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DEVELOPMENT OF PREFORMULATION PARAMETES OF CELECOXIB: SOLUBILITY, PARTITION COEFICIENT, CRYSTALLINE CHARACTERISTICS, FLOW PROPERTIES, FTIR AND DSC ANALYSIS

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ABSTRACT

Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, Celecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. The physicochemical parameters like solubility, partition coeficient, crystalline characteristics, flow properties, FTIR and DSC analysis were carried out. The aim of this research work was to develop the spectrophotometric methods for evaluation the celecoxib and to analyse the various physicochemical parameters of this drug. It is the part of investigation earlier to the design, development of pharmaceutical dosage forms. Drug was assayed for purity test and it was found 98.87±0.61 %. In presence of various solvents systems the regression co-efficient obtained from the standard plots were nearing about 1.0 and which proved the linearity of the analytical methods. All the models followed Beer-Lambert's law and therefore can be analyzed by UV spectrophotometer. The FT-IR spectra of pure celecoxib shown characteristic bands at 1229 & 1274 cm^{-1}($-CF_3$), 1446 cm^{-1} (-N-N-), 3417 cm^{-1} ($-SO_2NH_2$). Celecoxib showed a single sharp endothermic peak corresponding to the melting of the drug at 165.21°C (T_{onset}=161.15°C, T_{end}=167.73°C, area=1066.29 mJ, ΔH_f=0.1066 KJ/mol and ΔH=106.63 J/g).

Key words: Celecoxib, Solubility, FTIR, DSC, partition coeficient.

INTRODUCTION

Preformulation may be described as the process of optimizing a drug through determination of those physical and chemical properties considered important in the formulation of a stable, effective and safe dosage form. The possible interactions with the various components intended for use in the final drug product are also considered. It is an effort that encompasses the study of such parameters as dissolution, polymorphic forms and crystal size and shape, pH profile of stability, and drug excipients interactions, which may have a profound effect on a drug's physiological availability and physical and chemical stability. Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system [1-5].

Before beginning the formal preformulation programs the preformulation scientist must consider the following factors [5]:-

- The amount of drug available.
- The physicochemical properties of the drug already known.
- Therapeutic category and anticipated dose of compound.
- The nature of information, a formulation should have or would like to have.

Celecoxib is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of Celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase-2 (COX-2), and at therapeutic concentrations in humans, Celecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme. In animal colon tumor models, Celecoxib reduced the incidence and multiplicity of tumors. Main Indications of celecoxib are osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms [4-8].

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Celecoxib is thus, associated with a lower incidence of gastro duodenal ulcers than other nonsteroidal anti-inflammatory drugs, which are nonspecific inhibitors of cyclo-oxygenase. Celecoxib has site specific and saturable absorption kinetics. Earlier reported studies showed that celecoxib can exhibit chemoprotective effects on tumors of the colon and reduce the risk of colon cancer. Celecoxib exhibits poor water solubility, with biological half life; 6-11 hours, and conventional dosage form is administered twice daily to fulfill the therapeutic level of the patient. only 40% of administered drug is bioavailable through oral route and bioavailability may be greater if it is targeted to the colon [4-9].

The physicochemical parameters like solubility, partition coeficient, crystalline characteristics, flow properties, FTIR and DSC analysis were carried out. The aim of this research work was to develop the spectrophotometric methods for evaluation the celecoxib and to analyse the various physicochemical parameters of this drug. It is the part of investigation earlier to the design, development of pharmaceutical dosage forms.

MATERIALS & METHODS:

Procurement of API and Chemicals

Celecoxib was purchased from Exim-Pharm Interna-tional, Mumbai, India. All the others chemicals used were of analytical grade.

Physical appearance

Celecoxib was inspected visually for physical appearance. It was physically characterized on the basis of organoleptic properties like color, odor and texture [1-3].

Identification of drug

Melting point

This determination was obtained using a digital capillary melting point apparatus (Cambell Electronics, Bombay, India) by capillary fusion method. A capillary was taken and bringing it near the burner flame then sealed its one end. The open end of the capillary tube was pushed in to a small heap of drug, so that a small plug of the powder was collected in the open end and the tube was tapped gently, so that collected drug was settled down. This process was repeated several times. Then the capillary tube was placed in the melting point determination apparatus and observed the temperature at which sample changes its state from solid to liquid. The experiment was performed in triplicate. The temperature at which starts to melt was noted with the help of thermometer and it was compared with earlier reported value [1-3].

Ultraviolet spectrum:

10 mg drug was dissolved in 100 ml methanol to make the concentration of 100 µg/ml stock solution. Then from this solution 0.5 ml was taken and volume was made up to 10 ml with methanol to make solution concentration of 5µg/ml & the resulting solution was scanned between 200-400 nm using UV-Visible spectrophotometer (UV-1800, Shimadzu, Tokyo, Japan). The UV Spectra of the drug was recorded and compared with reported absorption maximum [1-5].

IR Spectrum:

The IR spectrum of pure drug was obtained in potassium bromide pellet by FTIR Spectrophotometer (Prestige-21, Shimadzu, and Tokyo, Japan) to monitor the identifications of drug between the ranges of 400 to 4000 cm^{-1}. The IR Spectra of the drug was recorded and compared with reported spectrum [1-7].

Assay:

A simple, economic, selective, precise, and stability-indicating HPLC method [8-11] has been developed and validated for analysis of celecoxib (CXB). Reversed-phase chromatography was performed on a C18 column with methanol–water, 75:25 (%, v/v), as mobile phase at a flow rate of 1.25 mL min^{-1}. Detection was performed at 250 nm and a sharp peak was obtained for CXB at a retention time of 4.8 ± 0.01 min.

Development of analytical methods:

Scanning of celecoxib solutions in various solvents systems:

10 mg of celecoxib was dissolved in 100 ml of various solvents system individually, so as solutions of 100µg/ml were prepared as a stock solutions. It was further diluted to make suitable concentration to run out the scanning processes and different concentration was used for scanning of all solvents system which is tabulated in table 1. The resulting solution was scanned by using UV-Visible spectrophotometer (UV-1800, Shimadzu, Tokyo, Japan). The each experiment was carried out in triplicate manner and the absorbance maxima (λ_{max}) were noted.

Preparation of Standard Curves of celecoxib in different solvents systems:

In purified Water:

10 mg of celecoxib was dissolved in 100 ml of respective solvents systems separately, so as solution of 100µg/ml were prepared as a stock solutions. From this suitable volume was taken and the volume was made up to 10 ml to make solutions concentration 0.2, 0.4, 0.6, 0.8, 1 & 2µg/ml. Absorbance of the resulting solutions were measured by using UV-Visible spectrophotometer (UV-1800, Shimadzu, Tokyo, Japan) at respective absorbance maxima (λ_{max}). The each experiment was carried out in triplicate manner and concentrations vs. absorbance were plotted for preparation of calibration curves.

In 0.1 N HCl (pH 1.2):

10 mg of celecoxib was dissolved in 100 ml of respective solvent systems separately, so as solution of 100µg/ml were prepared as stock solutions. From this suitable volume was taken and the volume were made up to 10 ml with respective solvent system to make solutions concentration 0.2, 0.4, 0.6, 0.8 & 1µg/ml. Absorbance of the resulting solutions were measured by using UV-Visible spectrophotometer (UV-1800, Shimadzu, Tokyo, Japan) at respective absorbance maxima (λ_{max}). The each experiment was carried out in triplicate manner and concentrations vs. absorbance were plotted for preparation of calibration curves.

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Solubility Study:
The drug was tested for its solubility because solubility is directly related with the release of the drug from the formulation, hence absorption of the drug into blood stream.

Solubility study was carried out by **"Shake flask method"** as given by some researchers [5, 10]. The solubility of drug was studied in different solvents. Standard buffers solutions were prepared as per the procedure given in IP 2007 [1].

The solubility of drug was determined by adding excess amount of drug in vials with respective solvent system and kept under agitated conditions at 25°C in a water bath shaker for 24 hours. The dispersions were filtered through a 0.45 µm pore filter and analyzed for the quantity of drug dissolved.

Determination of Partition Coefficient:
The partition coefficient is the measure of lipophilicity of drugs. The partition coefficient is generally carried out by using two immiscible solvents and the most suitable and common solvents like n-octanol, ethyl acetate, ether and oleyl alcohol are employed with water for determining the partition coefficient of drug intended for GIT.
The partition coefficient [5, 8-10] of drug was determined in n-octanol and water solvent systems. Accurately weighed amount of drug (30 mg) was transferred in to a rubber stopper (wrapped with butter paper) containing 30 ml each of octanol and water and the resulting mixture was shaken onrush action shaker for 1 hour. Both the phases were separated using separating funnel and it was analyzed by spectrophotometer, to determine the amount of drug after suitable dilution.
The partition coefficient of the drug in phases was calculated by using the following formula as given below:

$$\text{Partition Coefficient, (K)} = \frac{\text{Amount of drug in organic layer}}{\text{Amount of drug in aqueous layer}}$$

Crystal Characteristics:
X-ray diffractometry of drug sample was investigated using Philips XRD Machine set up with generator (PW1830), Goniometry (PW 1820) and diffractometer (PW1710, Eindhoven & Almelo, Netherlands, Europe). Cu K_α radiation was used (30 kV, 50mA with a α_1/α_2 ratio of 0.5) to study it. The XRD patterns were recorded at diffraction angels (2θ) with 4°/min scanning speed, and 5°-45° 2θ range.

Determination of bulk properties of pure drug:
Bulk Density:
Bulk density was determined by measurement in graduated cylinder [8]. A quantity of 25 gm of material was weighed (M) accurately and passed through sieve (# 22) to break up any agglomerates and introduced into a 100 ml measuring cylinder without compacting.

The powder was leveled carefully and the unsettled apparent volume V_0 was noted to the nearest graduated unit. The bulk density was calculated in gm/ml by the formula: $\mathbf{M/V_o}$.

Tapped Density:
After determination of the bulk density, the cylinder was tapped mechanically by mounting on a holder in a mechanical tapped density tester that provided a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and the tapped volume V_t was measured to the nearest graduated unit. The tapping was repeated for an additional 750 times and the tapped volume was measured. Final tapped volume was measured and tapped density was calculated by the formula: $\mathbf{M/V_t}$.

Compressibility Index and Hausner's Ratio:
The Compressibility Index and Hausner's Ratio [12] are measured to check the propensity of a powder to be compressed. These differences are reflected in the % Compressibility Index (% CI) and the Hausner's Ratio (HR) and it which were calculated using the following formulas:

$$\%CI = \left[\frac{Vt - Vo}{Vt}\right] X\ 100$$

$$HR = Vt/\ Vo$$

Angle of repose:
A glass funnel was held in place with a clamp on a ring support over a glass plate. Approximately 50 gm of material was transferred into the funnel keeping the orifice of the funnel blocked by thumb. As the thumb was removed, the powder was emptied from the funnel. The height of the pile (h) and radius of the base (r) measured with the ruler. The angle of repose (ɵ) was determined by the following equation [12-17].

$$\theta = \tan^{-1}(h/r)$$

DSC studies:
The thermal analysis of pure drug was carried out by differential scanning calorimetry (DSC) equipped with a thermal analysis data system (Perkin Elmer, California, USA). Samples weighing 3-5 mg were heated in flat-bottomed sealed aluminum pans over a temperature range of 40-250°C at a constant rate of 10°C/min under nitrogen purge (50 ml/min).

RESULTS & DISCUSSION

The drug celecoxib was characterized for the physical appearance and it was found a white odorless powder with fluffy texture. The melting point of celecoxib tabulated in **table 1.**

The maximum wave length of UV spectra of celecoxib in methanol is tabulated in **table 1** & it was also compared with the earlier reported data. The FTIR peaks of celecoxib responsible for characteristic functional group were identified and interpreted (**table 2**) & it was also compared with the earlier reported data. FTIR spectra of celecoxib are shown in **figure 1**. The assay result of celecoxib on the dried basis tabulated in **table 1.**

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Table 1: Physico-chemical Properties of celecoxib.

S.no.	Parameter	Reported / standard	Observed
1	Physical appearance	White odorless powder	Fully complied
3	Melting point	158 °C-162°C	160-162°C
4	Partition Coefficient (Log P) (Octanol /water)	3.9± 0.024	3.66±0.011
5	UV Spectra	λ_{max} at 254 nm in methanol	Fully complied
6	Drug Assay (%)	98-101%	98.87±0.61%
7	DSC Study	163.08°C	165°C

Table 2: Interpretation of FTIR Spectra of Celecoxib.

S.NO.	Reported values (cm^{-1})	Observed values (cm^{-1})	Responsible Functional groups
1	1120-1350	1229,1273	$-CF_3$
2	1440	1446	-N-N-
3	3400	3417	$-SO_2NH_2$
4	1550-1600	1550-1600	N-H Stretching
5	3300-3500	3300-3500	-NH2 Stretching

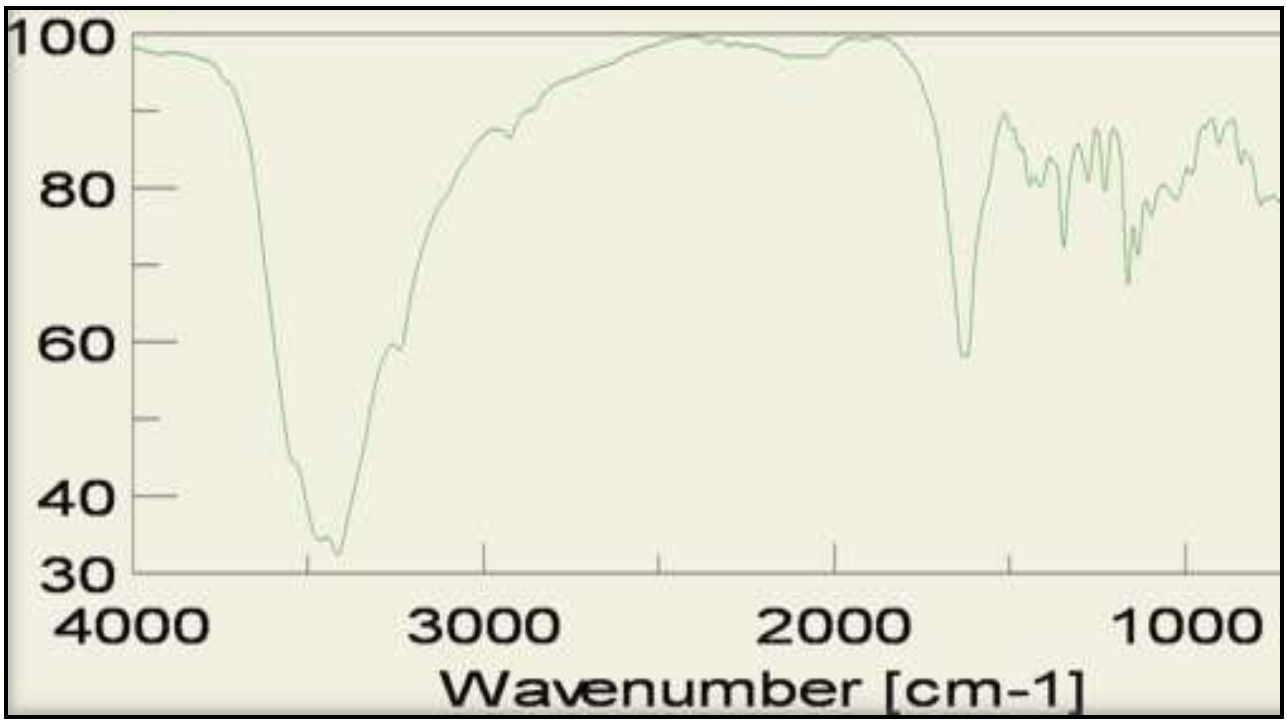

Figure 1: FTIR spectra of celecoxib.

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Table 3: Data for preparation of Calibration curve of celecoxib in purified water (λ_{max} 250 nm).

Concentration (µg/ml)	Absorbance at 250 nm
0.2	0.095 ± 0.002
0.4	0.106 ± 0.010
0.6	0.117 ± 0.014
0.8	0.131 ± 0.016
1.0	0.144 ± 0.021
2 .0	0.207 ± 0.024

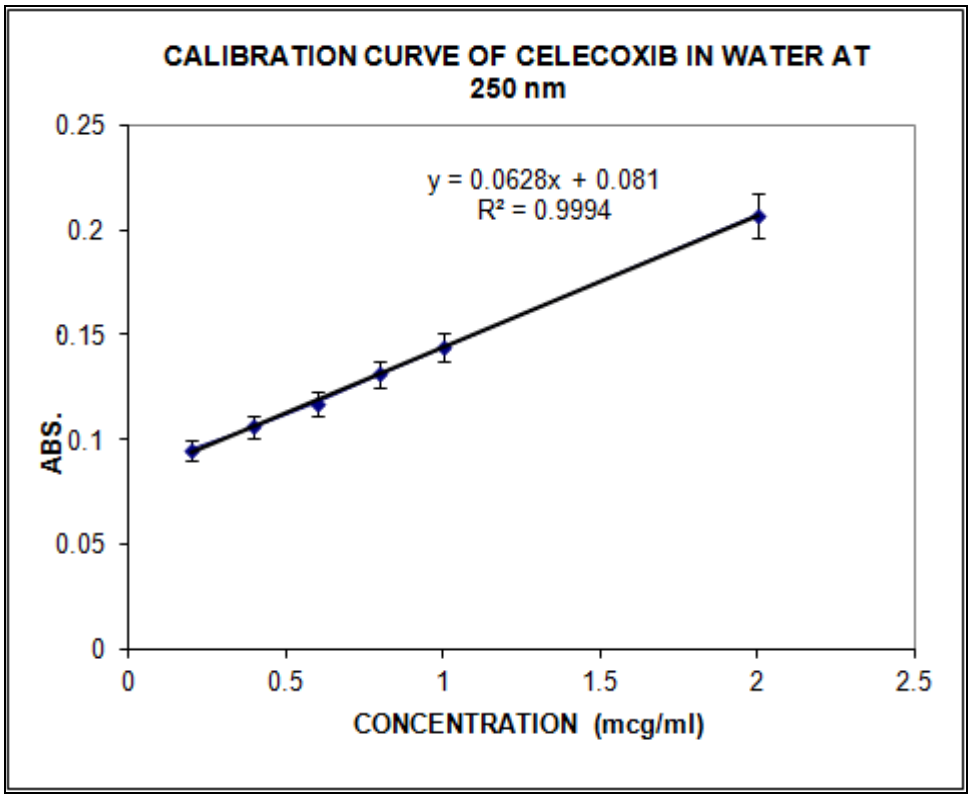

Figure 2: Calibration curve of celecoxib in purified water (λ_{max} 250 nm).

Table 4: Solubility studies of celecoxib in various solvent systems.

S.No.	Solvent System	Solubility of celecoxib (mg/ml) at 35 °C
1.	Purified water	0.005±0.002
2.	0.1 (N) HCl (pH 1.2)	0.004±0.01

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Table 5: Solution Stability studies of the celecoxib in 0.1 N HCl.

Medias	Theoretical drug concentration (µg / ml)	Time interval (hour)	% Drug content (Mean ± S.D.)	% Coefficient variation
0.1 N Hydrochloric acid (pH 1.2)	1	0	99.91 ± 0.315	0.3160
		24	98.16 ± 0.176	0.1871
		48	97.94 ± 0.315	0.3467
	2	0	99.51 ± 0.140	0.1410
		24	98.45 ± 0.245	0.2621
		48	98.04 ± 0.225	0.2487
		48	97.43 ± 0.028	0.0290

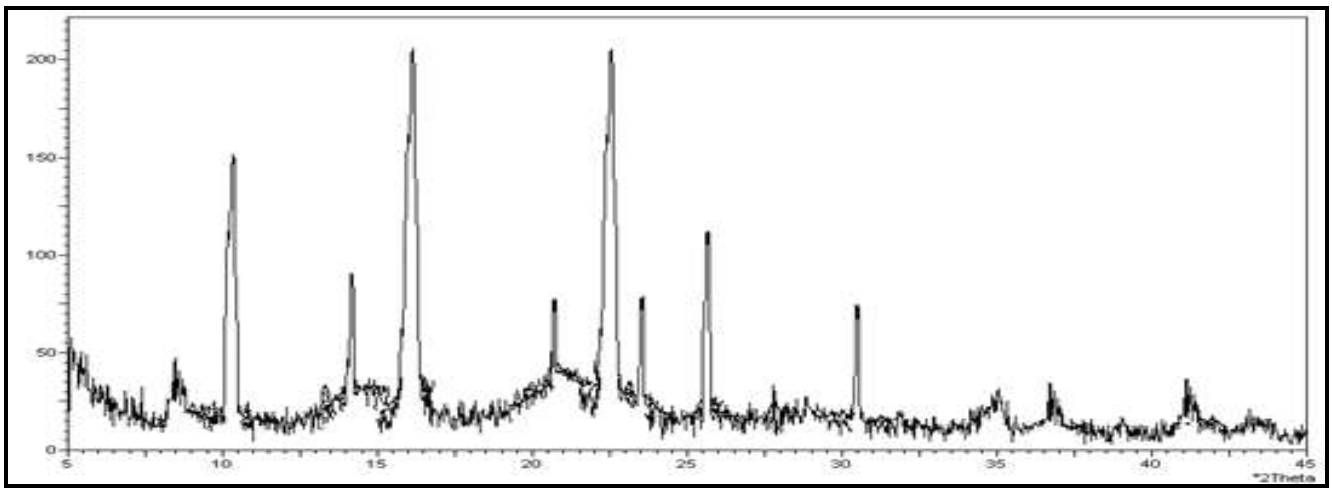

Figure 3: XRD graph of bulk Celecoxib.

Table 6: Bulk properties of pure drug celecoxib

Bulk properties	Celecoxib
Bulk Density	0.172 gm/ml
Tapped Density	0.384 gm/ml
% Carr's Index	55.2
Husnar's Ratio	2.23
Angle of Repose	69.68°

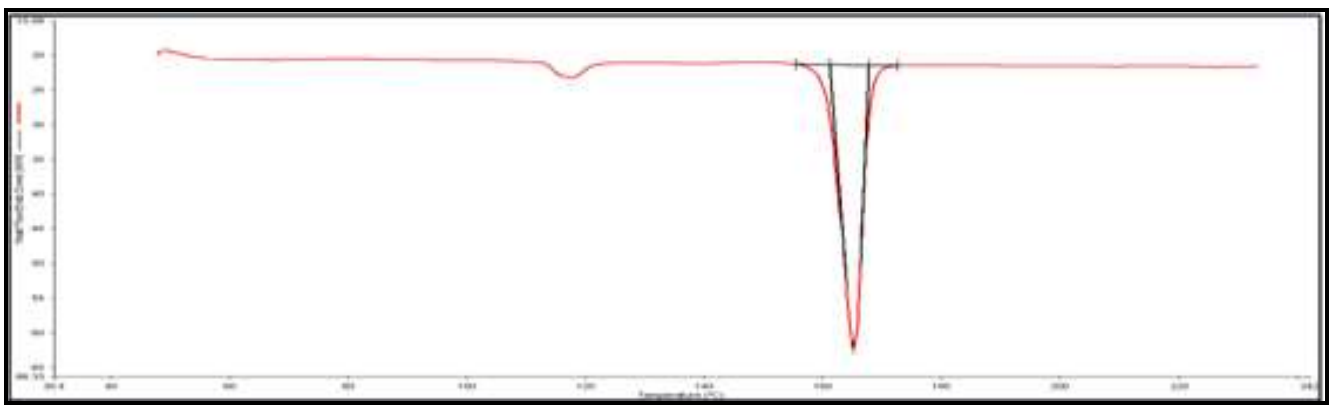

Figure 4: DSC curve of Celecoxib.

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The melting point (table 1) of celecoxib was 160-162°C, matched with reported melting point which was 158°C-162°C.

The FTIR spectra (figure 1) of drug was compared with that of the standard peaks (table 2) available in unofficial monograph and identified as celecoxib. The model drug obtained was authentic. The FT-IR spectra of pure celecoxib (figure 1) shown characteristic bands at 1229 & 1274 cm^{-1}(-CF_3), 1446 cm^{-1} (-N-N-), 3417 cm^{-1} (-SO_2NH_2). The UV spectra of the drug were recorded and the obtained λ_{max} value (table 1) was compared with the peaks those are given in reference books.

From the UV spectra the drug was identified as celecoxib. Drug was assayed (table 1) for purity test and it was found 98.87±0.61 %. In presence of various solvents systems the regression co-efficient obtained from the standard plots were nearing about 1.0 and which proved the linearity of the analytical methods. All the models followed Beer-Lambert's law and therefore can be analyzed by UV spectrophotometer.

The solubility values (table 1) were observed in 0.1 (N) HCl (pH 1.2) & purified water. The model drug has low solubility and high permeability and hence falls in BCS class II [3-7]. The drug content observed after stipulated time period in the stability study (table 5) in 0.1 (N) HCl (pH 1.2), and it was revealed that the drug was stable in 0.1 (N) HCl (pH 1.2). Intensed peaks were obtained in XRD analysis (figure 3) and 2θ values proved the crystalline nature of the drug and all the values were found matching to that present in the literature.

All the flow parameters like angle of repose, compressibility index and Hausner's Ratio were evaluated and shown in table 6. The Carr's index, angle of repose values revealed that the API was having poor flow ability which was confirmed by referring to standard literature. Bulk density and Tapped density values confirming with the API specification reported earlier. Celecoxib (figure 4) showed a single sharp endothermic peak corresponding to the melting of the drug at 165.21°C (T_{onset}=161.15°C, T_{end}=167.73°C, area=1066.29 mJ, ΔH_f=0.1066 KJ/mol and ΔH=106.63 J/g).

CONCLUSION

All these parameters can be useful before to design and develop the formulations of celecoxib, specially for development of conventional and NDDS.

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