Enhancing dissolution behavior of Nabumetone through coamorphous systems with cysteamine.

Running title: Coamorphous formulations of nabumetone with cysteamine

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Coamorphous formulations of nabumetone with cysteamine

Abstract

Nabumetone is a BCS class II, nonsteroidal anti-inflammatory drug (NSAID) used to treat mild-moderate pain and arthritis. It suffers from poor oral bioavailability. This work attempts to overcome this problem, through the formation of a Co-amorphous system of Nabumetone with Cysteamine hydrochloride. Hanson Solubility parameter a science based method was used for the selection of the co-former. The Nabumetone cysteamine coamorphous systems were prepared by various methods like solvent evaporation, Quench cooling, and Spray drying. The prepared Co-amorphous form was evaluated by differential scanning (DSC), Fourier transforms infrared spectrometry (FTIR), and Powder X-ray diffraction (PXRD). Interaction between drug and co-former or hydrogen bond was confirmed from the FTIR. The increase in t_g of the system as determined by Gordon Taylor Equation points to increased interaction between drug and co-former. The deviation of the endotherm of the co-amorphous system compared to the drug and alteration in the intensity and appearance of new peaks in PXRD patterns corroborates the findings. The prepared nabumetone cysteamine Co-amorphous system was found to have a 2 times improvement in solubility and dissolution over Nabumetone. This improvement will be able to enhance the oral bioavailability of nabumetone which is the direct impact of amorphization of drug.

Key Words: Co-amorphous, Dissolution, Nabumetone, Solubility

INTRODUCTION:

Nabumetone (NAB), is a nonsteroidal anti-inflammatory drug classified as BCS class II. Nabumetone is a prodrug that is extensively metabolized during its first pass in the body, resulting in the formation of 6-methoxy-2-naphthylacetic acid (6-MNA), which is the primary circulating metabolite . This metabolite, 6-MNA, is mainly responsible for the therapeutic effects of Nabumetone[*Hedner T,et.al*]. It works by reducing prostaglandin synthesis through the inhibition of cyclooxygenase, an enzyme involved in the conversion of arachidonic acid. Although Nabumetone is effective when taken orally, its therapeutic effectiveness is limited by its poor solubility in water. This poor solubility and wettability of Nabumetone create challenges in developing pharmaceutical formulations for oral or parenteral administration, potentially leading to variations in absorption and bioavailability[*Fink C, et.al]*

There are various conventional and innovative methods for enhancing the solubility of BCS Class II drugs. Conventional techniques include the use of co-solvents, amorphous forms, chemical modification of the drug, formation of inclusion complexes, use of hydrates or solvates, and employing soluble prodrugs [*Shi Q, Moinuddin SM, Cai T*]. Recent advancements in drug delivery include size reduction technologies, lipid-based delivery systems, micellar technologies, and crystal engineering technology, but have drawbacks like use of high end technology, stability [*Liu J, et.al*].

One commonly used method for increasing the dissolution rate and apparent solubility of poorly water-soluble drugs is to convert a crystalline drug into its amorphous form. Recently, the Co-amorphous drug delivery system has been established as a promising formulation approach for delivering poorly water-soluble drugs [*Dengale SJ, et.al- Savjani KT, et.al].* These systems consist of completely miscible single-phase amorphous solid forms, made up of two or more components in a solid state. The second component co-former is used to maintain drug in amorphous state for long duration through establishment of noncovalent interactions.[*Khatri H, Hussain MS, Tyagi S.]* The interaction between components in a co-amorphous system occurs at a specific favorable molar ratio on a molecular level [*Bhairav BA, Bachhav JK, Saudagar RB*]. It has been observed that co-amorphous formulations prepared using different methods may show significant variations in their physical stability and dissolution behavior *[P. J. Brandrup, EH Immergut and EA Grulke*]. Therefore, it is essential to carefully choose the molar ratio and preparation method to create uniform powdered co-amorphous formulations, ensuring satisfactory performance of the end product[*Stefanis E, Panayiotou CJ.*

This research aimed to create a Co-amorphous form of Nabumetone using a co-former Cysteamine (CYST) selected based on the Hansen Solubility Parameter to improve its solubility and dissolution. Co-amorphous preparations were made using different methods such as solvent evaporation method and Spray drying. Various drug and co-former ratios were used to prepare a co-amorphous form to determine the optimal stoichiometric ratio with the highest dissolution and improved flow property. The Co-amorphous forms were characterized using DSC, IR, and XRPD techniques.

MATERIAL AND METHOD

Nabumetone was obtained as a gift from Mylan Pharmaceutical Private Limited. The required excipients and solvents were purchased from LOBA CHEMIE Pvt Ltd.

Selection of Co-former

The co-former selection process based on Hansen Solubility Parameters (HSP) involves comparing the HSP values of potential co-formers with the pure drug and the difference between the HSP values of Nabumetone and Selected conformer should be less than 7. Cohesive energy is the sum of the forces (Van der Waals interactions, covalent bonds, hydrogen bonds, and ionic bonds) that hold the material intact. Cohesive energy can also be defined as the energy needed to break all these interactions, allowing atoms or molecules to detach and resulting in solid-to-liquid/gas or liquid-to-gas transformations [Hu D, et.al]. The cohesive energy per unit volume is termed the cohesive energy density (CED). The CED can be used to calculate the solubility parameter (δ) based on regular solution theory restricted to non-polar systems, as follows

$$\delta = (CED)^{0.5} = (\Delta Ev/Vm)^{0.5} \quad (1)$$

Where ΔEv is the energy of vaporization, and Vm is the molar volume. δ is measured in units of $(J/cm^3)^{0.5}$, $MPa^{0.5}$ or $(cal/cm^3)^{0.5}$ is equivalent to 2.0421 $MPa^{0.5}$ or $(J/cm^3)^{0.5}$ The total solubility parameter also called the three-dimensional solubility parameter can be defined as follows

$$\delta d = \frac{\sum_i Fdi}{\sum_i Vi} \quad (3)$$

$$\delta p = \frac{\sqrt{\sum_i F2pi}}{\sum_i Vi} \quad (4)$$

$$\delta h = \left[\frac{\sum_i Fdi}{\sum_i Vi}\right]^{0.5} \quad (5)$$

Where *I* is the structural group within the molecule, Fdi is the group contribution to the dispersion forces, Fpi is the group contribution to the polar forces, Fhi is the group contribution to the hydrogen bonding energy, and vi is the group contribution to the molar volume. The difference in the total solubility parameter between the drug and the cocrystal former (Δδt) as a tool to predict miscibility, as demonstrated in Eq. (6)

$$\Delta\delta t = \left| \delta_{t2} - \delta_{t1} \right|$$

Where δ_{t1} and δ_{t2} are co-former and drug respectively. Δδt <7 $MPa^{0.5}$ are miscible [*Löbmann K, et.al*].

PREPARATION OF NABUMETONE-CYSTEAMINE (NAB-CYST) CO-AMORPHOUS SYSTEM:

Solvent evaporation method[*Fael H, Demirel AL]*

NAB-CYST co-amorphous forms at a molar ratio of 1:1, 1:2, 1:3 and 1:4 were prepared by solvent evaporation process. NAB and Co-former were dissolved in methanol separately and mixed with stirring for 10 min. The resulting solution was transferred to the Petri plate and subjected to evaporation resulting in the formation of Co-amorphous NAB-CYST. These Co-amorphous product was subsequently air-dried and used for further analysis.

Spray drying [*Alhajj N, O'Reilly NJ, Cathcart H - Lu W, Rades T, Rantanen J, Yang M.]*

Accurately weighed amount of Nabumetone and cysteamine were dissolved in ratios of 1:1 and 1:2 based on their respective molar masses using methanol. This solution was spray-dried with an inlet and outlet of 60 ºC and 55 ºC respectively. Furthermore, the feed rate was maintained at 3 ml/min with a pump rate of 5± 0.2ml/min[*Alhajj N, O'Reilly NJ, Cathcart H - Lu W, Rades T, Rantanen J, Yang M.]*.

CHARACTERIZATION OF CO-AMORPHOUS:

Drug content determination

The total amount of the drug in the co-amorphous was analysed by dissolving the 10 mg co-amorphous product in 10 ml methanol. The flask was subjected to sonication for 30 minutes. The solution was filtered and analysed spectrophotometrically at the predetermined analytical wavelength of 262 nm using a UV-visible double-beam spectrophotometer [Park H, et.al]

Aqueous solubility studies:

The sample was tested for solubility in distilled water using the shake-flask method. Approximately 100 mg of the sample was placed into a 250 mL conical flask containing 100 mL of distilled water. The flask was then shaken using an incubator orbital with a stirring speed of 50 RPM at 37 ± 0.5°C for 72 hours. Following this, the Nabumetone concentration in the filtered solution (0.45 µm filters) was determined from a calibration curve in water. The testing was carried out with three repetitions [Hirakawa Y, et.al].

DSC analysis:

DSC thermogram was recorded on HITACHI DSC 7020 instrument and an empty standard aluminium pan was used as a reference. DSC scans were recorded at a heating rate of 10 ºC/min in the temperature range of 30-200ºC. The nitrogen gas flow was 50 mL/min. Routine calibration of the instrument was carried out using an indium standard. The Gordon-Taylor equation can be used to understand how the composition affects co-amorphous materials. When experimental values are higher than predicted values, it suggests possible intermolecular interactions between the drug and the co-former. Conversely, when experimental values are lower than predicted, it indicates cohesive intramolecular interactions [Wu W, Löbmann K, Rades T, Grohganz H.].

Prediction of theoretical T_g value by Gorden-Taylor equation[Holzapfel K, Rades T, Leopold CS.],

$$Tg_{12} = \frac{(W1 \times Tg1) + (K \times W2 \times Tg2)}{(W1) + (k \times W2)}$$

Where Tg_1 and Tg_2 are the glass transition temperature of pure drug and co-former respectively, W_1 and W_2 is the mass fraction of the component of pure drug and co-former respectively.

K is constant can be calculated from the equation,

$$K = \frac{(Tg1 \times \rho 1)}{(Tg2 \times \rho 2)}$$

where ρ_1 and ρ_2 are the densities of the two components.

FT-IR analysis:

The IR of pure Nabumetone, Co-former, and co-amorphous, were captured using a Shimadzu IRSPIRT 00344 FTIR spectrophotometer. The IR spectra were recorded over the range of 3500-500 cm^{-1} in 32 scans, with a resolution of 4 cm^{-1} for the sample *[Liu J, Grohganz H, Rades T.]*.

PXRD analysis:

The powder X-ray diffraction patterns (XRD) of pure Nabumetone, co-amorphous, and used co-former were recorded using an X-ray diffractometer. Copper was used as the X-ray source, with a voltage of 40 KV and a current of 40 mA. The samples were scanned in the 2θ range from 0 to 800000º at a scanning speed of 10.0 degrees per minute, with a scan step time of 0.8 seconds *[Ueda H, et.al - Li B, et.al]*.

In vitro dissolution studies:

The in-vitro dissolution study of the drug and its NAB-CYST was carried out, using a USP type II dissolution apparatus with 50 RPM speed in 900 mL of 2 % SLS solution in water as the dissolution at 37ºC ± 0.5 º C. Aliquots were withdrawn at 15 min intervals, filtered through 0.45 µm membrane immediately. An equal volume of 2% SLS was added to replenish the dissolution medium. The amount of dissolved Nabumetone in NAB-CYST was determined at 262 nm using a UV spectrophotometer *[da Costa NF, Fernandes AI, Pinto JF.]*.

RESULTS

Hansen Solubility Parameter

The co-former chosen in this work was Cysteamine hydrochloride which is basic. As calculated by Hoftyer Van Krevelen's group contribution method the difference in total solubility parameter of the drug and co-former should be less than 7 $MPa^{0.5}$. The HSP values of Nabumetone and co-former are 18.37 and 22.95 respectively which have differences of less than 7. Based on values and compatibility cysteamine is selected as co-former for NAB-CYST Co-amorphous.

Formulation of Co-amorphous forms

Spray drying has a low yield. The solvent evaporation method is a superior approach for creating Co-amorphous compared to alternative methods due to its simplicity and effectiveness. These techniques involve dissolving the desired components in a solvent and allowing the

solvent to evaporate, leading to the controlled formation of Co-amorphous. This method offers advantages, including ease of implementation, the minimal requirement for specialized equipment, and the ability to produce Co-amorphous. The dry powder and co-amorphous are used for further study

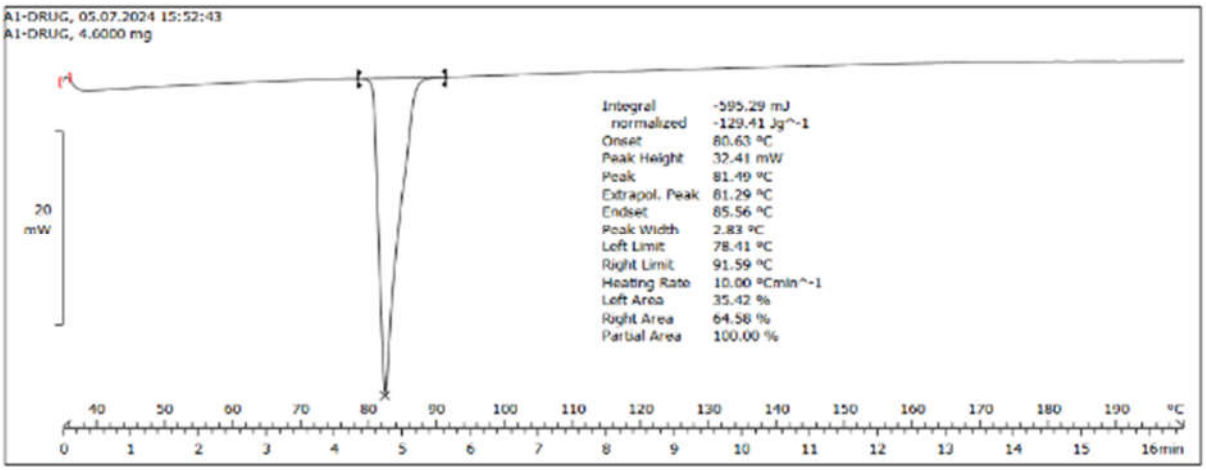
CHARACTERIZATION OF CO-AMORPHOUS FORMATION:

DSC Analysis:

The DSC approach was used for preliminary screening since it is the easiest and fastest way to choose systems that form Co-amorphous. as shown in Fig.1

From the DSC study, the Co-amorphous formation can be confirmed for that formulation, which shows a characteristic change in the melting behaviour, confirming the formation of a Co-amorphous structure. The thermogram of Nabumetone Co-amorphous showed an endothermic peak at 78°C which was reduced from that of the endotherm for Nabumetone at 81.49°C, suggesting that the cohesive energy of cocrystal is decreased from that of the pure drug indicating the increase in solubility of as Co-amorphous compared to pure drug Nabumetone.

The practically observed glass transition temperature (Tg.) of Nabumetone co-amorphous is 81.35°C, which is higher than the theoretical Tg of 71.36°C. This discrepancy in the Gorden-Taylor equation suggests a strong interaction between Nabumetone and cysteamine, possibly due to the formation of hydrogen bonds or π-π interactions [*USP 2021 Vol.III*].



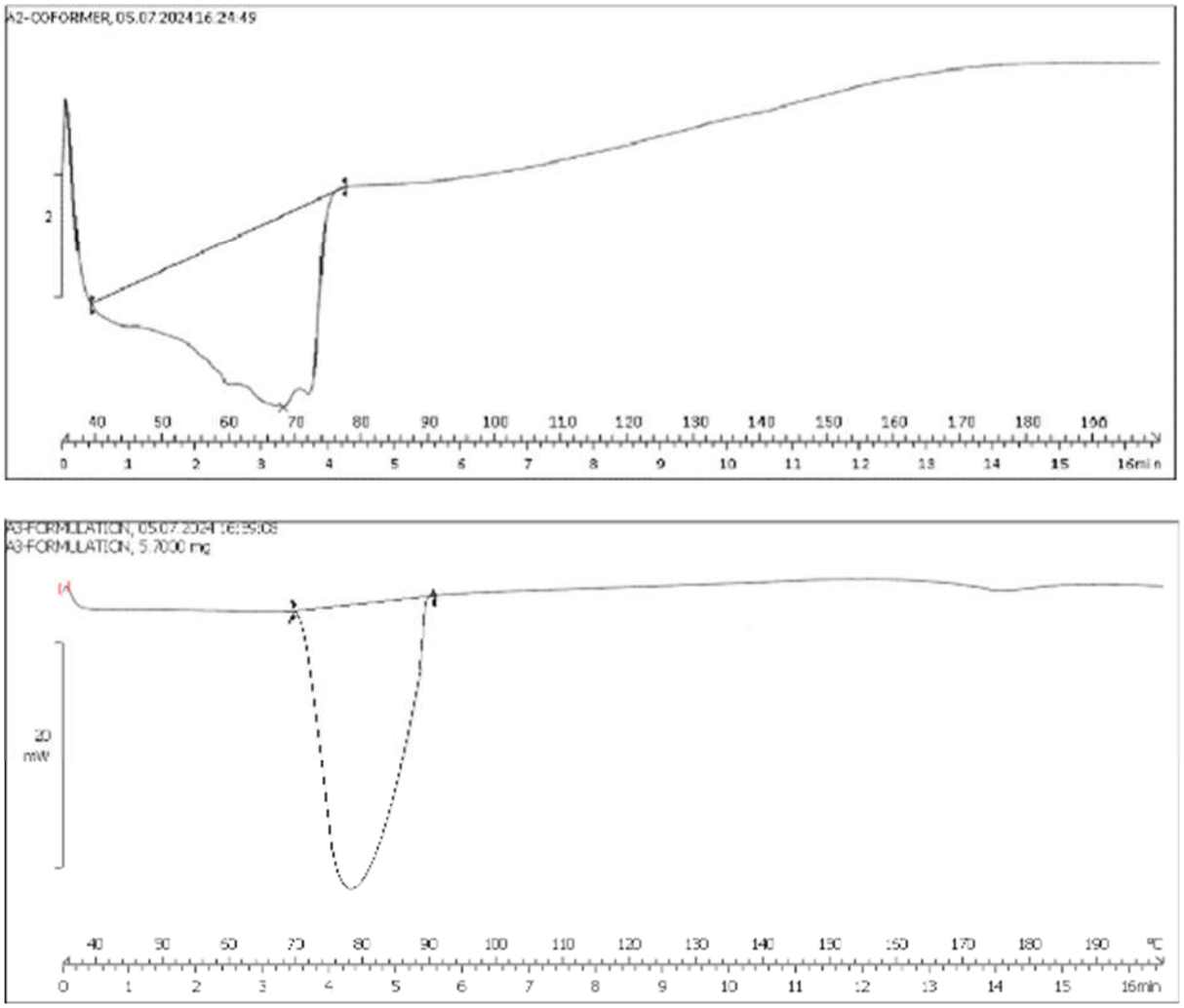
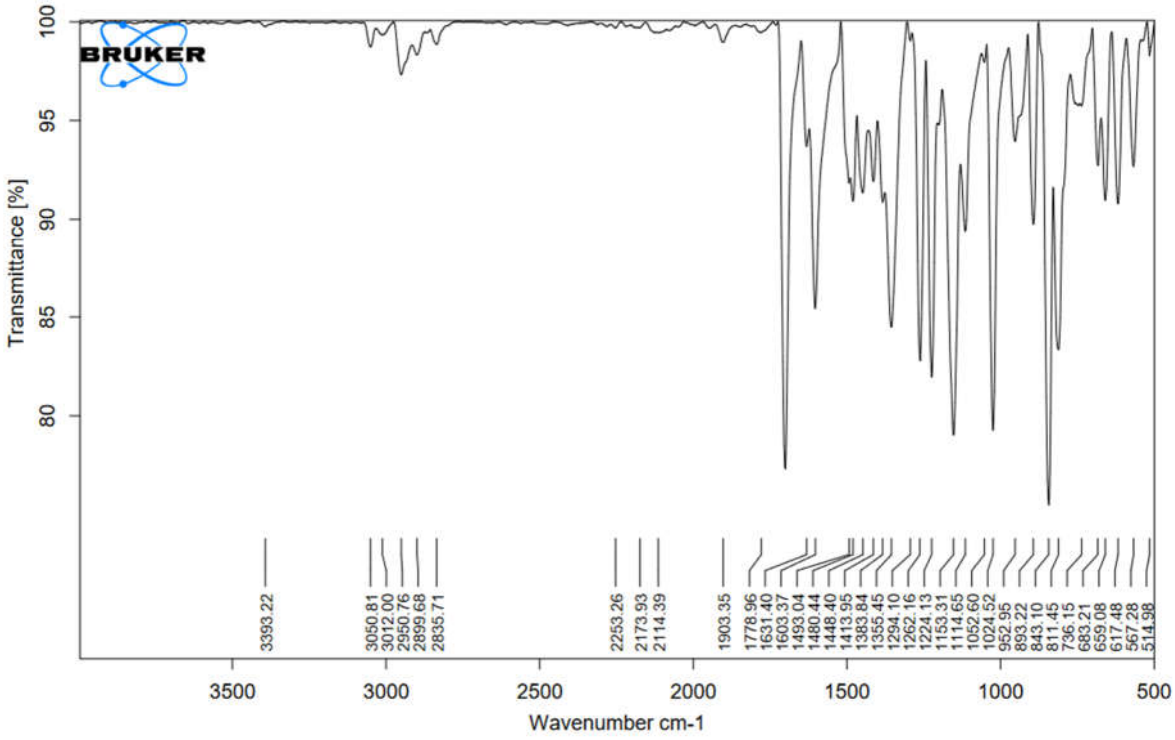


Fig.1 DSC thermograms of a) NAB b) CYST c) NAB-CYST Co-amorphous.

FTIR Analysis:

The pure drug and Co-amorphous infrared (IR) spectra were recorded and analysed. Specific wavenumbers corresponding to characteristic peaks of pure Nabumetone were identified, including peaks at 2899 cm^{-1} (C-H stretching), 1480 cm^{-1} (C=C stretching), 1383 cm^{-1} (CH_3 bend), 1778.96cm^{-1} (C=O), 1024 cm^{-1} (O-CH_3).

The FTIR spectrum (Fig.2) of the Co-amorphous with cysteamine showed changes in certain functional groups compared to pure Nabumetone. Specifically, the (C=C stretching) peak was observed at 1493 cm-^{1}, and at 2602 cm^{-1} new peak was observed which is not observed in Nabumetone spectra. The shift in characteristic peaks in FTIR spectra indicates changes in the bonding environment of specific functional groups.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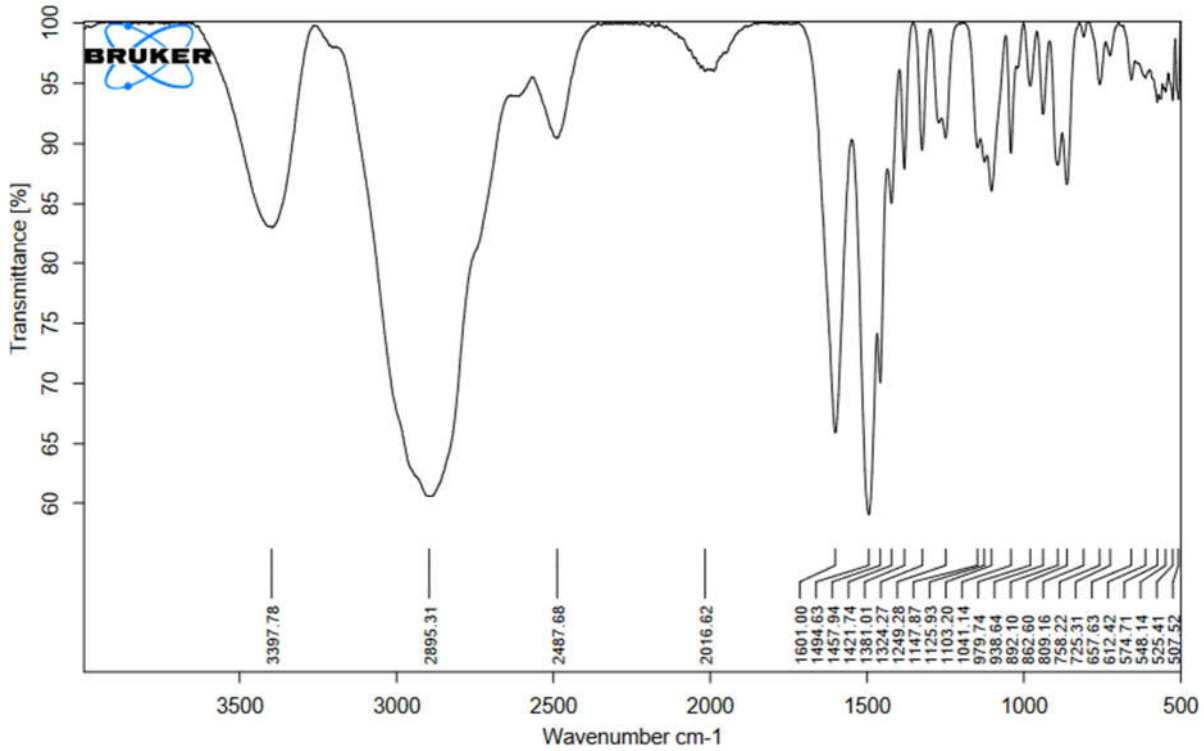
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1421.74
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1324.27
1249.28
1147.87
1125.93
1103.20
1041.14
979.74
938.64
892.10
862.60
809.16
758.22
725.31
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Wavenumber cm-1

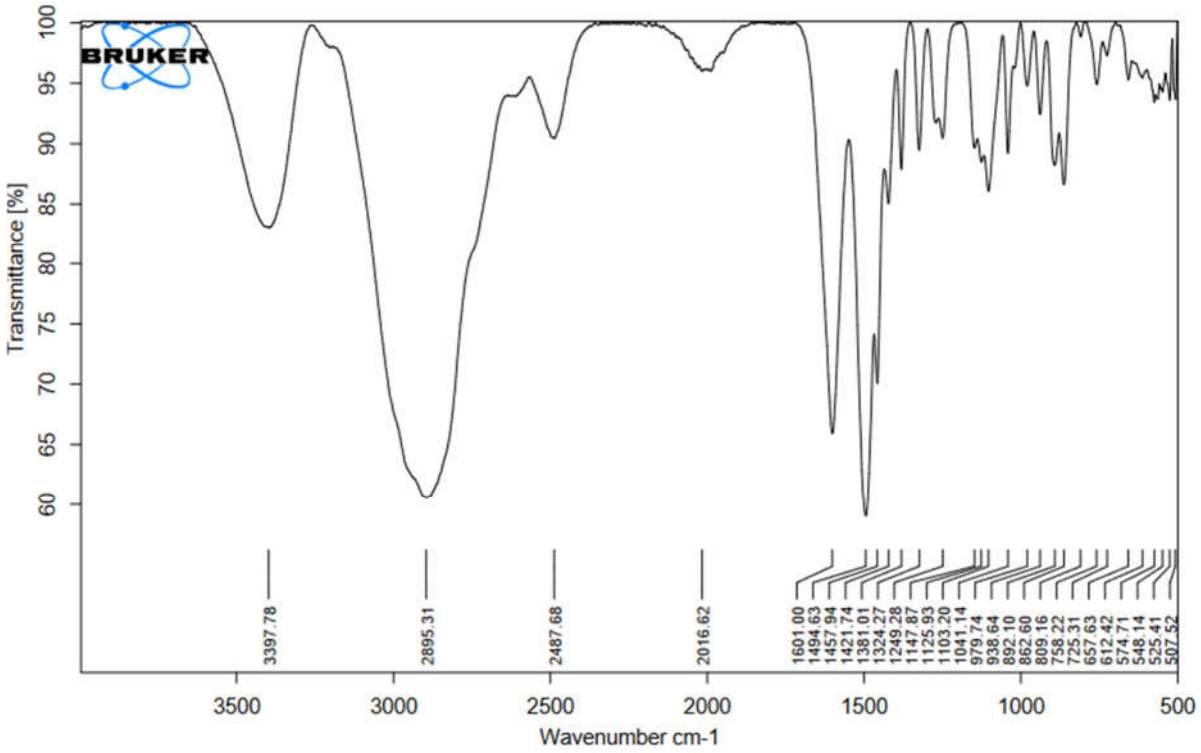

Fig.2 FT-IR spectrum a) NAB b)CYST c) NAB-CYST Co-amorphous

PXRD Analysis:

The Powder X-ray diffraction (PXRD) study helped to identify the characterization of the structure of crystalline and amorphous materials by analysing the diffraction peaks

The crystalline nature of Nabumetone (Fig.3) was confirmed by the distinct peaks at 2θ values of 19.92°, 21.56°, 24.32°, 27.22°, and 29.98° in Nabumetone, and 21.42°, 24.00°, 32.06°, and 40.02° in Nabumetone Co-amorphous Form (Fig.4). This indicates the formation of a new solid phase, as shown by the appearance of unique peaks in the Co-amorphous and the absence of Nabumetone peaks *[Schugmann M, Foerst P.*].

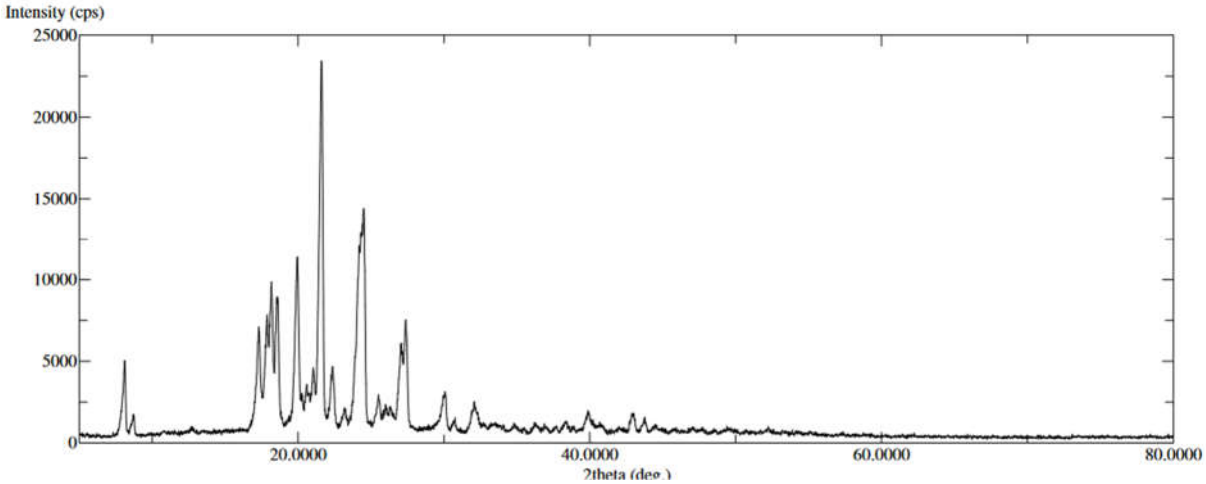

Fig.3 PXRD Pattern of Nabumetone

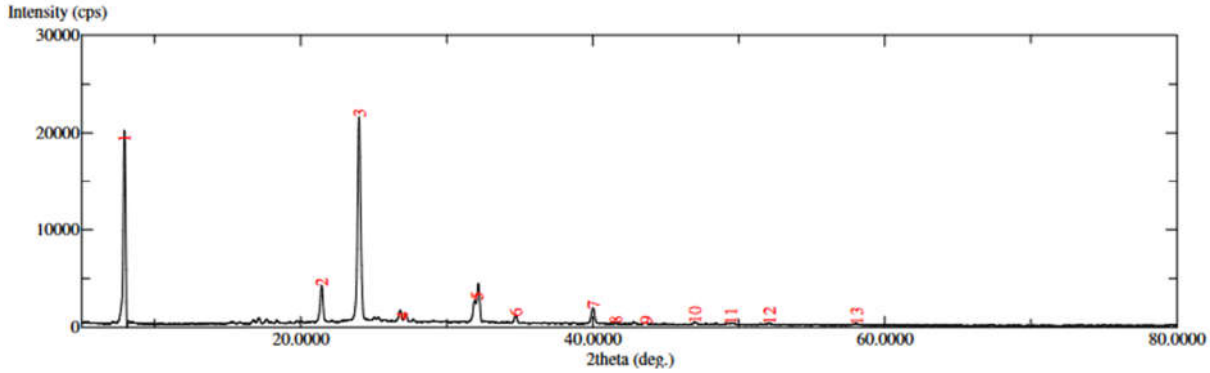

Fig.4 PXRD pattern of Nabumetone Co-amorphous form

EVALUATION OF NAB- CYST COAMORPHOUS FORM

Solubility study:

Nabumetone water solubility was 0.073 mg/ml, while NAB-CYST Co-amorphous exhibited higher solubility at 0.144 mg/ml, marking a 2-fold increase. Nabumetone Co-amorphous 1:1, prepared through solvent evaporation, demonstrates significantly higher solubility compared to quench cooling and spray drying. Results shown in Table. I

Table. I Solubility Studies

Sr. No	Name of Method	Drug and co-former ratio	Solubility (mg/ml)
1	Solvent Evaporation	1:1	1.44
		1:2	1.02
		1:3	0.98
		1:4	0.85
2	Spray drying	1:1	1.13
		1:2	0.89

Determination of drug content:

NAB content in the NAB-CYST Co-amorphous was determined by UV-spectrophotometry. The percentage drug content of NAB-CYST Co-amorphous was found to be 89.92%.

In Vitro Drug Release:

Dissolution rate tests for NAB-CYST Co-amorphous and NAB were carried out in 2% SLS, the drug release from Co-amorphous was rapid compared to that of the plain drug. Plain NAB shows slow and incomplete dissolution which was 37.99 % in 2 h, while 89.47 % drug was released in 2 hr when amorphization with a drug: co-former ratio of 1:1 by solvent evaporation was used. The amount of drug released from the Co-amorphous continuously surpassed the amount of the pure drug at each time point. According to the acquired results, there was a noticeable improvement in the dissolution rate of Co-amorphous when compared to pure drugs. It was found that the dissolution of NAB could be modified through amorphization. Therefore, Nabumetone permeability will change as its rate of dissolution increases [*Thakral NK, et.al]*.

Dissolution profiles were compared using spectrophotometric analysis at 262 nm. The NAB-CYST Co-amorphous displayed significantly improved dissolution compared to Nabumetone, with a dissolution of 89.47% for the 1:1 Co-amorphous prepared through solvent evaporation. This enhanced dissolution is attributed to a change in NAB-CYST amorphous nature due to hydrogen bond interaction with Cysteamine. Results as mentioned in Table II

Table II. Results of Drug Release

Time (min)	Nabumetone	% Release					
		Solvent Evaporation				Spray drying	
		1:1	1:2	1:3	1:4	1:1	1:1
15	29.94	69.90	60.59	46.31	43.12	52.53	51.53
30	30.98	73.08	62.83	58.32	46.22	55.12	52.12
45	32.56	77.16	65.16	66.45	51.41	59.42	54.12
60	33.77	78.01	68.82	76.36	72.54	66.14	61.13
75	33.99	82.15	71.42	76.41	74.85	72.92	69.72
90	34.49	85.61	71.72	76.49	75.22	72.76	70.70
105	35.91	86.87	75.69	78.51	76.25	82.44	75.41
120	37.99	89.47	85.23	84.40	81.57	82.91	79.24

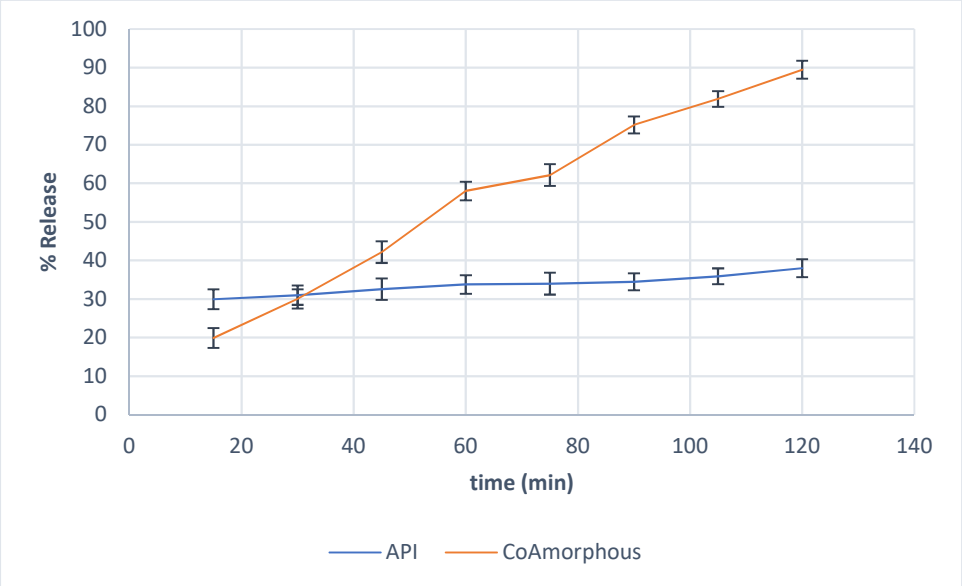

Figure 5 In-vitro drug release of Nabumetone and Nabumetone Co-amorphous (1:1 solvent evaporation)

Flow Property Evaluation studies:

These evaluations are crucial for understanding how the material behaves during manufacturing processes and their potential impact on the drug's performance in solid dosage forms [*Fael H, Demirel AL*]. Results are shown in Table No. III

Table III . Flow Property studies

Formulation	Bulk Density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio	Angle of Repose (Ɵ)
Nabumetone	0.15	0.24	35 Poor	1.42 Poor	40 Poor
Nabumetone-Coamorphous	0.22	0.25	12 Good	1.17 Good	34 Good
Nabumetone Coamorphous Granules	0.30	0.34	11 Excellent	1.10 Excellent	21 Excellent

DISCUSSION:

The co-former for the Co-amorphous study was chosen to be Cysteamine hydrochloride based on the Hansen solubility parameter (HSP). Different methods like solvent evaporation and spray drying were used to prepare Co-amorphous with varying drug and co-former ratios. Among these methods, the 1:1 ratio of Co-amorphous form prepared through solvent evaporation was selected for further studies due to a noticeable change in dissolution compared to the pure drug form. The alteration in the structure may have affected the hydrogen bonding between the drug and the co-former. In the FTIR analysis, a change in the chemical structure was observed, with a new band appearing at 1493 cm-1 in the NAB-CYST Co-amorphous and a new band at 2602

cm-1. The melting point of the pure drug decreased and became slightly broader in the Co-amorphous, indicating the formation of an amorphous structure. Analysis of the PXRD pattern of NAB-CYST showed the appearance of new unique peaks, the disappearance of peaks from NAB and CYST, and a change in peak intensity. These changes suggest an interaction between the drug and the co-former, resulting in the formation of a new solid phase.

A series of comparative studies were conducted to analyze the solubility and dissolution of NAB-CYST Co-amorphous compared to NAB. The results indicated that NAB-CYST Co-amorphous has nearly doubled solubility and dissolution rate compared to NAB. Additionally, the micrometric properties of NAB-CYST Co-amorphous, including the angle of repose, Carr's compressibility index, compressibility index, and Hausner’s ratio, were found to be superior to those of NAB.

CONCLUSION:

In this study, a NAB-CYST Co-amorphous was successfully prepared using solvent evaporation techniques. The formation of Co-amorphous was characterized by a shift in melting temperature as observed by DSC. The crystal structure and the formation of a new solid phase were characterized using PXRD and FT-IR. When compared with NAB, NAB-CYST Co-amorphous demonstrated a significant increase in vitro performance, suggesting that Co-amorphous preparation is an advanced strategy for enhancing the dissolution rate and bioavailability of poorly soluble drugs such as NAB.

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CONFLICT OF INTEREST:

No conflict of interest was declared by the authors. The authors are solely responsible for the content and writing of this paper.

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