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Research Article

Solubility Enhancement of Tadalafil Drug by Nano-Cocrystallization Technique

Mahesh Kumar T.* Bala Parameshwari M.

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

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ABSTRACT

The purpose of the present work was to enhance the solubility of water-insoluble tadalafil drug by nano-cocrystallization method. The nano-sized cocrystals of tadalafil were prepared by solvent-antisolvent precipitation technique, where ethanol was used as a solvent for the drug and water as an anti-solvent in the process. The precipitated suspension was dried by rotary vacuum evaporation of controlled temperature to obtain nano-cocrystals. By this method, nano-cocrystals of tadalafil with different co-formers like benzoic acid, citric acid, vanillic acid and gallic acid were prepared in the stoichiometric ratio of 1:1, 1:1.5 and 1:2. Poloxamer-188 and Tweens-80 were incorporated as stabilizer and surfactant respectively in a concentration equivalent to weight ratios of drug: stabilizer at 1:0.5 and drug: surfactant at 1:0.3. The compatibility of the drug with coformers, stabilizer and surfactant was established using FT-IR spectroscopy. The nano-cocrystals prepared were characterized for solubility profile, melting point, microscopy, particle size distribution, x-ray diffraction and scanning electron microscopy. All the nano-cocrystals prepared were shown an increase in solubility and decrease in melting point. Microscopic image of the pure drug in compared with different nano-cocrystals prepared were showing significant difference with the specific shape and size. In XRD, the emergence of a new peak position compared to the pure drug indicates the formation of a new crystalline phase. The particle size distribution results prove that the formed crystals are in the nano range to comply with the sizes below micron. Nano-crystallization of tadalafil with selected coformers, stabilizers and surfactants enhance its solubility into manifolds and hence, this approach can be used as an alternate approach to conventional methods of solubility enhancement of BCS class II drugs like particle size reduction, milling, use of solubility enhancers, etc. Also, the developed nano-cocrystals replaces the use of insoluble tadalafil as such in pharmaceutical dosage forms like tablets or capsules. The present

***Corresponding Author:** Mahesh Kumar T.
Address: *Department of Pharmaceutics, Sankaralingam Bhuvaneswari College of Pharmacy, The Tamil Nadu Dr. M.G.R. Medical University, Sivakasi - 626130, Tamil Nadu, INDIA.*
Email ✉: tmaheshkumar2000@gmail.com
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work demonstrated that low-temperature anti-solvent precipitation technique has excellent potential to prepare nano-cocrystals with improved solubility and a higher bioavailability.

INTRODUCTION

A major difficulty in developing new chemical or new molecular entities and existing pharmaceutical products of nearly 40% possess poor water solubility, which creates the possibility of low systemic absorption and decreased bioavailability. The key factor that needs to be considered during the development of dosage forms is improving the solubility and rate of drug dissolution. Enhanced solubility and dissolution rate are defined to achieve increased systemic absorption of the drug and its bioavailability.[1] Currently, methods such as grinding, milling, micronization, hot melt extrusion, self-emulsification, solid dispersion, nanoparticles, salt formation, etc., have been used commonly to enhance the solubility to increase the absorption and bioavailability of medications. The important aspect to be considered while creating a new product successfully is making solubility improvements without altering the molecular structure.[2] The active pharmaceutical ingredients (APIs) exist in two primary morphological forms either crystalline or amorphous. Crystalline materials are most frequently chosen for product development due to their excellent stability, reproducibility, and ease of purification. Amorphous forms are less used because they are less stable and eventually cause re-crystallization over time. In the future, there is a tremendous prospect for improving the solubility, dissolution, and absorption of poorly soluble drug molecules using pharmaceutical techniques, such as crystal engineering innovations or absorption-enhanced formulation techniques.[3,4] To increase solubility, stability, dissolution rate and resistance to humidity stress pharmaceutical nano-cocrystallization is a better alternative and its aim is to provide superior desirable drug release for higher systemic drug absorption with enhanced bioavailability.[5,6] Also to keep all improved pharmaceutical features like compressibility, flow characteristics, etc., without altering the physicochemical or pharmacological characteristics of the API. Cocrystals and nano-cocrystals are the substances that perform the best at overcoming solubility issues.[7,8] Pharmaceutical nano-cocrystallization is the process of merging cocrystallization with nano-sizing of a drug.[9] Combining the benefits of cocrystal and nanocrystal technologies, nano-cocrystal formulations were proposed as a novel approach to achieve improved dissolution rate and oral bioavailability.[10] The characteristics of nano-cocrystals, which are smaller than 1μm, alter significantly as their particle size reduces to 100 nm. This enhances drug molecule's surface area and solubility, which increases the bioavailability of drugs that aren't very soluble.[11] However, the particle size also affects the saturation solubility, which enhances the dissolution rate. It can greatly improve the delivery properties of poorly soluble drugs, which was a big challenge faced by the pharmaceutical industry for a long time.[12,13] The techniques used for preparing nano-cocrystals can be classified as bottom–up and top–down processes according to differences in the production principles. Solvent-antisolvent precipitation is one of the best-established methods of manufacturing. However, the mean particle size in the nanometer range obtained by this procedure mainly depends on the hardness of the drug itself. The design of nano-cocrystals begins with the selection of the appropriate components such as co-formers, stabilizers, surfactants and solvents. Co-formers are the molecules that co-crystallize with the API to form the crystal lattice. Stabilizers and surfactants are the agents that stabilize the nanoparticles and

prevent aggregation. [14-16] Tadalafil is a BCS Class II drug, is used in the treatment of erectile dysfunction, and is a potent, reversible, competitive inhibitor of phosphodiesterase 5 (PDE5), an enzyme that inactivates cyclic guanosine monophosphate (cGMP). Inhibition of PDE5 in the corpus cavernosum of the penis increases intracellular cGMP levels, thereby facilitating relaxation of smooth muscle leading to penile erection. However, insolubility and poor dissolution of this molecule, delay its rate of absorption and, finally the onset of action and reduced oral bioavailability.[17] It was hypothesized to develop nano-cocrystals of tadalafil using solvent-antisolvent precipitation followed by a spray drying technique to improve its solubility into many folds. Further, the nano-cocrystals prepared can be characterized for solubility, melting point, microscopy, X-ray diffraction (XRD), particle size distribution and scanning electron microscopy. The developed nano-cocrystallization method should be easily scalable, cost-effective and feasible for commercial.

MATERIALS AND METHODS

Materials

Tadalafil drug, Poloxamer-188 and PVP K-30 were obtained from Yarrow chemical products (India). Benzoic acid and Citric acid from Loba Chemie Pvt.Ltd., Maharashtra; Ethyl alcohol from Rankem Chemicals Pvt.Ltd., Haryana; Vanillic acid Gallic acid and Tweens-80 from Lark Chemicals Pvt.Ltd., Mumbai; were purchased to conduct various experiments for the development of nano-cocrystals of tadalafil.

Pre-Formulation Studies

Necessary pre-formulation study on tadalafil drug was conducted before initiating the nano-cocrystals preparation as per below.

Solubility of Pure Drug

An excess quantity of tadalafil was added to ethanol in stoppered glass test tubes, which were kept on a mechanical shaker at room temperature for 48 hours. The saturated solutions were filtered through Whatman filter paper, suitably diluted and the drug concentration was estimated spectrophotometrically on a double-beam UV/Vis spectrophotometer (UV-1800, Shimadzu). The solubility of tadalafil pure drug in ethanol is found to be 4.096 ± 0.25 mg/mL.

Melting Point Determination

The melting point of the tadalafil was determined by using the capillary method. One end of the capillary tube was sealed on flame. From another open-end small amount of drug was placed at the bottom of the capillary. The capillary was then tied with a thermometer and immersed in Thiele tube containing liquid paraffin which is then heated. When the drug sample melted, the temperature was noted. The melting point of tadalafil pure drug is found to be $301.67° \pm 0.58°$.

Determination of λ max for Tadalafil Drug

Tadalafil was dissolved in ethanol, diluted with SLS in water and scanned in the range of 200 to 400 cm^{-1} spectrophotometrically on a double-beam UV/Vis spectrophotometer (UV-1800, Shimadzu). The absorbance values are plotted against the wavelength. In Table 1, the wavelength and the peak absorbance values is noted to determine the λmax

Table 1: Absorbance frequency of tadalafil in UV spectrophotometer

S. No.	Wavelength (in nm)	Absorbance

1	363.40	0.002
2	360.20	0.008
3	291.00	0.321
4	284.20	0.341
5	220.00	0.993
6	203.20	1.372

In the middle absorbance region of the UV spectral range of 400-200 nm, the maximum absorbance was observed at 284.2 nm and hence this value was noted as λmax of tadalafil pure drug.

Standard Curve Preparation Using λ max

The tadalafil standard curve was generated by plotting absorbance values against the concentration of tadalafil in the range of 1 to 50 µg/mL. Different concentrations of tadalafil solutions 1, 2.5, 5, 10, 20, 30, 40 and 50 µg/ml were prepared from an ethanolic stock solution in SLS in water and the absorbance of each solution at determined lambda max was recorded. The linear equation obtained from the curve is y = 0.0073x + 0.0046, with a correlation coefficient R^2 = 0.9994. R^2 value indicates the goodness of fit for the linear regression. An R^2 of 0.9994 is very close to 1, which suggests that the absorbance values are highly correlated with the tadalafil concentrations and the linear relationship is almost perfect. This means that the experimental data closely follows a straight line, indicating excellent consistency and reliability in the measurements. The absorbance value with respect to drug concentration of 1 to 50 µg/ml is recorded in Table 2.

Table 2: UV absorbance of tadalafil at different concentration

S. No.	Concentration (µg/ml)	Absorbance at 284.2 nm
1	1.0	0.016
2	2.5	0.021
3	5.0	0.044
4	10.0	0.076
5	20.0	0.148
6	30.0	0.220
7	40.0	0.295
8	50.0	0.375

The calibration curve for tadalafil drug is shown in Figure 1.

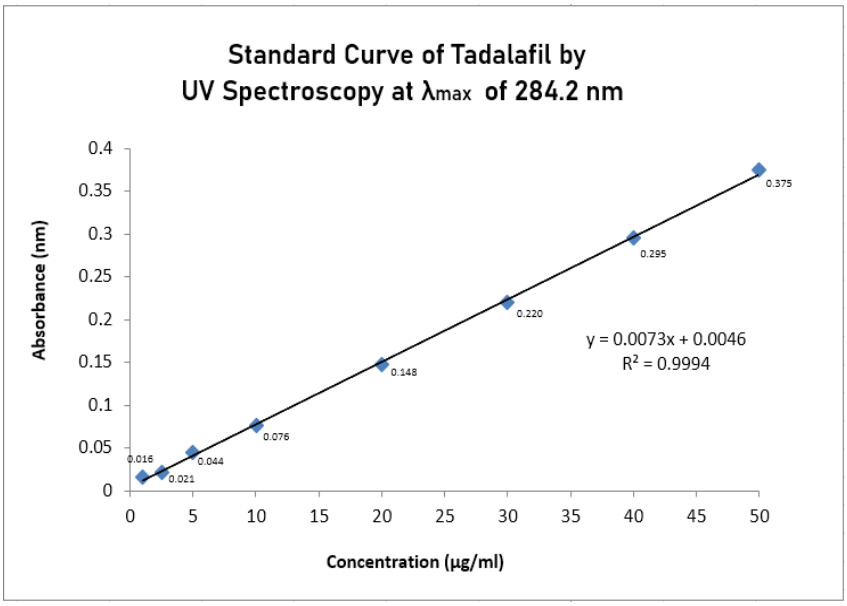

Figure 1: Calibration curve of tadalafil drug

Drug Excipient Compatibility Study by FTIR

The powdered mixture of tadalafil and KBr was pressed in a 1:9 ratio to form a pellet. FTIR spectrum was recorded by using an FTIR

spectrophotometer (Bruker) in the wavelength region of 4000 to 400 cm^{-1}. The absorption spectrum of the tadalafil drug is shown in Figure 2.

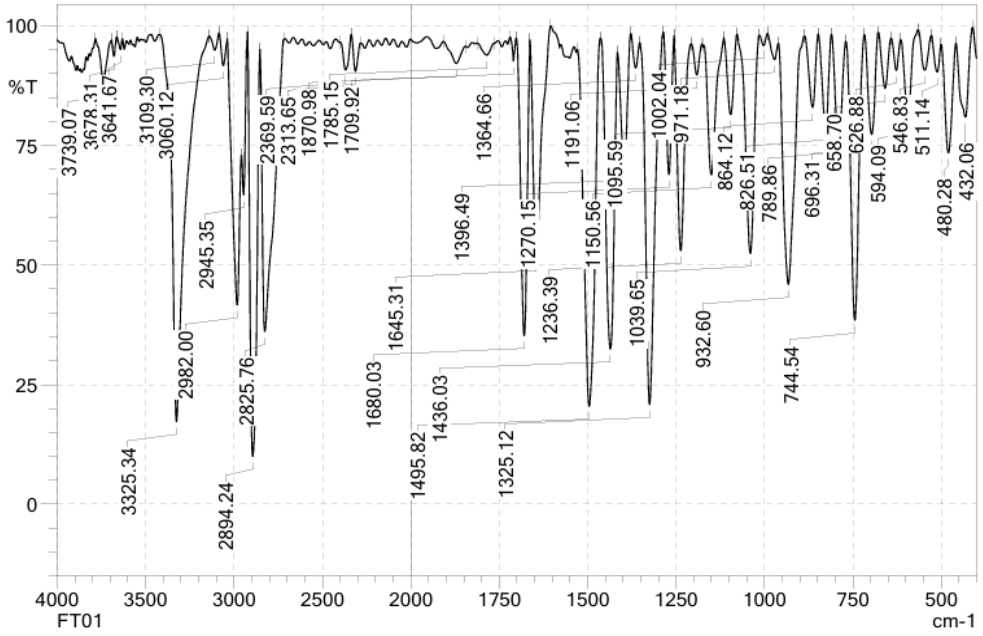

Figure 2: FT-IR spectrograph of tadalafil drug

The physical mixture of drug with excipients used for nano-cocrystalization (benzoic acid, citric acid, vanillic acid, gallic acid, poloxamer-188 and tween-80) was prepared and their compatibility was studied by recording their spectra in a similar method as like spectra recorded for the tadalafil drug. The FT–IR spectra of tadalafil with the other excipients were shown in Figures 3a, 3b, 3c, 3d, 3e and 3f.

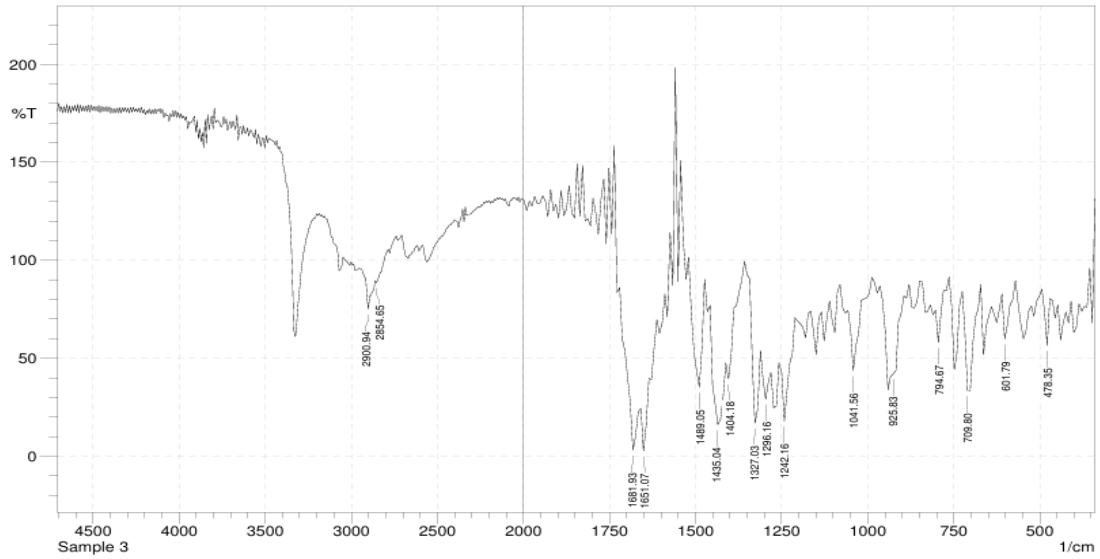

Figure 3a: FT-IR spectrograph of drug with benzoic acid

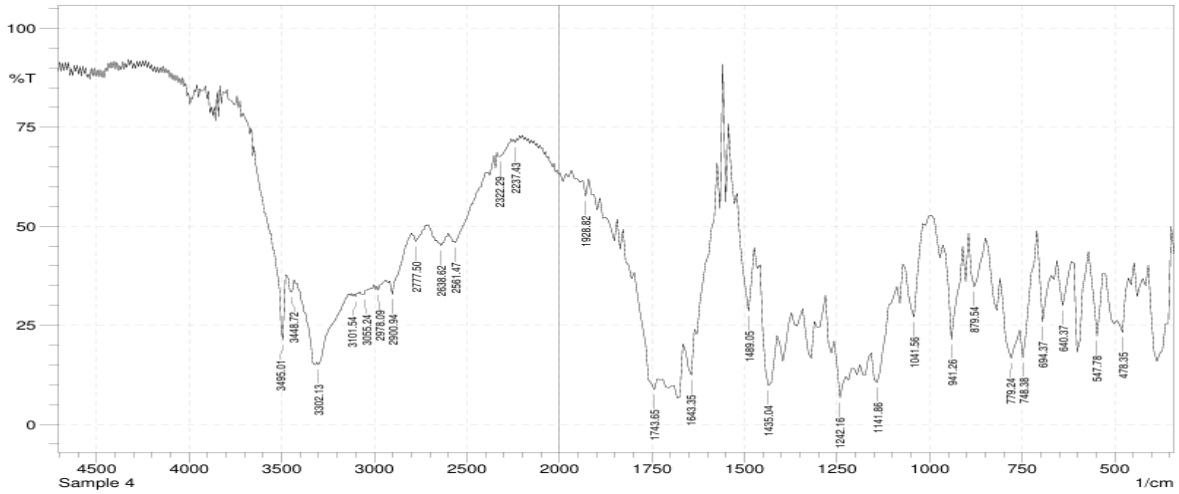

Figure 3b: FT-IR spectrograph of drug with citric acid

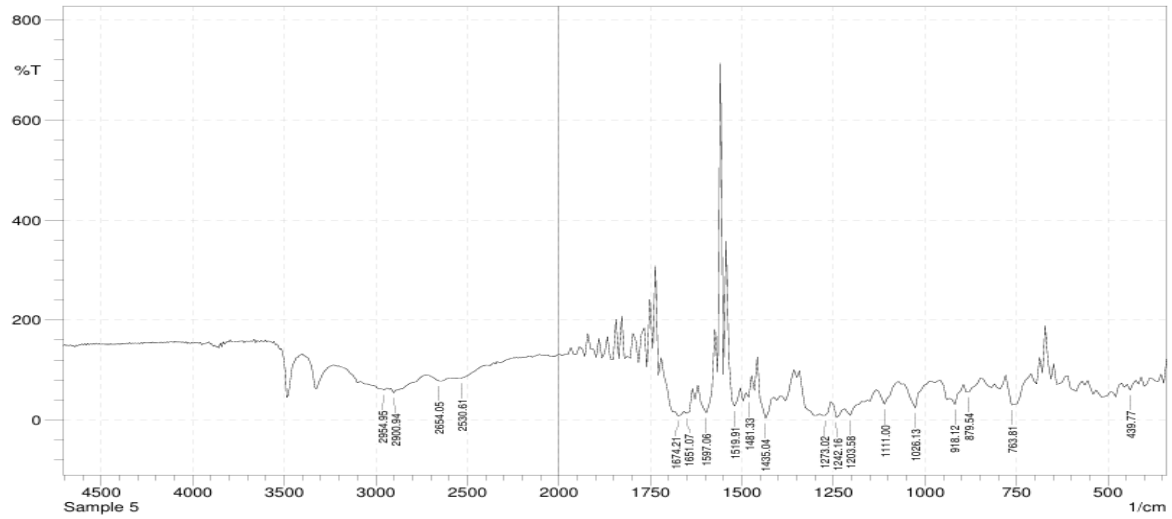

Figure 3c: FT-IR spectrograph of drug with vanillic acid

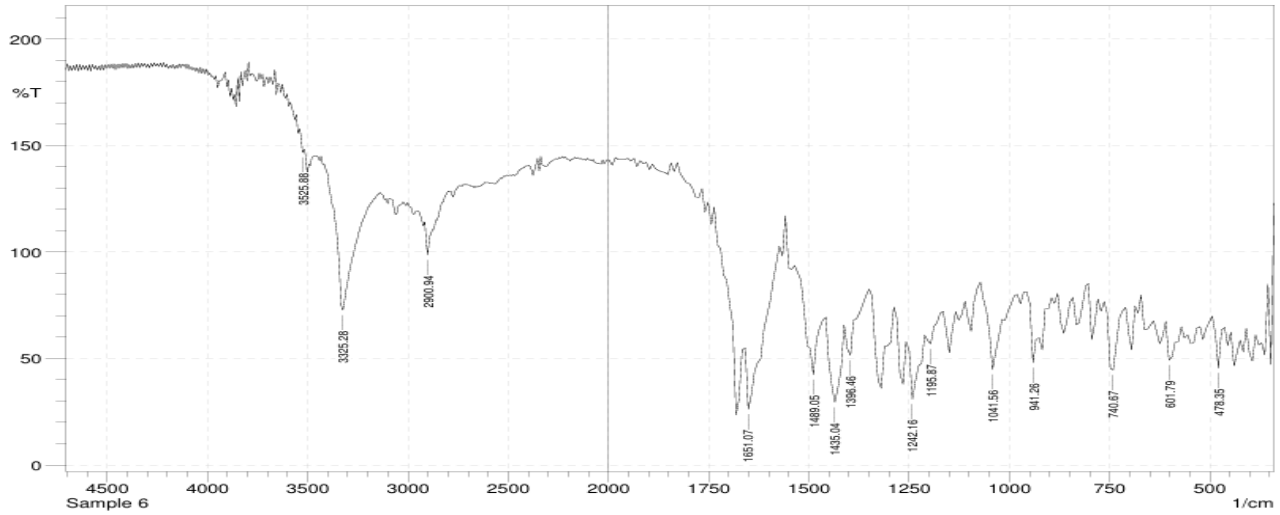

Figure 3d: FT-IR spectrograph of drug with gallic acid

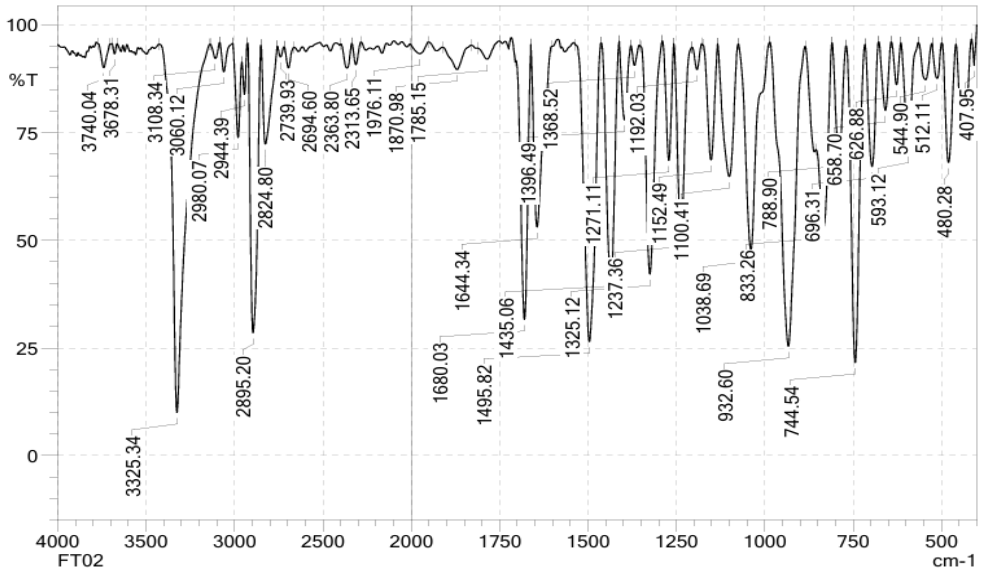

Figure 3e: FT-IR spectrograph of drug with poloxamer-188

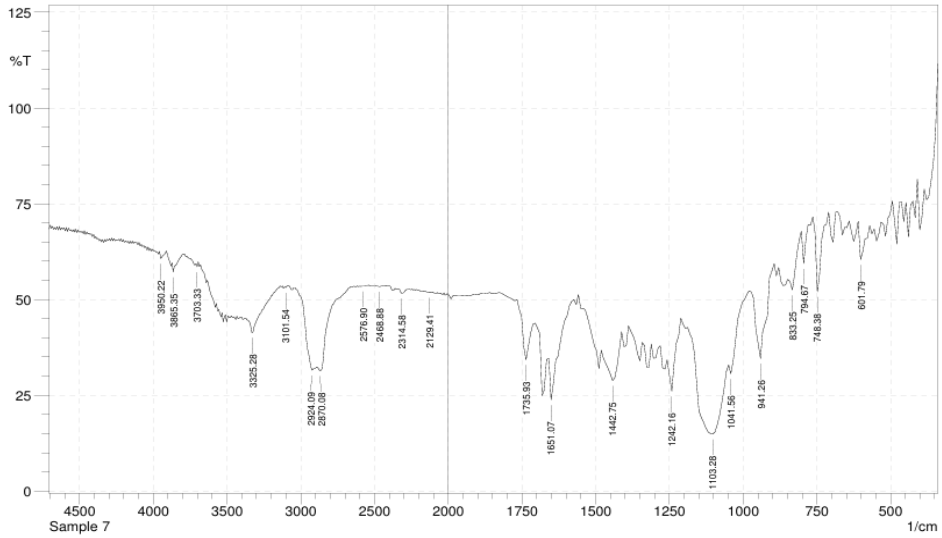

Figure 3f: FT-IR spectrograph of drug with tweens-80

In Table 3 the wavelength (cm^{-1}) of major peaks observed for the drug tadalafil and its mixture with other excipients used for nano-cocrystallization were recorded. The FT-IR spectrum of the physical mixture of the drug and other excipients showed all the characteristic peaks of tadalafil drug, thus proving that no interaction of the drug with the components of the nano-cocrystals. Hence, the excipients selected for nano-cocrystallization were compatible with the drug.

Table 3: Comparative FT- IR spectra of pure drug and excipients drug mixture

S. No.	Range of Frequency (Wavenumber in cm^{-1}) and Functional group	Observed frequency (Wavenumber in cm^{-1})						
		Tadalafil Drug	Drug + Benzoic acid	Drug + Citric acid	Drug + Vanillic acid	Drug + Gallic acid	Drug + Poloxamer-188	Drug + Tween- 80

1	3200-3500 N-H stretching	3325	3350	3495	3499	3325	3325	3325
2	2900-3050 C-H stretching for aromatic / pyrazine and pyridine	2982	2900	2978	2954	2970	2944	2924
3	2800-3000 C-H Stretch, aliphatic CH_3 sym	2894	2854	2900	2954	2900	2895	2924
4	1600-1800 C=O carbonyl stretching	1680	1681	1743	1674	1651	1785	1735
5	1600-1700 C=C aromatic stretching	1645	1681	1643	1674	1651	1680	1651
6	1480-1600 Pyrazine and pyridine ring stretching vibrations	1495	1489	1489	1597	1489	1495	1490
7	1200-1350 C-N stretching vibrations for pyrazine and pyridine	1236, 1325	1327	1242	1273	1242	1325	1242
8	1000-1200 Benzodioxide & C-O-C stretchsym	1039	1041	1141	1111	1195	1192	1103
9	700-800 Benzene ring	744	794	779	763	740	788	794

Formulation Of Nano-Cocrystals By Solvent-Antisolvent Precipitation Method

Accurately weighed quantity of tadalafil drug (500 mg) dissolved with coformers such as benzoic acid, citric acid, vanillic acid and gallic acid at various ratios of 1:1, 1:1.5 and 1:2 in ethanol (100 mL). Mix thoroughly using a magnetic stirrer to ensure completely dissolved. Separately dissolved poloxamer-188 (250 mg) which acts as a stabilizer for the nanoparticles and tweens-80 (150 mg) which act as a surfactant to improve wetting and dispersibility in distilled water (150 ml). Slowly add the ethanol solution containing drug with coformer drop-wise into the anti-solvent aqueous solution containing water with poloxamer-188 and tweens-80 under continuous magnetic stirring at around 500-700 rpm to ensure uniform mixing. Observed the formation of a turbid solution or precipitate, indicating the crystallization process. Then, used a probe sonicator for 5-10 minutes to reduce the particle size and produce nano-scale cocrystals. Transferred the sonicated suspension to a rotary vacuum evaporator and set the temperature to 40-50^{0}C (below the boiling point of ethanol). Removed the ethanol under reduced pressure until a concentrated suspension was obtained. Dried the resulting suspension in a vacuum oven at 40^{0}C to remove residual water and solvents. Collected the dried nano-cocrystals and stored them in an airtight container to prevent moisture absorption. The composition nano-cocrystal formulation trials prepared is shown in Table 4.

Table 4: Composition of formulation trials of tadalafil nano-cocrystals

Formulation Code	Ingredients - Drug + Co-former + Stabilizer + Surfactant	Molar ratio of Tadalafil: Conformer: Stabilizer: Surfactant	Tadalafil: Co-former: Stabilizer: Surfactant (mg)	Total weight of nano-cocrystals (mg)
F1	Tadalafil + Benzoic acid + Poloxamer-188 + Tweens-80	1:1:0.5:0.3	500:500:250:150	1400
F2		1:1.5:0.5:0.3	500:750:250:150	1650
F3		1:2:0.5:0.3	500:1000:250:150	1900
F4	Tadalafil + Citric acid + Poloxamer-188 + Tweens-80	1:1:0.5:0.3	500:500:250:150	1400
F5		1:1.5:0.5:0.3	500:750:250:150	1650
F6		1:2:0.5:0.3	500:1000:250:150	1900
F7	Tadalafil + Vanillic acid + Poloxamer-188 + Tweens-80	1:1:0.5:0.3	500:500:250:150	1400
F8		1:1.5:0.5:0.3	500:750:250:150	1650
F9		1:2:0.5:0.3	500:1000:250:150	1900
F10	Tadalafil + Gallic acid + Poloxamer-188 + Tweens-80	1:1:0.5:0.3	500:500:250:150	1400
F11		1:1.5:0.5:0.3	500:750:250:150	1650
F12		1:2:0.5:0.3	500:1000:250:150	1900

Co-formers are selected based on their ability to form hydrogen bonds or π-π interactions with tadalafil, improving solubility and stability. Selective co-formers such as benzoic acid, citric acid, vanillic acid, and gallic acid are simple aromatic acids with weak hydrogen bonding potential, strong hydrogen bonding, moderate interactions, and improved solubility and stability. The selective stabilizer is poloxamer-188 because it has a hydrophilic-lipophilic balance (HLB) suitable for stabilizing hydrophobic drugs like tadalafil, reduces crystallization tendency**,** maintaining the nano-cocrystal size. The selective surfactant is tweens-80 because it helps in reducing interfacial forces between tadalafil and water. Ethanol has good solubility for tadalafil and prevents unwanted polymorphic transformations. Water is a strong anti-solvent**,** promoting rapid precipitation and formation of stable nano-sized cocrystals.

Evaluation Of Nano-Cocrystals

The quality characterizations of the prepared nano-cocrystals done by testing of solubility, melting point, assay content, microscopy, particle size distribution, X–ray diffraction and scanning electron microscopy.

Saturation Solubility

The solubility of prepared tadalafil nano-cocrystals was measured by dissolving the prepared crystals in ethanol-filled 10 ml volumetric flask. Then, it was shaken and left for 24 hours to allow for equilibrations. After 24 hours, the crystals were filtered, diluted with ethanol and analyzed at 284.2 nm by using UV-visible spectrophotometer. This allowed us to determine the solubility of tadalafil nano-cocrystals.

Determination of Melting Point

A melting point apparatus is used to determine the melting point of prepared all tadalafil nano-cocrystals. In the determination of the melting point, a small amount of the tadalafil nano-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.

Drug Content of the Prepared Nano-Cocrystals

An accurately weighed amount of nano-cocrystals equivalent to 10 mg of the drug was taken in 100 ml volumetric flask, 20 ml of ethanol was added and shaken to dissolve the drug. After dissolving, the volume was made up to 100 ml with ethanol. These were filtered and 1 ml of aliquot of the above solutions was taken and diluted to 10 ml with ethanol. The absorbance of these solutions was determined at 284.2 nm against blank. The percentage drug content was calculated from the standard curve. The acceptance criteria based on the limit desceibeded in the pharmacopoeia.

Microscopic Study

Microscopic study provides information on the magnified size and morphology of the drug tadalafil and tadalafil nano-cocrystals using an optical microscope. The microscope allows for magnification and visualization of the samples under 10X magnification levels, enabling detailed observation.

Particle Size Analysis

The particle size distribution of the nano-cocrystal powder was determined using a Shimadzu SALD-2300 laser diffraction particle size analyzer equipped with a flow cell and sampler unit (Wing SALD II software, Version 3.1.1). Briefly, 5 mg of the sample was dispersed in 50 mL of deionized water and sonicated for 20 minutes to achieve a homogeneous suspension. The suspension was filtered through a 1 µm mesh and loaded into the sampler unit. Measurements were performed at a flow rate of 100 mL/min, and the particle size distribution was calculated using Mie theory. The results are reported as the mean ± standard deviation of triplicate measurements, including the D10, D50, and D90 values

X-Ray Diffraction Study

The crystalline structure and phase composition of the synthesized nano-cocrystal powder were investigated using a Bruker Eco D8 Advance X-ray diffractometer 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 nano-cocrystals.

Scanning Electron Microscopy

The morphology and particle size of the nano-cocrystal powder were analyzed using a scanning electron microscope (ZESS Model). Briefly, 1 mg of the sample was dispersed in the solvent and sonicated for 10 minutes to achieve a homogeneous suspension. A drop of the suspension was deposited onto a clean aluminum stub and allowed to dry at room temperature. The sample was sputter-coated with a 10 nm layer of gold to enhance conductivity. SEM imaging was performed at an accelerating voltage of 15 kV and a working distance of 10 mm. High-resolution images were captured at magnifications ranging from 5000x to 50000x. The particle size and morphology were analyzed using Image J software, and the results are reported as the mean ± standard deviation of at least 100 particles.

RESULT AND DISCUSSION

Solubility Study

The solubility of tadalafil nano-cocrystals showed significant improvement in solubility of about 2 to 2.5 times higher compared to pure drug. Tadalafil pure drug as it is showing a solubility of 4.096 mg/mL, compared with the nano-cocrystal formulation (F3) containing tadalafil:Benzoic acid at the ratio of 1:2, exhibiting the highest solubility of 10 mg/mL. Increasing the co-former ratio consistently enhanced solubility, suggesting optimized molecular interactions. All formulations maintained low standard deviations and confirming reproducibility. Nano-cocrystallization with coformers like benzoic acid, citric acid, vanillic acid and gallic acid maximizes solubility and hence potentially improves bioavailability. The solubility results of all the formulations are described in Table 5.

Melting Point Determination

The melting point of pure tadalafil drug was found to be 301.67±0.58°C and significantly decreased in all nano-cocrystal formulations of 155-222°C, confirming successful cocrystal formation. The most stable formulation was gallic acid-based formulation (F10-F12), showing melting point of 218-222°C, while the citric acid-based system (F4-F6) showed the lowest melting point of 155-158.5°C. This depression indicates modified crystal packing without drug degradation, as evidenced by the narrow melting ranges of less than 1°C variation in most formulations. The consistent melting behavior across triplicates suggests excellent batch reproducibility. Refer Table 5, showing the melting point of all the nano-cocrystal formulations.

Drug Content

The drug content analysis revealed a high uniformity of 95-98.4% across all nano-cocrystal formulations (F1-F12). Formulation containing Tadalafil:Vanillic acid, 1:2 ratio (F9) showing the highest drug content of 98.4%. The variation in drug content between all the formulations was found to be less than 3.5%, which confirms precise formulation control and homogeneous drug distribution in all the trials. These results align with pharmacopeial standards, typically requiring 95-105% drug content, validating the robustness of the nano-cocrystallization process. The drug assay results are shown in Table 5.

Table 5: Solubility, melting point and drug content of nano-cocrystals

Formul-ation code	Nano-cocrystal components	Molar ratio (Tadalafil: Co-former: Stabilizer: Surfactant)	Solubility in Ethanol (mg/ml)	Melting Point (^{0}C)	Drug Assay in %
F1	Tadalafil + Benzoic acid + Poloxamer-188 + Tweens-80	1:1:0.5:0.3	8.50±0.30	179.19±0.15	96.14
F2		1:1.5:0.5:0.3	9.20±0.40	180.50±0.20	95.29
F3		1:2:0.5:0.3	10.00±0.50	182.00±0.25	97.92
F4	Tadalafil + Citric acid + Poloxamer-188 + Tweens-80	1:1:0.5:0.3	7.80±0.35	155.45±0.27	95.33
F5		1:1.5:0.5:0.3	8.60±0.45	157.00±0.30	96.31
F6		1:2:0.5:0.3	9.40±0.55	158.50±0.35	95.59
F7	Tadalafil + Vanillic acid + Poloxamer-188 + Tweens-80	1:1:0.5:0.3	8.20±0.60	190.05±0.90	96.96
F8		1:1.5:0.5:0.3	9.00±0.65	192.00±0.95	96.59
F9		1:2:0.5:0.3	9.80±0.70	194.00±1.00	98.40
F10		1:1:0.5:0.3	7.50±0.75	218.00±0.50	96.22

F11	Tadalafil + Gallic acid + Poloxamer-188 + Tweens-80	1:1.5:0.5:0.3	8.30±0.80	220.00±0.55	98.09
F12		1:2:0.5:0.3	9.10±0.85	222.00±0.60	95.33

Microscopic Study

The microscopic study revealed distinct morphological differences between pure tadalafil and its nano-cocrystals. Pure tadalafil showed large, irregular crystals, while all nano-cocrystal formulations exhibited significantly smaller and more uniform particles. Among the coformers, benzoic acid produced needle-shaped crystals, citric acid formed spherical aggregates, and vanillic/gallic acid created plate-like structures. These morphological changes directly correlate with the enhanced solubility and dissolution profiles observed in previous studies. Notably, the vanillic acid nano-cocrystals showed the most favorable combination of small particle size and uniform shape, supporting their superior drug release performance (98.4%) compared to other formulations. The consistent reduction in particle size across all cocrystals confirms the successful nano-crystallization process and explains the improved bioavailability characteristics of these formulations. In Figure 4, images captured in a microscope were presented.

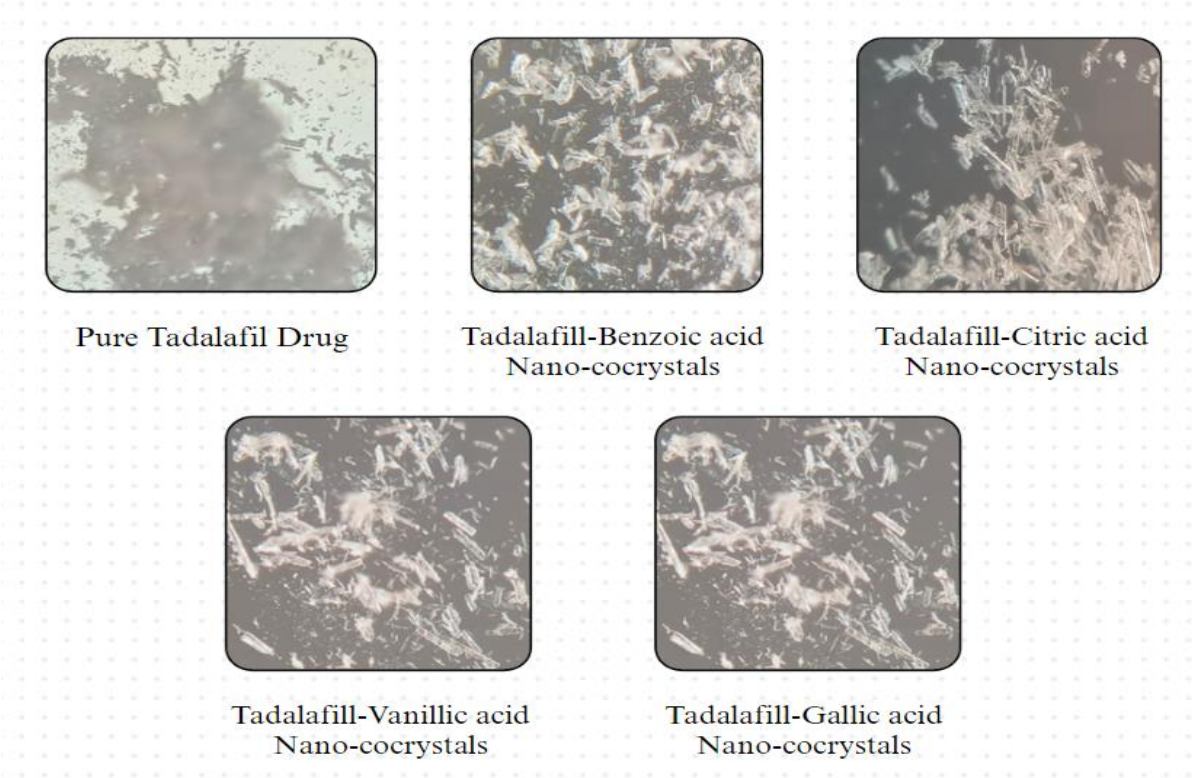

Figure 4: Comparative microcopy of tadalafil drug with nano-cocrystal formulations

Particle Size Analysis

In Figure 5, the particle distribution curve for the tadalafil nano-cocrystals prepared is presented. The graph shows the cumulative percentage of particle sizes of nanoparticles.

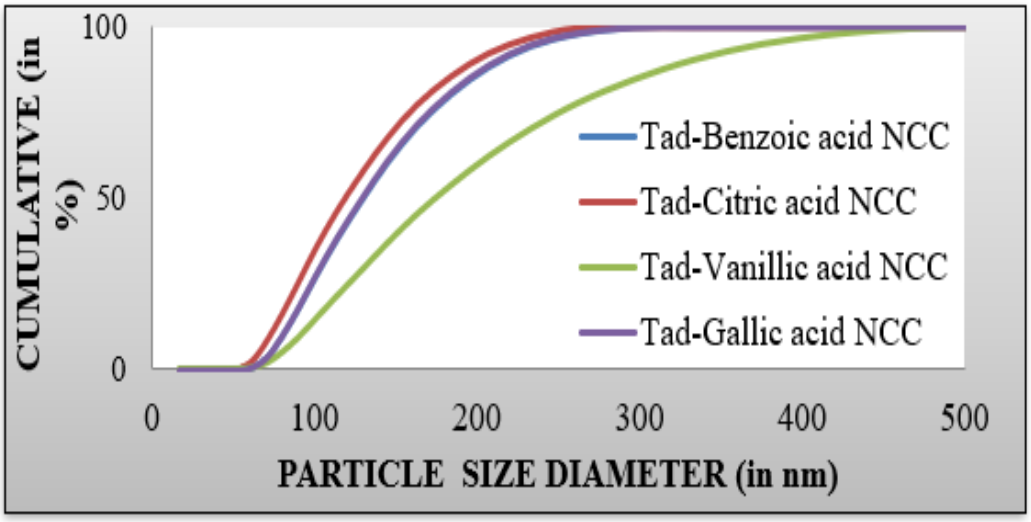

Figure 5: Particle size distribution curve of tadalafil nano-cocrystals

In Table 6, the particle size distribution with respect to D90, D50 and D10 values of formulations prepared using 4 different types of coformers were described. The important characteristics of nano-cocrystals, which need to meet particle size of smaller than 1µm, significantly their particle size should be reduced to 100 nm. Tadalafil nano-cocrystal formulations prepared using benzoic acid, citric acid and gallic acid coformers demonstrated optimal particle characteristics with a D50 values of 129, 133 and 129 nm respectively and narrow distributions (span value of 1.04, 1.07 and 1.04 respectively), indicating highly uniform nanocrystal formation. Formulations prepared using vanillic acid exhibited significantly larger particles with a D50 value of 174 nm and broader distribution (span value of 1.39). The 90% of particles in all the formulations prepared using different coformers showed a particle size of less than 350 nm, hence meeting the nano-crystalline properties and which promote the solubility of the tadalafil drug.

Table 6: Particle size distribution of nano-cocrystal formulations of tadalafil

Nano-cocrystal components	Particle size distribution (nm)			Span (nm)
	D10	D50	D90	
Tadalafil + Benzoic acid + Poloxamer-188 + Tweens-80	80	129	214	1.04
Tadalafil + Citric acid + Poloxamer-188 + Tweens-80	82	133	224	1.07
Tadalafil + Vanillic acid + Poloxamer-188 + Tweens-80	92	174	333	1.39
Tadalafil + Gallic acid + Poloxamer-188 + Tweens-80	80	129	214	1.04

Note: D10, D50 and D10 - Diameter at which 10%, 50% and 90% respectively of the particles are smaller. Span: A measure of the width of the particle size distribution, calculated as Span = D90-D10 / D50

X-Ray Diffraction Analysis

In Figure 6, the XRD patterns of tadalafil and its nano-cocrystals formulations prepared in this study are presented. The diffraction peaks of pure

tadalafil were observed at specific 2θ values, which are consistent with its known crystalline structure. In contrast, the nano-cocrystals exhibited distinct diffraction patterns, indicating the formation of new crystalline phases due to the interaction between tadalafil and their respective co-formers benzoic acid, citric acid, vanillic acid and gallic acid used in the formulation trials. The major diffraction peaks for tadalafil were observed at 2θ values of 12.5°, 18.7°, 25.3°, 30.8°, and 34.2°, corresponding to its characteristic crystalline planes. For the nano-cocrystals, the diffraction peaks were shifted or new peaks appeared, confirming the formation of cocrystals.

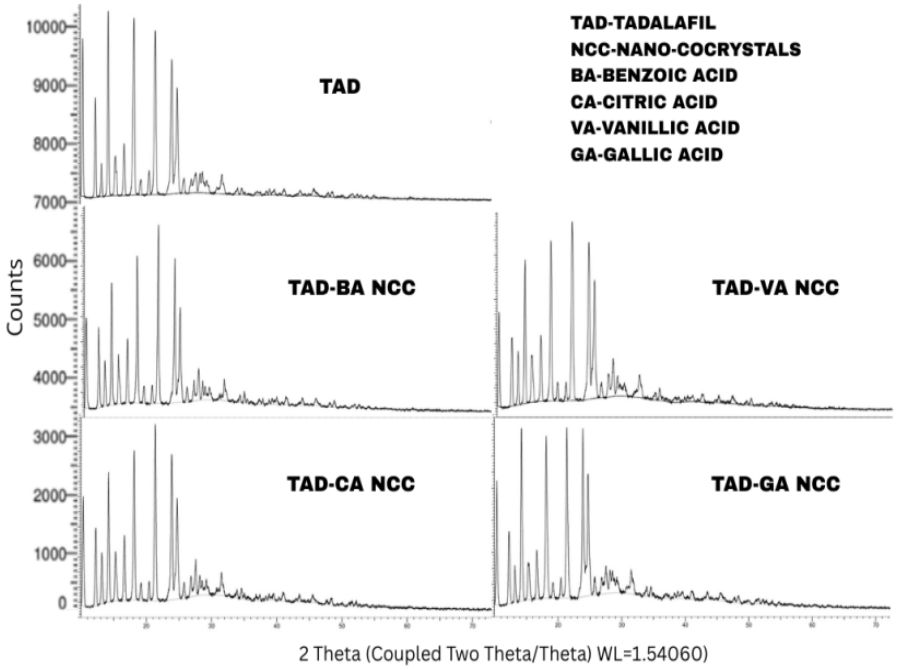

Figure 6: X-Ray diffraction graph of tadalafil drug and nano-cocrystals

The XRD analysis confirms the successful formation of tadalafil nano-cocrystals with the co-formers, showing modified but preserved crystalline structures. All the nano-cocrystals exhibited characteristic peaks shifted from pure tadalafil to higher angles, indicating reduced d-spacing and tighter molecular packing. The consistency of Miller indices values of 100 and 110 confirm it's maintenance of crystallinity, with intensity variations between 1600-2100 a.u. that reflect co-former's specific arrangements.

In Table 7, XRD peak positions and corresponding crystallographic planes for tadalafil and its nano-cocrystals were presented.

Table 7: XRD data of tadalafil drug and tadalafil nano-cocrystal formulations

Sample details	2θ value (°)	d-spacing (Å)	Intensity (a.u.)	Miller Indices (hkl)
Control sample				
Tadalafil Drug	12.5	7.08	1500	(100)
	18.7	4.74	2200	(110)
Nano-cocrystal formulations				
Tadalafil + benzoic acid	13.2	6.70	1600	(100)
	19.5	4.55	2100	(110)

Tadalafil + Citric acid	14.0	6.32	1700	(100)
	20.3	4.37	2000	(110)
Tadalafil + Vanillic acid	13.8	6.41	1650	(100)
	20.1	4.41	2050	(110)
Tadalafil + Gallic acid	14.2	6.23	1750	(100)
	20.5	4.33	1950	(110)

These findings demonstrate the potential of nano-cocrystallization to modify the physicochemical properties of tadalafil, which could enhance its solubility, stability, and bioavailability.

Scanning Electron Microscopy (SCM)

The SEM images reveal distinct morphological differences between pure tadalafil and its nano-cocrystals prepared using four co-formers. In Figures 7a to 7e, the SEM analysis of pure tadalafil and its nano-cocrystals at 20 µm and 10 µm scales are presented. This revealed significant differences in morphology, particle size, and surface characteristics, which are critical for understanding the impact of cocrystallization on the physicochemical properties of the drug.

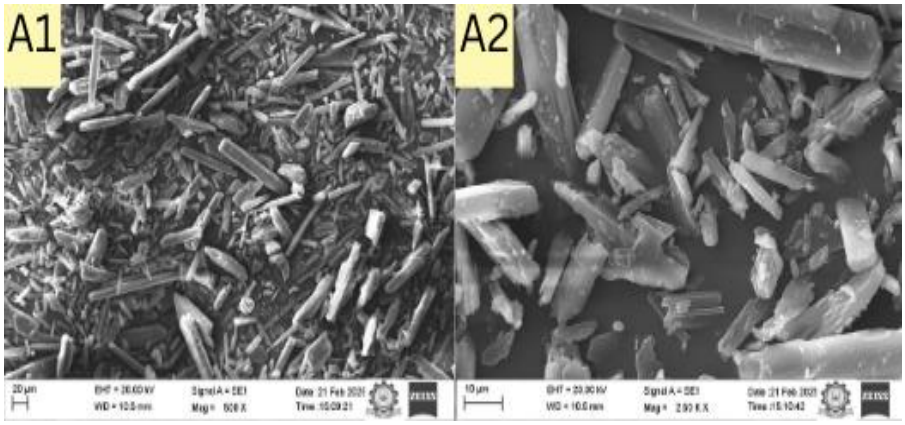

Figure 7a: SEM image of tadalafil

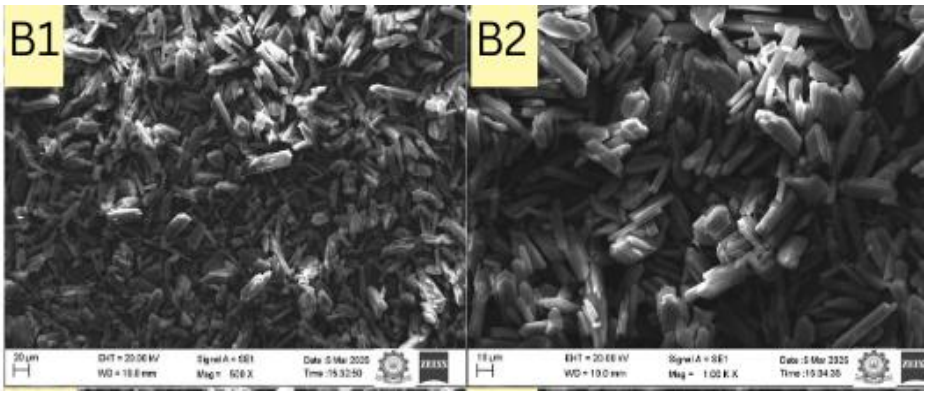

Figure 7b: SEM of tadalafil nano-cocrystals having benzoic acid

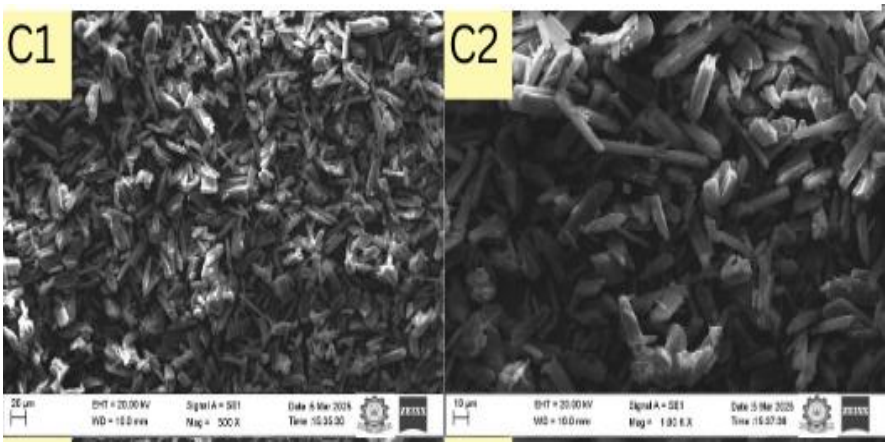

Figure 7c: SEM of tadalafil nano-cocrystals having citric acid

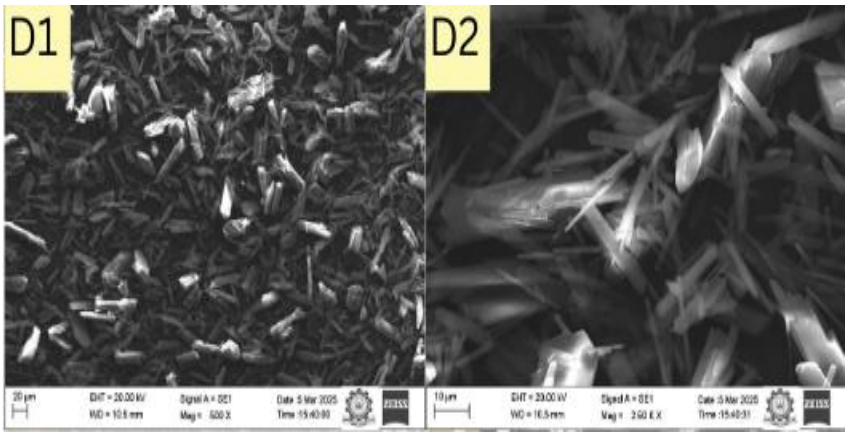

Figure 7d. SEM of tadalafil nano-cocrystals having vanillic acid

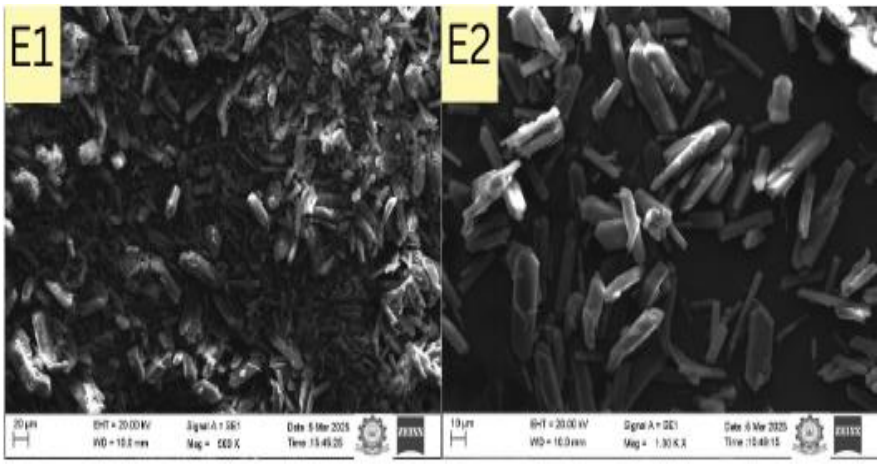

Figure 7e: SEM of tadalafil nano-cocrystals having gallic acid

The micrographs of pure tadalafil A1 and A2 (at 20 µm and 10 µm scale) show irregularly shaped particles with a rough and porous surface. The particles are highly agglomerated, indicating poor flowability and potential challenges in formulation processing. The rough surface morphology is typical of crystalline drugs and may contribute to low solubility and dissolution rates. In contrast, the nano-cocrystals of tadalafil containing benzoic acid coformer B1 and B2 exhibit a more uniform

particle size distribution and reduced agglomeration. The particles appear smoother and more homogeneous, suggesting the formation of a new crystalline phase. This improved morphology is likely to enhance flowability, solubility, and dissolution properties compared to pure tadalafil. The micrographs of tadalafil containing citric acid C1 and C2 reveal smaller, spherical particles with a compact and less porous surface. The spherical morphology and reduced particle size indicate improved solubility and dissolution rates, which are critical for enhancing the bioavailability of the drug. The absence of large agglomerates further suggests better flowability and stability. The nano-cocrystals with vanillic acid (D1 and D2) display a unique morphology, with a mix of spherical and rod-shaped particles. The surface is smooth with minimal porosity, indicating a stable crystalline structure. This unique morphology may contribute to improved mechanical properties and enhanced dissolution behavior compared to pure tadalafil. The micrographs of tadalafil containing gallic acid (E1 and E2) show irregular but less agglomerated particles compared to pure tadalafil. The surface is smooth and homogeneous, suggesting the formation of a stable cocrystal structure. This improved morphology is expected to enhance flowability and dissolution properties.

CONCLUSION

Tadalafil categorized into highly permeable and low soluble drug, hence this present research work aims to overcome its poor solubility during pharmaceutical drug or dosage form development. By converting the tadalafil drug into nano-cocrystals, its solubility is increased and enhances its absorption for systemic bioavailability. Tadalafil in the presence of a stabilizer and surfactant binds with the coformers to form nano-cocrystals by controlled process showing a remarkable increase in solubility than the parent tadalafil drug. The formation of nano-cocrystals was evidenced through various analytical techniques such as solubility measurement, melting point analysis, microscopic study, particle size analysis by laser diffraction, X-ray diffraction (XRD), and scanning electron microscopy. The SEM analysis revealed significant differences in the morphology and surface characteristics of tadalafil. The nano-cocrystals exhibited more uniform particle size distribution, smoother surfaces, and reduced agglomeration compared to pure tadalafil. These changes are indicative of successful nano-cocrystallization and suggest improved physicochemical properties, such as enhanced solubility, dissolution, and flowability. The results demonstrate the potential of nano-cocrystallization as a strategy to optimize the performance of tadalafil in pharmaceutical formulations. Hence, it can be concluded that nano-cocrystallization is one of the effective strategies to increase the solubility of class-II category drugs, thereby improving the absorption of the drug while administering to humans, which could maximize the bioavailability and therapeutic efficacy of the drug. The present study describes the formulation and evaluation of tadalafil into nano-cocrystals, and hence it is further necessary to formulate the prepared nano-cocrystals into suitable pharmaceutical dosage forms for its delivery to humans.

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