IJMPR, 2026, 10(5), 29-40

ISSN: 2319-5878

INTERNATIONAL JOURNAL OF
MODERN PHARMACEUTICAL RESEARCH

www.ijmpronline.com

Research Article
Impact Factor: 7.533
Coden USA: IJMPR3

SOLUBILITY ENHANCEMENT OF A POORLY SOLUBLE HEPATOPROTECTIVE DRUG SILYMARIN USING COCRYSTALLIZATION TECHNIQUE

Mahesh Kumar T.*, Dhivya G., Mohana Bharathi V., Malar Mannan U., Ananthi P.

Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University), Sivakasi - 626130, Tamil Nadu, INDIA.

Article Received on: 21/03/2026 **Article Revised on: 11/04/2026** **Article Published on: 01/05/2026**

***Corresponding Author**
Mahesh Kumar T.
Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy (Affiliated to The Tamil Nadu Dr. M.G.R. Medical University), Sivakasi - 626130, Tamil Nadu, India.

https://doi.org/10.5281/zenodo.19883429

How to cite this Article: Mahesh Kumar T.*, Dhivya G., Mohana Bharathi V., Malar Mannan U., Ananthi P. (2026). Solubility Enhancement Of A Poorly Soluble Hepatoprotective Drug Silymarin Using Cocrystallization Technique. International Journal of Modern Pharmaceutical Research, 10(5), 29–40.

ABSTRACT

Silymarin, a flavonolignan complex obtained from *Silybum marianum*, is widely used for its hepatoprotective antioxidant & anti-inflammatory activities. However, its clinical application is limited due to poor aqueous solubility and low oral bioavailability, as it belongs to the Biopharmaceutics Classification System of class II drug category. The present study aims to enhance the solubility characteristics of silymarin through the pharmaceutical cocrystallization technique. Cocrystals of silymarin were prepared by the antisolvent precipitation technique using coformers generally recognised as safe. The FTIR result establishes the compatibility of the drug silymarin with selected coformers in this study. The prepared cocrystals were evaluated using techniques like saturated solubility, melting point, microscopy and XRD. The saturated solubility of silymarin cocrystals increases many-fold in compared to the pure drug. The decrease in melting point of cocrystals and peak shifts in XRD towards higher 2θ values with reduced d-spacing of more crystalline percentages proved the formation of new crystalline phases. Microscopic image of pure silymarin drug compared with different cocrystals prepared, showing significant differences. Among all formulations, the silymarin–ascorbic acid cocrystal exhibited the highest solubility, improved particle morphology, and favourable crystalline characteristics. These results of this study confirm that the cocrystallization is an effective and promising approach to enhance the solubility and oral bioavailability of poorly water-soluble drugs like silymarin.

KEYWORDS: hepatoprotective, solubility, cocrystal, antisolvent precipitation, silymarin.

INTRODUCTION

Silymarin is an extract from the milk thistle plant that is used in the treatment of liver diseases, exhibiting hepatoprotective properties by mitigating mitochondrial dysfunction, oxidative stress, liver fat accumulation and insulin resistance. It is primarily used to support liver health, manage fatty liver, cirrhosis, and Hepatitis C. It protects the liver from toxins, aids in liver cell regeneration, and may also support kidney health, manage diabetes-related liver issues, and provide anti-cancer properties. It has very poor oral bioavailability (typically less than 1% of absolute oral bioavailability) due to low aqueous solubility, poor intestinal permeability, extensive hepatic phase II metabolism and rapid excretion via bile and urine. While 20–50% may be absorbed in the gut, rapid first-pass metabolism limits its systemic availability. To overcome these limitations, it is necessary to develop formulation strategies to enhance its therapeutic performance.[1,2] Several formulation approaches, such as micronization, solid dispersions, salt formation, nanosuspensions, liposomes, and inclusion complexes, have been explored to tackle the solubility-related challenges. Among all approaches, pharmaceutical cocrystallization has emerged as a promising and efficient technique.

Cocrystals are multicomponent crystalline systems consisting of an active pharmaceutical ingredient and a suitable coformer in a definite stoichiometric or mass ratio, held together by non-covalent interactions such as hydrogen bonding.[3,4] This approach enables modification of physicochemical properties without altering the pharmacological activity of the drug. Cocrystallization offers multiple advantages, including enhancement of solubility, dissolution rate, and bioavailability. It can also improve physicomechanical properties such as compressibility, flowability, and stability, which are essential for formulation research and development.[5,6]. Due to these benefits, cocrystallization is increasingly considered as an alternative to conventional solubility enhancement techniques. Despite its advantages, cocrystallization presents certain limitations and challenges. The selection of an appropriate coformer is critical and requires careful consideration of compatibility and stability. Additionally, maintaining consistency in crystal formation and ensuring stability under different environmental conditions can be difficult. Scale-up of cocrystal production from laboratory to industrial level also poses challenges due to the need for precise control of crystallization parameters.[7,8] Furthermore, regulatory and intellectual property considerations play a significant role in the development and commercialization of cocrystal-based formulations.[9,10]. Various methods are employed to manufacture the desired cocrystals. The choice of selection of methods depends on the material characteristics, such as solubility, thermal stability, and the need of stoichiometric purity. The solid state method uses no or minimal solvents in the process, like dry grinding, liquid-assisted grinding and high-shear wet granulation. Another strategy of manufacturing is solution-based/solvent-intensive wet process, such as solvent evaporation, antisolvent addition crystallization, cooling crystallization, and slurry cocrystallization. Also, various advanced methods have emerged includes hot-melt extrusion, spray drying/congealing, supercritical fluid technology, sonocrystallization and laser irradiation. The antisolvent crystallization method is widely preferred due to its simplicity, cost-effectiveness, and suitability for large-scale production. However, factors such as solvent selection, supersaturation control, and crystal growth conditions must be carefully optimized to achieve desired characteristics.[11,12]

The application of cocrystallization extends beyond solubility enhancement. It can be used to improve drug permeability, modify drug release profiles, enhance stability, and mask unpleasant taste. Cocrystals have been successfully applied in various therapeutic areas such as anticancer, antiviral, and cardiovascular treatments, demonstrating their wide pharmaceutical applicability.[13,14] In recent years, the market potential of pharmaceutical cocrystals has increased significantly due to growing industrial interest. Several cocrystal-based drug products have been developed, highlighting their commercial feasibility. Additionally, cocrystals offer opportunities for patent extension and lifecycle management, which are beneficial for the pharmaceutical industry.[15,16] Future research in cocrystallization is focused on the development of predictive tools for coformer selection, environmentally friendly manufacturing processes, and continuous production techniques. Advances in crystal engineering and computational modelling are expected to support the rational design of cocrystals with improved properties. Integration with advanced drug delivery systems may further enhance their applications.[17,18]. However, challenges such as large-scale manufacturing difficulties, reproducibility issues, and a lack of standardized regulatory guidelines must be addressed. Continued research is essential to overcome these barriers and establish cocrystallization as a reliable pharmaceutical strategy.[19]

The present research work focuses on the formulation and characterization of silymarin cocrystals using suitable coformers, which are generally recognized as safe (GRAS). The study aims to enhance the solubility rate of silymarin through cocrystallization. By improving the physicochemical properties of silymarin, this approach seeks to enhance its oral bioavailability and therapeutic efficacy. The successful development of silymarin cocrystals could provide a promising and practical solution for overcoming solubility-related challenges associated with essential natural drug moieties.

II. MATERIALS AND PREPARATION METHODS

2.1. Materials

Silymarin drug was received from Yarrow chem products, Mumbai. The other excipients including ethanol, ascorbic acid, oxalic acid, tartaric acid, succinic acid and nicotinamide, were purchased from Rankem Chemicals Pvt.Ltd, Haryana and Lark Chemicals Pvt.Ltd, Mumbai for conducting various experiments to develop silymarin cocrystals.

2.2. Preparation of silymarin cocrystals

The coformers selected from the list of substances which are approved as GRAS (Generally Recognized As Safe) by the USFDA and do not affect its pharmacological activities of an active molecule. The mass ratio of drug to coformer and the quantitative composition of trial bathes of cocrystals are shown in Table 1.

Table 1: Composition of silymarin cocrystals.

Cocrystal formulation code		**Cocrystal composition**		**Batch qty (gm)**	
		Drug + Coformer	**Mass ratio of Drug:Coformer**	**Drug**	**Coformer**
F1	A	Silymarin + Oxalic acid	1:1.5	5.0	7.5
	B	Silymarin + Oxalic acid	1:2.0	5.0	10.0
	C	Silymarin + Oxalic acid	1:2.5	5.0	12.5
F2	A	Silymarin + Tartaric acid	1:1.5	5.0	7.5
	B	Silymarin + Tartaric acid	1:2.0	5.0	10.0
	C	Silymarin + Tartaric acid	1:2.5	5.0	12.5
F3	A	Silymarin + Ascorbic acid	1:1.5	5.0	7.5

	B	Silymarin + Ascorbic acid	1:2.0	5.0	10.0
	C	Silymarin + Ascorbic acid	1:2.5	5.0	12.5
F4	A	Silymarin + Succinic acid	1:1.5	5.0	7.5
	B	Silymarin + Succinic acid	1:2.0	5.0	10.0
	C	Silymarin + Succinic acid	1:2.5	5.0	12.5
F5	A	Silymarin + Nicotinamide	1:1.5	5.0	7.5
	B	Silymarin + Nicotinamide	1:2.0	5.0	10.0
	C	Silymarin + Nicotinamide	1:2.5	5.0	12.5

The method adopted for the preparation of cocrystals of silymarin with various coformers was antisolvent precipitation method. In this method, silymarin drug with coformers such as oxalic acid, tartaric acid, ascorbic acid, succinic acid and nicotinamide were weighed individually at three concentration levels of 1:1.5, 1:2.0 and 1:2.5 ratios and used for the preparation of cocrystals. Water was selected as an antisolvent because silymarin is insoluble in it, and ethanol was chosen as the solvent because it is miscible with water. Silymarin and coformer were dissolved completely in ethanol with stirring. Subsequently, water was added slowly to the solution under continuous stirring. The addition of water causes precipitation and the formation of cocrystals. The colloidal solution containing cocrystals was kept in a hot air oven at 40ºC±2ºC for up to 12 hours. The dried powder materials were collected, labelled, tightly closed and stored at room temperature for further studies.

III. PREFORMULATION STUDIES

Preformulation studies were carried out to evaluate the physicochemical properties of the drug before formulation development. Solubility studies were performed to determine a suitable solvent system for drug analysis and formulation. The absorption maximum (λ_{max}) and calibration curve were established using UV-Visible spectrophotometry for quantitative estimation of the drug. Fourier Transform Infrared (FTIR) spectroscopy was conducted to identify functional groups and to assess drug–excipient compatibility.

3.1 Determination of λ_{max} (Wavelength of maximum absorption)

The wavelength of maximum absorption (λmax) of the drug was determined using UV- Visible spectrophotometer (Shimadzu UV-1800 series) by scanning the prepared sample solution over an appropriate wavelength range. The drug was accurately weighed, dissolved in a solvent, and subjected to spectral analysis to identify the peak absorbance value. The wavelength corresponding to the highest absorbance was considered as λmax and was selected for further quantitative analysis.

3.2 Standard calibration curve of silymarin

A standard calibration curve of the drug was prepared using UV-Visible analysis. An accurately weighed quantity of the drug (10 mg) was transferred into a volumetric flask (100 ml), dissolved in a suitable solvent with sonication, and the volume was made up to obtain a standard stock solution of 100 µg/ml concentration. From this stock solution, a series of solutions of different concentrations (10 – 80 µg/ml) was prepared using the same solvent. The prepared solutions were scanned within the wavelength range of 400–200 nm, and absorbance values were recorded at the predetermined λmax using the solvent as a blank. A calibration curve was constructed by plotting absorbance against concentration.

3.3 Drug excipient compatibility study by Fourier Transform-Infrared spectroscopy

The drug and excipients must be compatible with one another to produce a desired product that is highly stable, efficacious and safe. FT-IR spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. FT-IR spectra of the silymarin and other mixtures of drug with excipients used in the formulation were recorded by using an FT-IR spectrophotometer in the region between 4000-400 cm^{-1}. The samples were crushed and mixed with potassium bromide and pressed at 10 tons of pressure to make a disc. These compressed discs were scanned using an FT-IR spectrophotometer (PerkinElmer Spectrum IR Version 10.7.2) between 4000-400 cm^{-1}. After running the spectra, significant peaks relating to major functional groups were identified.

IV. CHARACTERIZATION OF COCRYSTALS

Characterization of the prepared cocrystals was carried out to evaluate their physicochemical properties and confirm cocrystal formation. Saturation solubility studies were performed to assess the improvement in drug solubility compared to the pure drug. Melting point determination and microscopic analysis were conducted to observe changes in thermal behaviour and crystal morphology. X-ray diffraction (XRD) analysis was further performed to confirm modification in crystallinity and the formation of new crystalline phases.

4.1 Saturation solubility study

The saturated solubility of prepared silymarin cocrystals was measured by dissolving in purified water in a 10 ml volumetric flask. Then, it was shaken in an orbital shaker and left for 24 hours to allow for equilibration. After 24 hours, the solution was filtered, diluted if necessary and analysed at 288.40 nm by using a UV-Visible spectrophotometer. In this way, the aqueous solubility of silymarin and its cocrystals prepared can be determined in this research work.

4.2 Melting point determination

The melting point apparatus is used to determine the melting point of all the silymarin cocrystals. In the determination of the melting point, a small amount of the silymarin cocrystals sample was placed into a capillary tube or melting point capillary. The capillary is then inserted into the melting point apparatus, which allows for controlled heating of the sample. As the temperature rises, the solid sample begins to melt, and the transition from solid to liquid phase occurs. The temperature at which this transition occurs is recorded as the melting point.

4.3 Microscopic study

It was used to study the information on the magnified size and morphology of the drug silymarin and silymarin cocrystal particles using an optical microscope (Monocular microscope, Coslab). The microscope allows for magnification and visualization of the samples under 10X magnification levels, enabling detailed observation.

4.4 XRD (X-RAY diffraction analysis)

The crystalline structure and phase composition of the synthesized cocrystal powder were investigated using a X-ray diffractometer (Bruker D8 Advance ECO) equipped with Cu Kα radiation (λ = 1.5418 Å). The instrument was operated at 40 kV and 40 mA, with a scan range of 5° to 80° (2θ), a step size of 0.02°, and a scan speed of 1° per minute. The powdered sample was finely ground and uniformly loaded onto a zero-background holder to ensure a smooth surface for analysis. The obtained XRD pattern revealed distinct diffraction peaks, indicating the crystalline nature of the cocrystals.

V. RESULTS AND DISCUSSION

The results obtained in developing and evaluating the silymarin cocrystals are presented with their scientific discussions as given below.

5.1 Determination of λ max (Maximum absorption wavelength) and standard curve preparation

For the determination of λmax, the stock solution of silymarin (concentration 1000µg/ml) in ethanol was prepared. 1 ml of the prepared stock solution was further diluted to 100 ml. Resulting solutions were scanned in the range of 400 to 200 nm using ethanol as a blank with the help of a UV-Visible spectrophotometer. The average of triplicate readings was taken. The λmax of the drug was found to be 288.40nm. The maximum absorbance wavelength of pure silymarin is shown in Figure 1. In Table 2, the absorbance with respect to drug concentration is recorded.

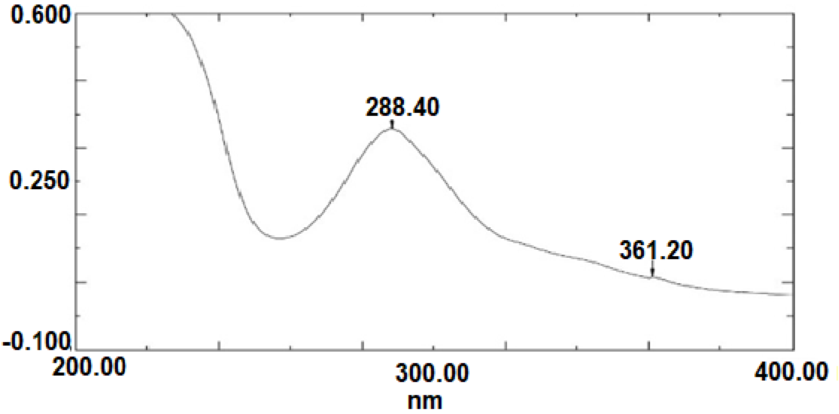

Figure 1: Maximum absorbance wavelength of silymarin drug.

Table 2: UV absorbance of silymarin drug at different concentration.

Sample No.	1	2	3	4	5	6	7	8
Drug Concentration (µg/ml)	10	20	30	40	50	60	70	80
Absorbance (nm)	0.345	0.740	1.065	1.451	1.792	2.094	2.491	2.810

The UV spectroscopic analysis of silymarin at λmax 288.40 nm showed linearity in the concentration range of 10–80 µg/ml. As shown in Figure 2, the calibration curve obeyed Beer-Lambert's law with a regression equation of:

$Y = 0.035x + 0.0215$

and a high correlation coefficient ($R^2 = 0.9993$), indicating a strong linear relationship between concentration and absorbance. The high R^2 value confirms the accuracy, precision, and reliability of the UV method for quantitative estimation of silymarin. Therefore, the developed method is suitable for routine analysis and drug content determination in formulation studies.

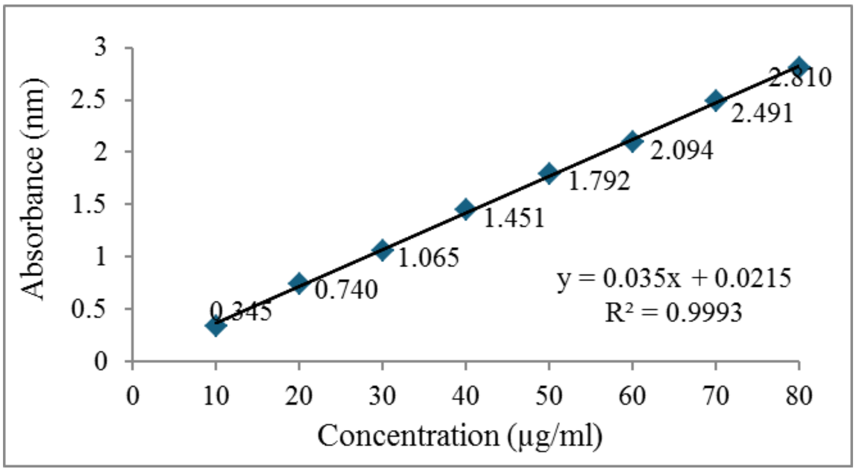

Figure 2: Standard curve of silymarin by UV spectroscopy.

5.2 Preformulation study for drug and coformers compatibility

Using Fourier Transform Infrared (FTIR) spectroscopy, the compatibility between drug and coformers oxalic acid, ascorbic acid, tartaric acid, succinic acid and nicotinamide were studied. The absorption spectrum of silymarin is shown in Figure 3. The FT–IR spectra of silymarin with the other selected coformers are shown in Figures 3(a), 3(b), 3(c), 3(d) and 3(e).

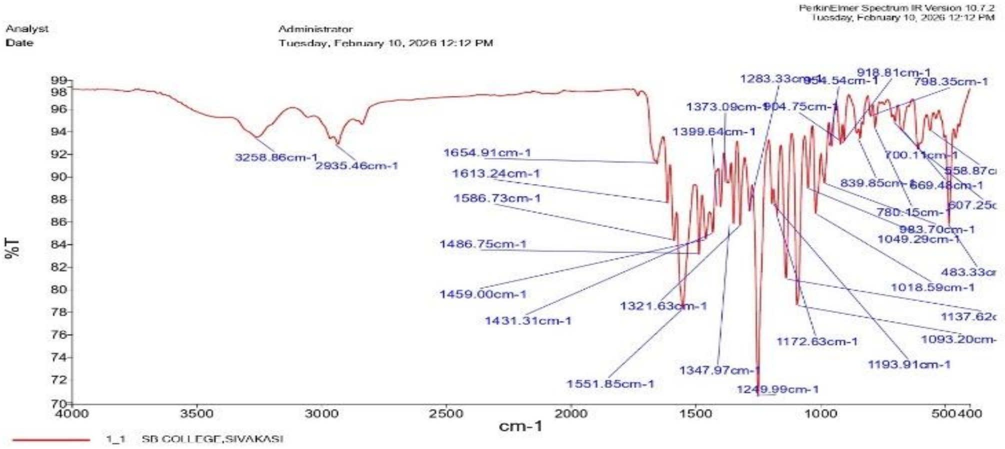

Figure 3: FT-IR spectrum of pure silymarin drug.

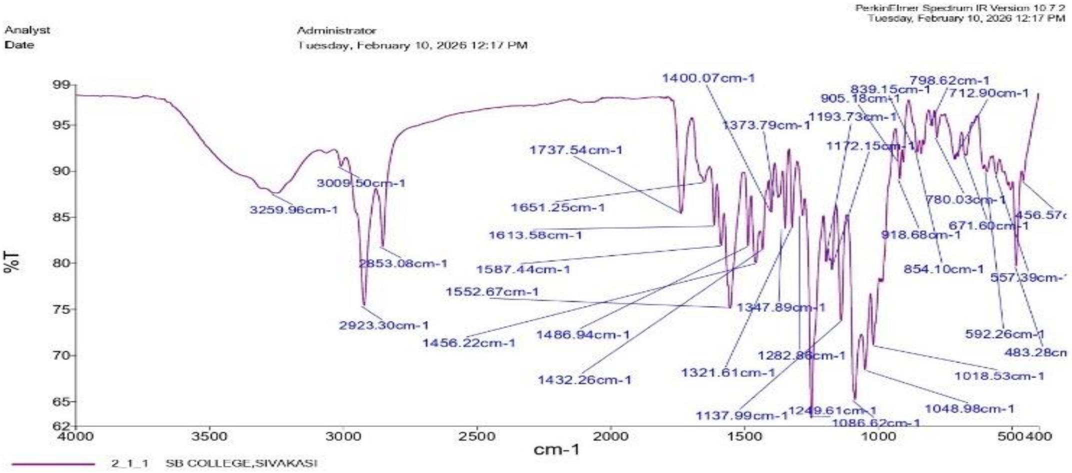

Figure 3(a): FT-IR spectrum of silymarin + Oxalic Acid.

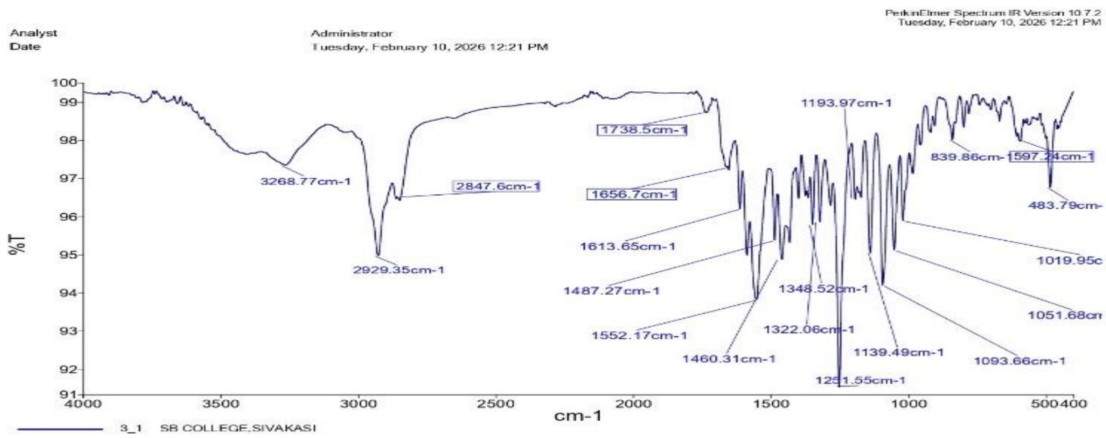

Figure 3(b): FT-IR spectrum of silymarin + Tartaric acid.

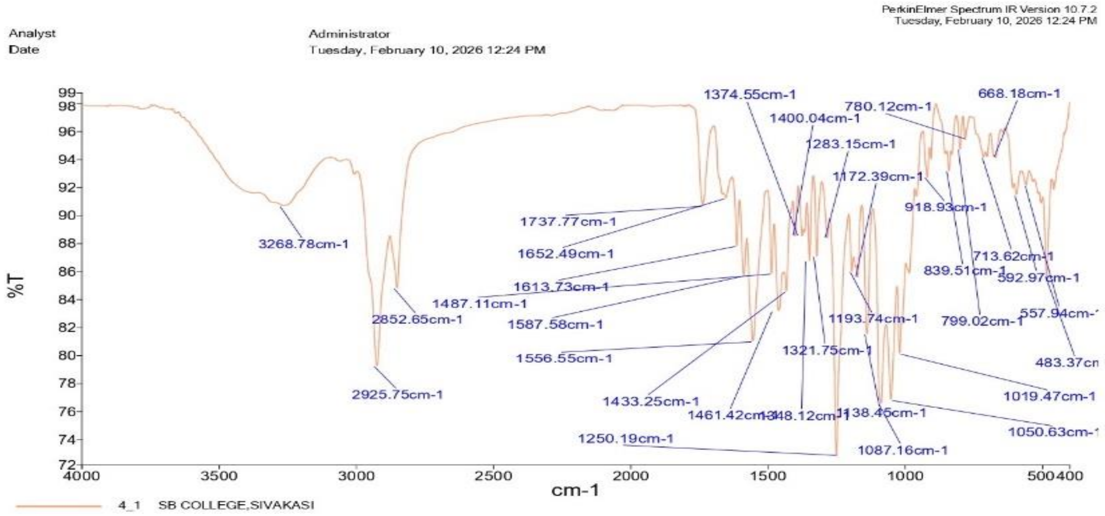

Figure 3(c): FT -IR spectrum of silymarin + Ascorbic acid.

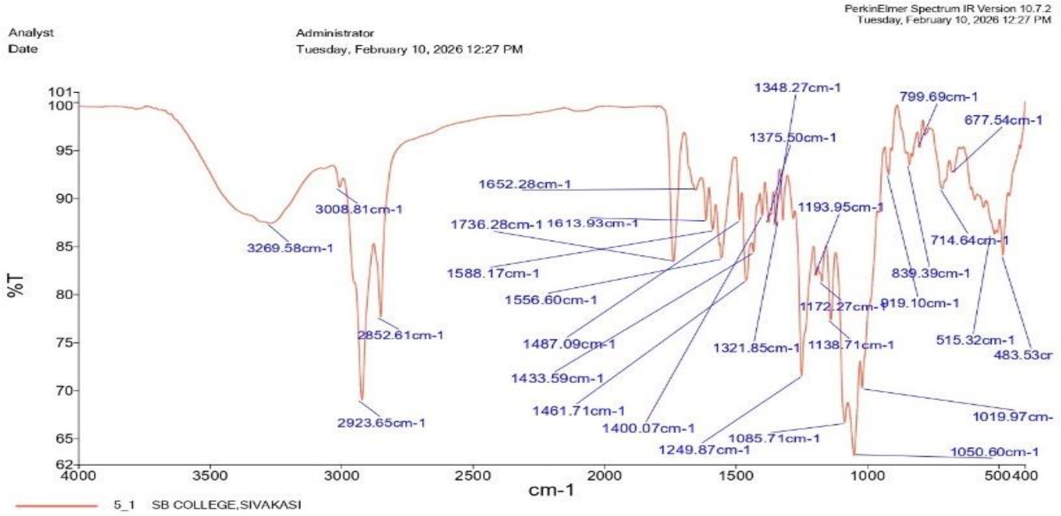

Figure 3(d): FT-IR spectrum of silymarin + Succinic acid.

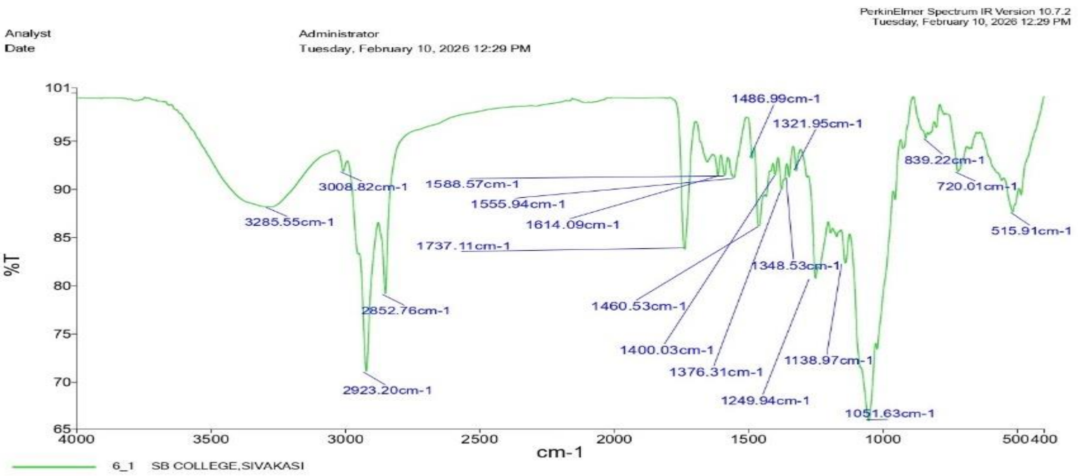

Figure 3(e): FTIR spectrum of silymarin + Nicotinamide.

In Table 3, the wavelength (cm^{-1}) of major peaks observed for the drug silymarin and its mixture with coformer is recorded.

Table 3: Comparative FT-IR spectra of drug and drug coformer mixtures.

Functional group of silymarin & conformer mixtures		O-H stretching phenolic OH group	Aliphatic C-H stretching	C=O stretching: chromanone ring	C=C aromatic stretching	C-O phenolic stretching	C-O-C ether stretching
Frequency range (cm^{-1})		3500 – 3200	3000 – 2900	1700 – 1600	1600 – 1500	1320 – 1220	1100 – 1000
Observed frequency (cm^{-1}) for the samples*	S1	3258.86	2935.46	1613.24	1551.85	1249.99	1093.20
	S2	3259.96	2923.30	1613.58	1552.67	1249.61	1086.62
	S3	3268.77	2929.35	1613.65	1552.17	1251.55	1093.66
	S4	3268.78	2925.75	1613.73	1556.55	1250.19	1087.16
	S5	3269.58	2923.65	1613.93	1556.60	1249.87	1085.71
	S6	3285.55	2923.20	1614.09	1555.94	1249.94	1051.63

***Note:** S1: Silymarin drug, S2: Silymarin+Oxalic acid, S3: Silymarin+Tartaric acid, S4: Silymarin+Ascorbic acid, S5: Silymarin+Succinic acid, and S6: Silymarin+Nicotinamide.

The FTIR spectrum of pure silymarin (S1) showed characteristic peaks corresponding to its functional groups. A broad peak observed at 3258.86 cm^{-1} confirmed O–H stretching of phenolic hydroxyl groups. The peak at 2935.46 cm^{-1} corresponds to aliphatic C–H stretching vibrations. The absorption band at 1613.24 cm^{-1} indicates C=O stretching of the chromanone ring, while the peak at 1551.85 cm^{-1} represents aromatic C=C stretching. Further, the bands at 1249.99 cm^{-1} and 1093.20 cm^{-1} correspond to C–O phenolic stretching and C–O–C ether stretching, confirming the structural integrity of silymarin.

In the physical mixtures with different coformers (S2–S6), slight shifts in peak positions were observed. The O–H stretching peaks appeared in the range of 3259.96–3285.55 cm^{-1}, indicating possible hydrogen bonding interactions. Aliphatic C–H stretching was observed between 2923.20–2929.35 cm^{-1}. The characteristic C=O stretching peaks were retained in the range of 1613.58–1614.09 cm^{-1}, and aromatic C=C stretching appeared between 1552.17–1556.60 cm^{-1}. Similarly, C–O phenolic stretching (1249.61–1251.55 cm^{-1}) and C–O–C ether stretching (1051.63–1093.66 cm^{-1}) were present in all formulations.

The retention of all major characteristic peaks without disappearance or significant shift confirms that there is no chemical incompatibility between silymarin and the selected coformers: oxalic acid, tartaric acid, ascorbic acid, succinic acid, and nicotinamide. The minor shifts observed may be attributed to intermolecular hydrogen bonding interactions rather than structural degradation.

Overall, the FTIR compatibility study demonstrates that silymarin is compatible and stable with the selected coformers, indicating suitability for further formulation development.

5.3 Saturated solubility studies

The saturation solubility of pure drug and prepared co-crystals was determined and reported in Table 4.

Table 4: Saturated solubility of silymarin cocrystals.

Sample No.	Sample details	Saturation solubility (mg\ml)
S1	Silymarin drug	0.027 ± 0.004
S2	Silymarin oxalic acid cocrystal	0.078 ± 0.006
S3	Silymarin tartaric acid cocrystal	0.092 ± 0.006
S4	Silymarin ascorbic acid cocrystals	0.136 ± 0.007
S5	Silymarin succinic acid cocrystal	0.082 ± 0.005
S6	Silymarin nicotinamide cocrystal	0.098 ± 0.006

The saturation solubility study was carried out using purified water. Pure silymarin exhibited a solubility of 0.027± 0.004 mg/mL, indicating its limited solubility in water. However, all prepared cocrystals showed enhanced solubility compared to the pure drug. Among the formulations, the silymarin–ascorbic acid cocrystal (S4) demonstrated the highest solubility of 0.136 ± 0.007 mg/mL, showing a 5-fold increase over the pure drug. This significant enhancement may be attributed to strong hydrogen bonding interactions and the highly hydrophilic nature of ascorbic acid, which improves solvent affinity and wettability. The formulations with nicotinamide and tartaric acid also showed considerable improvement, followed by succinic acid and oxalic acid.

The increase in saturation solubility indicates successful modification of the crystal lattice structure of silymarin through cocrystal formation, leading to reduced lattice energy and improved molecular interactions with ethanol. Overall, the study confirms that cocrystallization, particularly with ascorbic acid, is an effective strategy to enhance the solubility of silymarin and may improve its dissolution behaviour and bioavailability.

5.4 Melting point determination

The melting point of pure drug and prepared co-crystals were determined and is reported in Table 5.

Table 5: Melting point of silymarin cocrystals.

Sample No.	Sample details	Melting point (ºC)
S1	Silymarin drug	164 - 166
S2	Silymarin oxalic acid cocrystal	158 - 160
S3	Silymarin tartaric acid cocrystal	150 - 152
S4	Silymarin ascorbic acid cocrystal	145 - 147
S5	Silymarin succinic acid cocrystal	153 - 155
S6	Silymarin nicotinamide Cocrystal	140 - 143

The melting point of pure silymarin was found to be 164–166°C, which agrees with its reported melting range, confirming the purity of the drug. The prepared cocrystals exhibited a noticeable change in melting point compared to the pure drug. All formulations showed a reduction in melting point, indicating modification of the crystal lattice structure due to cocrystal formation. Among the formulations, the silymarin–nicotinamide cocrystal (S6) showed the lowest melting point (140–143°C), suggesting strong intermolecular interactions and formation of a new crystalline phase. The decrease in melting point may be attributed to reduced lattice energy and altered molecular arrangement in the cocrystal system. The shift in melting points confirms successful cocrystal formation rather than simple physical mixing. The modified thermal behaviour indicates improved physicochemical properties, which may contribute to enhanced solubility and physicochemical properties.

5.5 Microscopic study

Cocrystals formation was confirmed by observing the images of both the drug and the cocrystals prepared. The microscopic image of silymarin drug was presented in Figure 4. In Figure 4(a), 4(b), 4(c), 4(d) and 4(e) microscopic images of silymarin cocrystals were shown.

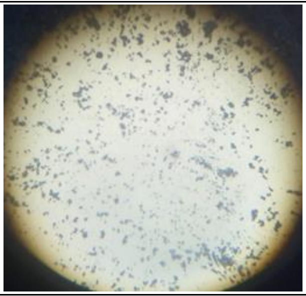	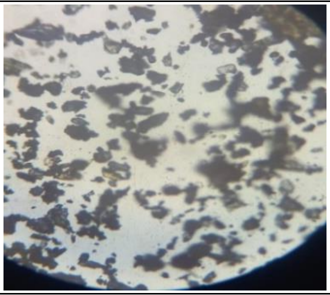	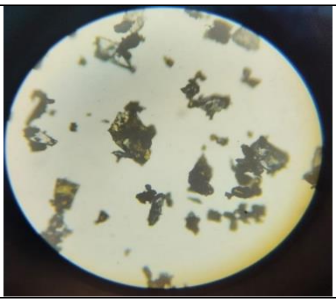
Figure 4: Silymarin drug	**Figure 4(a): Silymarin ascorbic cocrystal**	**Figure 4(b): Silymarin oxalic acid cocrystal**

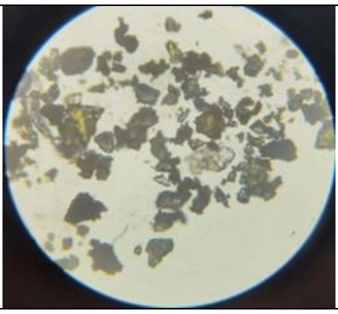		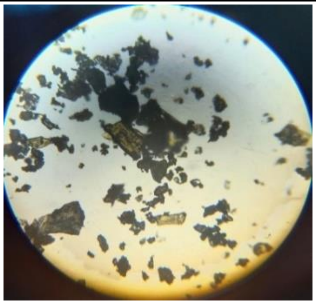
Figure 4(c): Silymarin tartaric acid cocrystal	**Figure 4(d): Silymarin succinic acid cocrystal**	**Figure 4(e): Silymarin nicotinamide cocrystal**

When comparing the microscopy image of pure silymarin drug with different cocrystals prepared using the antisolvent method, a significant difference was observed in the specific shape and size of the cocrystals.

5.6 X-Ray diffraction analysis

The XRD data results for silymarin and its cocrystals are reported in Table 6.

Table 6: XRD results of silymarin drug and it's cocrystals.

Sample No	Details	2θ value (°)	d-spacing (Å)	Intensity (a.u.)	Crystallinity (%)	Amorphous (%)
I	Silymarin drug	19.54	4.54	1641	32.8	67.2
		22.16	4.00	1625		
II	Silymarin oxalic acid cocrystals	26.58	3.35	2657	56.6	43.4
		27.86	3.20	2773		
III	Silymarin tartaric acid cocrystals	28.85	3.09	10323	72.9	27.1
		30.24	2.95	5283		
IV	Silymarin ascorbic acid cocrystals	21.86	4.06	8216	79.6	20.4
		26.01	3.42	9030		
V	Silymarin succinic acid cocrystals	37.57	2.39	28806	82.3	17.7
		31.53	2.64	3926		
VI	Silymarin nicotinamide cocrystals	25.55	3.48	4605	51.5	48.6
		27.08	3.29	4868		

The XRD pattern of the pure drug silymarin is presented in Figure 5.

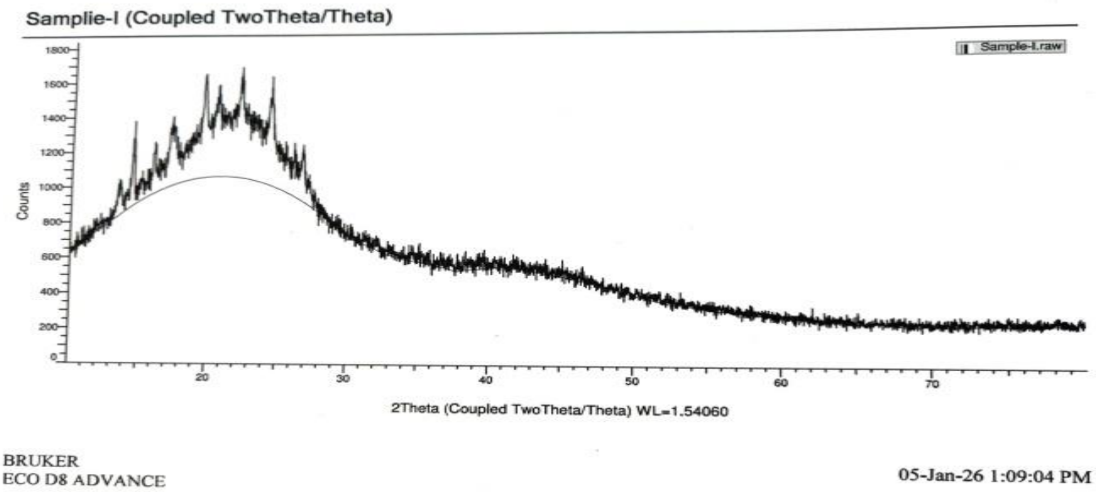

Fig 5: XRD of silymarin drug.

The XRD patterns of silymarin cocrystals from the antisolvent method were presented in Figure 5(a), 5(b), 5(c), 5(d) and 5(d), respectively.

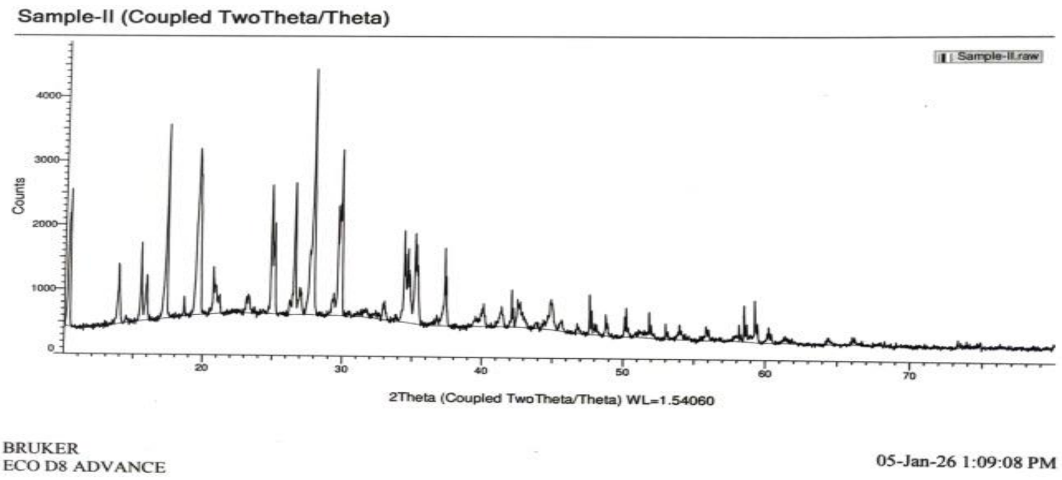

Fig 5(a): XRD of silymarin oxalic acid cocrystal.

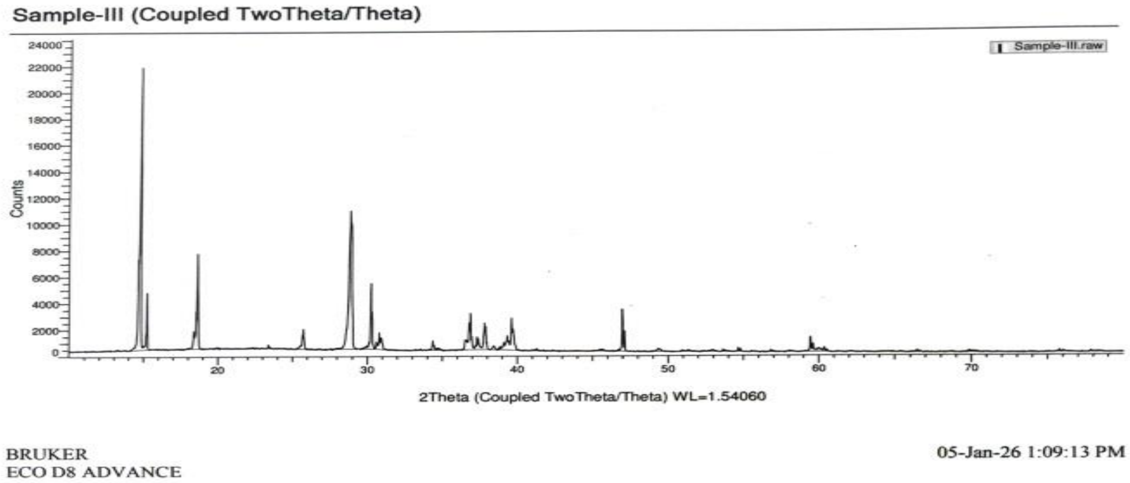

Fig 5(b): XRD of silymarin tartaric acid cocrystal.

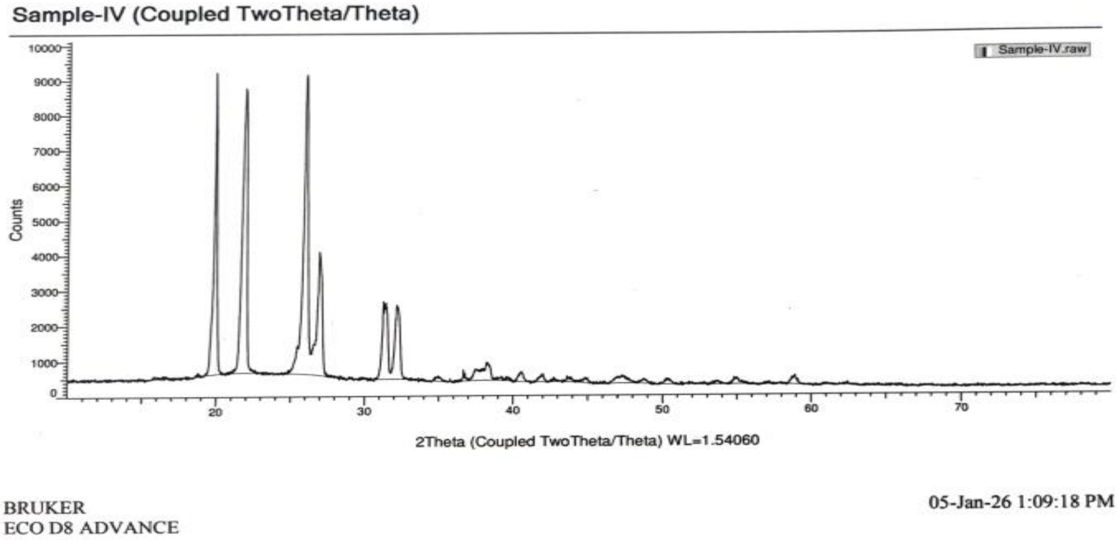

Fig 5(c): XRD of silymarin ascorbic acid cocrystal.

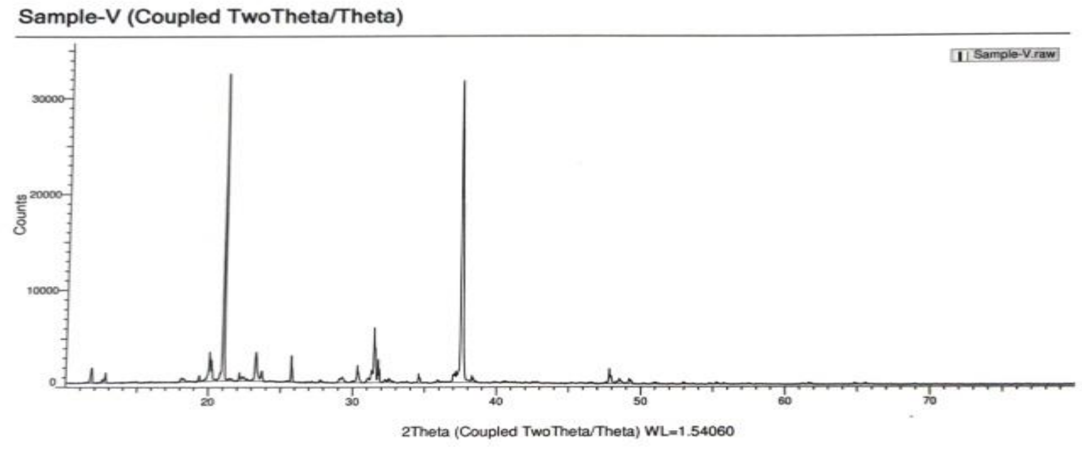
Sample-V (Coupled TwoTheta/Theta)

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Fig 5(d): XRD of silymarin succinic acid cocrystal.

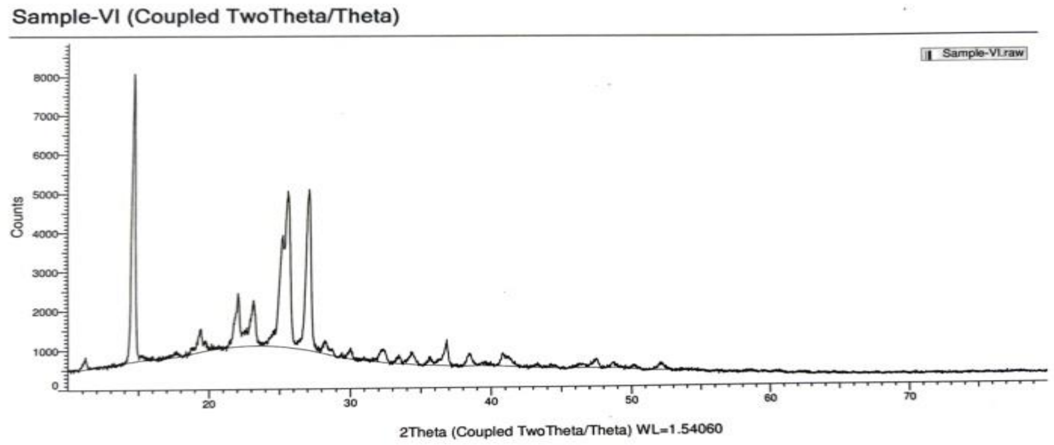
Sample-VI (Coupled TwoTheta/Theta)

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Fig 5(e): XRD of silymarin nicotinamide cocrystal.

The XRD analysis confirmed the successful formation of silymarin cocrystals with oxalic acid, tartaric acid, ascorbic acid, succinic acid, and nicotinamide. Pure silymarin showed characteristic peaks at 19.54° and 22.16° (d-spacing 4.54 Å and 4.00 Å) with moderate intensity and low crystallinity (32.8%), indicating a partial amorphous nature. All cocrystals exhibited noticeable peak shifts toward higher 2θ values with reduced d-spacing, confirming modification of the crystal lattice due to intermolecular interactions and improved molecular packing. Silymarin–oxalic acid cocrystals showed peaks at 26.58° and 27.86° with increased intensity and crystallinity (56.6%), indicating enhanced structural organization. Silymarin–tartaric acid cocrystals displayed sharp peaks at 28.85° and 30.24° with high intensity and crystallinity (72.9%), confirming strong crystal formation. Silymarin–ascorbic acid cocrystals demonstrated improved crystallinity (79.6%) with well-defined peaks at 21.86° and 26.01°.

Among all formulations, silymarin–succinic acid cocrystals exhibited the highest crystallinity (82.3%) and sharp, intense peaks, suggesting the most compact and stable lattice arrangement. silymarin–nicotinamide cocrystals showed moderate improvement with crystallinity of 51.5%. Overall, the shift in diffraction peaks, reduction in d-spacing, and increase in crystallinity confirm successful cocrystal formation and improved crystal lattice organization, which may enhance the physicochemical performance of silymarin.

VI. CONCLUSION

The present study successfully demonstrated the enhancement of solubility and physicochemical properties of silymarin through pharmaceutical cocrystallization using the antisolvent method. Preformulation studies confirmed the poor solubility nature of pure silymarin drug, validating the need for solubility enhancement approaches. Compatibility studies performed using FTIR analysis revealed the absence of chemical interaction between the drug and selected coformers, indicating stability of the developed systems. Saturation solubility studies showed a remarkable improvement in solubility for all prepared cocrystals when compared with pure silymarin. The formation of new crystalline phases was confirmed through microscopic evaluation and X-ray diffraction analysis, which demonstrated significant modification in crystal habit, lattice arrangement, and crystallinity compared to the pure drug. The melting point depression and diffraction pattern shifts further confirmed successful cocrystal formation resulting from intermolecular hydrogen bonding interactions between drug and coformer molecules. Overall, the study establishes pharmaceutical cocrystallization as an effective and promising crystal engineering strategy for improving solubility behaviour of poorly water-soluble drugs. The enhanced physicochemical performance observed in the silymarin cocrystals is expected to improve oral bioavailability and therapeutic effectiveness. The prepared silymarin cocrystals are considered to be a potential candidate for further formulation development into a suitable dosage form and in-vivo evaluation. Hence, this approach may also be extended as a practical and scalable technique for enhancing the solubility performance of other BCS Class II drugs in the domain of pharmaceutical research.

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