib, FTIR Spectra of Solid Dispersion of Celecoxib + PVP K-30

K = Kinetic constant incorporating structural and geometrical characteristic of the drug/polymer system (devices).

Λ = Diffusion exponents that characterizes the mechanism of drug release

T = Time

A plot of log (Q_t/ Q_∞) versus log t gives straight line of gradient λ and an intercept of log K. Values of exponent Λ and the corresponding release mechanism are given in Table 5.3.

Solid state studies

Fourier transform infra-red (FT-IR) analysis

A FT-IR spectrophotometer (JASCO FT/IR-4200 Spectrophotometer) in Tokyo, Japan was used to measure the FT-IR spectra of pure drugs, physical mixtures, and solid dispersions in the wave number range of 4000-200 cm-1.

Differential scanning Calorimetry study

A Shimadzu DSC-60 differential scanning calorimeter with a thermal analyser, located in Tokyo, Japan, was used to conduct the DSC measurements. In hermetically sealed aluminium pans, precisely weighed samples (about 5–10 mg) were heated in a nitrogen environment at a flow rate of 20 ml min–1 and a scanning rate of 15 °C min–1 between 60 and 250 °C. The reference was an empty aluminium pan.

X-ray diffraction study

The X-ray powder diffraction method was used to assess the crystalline condition of several samples. With minor adjustments, the X-RD analysis of the pure drug, best formulations S2, S22, and physical mixture W2 and W22 was carried out at the Centre for Earth Studies, Thiruvanthpuram, using the procedure described by Li et al., [108]. A Philips Analytical X-ray BV 1710 with a graphite monochromator and cobalt as the anode material was used to obtain the diffraction patterns at ambient temperature while operating at a voltage of 30 kV. The process parameters were set at a scan rate of 0.020 seconds-1, and the samples were examined within the 2θ angle range of 10 to 500.

Determination of in vitro drug release of solid Dispersions

Dissolution Parameters

Medium: Phosphate buffer (pH= 7.4)

Type: USP apparatus I (Basket) type

RPM: 75

Quantity: 900ml Temperature : 37± 0.2°C

Duration : 1 hr

Sampling time : 10 min, 20min, 30min, 40min.50min and 60 min.

Table 3: Melting Point Study of celecoxib

S. No	Drug	Observed Temperature	Literature Temperature
1.	Celecoxib	161.8^{0}C	161 – 164℃

Table 4: Observed Solubility of celecoxib and Polymer in aqueous condition

S. No	Category		
	Drug	Physical Mixture	Observed Solubility (µg/ml)
1.	Celecoxib	-	9.2
2.	-	Celecoxib + PVP K-30	15.30
3.	-	Celecoxib + Mannitol	15.50
4.	-	Celecoxib + PEG-6000	18.33

Table 5.: Observed DSC Thermograme of celecoxib SD and PM study

Category	Peak Temp (^{0}C)	Onset (^{0}C)	Endset (^{0}C)	Heat (mJ)
Celecoxib (Plain)	152.88	150.69	155.04	-154.57 mJ
Solid Dispersion	81.54	81.50	115.17	3.99 mJ
Physical Mixture	117.32 150.00	120.0 140.85	133.00 153.51	-5.63 mJ -45.50 mJ

Table 6: λ_{max} Studies of Celecoxib

S,No	Solvents (10µg/ml)	Experimental λmax	Literature λ_{max}	Observed absorbance
1.	Phosphate Buffer	273	272/273/274	0.155

SOLID STATE STUDIES

Differential scanning Calorimetry study

A Shimadzu DSC-60 differential scanning calorimeter with a thermal analyser, located in Tokyo, Japan, was used to conduct the DSC measurements. In hermetically sealed aluminium pans, precisely weighed samples (about 5–10 mg) were heated in a nitrogen environment at a flow rate of 20 ml min–1 and a scanning rate of 15 °C min–1 between 60 and 250 °C. The reference was an empty aluminium pan.

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Scanning electron microscopy (SEM)

The surface morphology of Drug-SD using polymer HPMC-AS (S2, S22) and PM (W_2, W22) were observed by scanning electron microscope (SEM) at JNU, New Delhi. Before hand, the samples were mounted on alumina stubs using double adhesive tape, coated with gold in Hitachi HUS-GB vacuum coating unit and observed in Hitachi S-300 N Scanning electronic microscope at a voltage of 10 Kv

Drug Content

Obtained SDs equivalent to 50 mg of drug prepared were weighed accurately and dissolved in a 50 ml of Phosphate buffer at pH 7.4. The stock solutions were filtered. The solutions were then diluted suitably in same solvent. The drug content was analyzed at 263 and 273 nm using a UV spectrophotometer (shimadzu-1700 series). Each sample was analyzed in triplicates

Dissolution Parameters

Medium: Phosphate buffer (pH= 7.4)

Type: USP apparatus I (Basket) type

RPM: 75

Quantity:900ml Temperature: 37± 0.2°C

Duration : 1 hr

Sampling time : 10 min, 20min, 30min, 40min.50min and 60 min.

RESULT DISCUSSION

Drug identification tests

Melting point: The melting point determined by the capillary method is the temperature at which the last solid particle of a compact column of a substance in a tube passes into the liquid phase. Melting point of celecoxib was observed in the following range enlisted below in table no 6.1 and get complies with the standard literature value.

Solubility Study

Drug excipient compatibility studies:

FTIR studies: The FT-IR analysis of the pure drug Celecoxib and drug polymer physical mixture (PVP K-30, Mannitol and PEG 6000) was carried out for Compatibility study. The FT-IR spectra for pure drug and polymer were obtained by powder diffuse reflectance on a FT-IR spectrophotometer (**JASCO-FTIR 4200)** in the wave number region of 4000-400 cm^{-1}. The same procedure is performed to analyze different vibration

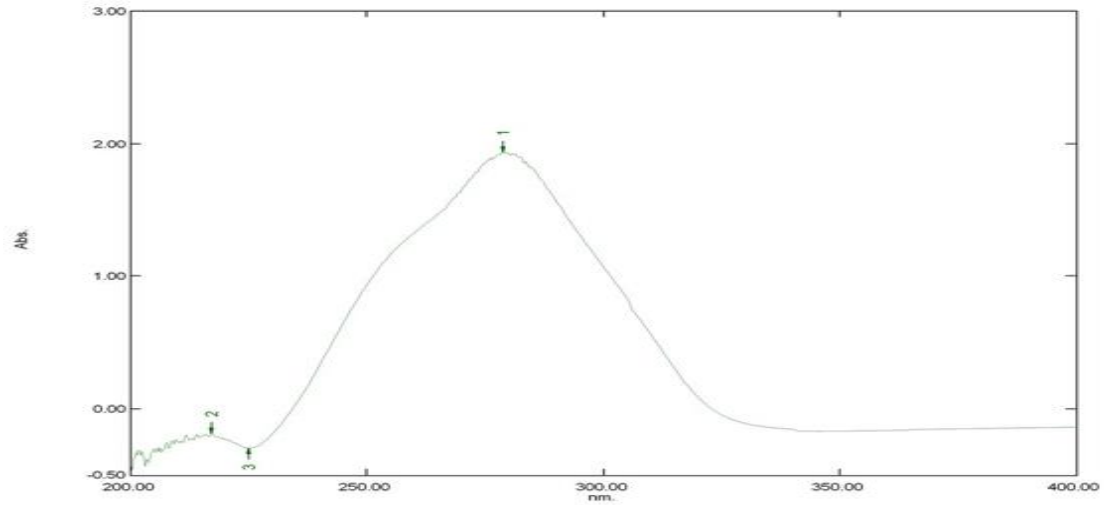

Figure 5.: UV Spectrum Studies of Celecoxib

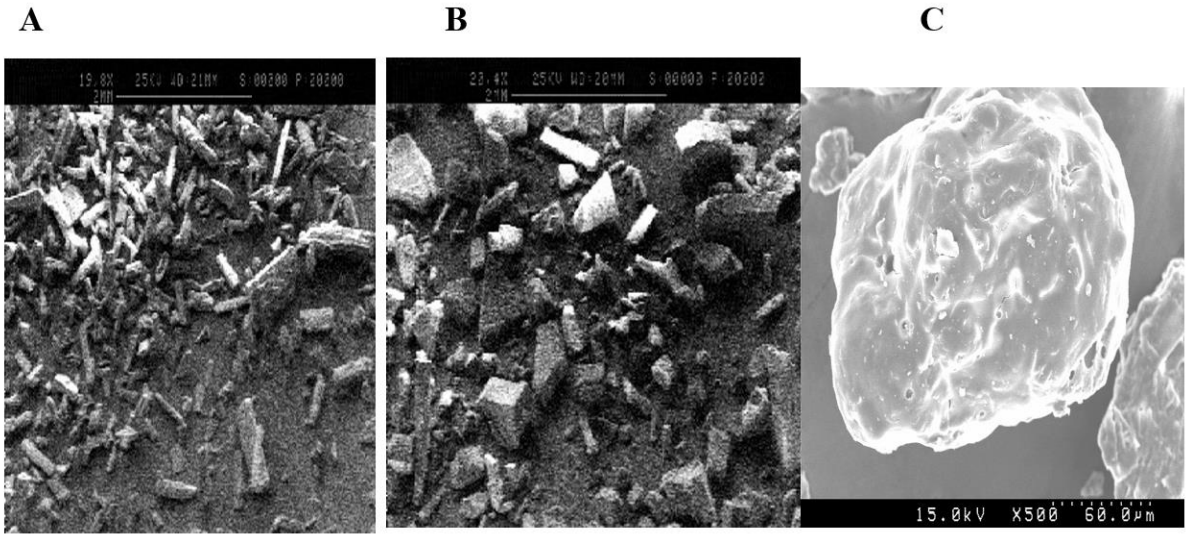

Figure 6 : Scanning electron microphotographs of (a) Celecoxib alone (b) Physical mixture of Celecoxib- PEG-6000 binary systems (c) Solid dispersion of Celecoxib

spectra for Celecoxib and drug polymer physical mixture to get compatibility study.

FTIR Spectra of Celecoxib, Polymer and Physical Mixture

Differential Scanning Calorimetry

DSC is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample is measured as a function of temperature. The temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The DSC thermogram of drug and polymer shows an endothermic peak at specific temperature thus retaining the peak of drug and the polymer. The DSC thermograms of pure drug and polymer reveals that polymer interactions or phase transformations have not occurred and the drug and excipient are chemically compatible with each other.

UV Spectrometric Studies

Assay and Determination of wavelength: An assay is refers for qualitatively assessing or quantitatively measuring the presence or amount or the functional activity of a target entity (the analyte) which can be a drug or biochemical substance. The assay of celecoxib was carried out by UV spectrometric method in different medium of methanol, O.1N NaOH and phosphate buffer at PH 7.4 in strength of 10µg/ml concentration individually as specified in I.P. in a scanning range of 230 to 360 nm. The λ_{max} obtained are recorded in table no 6.4 and comparison with the literature value authenticated the study.

SEM of Celecoxib, solid dispersion and physical mixture of Celecoxib-PEG-6000

Figure reveals that celecoxib of SEM Figure 6.24(A) was composed of irregular shaped particles. The physical mixture of celecoxib with PEG-6000 Figure 6.24 (B) showed the presence of drug attached on the surface of the carrier. Solid dispersion Figure 6.24(C) SEM showed that the drug might have dispersed within the carrier matrix which further supported DSC results.

CONCLUSION

The pre-formulation studies were conducted in the first phase to ascertain the drug's organoleptic properties, its solubility in distilled water, and its melting point. The drug complies with all of the organoleptic properties as well as physico-chemical properties; its solubility was found to be soluble in water, easily soluble in DMSO, and 95% alcohol; its melting point was determined to be 161°C, which falls within the range of 161-165 °C. The solubility studies of the drug in combination with various hydrotropic agents and in pure form were conducted at various temperatures to ascertain the impact of temperature on the drug's solubility with regard to the various hydrotropic agents. The solubility observed as 9.2 µg/ml for pure drug, 15.30 µg/ml in combination with PVP K-30 , 15.50 µg/ml with Mannitol and 18.33 µg/ml with PEG-6000. O on behalf of that, the drug shows excellent solubility in combination with PRG-6000. The FT-IR studies of optimized formulation show no interactions between the drug and the polymers- PEG-4000.

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7. CHAPTER 6 RESULTS AND DISCUSSION 6.1 RESULTS OF FORMULATION AND EVALUATION OF GEL LOADED WITH FLURBIPROFEN MICROSPONGES 6.1.1 Results of Preformulation studies of Flurbiprofen (FP) 6.1.1.1 Results of melting point of FP Table 6.1 Results of Melting Point of FP.
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