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Formulation and Evaluation of Solid Dispersion of Celecoxib

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ABSTRACT
The purpose of present study is to develop stomach specific Celecoxib solid dispersion using β cyclodextrin as a carrier for enhancing solubility as well as drug release rate in gastric environment. Enhanced dissolution rate and solubility in gastric pH was achieved by formulating Celecoxib solid dispersion by solvent evaporation method.The drug and β cyclodextrin in different ratios like 1:1,1:2,1:3 and 1:4 were used for formulating solid dispersion. Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC) estimated for determination of the compatibility of Celecoxib with polymer. All formulations evaluated for production yield, drug content, in-vitro drug release, scanning electron microscopy (SEM),Powder X ray diffraction and stability studies. FTIR spectra of Celecoxib in alone and combination showed compatibility of drug and excipient. The solid dispersion was evaluated for percentage yield, drug content and percent drug release and results found to be 95.33%,93.97% and 95.18% respectively. Stability study was performed in closed container at 40^{0}C±2˚C/75% RH ±5% RH. It was concluded that 1:2 ratio of celecoxib solid dispersion showed better in-vitro dissolution rate as compared to pure drug. The increased dissolution rate of celecoxib solid dispersion in gastric pH was attributed to the effect of β Cyclodextrin which was clearly shown by SEM, DSC and P-XRD studies.
Key words: Solid dispersion, Celecoxib, β Cyclodextrin, Solvent evaporation method

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INTRODUCTION

Celecoxib is 4-[5-(4-methyl phenyl)-3-(trifluoromethyl)pyrazole-1-yl]benzyl sulphonamide (IUPAC)The chemical formula of celecoxib is $C_{17}H_{14}F_3N_3O_2S$ and molecular weight is 381.373g/mol. Celecoxib belongs to the class of selective cyclooxygenase-2(COX-2) inhibitors and is poorly water-soluble. It is used clinically in the treatment of osteoarthritis, acute pain, rheumatoid arthritis and alkylosis spondylitis. Celecoxib belongs to the second class of the biopharmaceutical classification system (BCS) due to its low solubility and high permeability [1, 2]. Celecoxib has very low bioavailability as a classified class 2 compound according to the biopharmaceutical classification system. In addition, both the solubility and bioavailability of celecoxib should be enhanced. There are many ways to increase drug bioavailability aimed at increasing the drug surface area, including solvent deposition, solvent complexation, solid dispersion, solute solvent complexation. Solid dispersion formation is the most favourable process for fostering dissolution. The term solid dispersion is defined as dispersion of one or more active ingredient in an inert carrier or matrix in solid state prepared by solvent evaporation method [7].

Solvent evaporation method has proven to be a vigorous method for producing solid dispersion which increases the bioavailability of drug. Celecoxib and β-Cyclodextrin were triturated in ratio 1:1, 1:2, 1:3, and 1:4. w/w with addition of few drop of methanol to form a paste in a separate china dish. The solvent allowed evaporate at 40ºC to form a dry solid mass which is further crushed to fine particles and passes through sieve no.60 and kept in a desiccator for further use. The β-Cyclodextrin polymer with the non-proprietary name is BP: Alfadex betadex PhEur: Alphadex Betadexsynonyms is beta-cycloamylose, beta-dextrin, betadexum. The chemical formula of β-Cyclodextrin is $C_{42}H_{70}O_{35}$ and molecular weight is 1135 g/mol functional category is solubilizing agent and stabilizing agent [6].

The formulation with different drug polymer ratios 1:1,1:2,1:3 and 1:4 was prepared and solid dispersion was obtained by solvent evaporation method. In the dissolution study of solid dispersion 1:2 ratio showed highest dissolution rate. DSC,P-XRD and SEM were performed for physical characterization of Celecoxib solid dispersion [1].

MATERIAL AND METHODS

Materials

Celecoxib was provided by sigma laboratories Pvt. Ltd, Mumbai. All chemicals used in the formulation preparation were of analytical grade and used without further purification.

Methods

Celecoxib and β-Cyclodextrin were triturated in ratio 1:1, 1:2, 1:3, and 1:4. w/w with addition of few drop of methanol to form a paste in a separate china dish. The solvent allowed evaporate at 40ºC to form a dry solid mass which is further crushed to fine particles and passes through sieve no.60 and kept in a desiccator for further use. [9,17]

Sr. No.	Formulation code	Drug (mg)	Polymer (mg)
1	F1	100	100
2	F2	100	200
3	F3	100	300
4	F4	100	400

Table 1: Formulation of celecoxib solid dispersion

Preformulation studies of pure drug

1. The sample of drug observed for colour and stare. 2. Melting point 3. Determination of λ max. 4. Compatibility study of IR and DSC. [8,9]

Drug-excipient compatibility studies

The drug and excipient compatibility studies were carried out by Fourier transform-infrared spectroscopy (FT-IR). By using the KBr press method. The pellets were prepared by grounding the solid powder sample with 100 times the amount of KBr in the mortar. The spectra were recorded from 4000 cm^{-1} to 400 cm^{-1}. [3]

Evaluation of Prepared Celecoxib solid dispersion

From the results obtained by solubility and dissolution studies, solid dispersion which showed better result was selected. For further characterization, solid dispersion were performed to access interaction if any between the drug and polymer and also to find out what properties of polymer make them an effective material for solubility and bioavailability enhancement. In present study, the solid dispersion of Celecoxib with β Cyclodextrin were characterized by FT-IR, DSC, SEM, *in-vitro* drug release study, percentage yield, drug content etc.

Aqueous solubility study

The solubility studies were performed on pure drug and solid dispersion. This test conducted in orbital shaker for 24 hours at 37°C±5°C. Finally, the solution was filtered using Whatman filter paper and filtrate was diluted to 10µg/ml for determining drug concentration by UV visible spectrophotometer. The absorbance was measured at 245nm [1].

Percentage yield

The dried solid dispersion was collected and weighed accurately. The percentage yield was calculated by using formula given below.[10]

$$\%\ Yield = \frac{\text{mass of solid dispersion}}{\text{Total weight of drug + polymer}} \times 100$$

Determination of drug content

The accurately weighted quantity of solid dispersion equivalent to 100 mg of celecoxib taken into 100 ml volumetric flask and dissolved in methanol. The resulting solution was filtered through a Whatman filter paper. The celecoxib content in the methanolic extracts was analysed spectrophotometrically by using a UV- Visible spectrophotometer (UV JASCO V530) at a wavelength of 254 nm, against methanol as blank.[3, 7].

% drug content = (Wa/Wt) × 100

Where,

Wa = Actual drug content and

Wt = Theoretical drug content

In-vitro drug release studies

The *In-vitro* study of pure drug and its solid dispersion carried out using USP apparatus II (LABINDIA DS 8000). The dissolution medium was 900 ml 0.1 N HCL (pH1.2) kept at 37 ± 1 ^{0}C. The paddle was rotated at 100 rpm. The sample of 5 ml sample was withdrawn at specified time interval and analysed spectrophotometrically at 245 nm using UV visible spectrophotometer. The sample withdrawn replaced by fresh 0.1 N HCL solution. The dissolution study continued for next 2 hr. [9, 10]

Micromeritic studies

Bulk density(ρb) = Mass of powder(M) /bulk volume of powder (Vb)

Tapped density(ρt) = Mass of powder(M) / tapped volume of powder (Vt)
Carr's index **=** (Tap density – bulk density / Tap density) × 100
Housener's ratio **=** Tapped density(ρt) / Bulk density(ρb)
Angle of repose (θ) = Tan^{-1} (h/r)
Where, h= height, r= radius [4, 10]

Fourier transform infrared spectroscopy (FTIR) FTIR spectra of celecoxib and its solid dispersion was identical. The principal IR absorbance peaks of celecoxib solid dispersions were observed and found to be identical with the spectra of celecoxib pure drug. Thus, from the spectra it was understood that where was no interaction between celecoxib and the carriers used in the preparation of solid dispersion. The FTIR spectra of pure celecoxib, physical mixture and solid dispersion. The 1:2 ratio was recorded (SHIMADZU, BRUKER TENSOR 37) FTIR spectrophotomer. The sample scanned at 4000-400 cm^{-1}.[5, 15]

Differential scanning colorimetry

DSC studies of pure celecoxib, physical mixture and solid dispersion of drug celecoxib with β cyclodextrin was performed to assess what changes happen during the heat change and thermal behaviour of the drug is also determined. The pure drug sample shows sharp endothermic peak at melting point of drug. The sample were kept on DSC reference pan and DSC curve were obtained by differential scanning colorimetry (DSC-60 SHIMADZU, METTLER TOLEDO) The DSC pattern of solid dispersion in 1:2 ratio was recorded [3, 15]

Powder X-ray diffraction

Powdered X-ray diffraction of pure drug and solid dispersion in 1:2 ratio recorded on (ULTIMA IV X-RAY DIFFRACTOMETER). [9]

Scanning electron microscopy

The SEM of pure drug and solid dispersion in 1:2 ratio recorded on (NOVA NANOSEM450) [14].

Stability studies

The reason of stability testing is to provide evidence on how the quality of drug formulation varies with time under the influence various environmental condition such as temperature, humidity, light. Form this study recommended storage conditions humidity, light, re-test periods and self-life of the drug can be established. The selected formulations were subjected for 3 months for stability study as per ICH guidelines. The selected formulation was a placed in a wide mouth glass bottles, mouth of the bottle was tightly closed and packed in aluminium foil. In the present study, stability studies were carried out at 40 ^{0}C ±2 ^{0}C /75% RH ±5% RH for a specific period of 3 month for the selected formulation.(13)

RESULT AND DISCUSION

Preformulation studies of drug

The properties of drug related with the physical appearance, state solubility is given below table no.2

Table 2: Description of drug

Sr. No	Properties	Nature
1	Physical state	Crystalline
2	Colour	White
3	Solubility	Poorly soluble in water, Soluble in methanol, Chloroform, Acetonitrile, etc.

The melting point of celecoxib was found to be 162^{0}C.

Standard calibration curve of celecoxib

Concentration and absorbance obtained for calibration curve of celecoxib in methanol.

Table 3: Standard calibration curve of celecoxib

Sr No	Concentration (µg/ml)	Absorbance at (254) nm.
0	0	0
1	2	0.1012
2	4	0.2075
3	6	0.3102
4	8	0.4147
5	10	0.5081

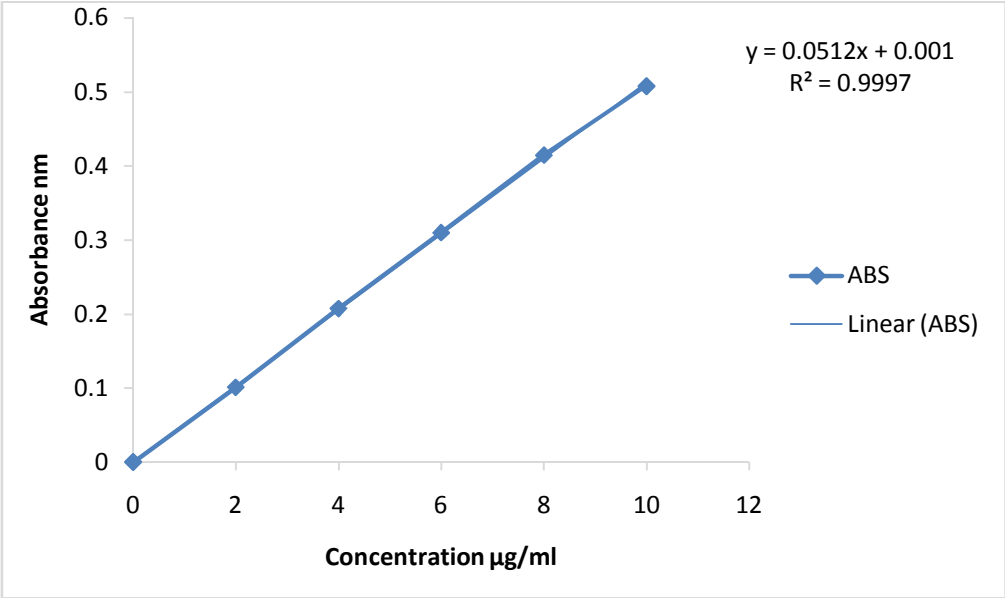


Figure 1: Standard graph of celecoxib in methanol

Drug excipient compatibility studies

Fourier transform infrared spectroscopy (FTIR)

The interaction between drug and physical mixture were studied by IR spectroscopy. Below spectra shows the peak of pure drug and physical mixture thatwas no chemical reaction occurs between polymer and drug sample as shown in figure no.2 and 3. FTIR spectra studies showed the following characteristic peak at1512 cm^{-1} -C=C- aromatic stretching vib. Frequency, 1260 cm^{-1} C-N stretching vibration frequency, 1150 cm^{-1} -S=O sulphoxide symmetric stretching vibration frequency, 1342 cm^{-1} -S=O sulphoxide asymmetric stretching vibration frequency, 1450 cm^{-1} Methyl --CH_3 bending vibration frequency, 1345 cm^{-1}-C-O-C- stretching vib. Frequency for cyclie ether link, 3334 cm^{-1}-OH stretching vib. Frequency.

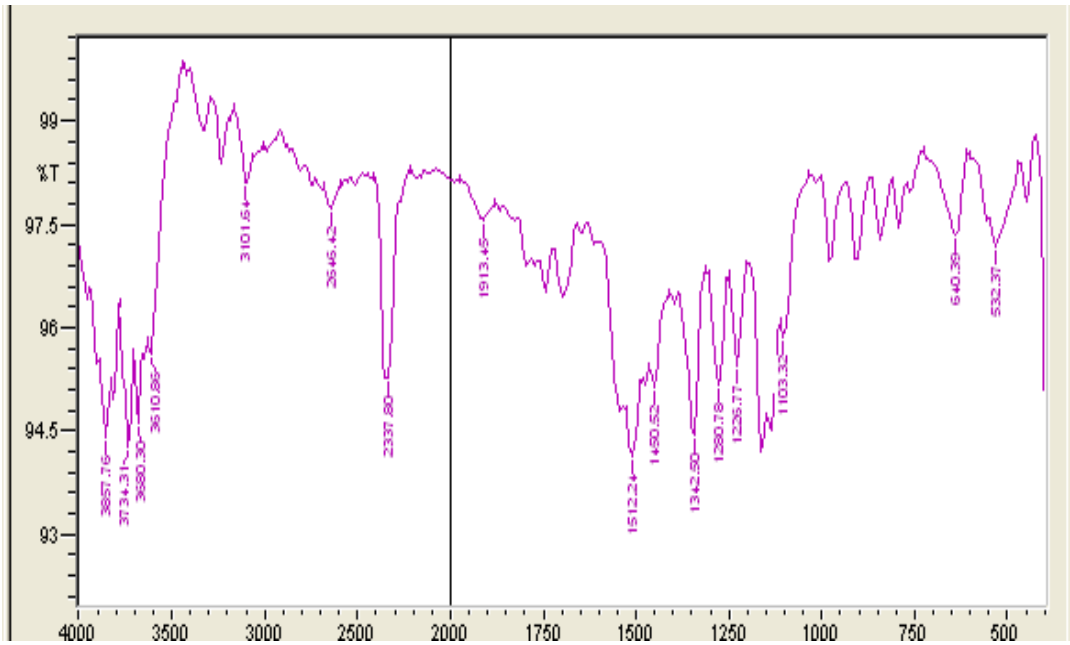


Figure 2: FTIR spectra of pure celecoxib

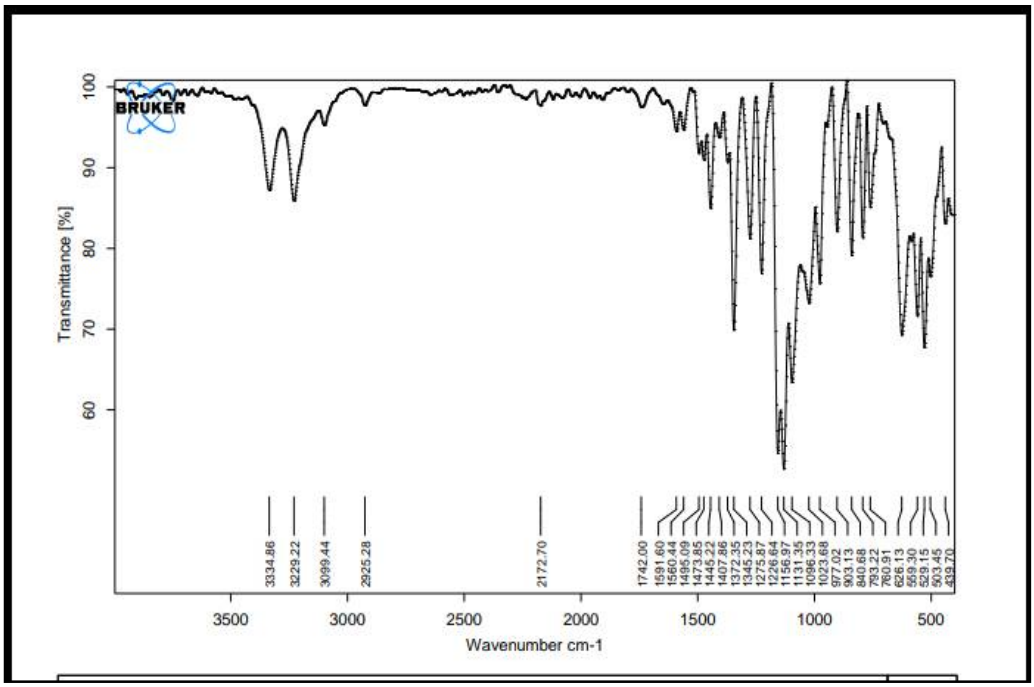


Figure 3: FTIR spectra of physical mixture

The peak obtained in the pure drug spectrum was comparable to that given in std.

Different scanning colorimetry

The DSC thermogram of Celecoxib and physical mixture was recorded and it shows one endothermic peak at 165^0 C. This was compared and accordance with reported DSC data of drug. Celecoxib was identified by DSC as shown in figure no.4 and 5.

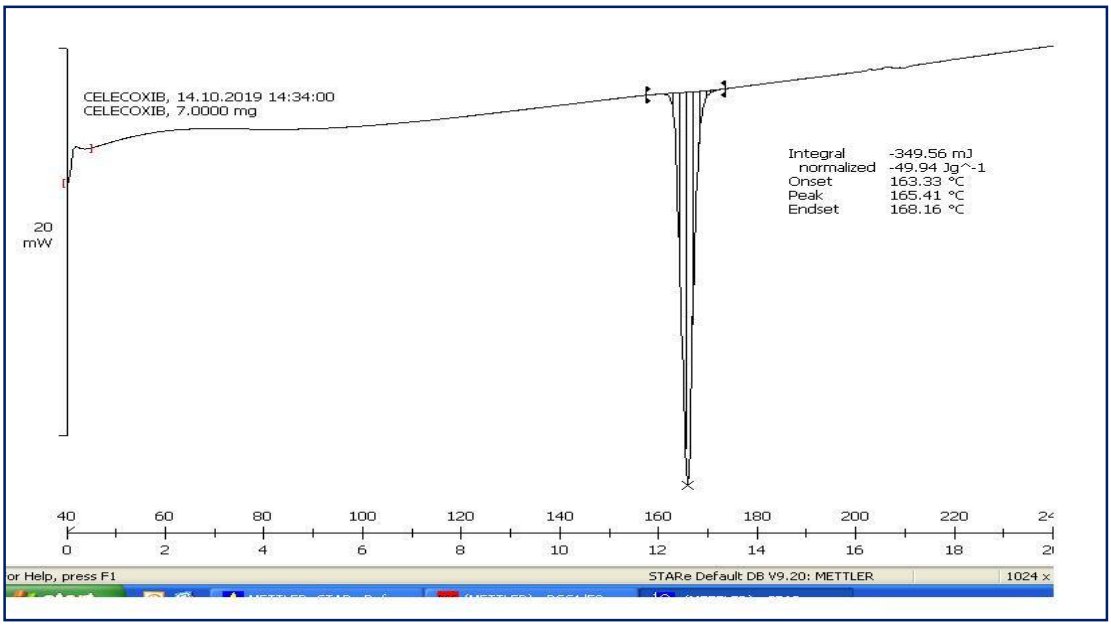


Figure 4: DSC thermogram of celecoxib

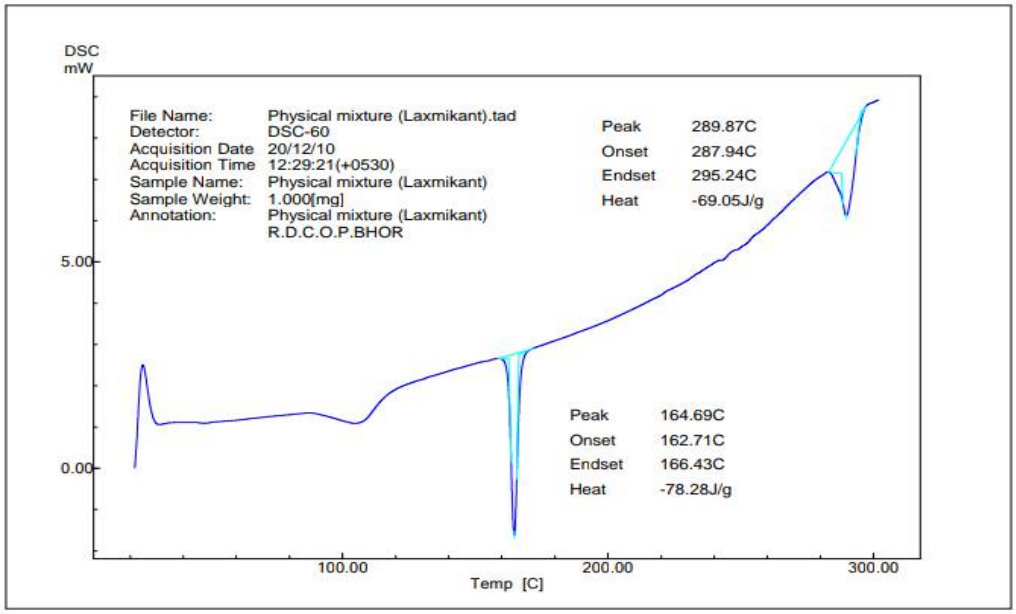


Figure 5: DSC thermogram of physical mixture.

From the above data on the basis of physical appearance, melting point, UV visible spectrum, FTIR spectrum and DSC thermogram of celecoxib. The procured sample of celecoxib was found to be acceptable purity and quality. The sample taken for further studies.

Evaluation tests:

Solubility studies

The solubility of Celecoxib and prepared solid dispersion is determined and shown in table no.4

Table 4: Solubility of celecoxib solid dispersion

Sr.No.	Formulation code	Solubility in 0.1 N HCL
1	API	4.347 ± 0.14
2	F1	27.32 ± 0.22
3	F2	57.84 ± 0.46
4	F3	21.17 ± 0.42
5	F4	24.22 ± 0.45

The solubility was found that solid dispersion prepared using β cyclodextrin in 1:2 ratio had good solubility as compared to another drug polymer ratio. For the further study 1:2 ratio of solid dispersion selected and evaluated.

Micromeritic studies

The micromeritic studies like the determination of the bulk density, tapped density, hausner's ratio, carr's index and angle of repose, were performed for all formulation and the obtained results are as shown in table no.5

Table 5: Micromeritic properties of celecoxib solid dispersion

Sample	Bulk density (gm/cm^3)	Tappeddensity (gm/cm^3)	Hausner's ratio	Carr's index (%)	Angleof repose$^{(0)}$
Pure drug	0.360	0.545	1.61	34.85	41^0.36
F1	0.479	0.537	1.12	12.54	22^0.13
F2	0.502	0.531	1.10	7.51	23^0.12
F3	0.472	0.539	1.09	10.42	25^0.10
F4	0.439	0.536	1.11	9.52	24^0.14

Percentage yield

The percentage yield of prepared solid dispersion is determined and shown in table no.6

Table 6: Percentage yield of solid dispersion

Sr. No.	Formulation code	Percentage yield
1	F1	95.50 %
2	F2	95.33 %
3	F3	96.75 %
4	F4	97.40 %

Drug content

The drug content of different solid dispersion is shown in table no. 7

Table 7:Drug content of solid dispersion

Sr. No.	Formulation code	Drug content
1	F1	90.25 %
2	F2	93.97 %
3	F3	91.20 %
4	F4	92.99 %

***In-vitro* drug release studied**

In-vitro drug release studies pure drug and formulation were performed. Celecoxib solid dispersion showed improve dissolution performance over corresponding to pure drug. Celecoxib with β cyclodextrin solid dispersion 1:2 ratio showed a significant increase in cumulative % drug release up to 95.18 % shown in table no.8

Table 8: *In-vitro* drug release of celecoxib solid dispersion compared with pure drug

Sr. No	Time (min)	0	15	30	45	60	75	90	105	120
1	Pure drug	0	2.22	2.28	3.39	4.37	5.50	5.89	6.71	7.23
2	F1	0	10.37	18.74	27.88	37.58	50.48	62.44	72.32	80.82
3	F2	0	13.62	25.65	36.95	48.54	60.83	73.32	85.01	94.18
4	F3	0	9.27	17.70	31.03	41.87	52.96	62.40	69.54	79.99
5	F4	0	7.91	15.91	26.88	35.53	46.53	57.87	71.10	83.01

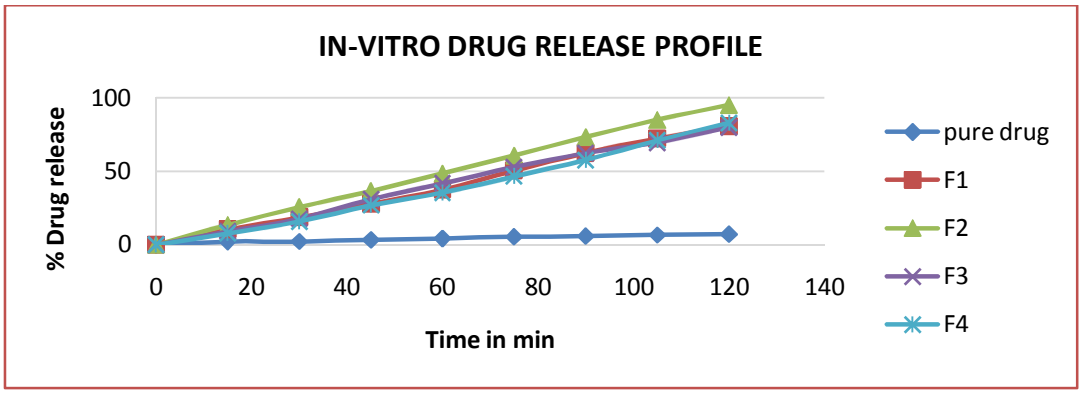


Figure 6: Comparative *in-vitro* drug release profile of pure drug and all formulation

As per the percentage yield, of drug content and dissolution tests, it was shown that F2 batch formulation given better yield, having best drug content and shows best dissolution release.

FTIR Spectra

The FTIR spectra of celecoxib and β cyclodextrin solid dispersion 1:2 ratio was recorded with FTIR spectrophotometer and show in figure no.7. It was revealed that no incompatibility seen between API and excipient.

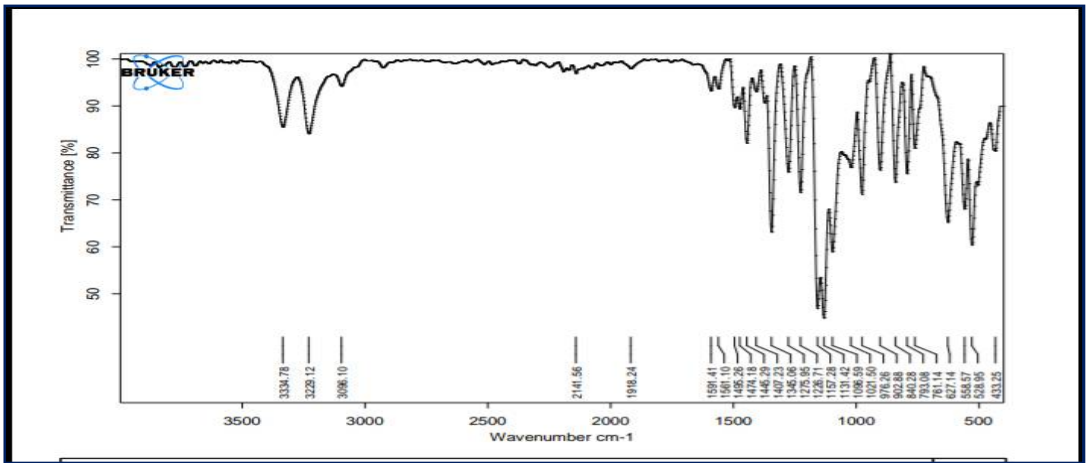


Figure 7: FTIR spectra of Celecoxib solid dispersion

From the FTIR spectra of celecoxib: β cyclodextrin solid dispersion (1:2) ratio was found that there was no functional group change when celecoxib reacts with β cyclodextrin. So, they are found to be compatible with each other.

Different scanning colorimetry

The DSC thermogram of celecoxib and β cyclodextrin solid dispersion shown in figure no.8

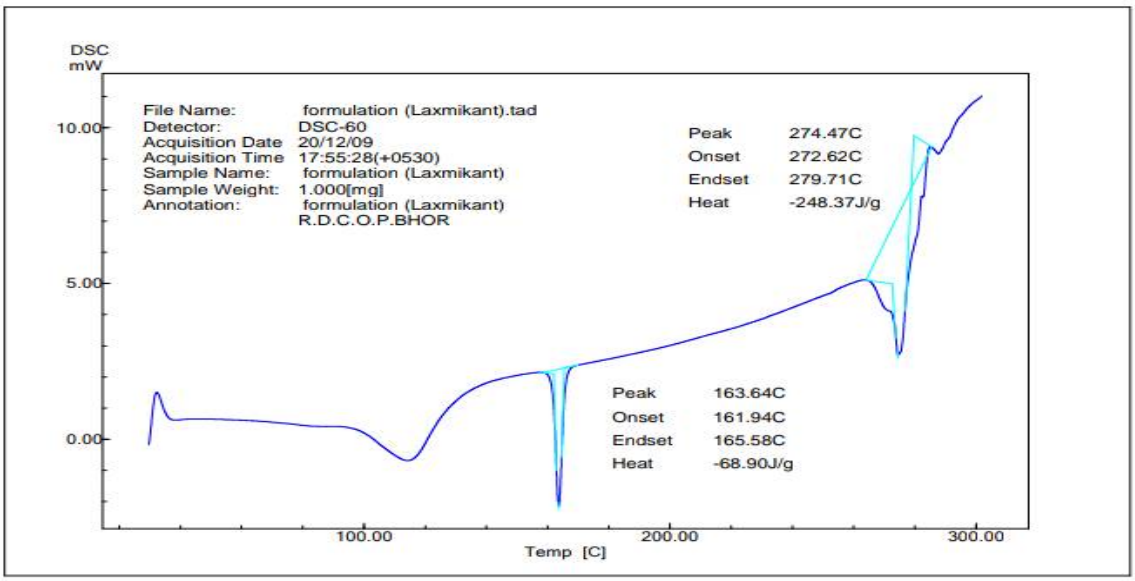


Figure 8: DSC of Celecoxib solid dispersion

Powdered X-ray diffractometry

The x-ray diffractogram of celecoxib and β cyclodextrin 1:2 ratio is shown figure no.9 and 10. Figure no.9 shown plane diffractogram of celecoxib.

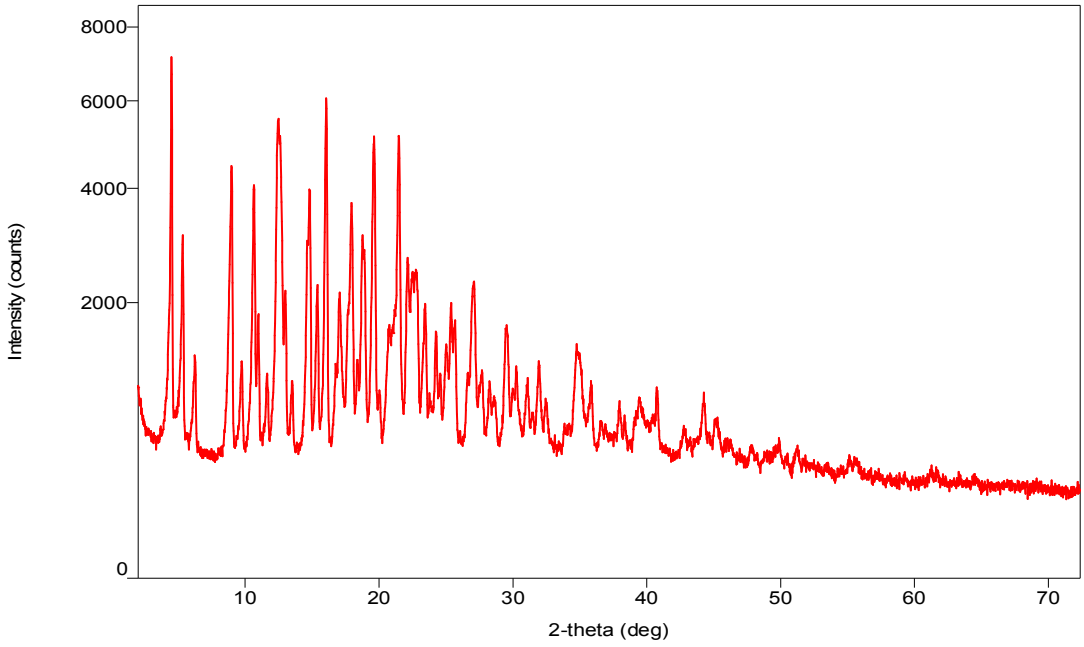


Figure 9: X-Ray diffractogram of pure celecoxib

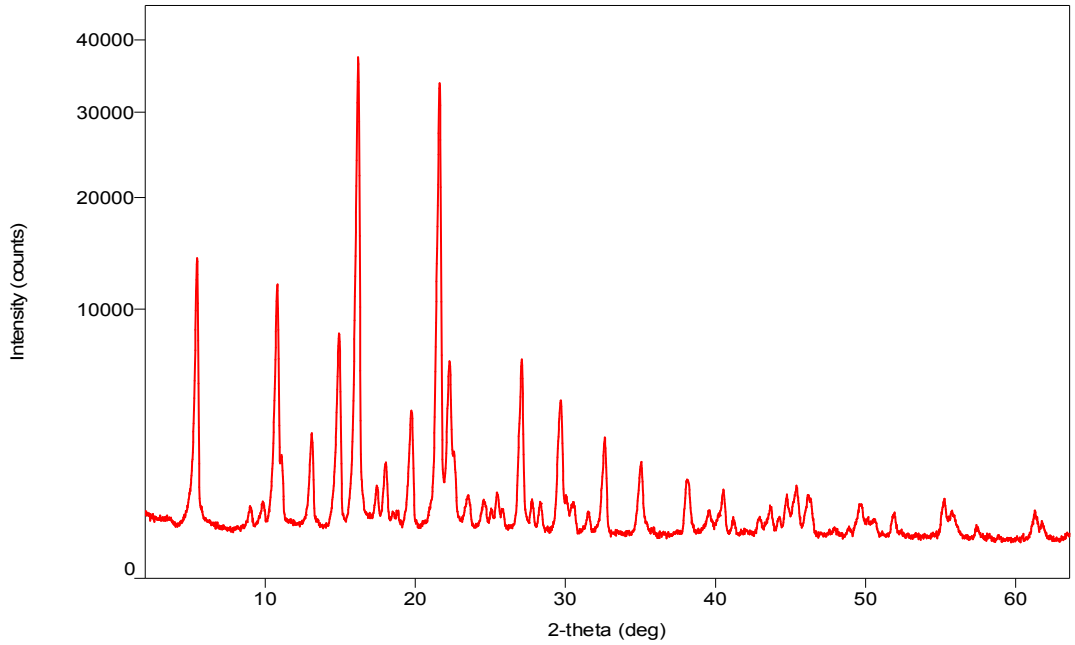
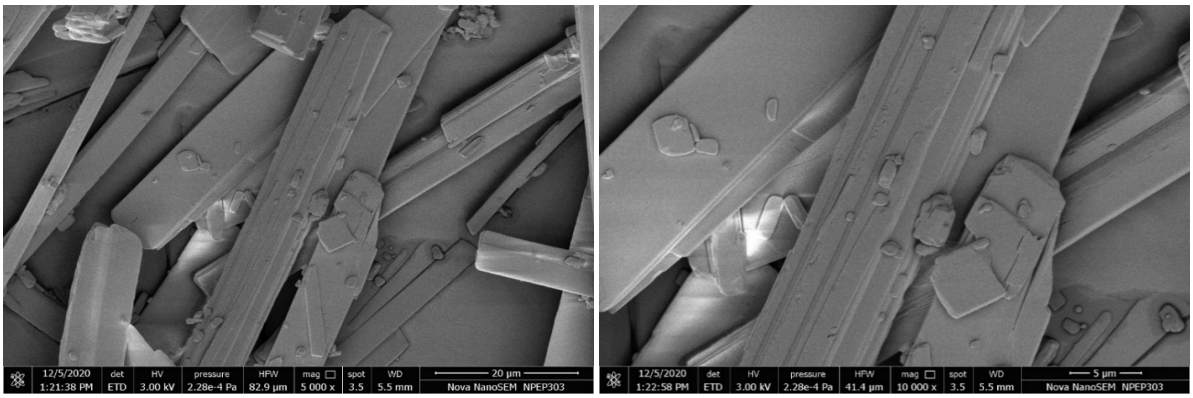


Figure 10: X-Ray diffractogram of Celecoxib solid dispersion.

The diffraction pattern of pure celecoxib showed its crystalline nature. Shown the figure no.9. and figure no. 10 diffraction pattern of celecoxib and β cyclodextrin solid dispersion peak of celecoxib with reduction in peak intensities indicating that conversion of crystalline to partial amorphous form.

Scanning electron microscopy

The particle size of pure drug and celecoxib: β cyclodextrin solid dispersion determine by SEM studies and shown in figure no. 11 and 12.



A **B**

Figure 11: S.E.M. images of pure Celecoxib (A) and (B)

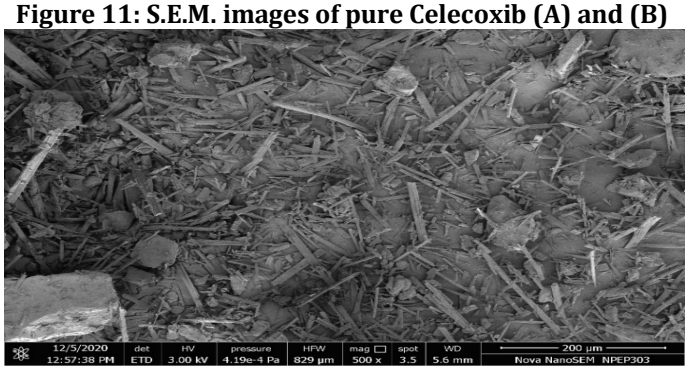


Figure 12: S.E.M. images of Celecoxib solid dispersion C.

The SEM micrographs of celecoxib powder showed irregular shaped particles. On the figure C, formulation F2 was spherical in shape and smooth morphology.

Stability study

Stability studies were carried out 40^0C ±2^0C /75 %RH± 5% RH for a period of 3 month. The optimized formulation F2 was selected for stability studies in order to study the effect of temperature and humidity on formulation. The formulation F2 was analysed for visual appearance, drug content and *iv-vitro* release studies. First month of stability revealed that there was no change in the physicochemical characteristic of formulation. In between2-to-3-month F2 formulation has shown slightly change in drug content and *in-vitro* release which was in acceptable limit (±0.5). No significant changes were observed in formulation during study period thus it can be concluded that the formulation was stable.

CONCLUSION

The celecoxib is BCS II poorly water-soluble drug having high permeability and low solubility. The aim of this study was to improve solubility as well as dissolution rate of celecoxib.We prepared solid dispersion of celecoxib with β cyclodextrinby using solvent evaporation method. Solid dispersion prepared by solvent evaporation method shown good drug content 90.25 to 93.97 and *in-vitro*drug release is 94.15%. The compatibility of drug and polymer determined by FTIR and DSC study. The solid-state characterization such that DSC, SEM, P-XRD studies gave information about smooth molecular morphology and strong molecular dispersion between celecoxib and β cyclodextrin solid dispersion exhibited an immediate release dissolution profile in 0.1 N HCL (pH 1.2) compared with pure celecoxib drug. Therefore, developed formulation with immediate drug release profile could be an effective drug delivery system in treatment of osteoarthritis, rheumatoid arthritis, acute pain etc.

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