PREFORMULATION STUDY OF CELECOXIB BY VARIOUS PARAMETER

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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. 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 14.0. 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. The PEG 400-ethanol system had the highest potential for solubilisation among the mixed solvent systems. 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.

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

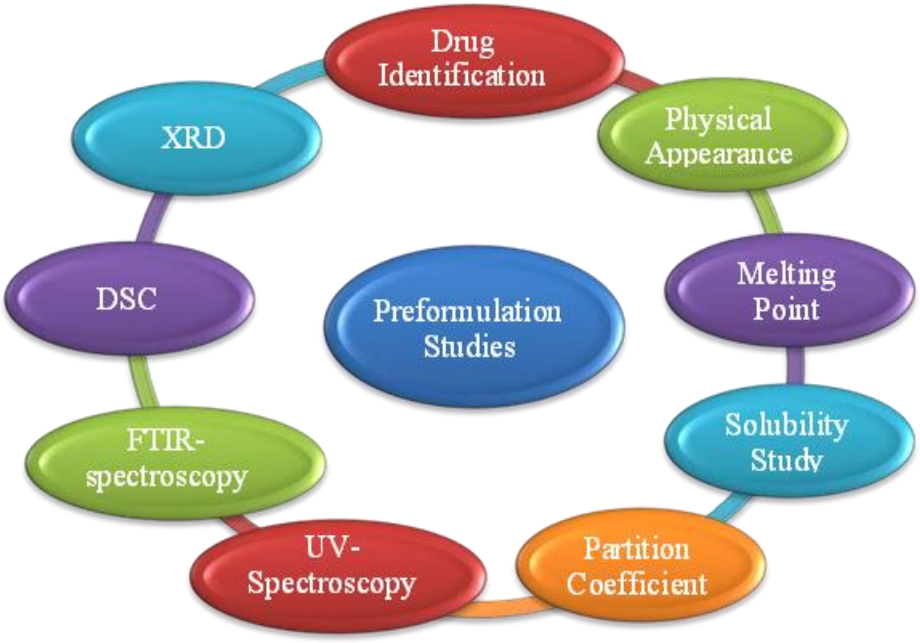
spare cox-1 activity, cox-2 selective NSAIDs are therefore the best anti-inflammatory medications with the fewest possible adverse effects(2).

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 celecoxib(3). There hasn't been much focus on improving the solubility of celecoxib 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. 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



Authentication of drug

The medication was confirmed using techniques such as melting point determination, UV spectroscopy, infrared spectroscopic analysis (FTIR), and differential scanning calorimetry (DSC) [5].

UV spectroscopy

The absorption maximum was determined by scanning 2.5µg/ml solution of Celecoxib in phosphate buffer pH 6.8 between 230-360nm [6].

Procedure

The standard stock solution of celecoxib was prepared using 6.8 pH phosphate buffer. Accurately weighed 100mg of drug was dissolved in 100 ml of phosphate buffer pH 6.8 in 100ml volumetric flasks with aid of sonication in bath sonicator for 20 min.
The concentration of celecoxib was 100µg/ml and for the analytical purpose concentration of celecoxib was taken 10µg/ml. This sample was scanned under ultra- violet spectrophotometer range from 230-360nm. From this spectrum of celecoxib drug, the wavelength with maximum absorbance was chosen for further analysis [7, 8].

Infrared spectroscopic study

Fourier Transform Infra- red spectroscopy used in this research work for the chemical identification of celecoxib. This is the most powerful analysis technique that provides useful information about the chemical structure of molecule quickly, without any lengthy and tiresome evaluation methods [9].

The main application of Infra- red spectroscopy is the determination of the identity of a compound by means of spectral comparison with that of an authentic sample and verification of the presence of functional groups in an unknown molecule. So, the identity of sample was established by taking the Infra- red of the drug sample and comparing with the pharmacopeial spectra [10].

Method of placing sample in FT-IR

For sample placing the disc of potassium bromide was employed. The powdered sample of celecoxib was intimately mixed with dry potassium bromide. The mixture of drug and potassium bromide was compressed into transparent disc under the high pressure [11]. This disc was placed in Fourier Transform Infra- red spectrophotometer using sample holder and the spectrum of celecoxib was recorded at FTIR was scanned from 4000-400 cm-1.
The spectrum of celecoxib obtained between the % transmittance and the wave number (cm^{-1}), that is inverse of λ [12].

Differential scanning calorimetry

Celecoxib's DSC thermogram was acquired using a DSC. Aluminium pans containing samples weighing 20–25 mg were inserted into the DSC cell. Samples were thermally analysed throughout a temperature range of 30 to 300 degrees Celsius at a scanning rate of 10 degrees Celsius per minute [13].

Melting point

The fused capillary method used to determine the melting point of the drug [14].

Procedure

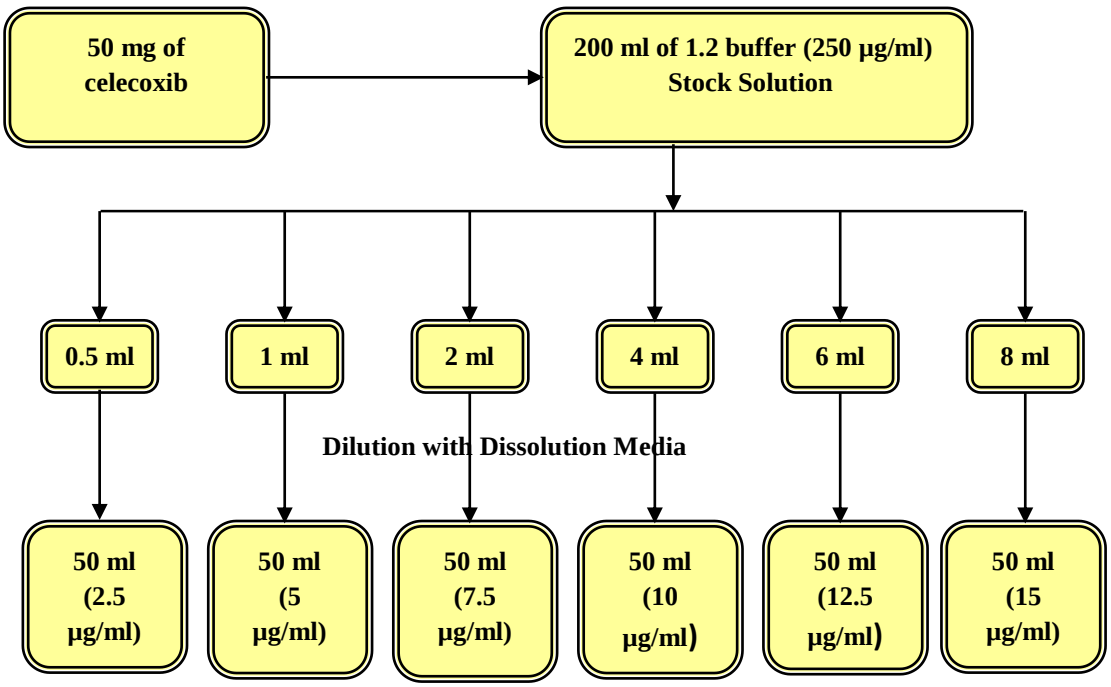
In this method a small amount of pure celecoxib was taken in a capillary tube. This tube is open at one and closed at another end. This capillary was placed in Thieles melting point apparatus. The apparatus was filled with liquid paraffin. This apparatus tied at stand and put over a Bunsen burner. The temperature at which the drug melted was noted and average of triplicate readings was taken [15, 16].

Standard Calibration Curve

Standard Calibration Curve of celecoxib in 1.2 pH Buffer

Stock solution of celecoxib was prepared by dissolving 50 mg of drug in 200 ml of 1.2 phosphate buffer [17]. Aliquots of 0.5, 1, 2, 4, 6, 8 ml (2.5 to 15 µg/ml) were transferred separately in to 50 ml volumetric flasks from the stock solution. Volume was adjusted up to the mark celecoxib the same solvent. Absorbance of the above solutions was taken at 249 nm against the blank. Graph of absorbance Vs concentration was plotted [18].

Standard (Stock) solution



Preparation of standard curve Preparation of phosphate buffer pH 1.2

Procedure for Reagents

Preparation of 0.2 M Sodium Hydroxide Solution

Accurately weigh 8 g of sodium hydroxide pellets and dissolve them in 1000 ml of distilled water mix thoroughly [19].

Preparation of 0.2 M Potassium Dihydrogen Phosphate

Accurately weigh 27.21 g of monobasic potassium dihydrogen phosphate and dissolve it in 1000 ml of distilled water mix well [20].

Procedure for buffer

Transfer 50 ml of 0.2 M potassium dihydrogen orthophosphate to a 200 ml volumetric flask. Add 39.14 ml of 0.2 M sodium hydroxide to the flask. Fill the flask to the mark with distilled water, mix thoroughly, and adjust the pH to 1.2 using 0.2 M sodium hydroxide [21].

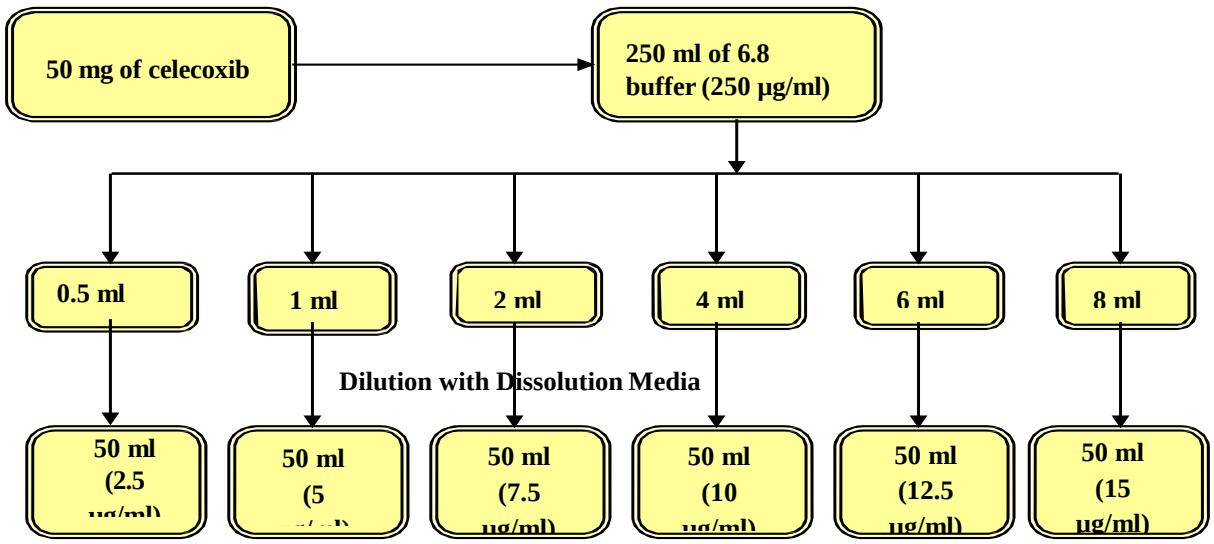
Preparation of standard curve of celecoxib in 6.8 pH Buffer

1st Stock solution

50 mg of celecoxib dissolved in up to 250 ml with 6.8 Phosphate buffer. This stock solution having concentration of 250µg/ml of celecoxib [22].

Aliquots of 0.5, 1, 2, 4, 6, 8 ml (2.5 to 15 µg/ml) were transferred separately in to 50 ml volumetric flasks from the stock solution. Volume was adjusted up to the mark celecoxib the same solvent.

The absorbance of each concentration was measured using UV-Visible spectrophotometer at 249 nm as λ max and the graph plotted against the concentration and absorbance [23].



Solubility determination

Solubility is defined in quantitative termed as the concentration of solute in a saturated solution at a certain temperature, in qualitative way, it can be defined as the spontaneous interactions of two or more substances to form a homogeneous molecular dispersion. The solubility of celecoxib was determined in different solvents. For solubility studies, a known amount of drug was dissolved in various solvents and the solubility was determined [24].

The drug celecoxib belongs to BCS type II, having poor solubility and high permeability. Solubilities study of the drug play an important to know about the characteristics of a drug in aqueous systems. Bioavailability of the drug completely depends on the aqueous solubility. Solubility of celecoxib was determined by shaking flask method. The absorbance is measured by UV spectroscopy and solubility is calculated [25].

Limits of Solubility as Per Indian Pharmacopoeia

S. No.	Descriptive term	Part of solvent required per part of solute
1	Very soluble	Less than 1
2	Freely soluble	1 to 10 ml
3	Soluble	10 to 30ml
4	Sparingly soluble	30 to 100ml
5	Slightly soluble	100 to 1000ml
6	Very slightly soluble	1000ml to 10,000ml
7	Practically insoluble or insoluble	10000 or above 10,000

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 ± 0.5 ºC in a shaker incubator. The vials were shaken and then incubated for 12 hours at 37 ± 0.5 ºC 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 [26].

Drug-Excipient interaction study

Celecoxib and excipient physical mixes at a 1:1 ratio were put into ampoules that had been previously cleaned, dried, and sealed. For 28 days, the sealed ampoules were kept in a stability chamber at 37 ± 0.5 ºC. After 28 days, the ampoules were taken out of the stability chamber and used for FTIR and DSC interaction studies [27].

Infrared spectroscopic study

The molecular interaction between celecoxib and polymers was ascertained using infrared spectroscopy. Using the diffuse reflectance scan sampling approach, the FTIR spectra of celecoxib and all physical combinations were acquired on an FTIR spectrophotometer (1 mg

sample in 100 mg KBr). With a resolution of 1 cm-1, the scanning range was 4000–400 cm–1 [28].

Differential scanning calorimetry

A DSC was used to obtain the DSC thermogram of the physical mixes and RG. Aluminium pans containing samples weighing 20–25 mg was inserted into the DSC cell. Samples were thermally analysed throughout a temperature range of 30 to 300 degrees Celsius at a scanning rate of 10 degrees Celsius per minute [29].

RESULT & DISCUSSION

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 1 and get complies with the standard literature value.

Table 1: Melting Point Study of celecoxib

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

Solubility

The solubility of a drug is one of the most important physiochemical properties. as it is essential components of pharmaceutical development programs. The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system. The observed solubility of plain drug, and Drug-Polymer physical mixture in aqueous solution are enlisted below in table no 2 for further studies.

Table 2: Observed Solubility of celecoxib and Polymer in aqueous condition

Sr. 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

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

FTIR Spectra of Celecoxib, Polymer and Physical Mixture

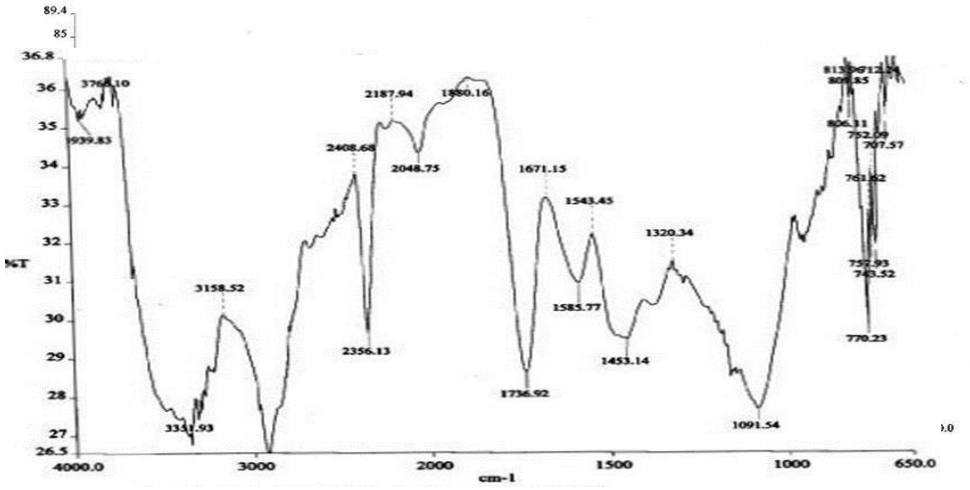


Figure 1: FTIR Spectra of Celecoxib

Figure 2: FTIR Spectra of Solid Dispersion of Celecoxib + PVP K-30

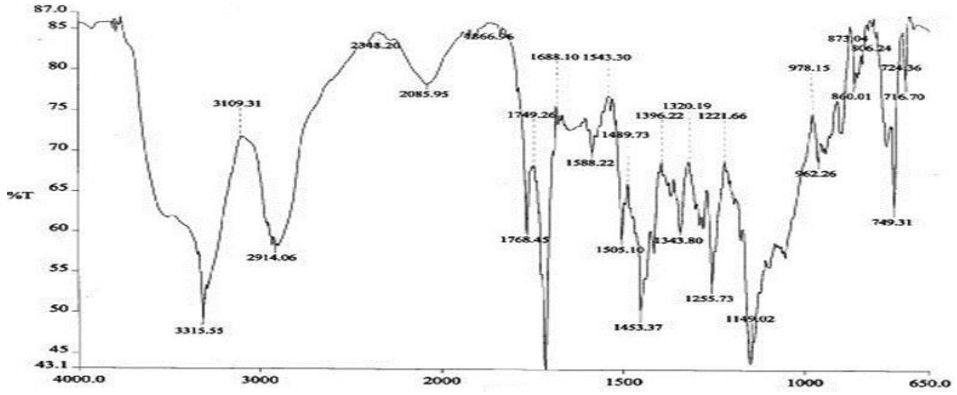


Figure 3: FTIR Spectra of Physical Mixture Celecoxib + Mannitol

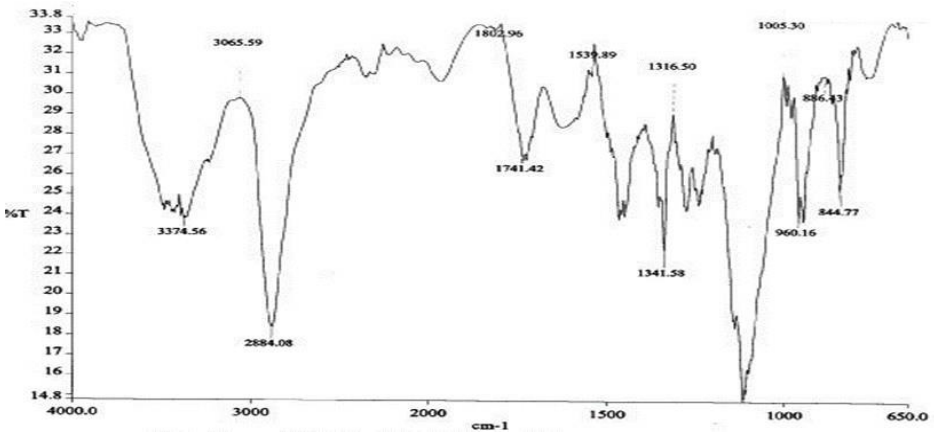


Figure 4: FTIR Spectra of Solid Dispersion of Celecoxib + PEG-6000

Based on the spectra of Celecoxib and its physical mixture, it can be concluded that the experimental vibrational spectra clearly indicate the presence of specific intermolecular interactions. Notably, the bands observed at 1714.71 cm^{-1} and 3315.53 cm^{-1}, attributed to the C10–O11 and O–H stretching vibrations respectively, show a shift to lower frequencies due to intermolecular hydrogen bonding interactions. Additionally, the presence of a carbonyl stretching band at 1737.70 cm^{-1}, which is a result of hydrogen bonding between dimers, further supports the presence of these interactions. These significant changes in the IR spectra confirm that Celecoxib is interacting with the polymers.

Differential Scanning Calorimetry

The difference in the amount of heat needed to raise a sample's temperature is measured as a function of temperature using the DSC thermos-analytic approach. The

sample holder temperature rises linearly with time thanks to the design of the temperature program for a DSC analysis. At a particular temperature, the drug and polymer's DSC thermogram displays an endothermic peak, maintaining the drug and polymer peak. The DSC thermograms of the pure drug and polymer show that there have been no phase changes or interactions between the polymers, indicating that the drug and excipient are chemically compatible. Below is a summary of the research on polymers, plain drugs, and their physical mixtures.

Figures 6.5, 6.6, 6.7, and 6.8 show the thermal behaviour of the pure drug and the matching polymer system, respectively. The crystalline nature of the pure medication Celecoxib is indicated by the DSC curve, which shows a prominent endothermic peak (T peak = 152.88° C) correlating to its melting. However, as seen in Figure 6.10, the distinctive endothermic peak that corresponds to drug melting was widened and moved towards lower temperatures with less intensity in both the solid dispersion and the physical combination of Celecoxib.

This may be explained by the polymer and the consistent dispersion of the drug in the crust polymer, which leads to the total miscibility of the molten drug in the polymer. Furthermore, the data suggest that the medication and polymer do not appear to interact. The fact that there is no discernible difference between the physical mixture and the dispersion's DSC pattern indicates that even the kneading process was unable to create molecular contact, and the solid dispersion that resulted was a physical mixture with a highly disseminated drug crustal in the polymer.

DSC analysis of Polymers and celecoxib are enlisted below

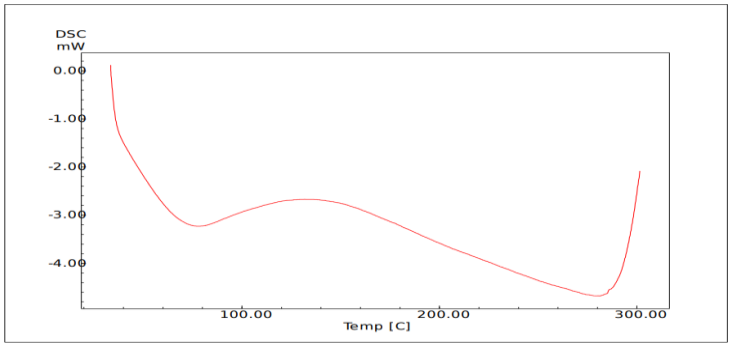


Figure 5: DSC Thermogram of PVP K-30

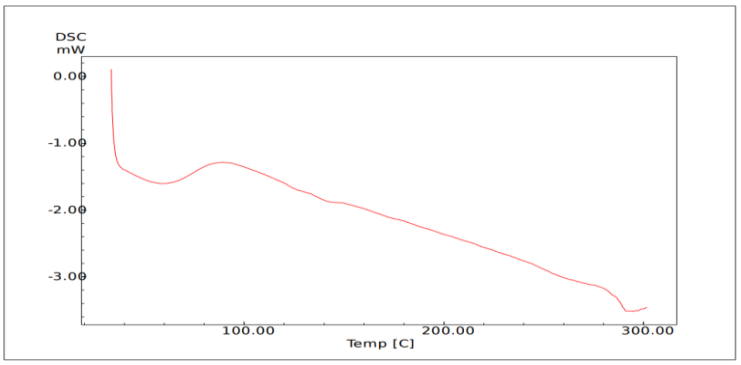


Figure 6: DSC Thermogram of Mannitol

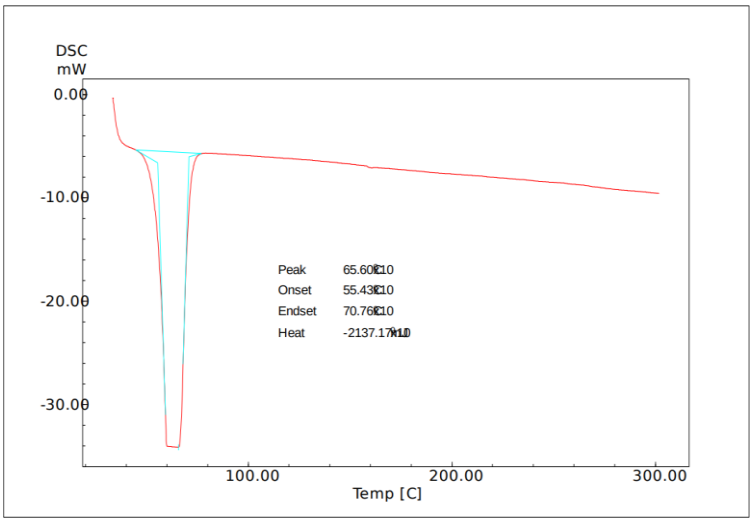


Figure 7: DSC Thermogram of PEG 6000

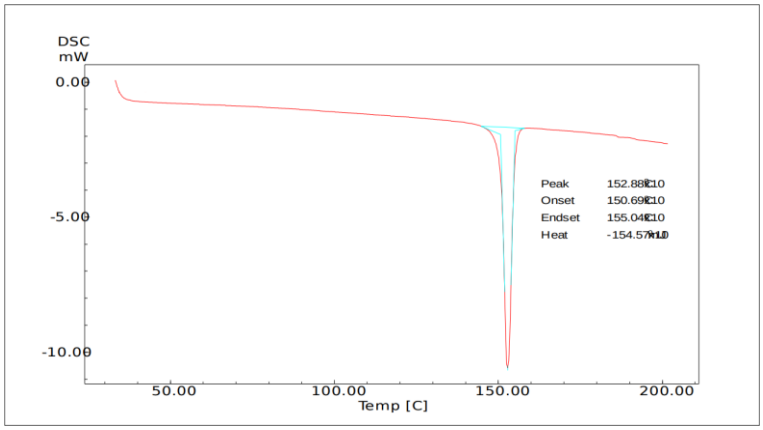


Figure 8: DSC Thermogram of Celecoxib

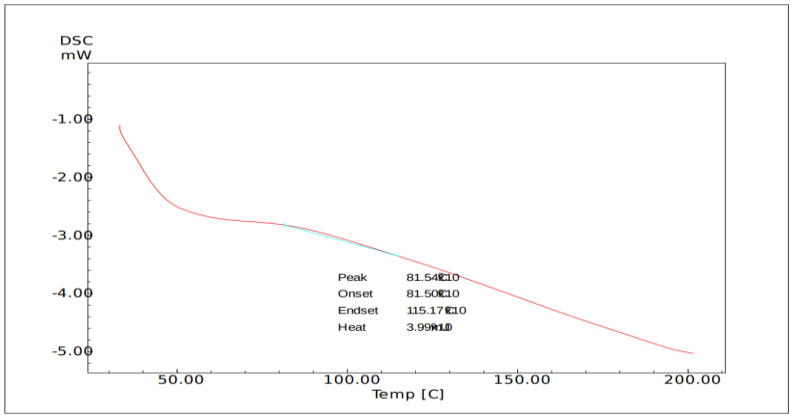


Figure 9: DSC Thermogram of Celecoxib Solid dispersion

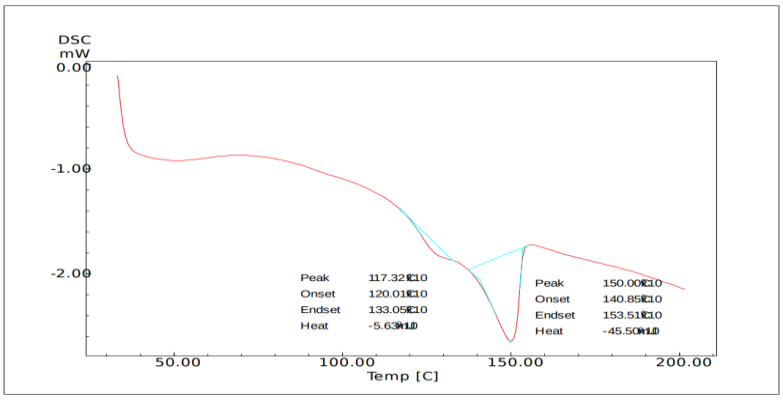


Figure 10: DSC Thermogram of Celecoxib Physical mixture

Table 3: 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

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 6.8 in strength of 2.5µg/ml concentration individually as specified in I.P. in a scanning range of 230 to 360 nm. The λmax obtained are recorded in table no 4 and comparison with the literature value authenticated the study.

Table 4: λmax Studies of Celecoxib

Sr. No.	Solvents (2.5µg/ml)	Experimental λmax	Literature λmax	Observed absorbance
1.	Phosphate Buffer	249	248/249/250	0.125

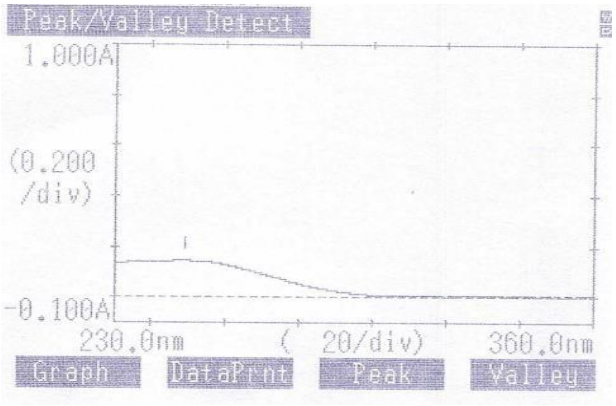


Figure 6.11: UV Spectrum Studies of Celecoxib

Analytical Method Development

Calibration curve for Celecoxib in pH 6.8 Phosphate buffer

Phosphate buffer pH 6.8 was used for the preparation of Celecoxib concentration and absorption was measure by Shimadzu UV-1700 UV/Vis double beam spectrophotometer. The λ max of Celecoxib was found to be 249 nm. The result was showed in the table no. 5 and figure 12.

Table 5: Standard CC of Celecoxib in Phosphate buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	2.5	0.125	0.121	0.130	0.125
2	5.0	0.250	0.255	0.252	0.257

3	7.5	0.377	0.378	0.380	0.374
4	10.0	0.502	0.499	0.498	0.507
5	12.5	0.633	0.630	0.631	0.627
6	15.0	0.762	0.763	0.760	0.767
Correlation Co-efficient (R^2) = 0.9995 **Absorbance (y)** = 0.0509x conc - 0.0025					

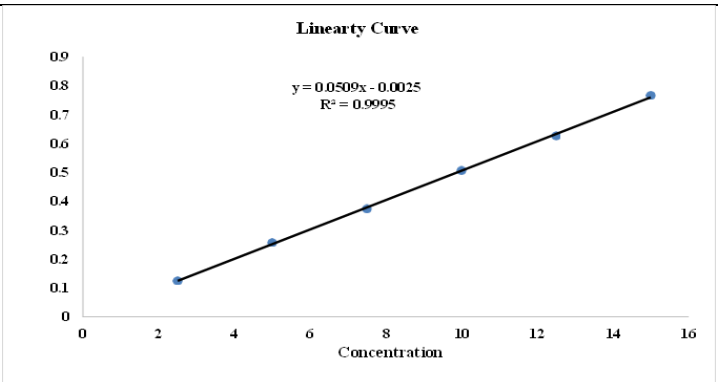


Figure 12: Drug calibration curve in Phosphate buffer pH 6.8

Calibration curve of Celecoxib in 0.1 N HCl

Celecoxib concentration was prepared in 0.1 N HCl and absorption were measure by Shimadzu-1700 UV/Vis double beam spectrophotometer. The λ max of Celecoxib was found to be 249 nm.

Table 6 Standard CC of Celecoxib in 0.1 N HCl

Sr. No.	**ıcentration (µg/ml)**	**Absorbance**			**Average Absorbance**
		1	**2**	**3**	
1	2.5	0.125	0.121	0.130	0.127
2	5.0	0.250	0.255	0.252	0.252
3	7.5	0.377	0.378	0.380	0.378
4	10.0	0.502	0.499	0.498	0.500
5	12.5	0.633	0.630	0.631	0.631
6	15.0	0.762	0.763	0.760	0.762
Correlation Co-efficient (R^2) = 0.9998 **Absorbance (y)** = 0.0507x conc - 0.0017					

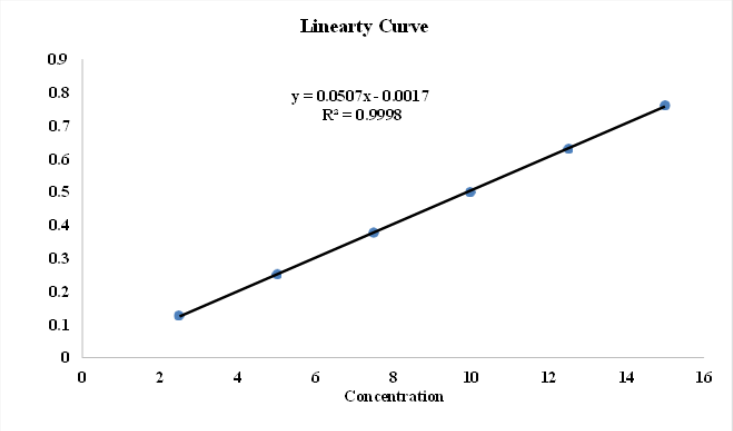


Figure 13: Drug calibration curve in 0.1 N HCl

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. On behalf of that, the drug shows excellent solubility in combination with PEG-6000. The FT-IR studies of optimized formulation show no interactions between the drug and the polymers- PEG-6000.

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