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DISSOLUTION ENHANCEMENT OF TADALAFIL: FORMULATION OF NANO-COCRYSTALS INTO DIRECTLY COMPRESSIBLE ORAL TABLETS

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ABSTRACT

The present work aimed to formulate tadalafil immediate release oral tablets using nano-cocrystals for enhanced drug dissolution rate with necessary pharmaceutical quality attributes, and ensure that the process of manufacturing is easily scalable. Tadalafil drug belongs to the BCS class II category of highly insoluble and highly permeable; its nano-cocrystals possess improved solubility, were used to formulate into tablets by the direct compression technique. Compatibility between tadalafil with other formulation excipients of tablet was established by FT-IR spectroscopy. The powder blends of tadalafil nano-cocrystals prepared with selected excipients were evaluated for precompression parameters, and the tablets prepared were evaluated for various physical properties, drug assay, disintegration and in-vitro drug release. Selected formulations were subjected to stability studies as per ICH guidelines. The precompression parameters revealed that the flow of the blend prepared was satisfactory for its direct compression process. Complete drug release in a short time was achieved when using the tadalafil nano-cocrystals in the formulation compared to the tadalafil plain drug formulation. It was concluded that in-vitro drug release was enhanced when formulating the nano-cocrystals form of insoluble drug tadalafil in a directly compressible tablet dosage form, and hence the systemic absorption of the drug in biological medium will be higher, which leads to increased bioavailability.

KEYWORDS: Nano-cocrystal, Direct compression, Disintegration, Dissolution, Stability.

INTRODUCTION

Oral route of drug administration is considered to be more convenient, economical, and any improvements in oral drug delivery technology can make significant differences in enhancing patient compliance and in-vivo drug bioavailability.[1] More than 70% of commercially launched dosage forms in the market exist in the form of oral tablets, and most pharmaceutical manufacturers prefer immediate release (IR) tablets due to their ease of manufacturing, better stability and consistency. Hence, oral IR tablets play a vital role in delivering pharmaceutical agents by rapidly releasing into the systemic circulation, making them an essential dosage form for drugs that require rapid onset of action or quick relief of symptoms. These tablets disintegrate and release their active ingredients promptly upon ingestion, allowing for efficient absorption and attainment of therapeutic levels in a shorter time frame compared to extended-release/other types of formulations.[2] Various techniques used for the manufacturing of oral IR tablets are wet granulation, dry granulation, direct compression, melt granulation, foam granulation, etc. The more preferable method of tableting is the direct compression method due to it requiring fewer processing steps, simplified validation, elimination of water/moisture, economical, high dilution potential, less chance of wear and tear of punches and improved drug stability compared with other techniques.[3-5]

During the pharmaceutical development of a new drug molecule or dosage forms, one of the important factors necessary to be considered is improving the active drug's solubility and rate of drug dissolution in formulation. Improving the solubility of the insoluble drug category is the thrust area of formulation research. To achieve increased systemic absorption of the drug and its oral bioavailability, it is mandatory to increase or improve the solubility and dissolution rate.[6-10]

Pharmaceutical nano-cocrystallization is used to enhance the solubility, stability, physical characteristics like hygroscopicity, crystallinity, particle size, flow, density, and flavour without altering the pharmacological characteristics of the active pharmaceutical ingredients

(APIs). It is the most effective method for active drugs, which fall under BCS class II category of drugs. Nano-cocrystallization is the process of merging cocrystallization with nano-sizing of a drug.[11] Nano-cocrystal formulations were proposed as a novel approach to achieve improved dissolution rate and oral bioavailability by combining the benefits of cocrystal and nanocrystal technologies.[12] Process of nano-cocrystalization reduces particle sizes to less than 1µm, significantly reduces to 100 nm, enhances the drug molecule's surface area and solubility, which increases the bioavailability of drugs that aren't very soluble.[13] 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.[14,15] 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.[16-18]

Tadalafil is a BCS Class II drug, 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.[19]

In our previous research work, nano-cocrystals of tadalafil were prepared using the coformers benzoic acid, citric acid, vanillic acid, and gallic acid; poloxamer-188 as stabilizer; and tween-80 as surfactant by the solvent antisolvent precipitation method and were evaluated for solubility, melting point, XRD, particle size and microscopy.[20] In this present work, the nano-cocrystals prepared were formulated into pharmaceutical dosage forms with the necessary characteristics of immediate release tablets, including physical properties, compressibility, hardness, friability, disintegration time, drug assay, in-vitro drug release, and stability on storage. The developing oral dosage form of tablets with nano-cocrystals and its manufacturing process needs to be less cumbersome and easily scalable, cost-effective, and feasible to commercialize at the industry level.

MATERIALS AND METHODS

Materials

Tadalafil drug, Poloxamer-188 and PVP K-30 were obtained from Yarrow chemical products, Mumbai; Benzoic acid, Citric acid, Lactose and Purified talc 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; Croscarmellose sodium (CCS) from Prachin chemical products, Magnesium stearate from Vijlak Pharma, Hyderabad; were purchased to conduct various experiments for the development of tablets of tadalafil nano-cocrystals.

Method of Preparation of Tadalafil Tablets using Nano-Cocrystals

Preparation of tadalafil tablets includes two stages, which include preparation of nano-cocrystals of tadalafil and formulation of the prepared nano-cocrystals into its tablet dosage form.

In stage 1, the required quantity of nano-cocrystals containing the drug tadalafil with coformers and stabilizers were prepared by the solvent-antisolvent precipitation method as described in our previous research work.[20] In this method of preparation, the drug and coformer excipients (benzoic acid, citric acid, vanillic acid and gallic acid) were mixed thoroughly in ethanol at 1:1, 1:1.5 and 1:2 molar ratios respectively, using a magnetic stirrer to make a complete solution. Dissolved the poloxamer-188 and tween-80 in distilled water, separately. Drop-wise added the drug+co-former solution into the anti-solvent aqueous solution containing poloxamer-188+tweens-80 slowly under continuous magnetic stirring at 500-700 rpm. Used a probe sonicator for 5-10 minutes to reduce the particle size and transferred the sonicated suspension into 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 is obtained. Dried the resulting suspension in a vacuum oven at 40^{0}C to remove residual water and solvents. Collected the dried nano-cocrystals, labelled and stored them in an airtight container.

In stage 2, the process of tablet preparation began by the blending of prepared tadalafil nano-cocrystals with lactose granules previously coated with PVP K-30 for 5 minutes by a mixing process. Subsequently, croscarmellose sodium (CCS) was added to the mixture and thoroughly blended for 5 minutes. Finally, purified talc and magnesium stearate were added to the mixture and blended for another 5 minutes. The resulting powder blend was subjected to pre-compression evaluation to assess its characteristic features. Following the pre-compression evaluation, the blend was compressed into tablets by the direct compression method. The 10-station rotary compression machine (Rimek mini press, India) was set with B tooling round punches. The blend was loaded in the hopper, and the machine was run at a low rpm of 10. The tablet compression parameters were set at optimum to produce a tablet with an average weight of 250 mg with the necessary hardness and thickness. During the compression process, the tablets were collected at different time intervals, and in-process quality checks were performed by keeping the target limits for the parameters as mentioned in Table 1.

Table 1: In-process compression parameters for tadalafil tablets.

S.No.	In-process compression parameters	Target limit
1	Average weight	250 mg ± 5%
2	Thickness of the tablets	3.5 ± 0.1 mm
3	Hardness of the tablets	Not less than 4.0 kg/cm^2
4	Friability	Not more than 1%

The unit composition of tadalafil immediate release tablets for direct compression which contains the nano-cocrystals of drug and excipients are in detailed in Table 2.

Table 2: Formulation composition of tadalafil tablets using nano-cocrystals.

Formulation code	Unit composition of tadalafil tablets in mg									
	Nano-cocrystals of tadalafil					Lactose	PVP K-30	CCS	Talc	Magnesium stearate
	Tadalafil	Co-formers*		Poloxamer-188	Tween-80					
Control	5.0	-		-	-	221.0	12.0	8.0	2.0	2.0
F1	5.0	Benzoic acid	5.0	2.5	1.5	212.0	12.0	8.0	2.0	2.0
F2	5.0		7.5	2.5	1.5	209.5	12.0	8.0	2.0	2.0
F3	5.0		10.0	2.5	1.5	207.0	12.0	8.0	2.0	2.0
F4	5.0	Citric acid	5.0	2.5	1.5	212.0	12.0	8.0	2.0	2.0
F5	5.0		7.5	2.5	1.5	209.5	12.0	8.0	2.0	2.0
F6	5.0		10.0	2.5	1.5	207.0	12.0	8.0	2.0	2.0
F7	5.0	Vanillic acid	5.0	2.5	1.5	212.0	12.0	8.0	2.0	2.0
F8	5.0		7.5	2.5	1.5	209.5	12.0	8.0	2.0	2.0
F9	5.0		10.0	2.5	1.5	207.0	12.0	8.0	2.0	2.0
F`0	5.0	Gallic acid	5.0	2.5	1.5	212.0	12.0	8.0	2.0	2.0
F11	5.0		7.5	2.5	1.5	209.5	12.0	8.0	2.0	2.0
F12	5.0		10.0	2.5	1.5	207.0	12.0	8.0	2.0	2.0
Average weight of tadalafil tablet = 250 mg										

**Note: ***Drug:coformer was used at three levels of 1:1, 1:1.5 and 1:2 ratios, respectively.

The finished tablet products were packed in tightly closed HDPE containers, labelled and subsequently evaluated through various post-compression tests to ensure their quality and performance.

PREFORMULATION STUDIES

Drug Excipient Compatibility Study by FT-IR Spectroscopy

Using Fourier Transform Infrared (FT-IR) spectroscopy, the compatibility between tadalafil and excipients used in the tablet formulation were studied. FT-IR spectrophotometer (Bruker) was used to record the FT-IR spectrum between the wavelengths of 600 and 4000 cm^{-1}, using the KBr disc technique. The baseline correlation was done using dried potassium bromide, and the spectrum of the dried mixture of the drug with potassium bromide was run, followed by the drug with various excipient mixture proposed in this research work.

EVALUATION OF PRE-COMPRESSION PARAMETERS FOR TABLET BLEND

Before compression, powder blends of the drug with excipient mixture were evaluated for various pre-compression parameters like bulk density, tapped density, Carr's compressibility index, Hausner's Ratio and angle of repose.

Bulk and Tapped Density

Bulk density is defined as the ratio of the total mass of powder and its bulk volume without any tapping and is expressed as g/cm^3. The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume, including the contribution of the inter-particulate void volume. Bulk density is often used to calculate the batch size for the blender and granulator. Weighed 10 gm of powder blend from each formulation was taken in a 50 mL measuring cylinder, and the initial volume of the powder blend in the measuring cylinder was noted. The bulk density of the powder blend was calculated by using the formula.

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

Tapped density is the ratio between the weight of powder mass and powder volume after tapping. It is expressed by g/cc. The tapped density is obtained by mechanically tapping a 10 g of powder blend in a graduated measuring cylinder. After observing the initial powder volume or mass, the measuring cylinder or vessel is mechanically tapped and volume readings are noted until little further volume change is observed. The mechanical tapping was achieved by raising the cylinder and allowing it to drop, under its mass, a specified distance.

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

Carr's Compressibility Index

The simple way of measuring the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow, is given by the compressibility index of the powders. Carr's compressibility index (CI) was determined by using the following formula.

$$CI(\%) = \frac{TD - BD}{TD} \times 100$$

Where, TD = Tapped Density, BD = Bulk Density, CI = Carr's Compressibility Index

The flow properties concerning compressibility index, as per USP, are shown in Table 3

Hausner's Ratio and Angle of Repose

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

The angle of repose is the angle made by the surface of a pile of powder to the horizontal surface. It is a micrometric parameter related to inner particulate friction or resistance to flow. The funnel technique was used to determine the angle of repose. About 10 g of the sample was slowly passed along the wall of the funnel till the tip of the pile formed. A rough circle was drawn around the pile base, and the radius of the powder cone and height were measured. The angle of repose was calculated using the following formula.

$$\text{Tan } \theta = \frac{h}{r} \; ; \quad \theta = Tan^{-1}\frac{h}{r}$$

Where, θ = Angle of repose; h = Height of the cone; r = Radius of the cone base

The flow properties concerning angle of repose, Hausner's ratio and compressibility index as per USP were listed in Table 3.

Table 3: Flow properties of powder as per USP.

S. No.	Compressibility index	Hausner's ratio	Angle of repose (θ)	Flow property
1	≤10	1.00-1.11	25-30	Excellent
2	11 – 15	1.12-1.18	31-35	Good
3	16 – 20	1.19-1.25	36-40	Fair
4	21 – 25	1.26-1.34	41-45	Passable
5	26 – 31	1.35-1.45	46-55	Poor
6	32 – 37	1.46-1.59	56-65	Very poor
7	>38	>1.60	>66	Very, very poor

EVALUATION OF POST-COMPRESSION PARAMETERS

The compressed tablets were evaluated for the parameters such as appearance, thickness, hardness, weight variation, friability, disintegration time and dissolution.

General Appearance

The organoleptic characters like general appearance, colour, shape, odor and texture were evaluated for all the tablet formulations.

Weight Variation Test

Twenty tablets were selected at random, and the average weight was determined. The individual tablets were weighed and it was compared with the average weight. Not more than two of the tablet's weights should deviate from the average weight by more than the percentage deviation listed in the accompanying table, and none should deviate from the average weight by more than twice that percentage deviation mentioned in Table 4.

Table 4: Uniformity of weight and percentage deviation.

Average weight of tablets (mg)	Percentage deviation allowed (%)
80 mg or less	± 10
More than 80 mg but less than 250 mg	± 7.5
250 mg or more	± 5

$$\text{Percentage devation} = \frac{(\text{Weight of tablet} - \text{Average weight of tablets})}{\text{Average weight of tablets}} \times 100$$

Thickness Test

The thickness of the tablet was measured by using a vernier caliper. To find the thickness, hold the tablet vertically against the jaws. Close the jaws until they touch the tablet and read the measurement on the main scale. Tablet thickness should be controlled within a ± 5% variation of the standard value. Thickness values were expressed in millimeters.

Hardness Test

The resistance of the tablet to the applied force, until it breaks, is the definition of hardness. 6 - 10 tablets are

selected randomly from each of the batches, and hardness was determined using a Monsanto Hardness tester. The tester is placed across the diameter between the spindle and the anvil. The knob is adjusted to hold the tablet in position. The pressure is increased slowly to break the tablet. The value was expressed in Kg/cm2.

Friability Test

A friability study is a quality control test performed on tablets to determine to ensure the durability and integrity of tablet formulations. It was measured using a Roche friability tester. The plastic chamber was linked to a motor. For this study, sample tablets weighing 6.5 g were initially weighed and taken in the chamber and rotated the drum 100 times (25 rpm). These tablets were dusted off, reweighed, and the % weight loss was computed using the formula below:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Drug Content

From each formulation of Tadalafil IR tablets, 10 tablets were taken randomly and powdered. A quantity equivalent to 100 mg of Tadalafil was transferred into a 100 ml volumetric flask, dissolved in 50 ml of ethanol. The volume was made upto 100 ml using ethanol. From the stock solution 10 µg/ml solution was prepared. The drug content was estimated by measuring the absorbance of the solution at 284.2 nm using a UV-Visible double-beam spectrophotometer.

In-Vitro Disintegration Time (DT)

The disintegration was determined by noting the time when the tablet was completely disintegrated and passed through the screen of the DT apparatus. Six tablets were placed in each of the tubes, in a medium of 900 mL distilled water, which was maintained at 37 ± 0.5°C. The time required for the complete passage of tablet fragments through the 10-mesh sieve was considered as the disintegration time of the tablet.

In-Vitro Dissolution Studies

The drug release study was carried out using USP - Type II dissolution apparatus with 900 mL of dissolution media (0.5 % w/v of SLS in purified water) at 37°C ± 0.5°C using paddle at 50 rpm. A sample volume of 5 mL was withdrawn at regular time intervals from a zone midway between the surface of the dissolution medium and the top of the rotating paddle, not less than 1 cm apart from the vessel wall, at every 5-minute interval. The volume withdrawn was replaced by a fresh volume of dissolution medium to maintain a constant volume of medium. The filtered samples after suitable dilution were analyzed using a spectrophotometer at 284.2 nm.

STABILITY STUDY

As per ICH guidelines for stability, selected formulations were stored at accelerated storage conditions of 40±2°C/75±5%RH for 3 months in a stability chamber (CHM-16S, Remi Sales & Engg.). Their physical appearance, hardness, drug content, disintegration time, and in vitro drug release were evaluated at specified intervals of time, every month.

RESULTS AND DISCUSSION

Drug Excipients Compatibility Studies

FT-IR study was performed and the absorption spectra observed for the drug excipient mixture prepared, which contains tadalafil drug, poloxamer-188, tweens-80, lactose, PVP K-30, purified talc and magnesium stearate, along with the coformers benzoic acid, citric acid, vanillic acid and gallic acid individually, were recorded.

Figure 1 represents FTIR spectra of pure drug tadalafil, and Figures 2,3,4 and 5 represents the drug mixture, which contains the coformers benzoic acid, citric acid, vanillic acid and gallic acid respectively, along with tadalafil drug and the other excipients, including poloxamer-188, tweens-80, lactose, PVP K-30, CCS, purified talc, and magnesium stearate.

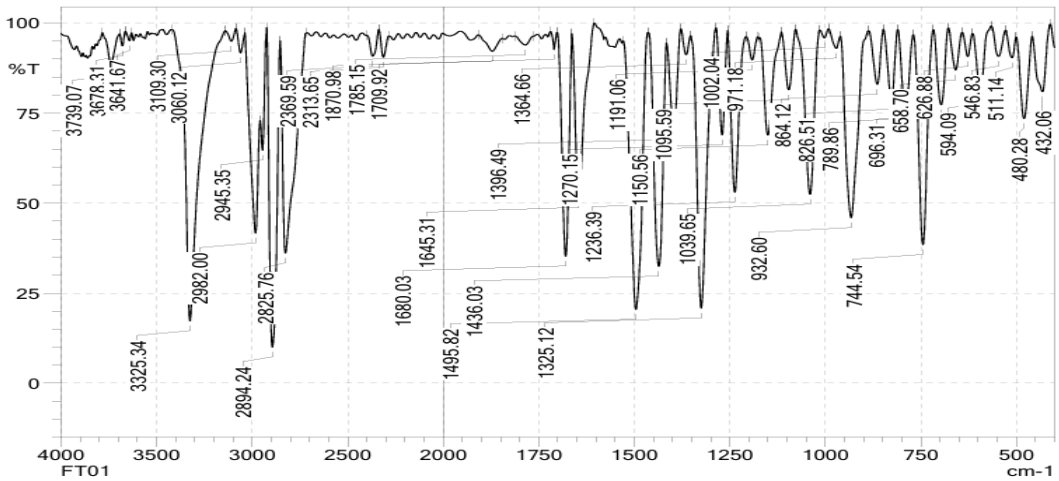

Figure 1: FT-IR Spectrograph of Tadalafil pure drug.

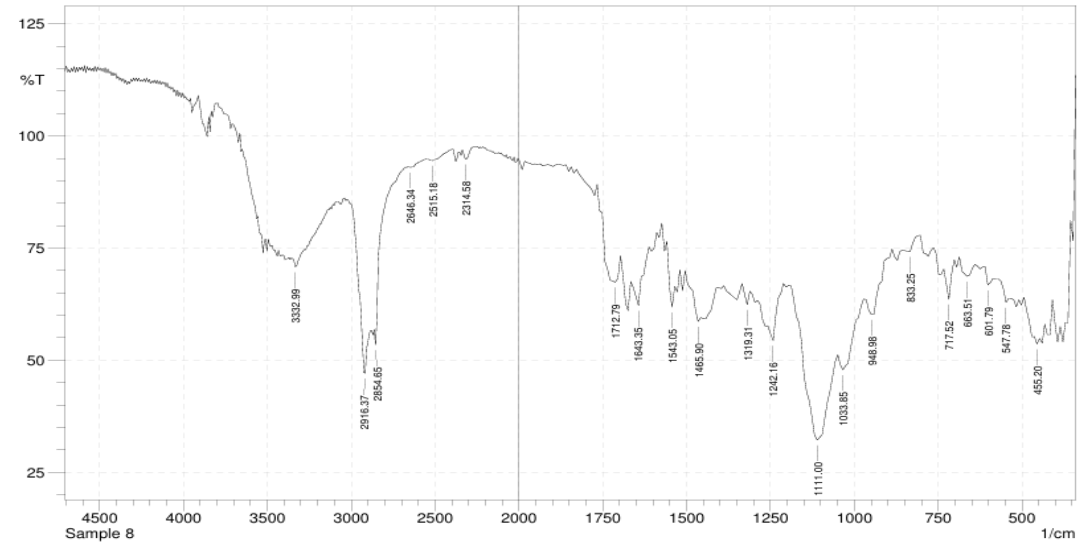

Figure 2: FT-IR Spectrograph of Drug + Poloxamer-188 + Benzoic acid + Tweens-80 + Lactose + PVP K-30 + CCS + Purifies talc + Magnesium stearate.

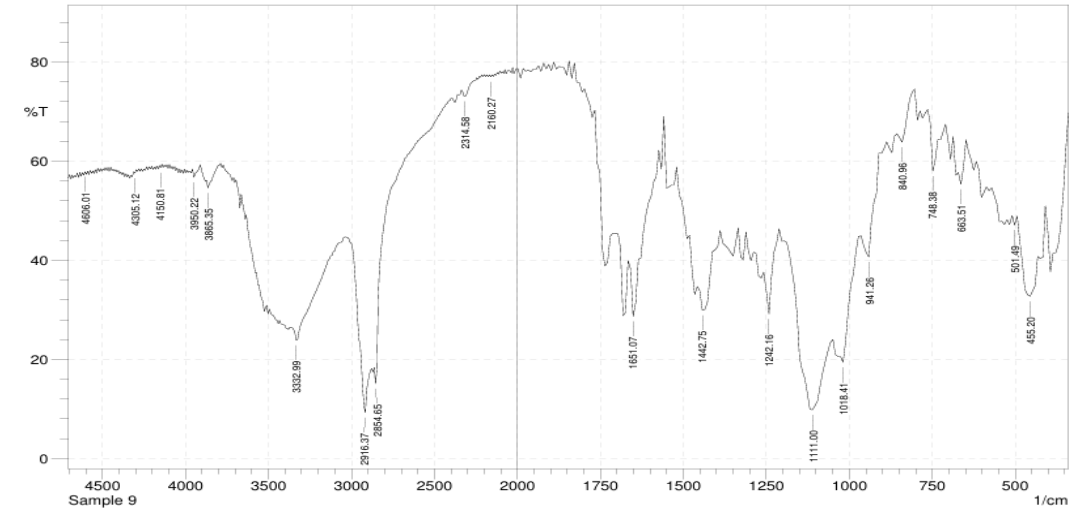

Figure 3: FT-IR Spectrograph of Drug + Poloxamer-188 + Citric acid + Tweens-80 + Lactose + PVP K-30 + CCS + Purifies talc + Magnesium stearate.

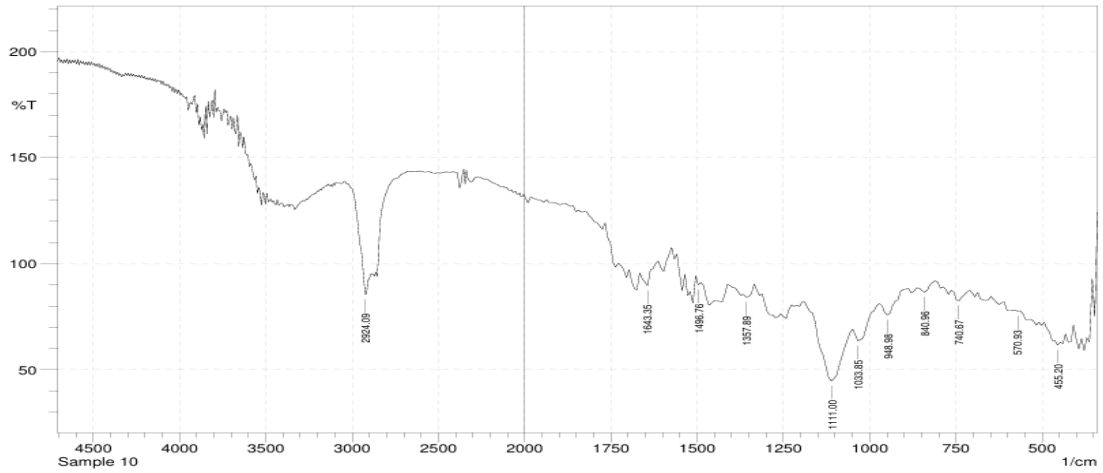

Figure 4: FT-IR Spectrograph of Drug + Poloxamer-188 + Vanillic acid + Tweens-80 + Lactose + PVP K-30 + CCS + Purifies talc + Magnesium stearate.

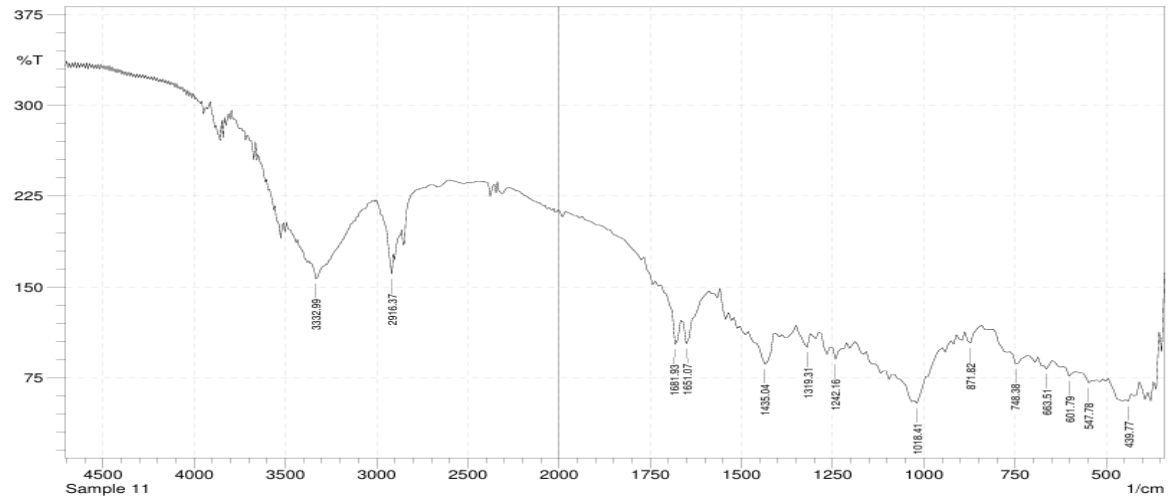

Figure 5: FT-IR Spectrograph of Drug + Poloxamer-188 + Gallic acid + Tweens-80 + Lactose + PVP K-30 + CCS + Purifies talc + Magnesium stearate.

In Table 5, the wavelength (cm^{-1}) of major peaks observed for the pure drug tadalafil and its mixture containing tablet excipients were recorded.

Table 5: FT-IR Spectral data of the drug with excipients mixture.

S. No.	Range of Frequency (cm^{-1})	Group	Observed frequency				
			Tadalafil Drug	Drug + excipient mixture*			
				B+Po+ Tw+L+ K30+Cs +T+Ms	C+Po+ Tw+L+ K30+Cs +T+Ms	V+Po+ Tw+L+ K30+Cs +T+Ms	G+Po+ Tw+L+ K30+Cs +T+Ms
1	3170-3500	N-H stretching	3325	3333	3333	3350	3333
2	2950-3050	C-H stretching for aromatic / pyrazine and pyridine	2982	2916	2916	2924	2916
3	2800-3000	C-H Stretch, aliphatic CH_3 sym	2894	2916	2916	2924	2916
4	1600-1800	C=O carbonyl stretching	1680	1713	1651	1643	1682
5	1600-1700	C=C aromatic stretching	1645	1643	1651	1643	1435
6	1480-1600	Pyrazine and pyridine ring stretching vibrations	1495	1543	1443	1497	1435
7	1200-1350	C-N stretching vibrations for pyrazine and pyridine	1236 & 1325	1242	1242	1250	1319
8	1000-1200	Benzodioxide & C-O-C stretch sym	1039	1111	1111	1111	1018
9	700-800	Benzene ring	744	718	748	741	748

**Note: ***B - Benzoic acid, C - Citric acid, V - Vanillic acid, G - Gallic acid, Po - Poloxamer-188, Tw - Tweens-80, L - Lactose, K30 - PVP K-30, Cs - Croscarmellose sodium, T - Purified Talc, Ms - Magnesium stearate.

It was observed that there was no change in absorption peaks in the drug mixture when compared to pure drug tadalafil. The drug had not undergone any kind of structural change or chemical reaction with the other excipients used in this development work. Therefore, it was confirmed that there was no chemical interaction of the drug with the excipients used in this current experimental study and they were compatible with each other. Also, the consistency in benzene ring (700–800 cm^{-1}) and pyridine vibrations (1200–1360 cm^{-1}) across all samples confirms tadalafil stability in nano-cocrystals and tablet formulations.

Evaluation of Pre-compression Parameters

The powder blends were evaluated for the following parameters such as bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose before formulating into tablets. The results are given below in Table 6.

Table 6: Pre-compression tablet parameters.

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})
F1	0.48±0.02	0.58±0.02	17.2±1.0	1.21±0.02	25.8±1.0
F2	0.49±0.02	0.59±0.02	16.9±1.0	1.20±0.02	26.0±1.0
F3	0.50±0.02	0.60±0.02	16.7±1.0	1.20±0.02	25.5±1.0
F4	0.47±0.02	0.56±0.02	16.1±1.0	1.19±0.02	24.0±1.0
F5	0.48±0.02	0.57±0.02	15.8±1.0	1.19±0.02	24.5±1.0
F6	0.49±0.02	0.58±0.02	15.5±1.0	1.18±0.02	25.0±1.0
F7	0.51±0.02	0.61±0.02	16.4±1.0	1.20±0.02	25.2±1.0
F8	0.52±0.02	0.62±0.02	16.1±1.0	1.19±0.02	25.8±1.0
F9	0.53±0.02	0.63±0.02	15.9±1.0	1.19±0.02	25.0±1.0
F10	0.46±0.02	0.55±0.02	16.4±1.0	1.20±0.02	23.5±1.0
F11	0.47±0.02	0.56±0.02	16.1±1.0	1.19±0.02	23.8±1.0
F12	0.48±0.02	0.57±0.02	15.8±1.0	1.19±0.02	24.2±1.0

The pre-compression evaluation of the tadalafil blend ready for compression showed excellent powder flow properties suitable for tablet manufacturing. All formulations (F1-F12) demonstrated acceptable test results with Carr's compressibility ratios (15.5-17.2%) and Hausner's ratios (1.18-1.21), indicating good to excellent flowability. The angle of repose observed between 23.5°-26.5° further confirmed optimal flow properties for all formulations. Bulk and tapped density of the formulations were recorded suggesting better particle packing. These results indicate that the nano-cocrystals of tadalafil drug with directly compressible excipients used in the formulation enhanced the powder's compressibility without negatively affecting flow properties, making all formulations suitable for the direct compression process of tablet manufacturing. The consistent values across different formulations (F1-F12) demonstrate the robustness of the preparation method.

Tablet Compression Parameters

The general appearance of the tablet was found to be round, biconvex, white to off-white and having a smooth, uniform surface with no cracks or sticking. After the compression of lubricated granules, the tablets were evaluated for post-compression parameters. The prepared tadalafil tablets were evaluated for various compression quality parameters such as weight variation, thickness, hardness, and friability. The results are described in Table 7.

Table 7: Tablet compression parameters.

Formulation Code	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (% weight loss)
F1	250.8±2.8	3.52±0.06	5.4±0.3	0.42
F2	249.5±3.0	3.51±0.07	5.6±0.4	0.40
F3	250.4±2.7	3.53±0.05	5.5±0.3	0.38
F4	248.5±2.9	3.50±0.04	5.3±0.2	0.45
F5	251.7±3.1	3.54±0.08	5.7±0.5	0.43
F6	250.9±2.6	3.52±0.06	5.4±0.4	0.41
F7	251.3±3.2	3.51±0.05	5.8±0.6	0.39
F8	250.5±2.4	3.53±0.07	5.5±0.3	0.44
F9	250.7±3.3	3.55±0.09	5.9±0.7	0.37
F10	248.9±2.3	3.50±0.03	5.2±0.2	0.46
F11	249.2±3.4	3.54±0.08	5.6±0.5	0.42
F12	250.3±2.2	3.51±0.06	5.7±0.6	0.40

The weight variation test results for all tadalafil tablet formulations (F1-F12) demonstrated excellent compliance with USP standards of ±5% limit. All batches showed weight variation ranging from 245 to 255 mg, well below the permissible limit of 238 to 262 mg. The weight control across all batches suggests that robust formulation and manufacturing processes, with all values meeting the pharmacopeial requirements for content uniformity. The thickness of the tablets was measured and was found in the range between 3.4mm to 3.6mm, and hence there is no significant difference. The hardness of the tablets was measured, and the values were found in the range between 5 to 6 kg/cm^2. These showed all batches of the prepared tablets had acceptable mechanical strength with sufficient hardness. Similarly, percentage friability values of the prepared tablets showed less than 0.5% weight loss, which is within the acceptable limit of <1%. Hence, all the tablet formulation trials comply with the friability test.

Drug Content of Compressed Tadalafil Tablets

The drug content or assay of tadalafil in all formulations was found to be in the range of 97% to 101% which was within the acceptable USP limits (Tadalafil tablets contain NLT 90.0% and NMT 110.0% of the labelled amount of tadalafil). Drug content remained satisfactory across all batches and well within pharmacopeial limits. These results demonstrate that the method of preparation and the characteristics of excipients used significantly enhanced the uniform distribution of tadalafil in the formulation for compliance. The drug content results of tadalafil tablet batches are given in Table 8.

Disintegration Testing of Compressed Tablets

For tablet disintegration testing, a disintegration apparatus consisting of a basket-rack assembly with tubes and a beaker containing the immersion liquid medium was used. The basket-rack assembly is immersed in a beaker containing water at 37 ± 2°C. One tablet was placed in each of the six tubes. The apparatus was operated to move the basket up and down, simulating the conditions in the gastrointestinal tract. The time taken for all the trial batch tablets to be disintegrated was noted. Disintegration test performed for the control sample tablets, which contains plain tadalafil drug as it is without any modification. The results are shown in Table 8.

Table 8: Drug content and disintegration of tablets.

Formulation code	Drug Content (%)	Disintegration time (min)
F0 (control)	---	10.0±1.0
F1	99.0±1.2	4.6±0.5
F2	99.3±1.1	4.3±0.4
F3	99.5±1.0	4.0±0.3
F4	98.8±1.3	4.8±0.6
F5	99.1±1.2	4.5±0.5
F6	99.4±1.1	4.2±0.4
F7	99.6±0.9	3.9±0.3
F8	99.2±1.0	4.1±0.3
F9	99.8±0.8	3.8±0.2
F10	98.9±1.4	4.9±0.7
F11	99.3±1.1	4.6±0.5
F12	99.5±1.0	4.3±0.4

The disintegration time (DT) of prepared tablets using the direct compression method was found to be between 3.8±0.2 min (F9) and 4.9±0.7 min (F10) compared to the control sample tablets having a DT of 10.0±1.0. The acceptable disintegration time of the uncoated tablet limit as per pharmacopoeia is not more than 15 minutes. Hence, all the tablets compiles the disintegration test.

In Vitro Dissolution Studies

The multiple point in vitro drug release of tadalafil tablet formulations (F1-F12) containing nano-cocrystals and the control formulation prepared in this study are given in Table 9.

Table 9: Comparative in-vitro drug release of tablets with tadalafil nano-cocrystals (F1 to F12) and tadalafil plain drug (F0).

Formulation Code		Time in minutes					
		5 min	10 min	15 min	20 min	25 min	30 min
F0	% Drug Release	25±2	45±3	60±2	70±3	73±3	75±3
F1		55±3	78±2	88±1	92±1	93±1	94±2
F2		58±3	82±2	92±1	95±1	95±1	95±2
F3		60±2	85±1	94±1	97±1	96±1	96±1
F4		53±2	75±2	85±1	90±1	92±1	93±2
F5		56±3	80±2	90±1	93±1	94±1	94±2
F6		59±2	83±1	93±1	94±1	95±1	95±1
F7		62±2	88±1	96±1	96±1	97±1	97±1
F8		61±3	86±2	95±1	95±1	96±1	96±1
F9		65±2	90±1	98±1	99±1	99±1	99±1
F10		52±3	74±2	84±1	89±1	91±1	92±2
F11		55±3	78±2	88±1	92±1	93±1	94±2
F12		57±2	82±1	91±1	95±1	95±1	95±1

The in-vitro dissolution study demonstrated that tadalafil nano-cocrystal formulations (F1-F12) exhibited significantly enhanced drug release compared to the conventional tablets (F0). All nano-cocrystal formulations achieved more than 90% drug release within 15-20 minutes, while the control (F0) reached only 60% release at 15 minutes and 75% at 30 minutes. Among the nano-cocrystals formulations, F9 (vanillic acid-based) showed the fastest and most complete release profile, achieving 65% release in just 5 minutes and reaching 99% by 20 minutes, representing a 2.6-fold improvement over F0 at the 5-minute mark. The benzoic acid-based formulations (F1-F3) also performed better drug release, with F3 reaching >90% release by 20 minutes, while citric/gallic acid formulations (F4-F6, F10-F12) showed slightly slower but still substantially improved dissolution compared to F0. These results indicate that in the presence of stabilizers, with co-formers, dramatically enhances the dissolution characteristics of tadalafil, which is crucial for improving its bioavailability as a poorly water-soluble drug. The consistent performance across all nano-cocrystal formulations (standard deviations ≤3%) further validates the reliability of the analytical method and solvent-antisolvent precipitation method of manufacturing for tadalafil nano-cocrystals with superior dissolution properties.

STABILITY STUDY OF TADALAFIL TABLETS

The physical appearance of tablets of all the formulations under stability was found to be white to off-white with a smooth surface and no remarkable changes. The stability results were compiled, and the results were shown in Table 10.

Table 10: Stability data for tadalafil tablet formulations.

Formulations code and sampling period		Stability indicating parameters at 40±2°C / 75±5%RH				
		Hardness (Kg/cm^2)	Drug content (%)	DT(min)	Drug release (%)	
					15 mins	30 mins
F2	Initial	5.6±0.4	99.3±1.1	4.3±0.4	92±1	95±2
	1 M	5.5±0.5	98.7±0.9	4.6±0.5	93±3	95±1
	2 M	5.6±0.8	99.5±1.3	4.5±0.2	92±2	95±1
	3 M	5.4±0.3	98.4±1.0	4.4±0.8	92±2	95±2
F5	Initial	5.7±0.5	99.1±1.2	4.5±0.5	90±1	94±2
	1 M	5.6±0.7	99.3±1.0	4.4±0.7	91±2	93±1
	2 M	5.5±0.9	98.7±1.5	4.5±0.3	90±1	95±2
	3 M	5.7±0.4	99.5±0.8	4.3±0.5	89±1	94±1
F8	Initial	5.5±0.3	99.2±1.0	4.1±0.3	95±1	96±1
	1 M	5.4±0.5	98.4±1.4	4.3±0.5	94±21	95±1
	2 M	5.5±0.2	99.4±1.2	4.5±0.6	95±2	94±2
	3 M	5.6±0.7	98.9±0.8	4.3±0.4	94±1	95±1
F11	Initial	5.6±0.5	99.3±1.1	4.6±0.5	88±1	94±2
	1 M	5.4±0.3	98.5±0.7	4.4±0.7	87±2	95±1
	2 M	5.4±0.4	99.5±1.6	4.2±0.4	85±1	93±2
	3 M	5.5±0.7	98.4±1.3	4.4±0.5	86±2	94±1

Note: F2, F5, F8 and F11 formulations contain the coformers benzoic acid, citric acid, vanillic acid and gallic acid, respectively.

The stability study revealed that there were no significant changes observed between the initial analysis results and during the period of 90 days storage at accelerated storage conditions.

CONCLUSION

In this present work, immediate release tablets containing tadalafil nano-cocrystals were prepared by the direct compression method, and their quality characteristics are evaluated. The powder blend prepared with tadalafil nano-cocrystals exhibits better flow and compressibility for the preparation of tablets by direct compression in a rotary tablet compression machine. The physical parameters, rapid disintegration and complete drug release of compressed tablets showed a remarkable increase in dissolution rate than the tadalafil plain drug formulation. Stability results revealed that the developed formulations of tadalafil were stable on storage. Hence, it can be concluded that the use of the nano-cocrystals of tadalafil in tablet formulation is a better alternative where size reduction, use of surfactants, solubilizers and other techniques of improving the solubility and dissolution were not feasible or difficult. Many existing and new drug molecules are heat unstable during particle size reduction by micronizer and yield is also reduced due to loss on the process, particularly handling of highly potent drugs at lower volumes. These difficulties are overcome by adopting the nano-cocrystallization technique and enhance the absorption of the insoluble drug, which leads to increased bioavailability and therapeutic efficacy of the drug. The developed composition and process for tadalafil is cost-effective and can be easily scalable for commercial manufacturing. Further necessary bioequivalence or

clinical studies can be performed to prove in-vivo efficacy of the developed formulation.

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