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Design, Formulation and Characterization of Sertraline Multicomponent Crystal Tablet as an Antidepressant

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Artikel Penelitian

Abstract: *Sertraline (BCS class II) has low solubility and dissolution rate. Modifying sertraline through multicomponent crystal formation is a strategy to enhance its physicochemical properties, particularly solubility and dissolution. This study aimed to design, formulate, and characterize sertraline tablets based on multicomponent crystals using L-tryptophan (S–L), saccharin (S–S), and nicotinic acid (S–N) as coformers. The crystals were synthesized by solvent evaporation and characterized using FTIR, DSC, PXRD, SEM, and solubility and dissolution studies, followed by evaluation of tablet properties using direct compression. The multicomponent crystals exhibited FTIR band shifts or broadening of –OH/–NH and C=O groups and new PXRD peaks, indicating the formation of multicomponent crystals. DSC showed distinct thermal transitions: S–L at 258 °C, S–S at 280.8 °C, and S–N at 242 °C. The highest solubility enhancement was observed for S–N (44.29 mg/10 mL, followed by S–L (15.44 mg/10 mL). In 0.1 N HCl medium, 60-minute dissolution reached >88% for S–N, 73% for S–L, 53% for S–S, and 52% for pure sertraline. The best tablet formulation (F6) demonstrated good flow and compressibility (compressibility index 23.55%, angle of repose 28.85°, flow rate 6.53 g/s) and met pharmacopeial criteria: uniform dimensions (8 mm diameter, 5.23 mm thickness), weight (284.22 mg), (friability (0.37%), hardness (6.66 kg/cm^2), disintegration (5.47 seconds), and dissolution at pH 4.5 ≥85% in 30 minutes. Multicomponent crystals of sertraline-nicotinic acid are able to increase solubility up to 8.8 fold and can be produced by direct compression method and produce good evaluation of tablet preparations (uniformity of weight, friability, hardness, disintegration time test, and dissolution test) in immediate release tablet formulation.*

Keywords: *Multicomponent Crystal, Sertraline, Solubility*

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Abstrak: Sertraline (BCS kelas II) memiliki kelarutan dan laju disolusi rendah. Modifikasi sertraline melalui pembentukan kristal multikomponen digunakan untuk meningkatkan sifat fisikokimia, terutama kelarutan dan disolusi. Penelitian ini bertujuan mendesain, memformulasi, dan mengkarakterisasi tablet sertraline berbasis kristal multikomponen dengan koformer L-triptofan (S–L), sakarin (S–S), dan asam nikotinat (S–N). Kristal multikomponen disintesis menggunakan metode *solvent evaporation* dan dikarakterisasi dengan FTIR, DSC, PXRD, SEM, serta diuji kelarutan, disolusi, dan sifat pra- serta pascakompresi tablet melalui kempa langsung. Kristal multikomponen menunjukkan perubahan pita FTIR (pergeseran/pelebaran –OH/–NH dan C=O) serta puncak PXRD baru yang mengindikasikan terbentuknya fase kristal baru. DSC memperlihatkan transisi termal khas: S–L endotermik 258 °C, S–S 280,8 °C, dan S–N 242 °C, sejalan dengan perubahan energi kisi. Kelarutan meningkat paling besar pada S–N (44,29 mg/10 mL, dan diikuti S–L (15,44 mg/10 mL). Pada media HCl 0,1 N, pelepasan 60 menit menunjukkan S–N >88%, S–L 73%, S–S 53%, dan sertraline murni 52%. Formula tablet terbaik (F6) memiliki sifat alir dan kompresibilitas baik (indeks kompresibilitas 23,55%, sudut istirahat 28,85°, laju alir 6,53 g/detik) serta memenuhi persyaratan mutu tablet: keseragaman ukuran (diameter 8 mm, tebal 5,23 mm), bobot 284.22 mg, kerapuhan 0,37%, kekerasan 6,66 kg, waktu hancur 5,47 detik, dan disolusi pH 4,5 ≥85% pada 30 menit. Kristal multikomponen sertralin-asam nikotinat

mampu meningkatkan kelarutan hingga 8.8 lipat dan mampu diproduksi dengan metode kempa langsung serta menghasilkan evaluasi sediaan tablet (Keseragaman bobot, kerapuhan, kekerasan, uji waktu hancur, dan uji disolusi) yang baik dalam formulasi tablet lepas cepat.

Kata kunci: Kelarutan, Kristal multikomponen, Sertraline

Pendahuluan

In drug development efforts, one of the current challenges is poor solubility. It is estimated that 40% of newly developed drugs have poor solubility and permeability issues. Furthermore, 50% of orally administered drug compounds have similar problems, namely formulations with low solubility (1). The Biopharmaceutics Classification System (BCS) regulates the solubility and permeability system, which is divided into four classes. Of these four classes, Active Pharmaceutical Ingredients (API) classes II and IV have low solubility. Low solubility affects the slow dissolution rate of a drug, and poor penetration will affect low bioavailability when passing through the gastrointestinal tract membrane (2). This causes more than 40% of new drug candidates to fail in the drug development process due to suboptimal biopharmaceutical properties (3).

ndrug with low solubility. The solubility of sertraline in water is 3.5 mg/L. Sertraline is highly lipophilic with a log P value of 5.1, but results in low bioavailability of around 44% (4,5). The limitations of sertraline's physicochemical properties can be overcome by modifying the crystal, one of which is by using cocrystallization techniques. Cocrystals are crystalline materials with two or more components bonded non-uniquely by noncovalent bonds (6,7). Interaction such as hydrogen bonds, Van der Waals forces, and π-π interactions (7,8). Hydrogen bonds are the dominant interaction because they have a relatively high interaction strength (9). Cocrystals are a method that can be used to increase the solubility & dissolution rate, stability, permeability, bioavailability, compressibility & tabletability and pharmacological efficacy of a drug (10–15).

Cocrystallization is an attractive approach in drug development because it can be used as an alternative in drug development to improve the physicochemical properties of APIs without changing their pharmacological activity. Coformers are co-components used in cocrystallization. The choice of coformer is important because the coformer used must not reduce the pharmacological activity of the API, but can improve the physicochemical properties of the API, namely increasing solubility, dissolution, permeability, bioavailability, hygroscopicity, stability, compressibility, and pharmacological efficacy (15,16). Coformers must have certain groups in forming a multicrystalline phase. Certain functional groups such as carboxylic acids, amides, carbohydrates, alcohols, or amino acids (17).

Modifications made by Anusha & Reddy (2019) with API sertraline using carboxylic acid coformers such as salicylic acid, benzoic acid, nicotinic acid and oxalic acid using the solvent evaporation method increased the solubility of sertraline up to 5 times (18). Sertraline in its structure has an amino group (-NH-) and an aromatic ring that has great potential to form hydrogen bonds with coformers with O and or H atoms such as saccharin, urea, tartaric acid, maleic acid, succinic acid, sorbic acid, fumaric acid and tyrosine. In addition, the π-π stacking interaction between sertraline and the coformer can occur hydrogen bonds because there is an aromatic ring. The formation of cocrystals is successful with the formation of hydrogen bonds using coformers that have O and or H atoms improving the physicochemical properties by the occurrence of proton donors and acceptors between the coformer and sertraline. Coformer screening is an in silico study that can be used to determine the molecular interactions that lead to hydrogen bonding and π-π stacking interactions between sertraline and coformers. Furthermore, this study aims to identify specific coformers that exhibit hydrogen bonding and π-π stacking interactions, allowing for further cocrystal preparation.

In a study conducted by Shi et al., using a carboxylic acid coformer for cocrystal formation with the API lbrutinib increased solubility through π-π stacking and hydrogen bonding interactions (9). A study conducted by Ji et al. using a carboxylic acid coformer for abacavir also showed increased solubility, dissolution, and permeability (19). In addition to the coformer, the preparation method influences the success of cocrystal formation. Acyclovir cocrystal formation using the solvent evaporation method was superior to the wet grinding method and the addition of an antisolvent (20).

Despite the growing interest in multicomponent crystal engineering as a strategy to improve the physicochemical properties of poorly water-soluble drugs, studies integrating in silico coformer screening, multicomponent crystal formation, comprehensive solid-state characterization, dissolution enhancement, and immediate-release tablet formulation within a single investigation remain limited, particularly for sertraline. Therefore, this study aimed to improve the physicochemical properties of sertraline through the preparation of multicomponent crystals using the solvent evaporation method and rational coformer selection based on in silico analysis. The obtained multicomponent crystals were subsequently evaluated through solubility and dissolution studies, as well as FTIR, DSC, PXRD, and SEM characterization. Furthermore, the optimized multicomponent crystal was formulated into immediate-release tablets and subjected to pre-compression and post-compression evaluations to assess its pharmaceutical performance.

Materials and Methods

Materials

The materials employed in this study included sertraline, L-tryptophan, saccharin, nicotinic acid, methanol, distilled water, hydrochloric acid (HCl) 0.1 N, and acetate buffer at pH 4.5. The instruments utilized in this research comprised an orbital shaker, UV-Vis spectrophotometer, dissolution tester, Fourier Transform Infrared (FTIR) spectrometer, Differential Scanning Calorimeter (DSC), Powder X-Ray Diffractometer (PXRD), Scanning Electron Microscope (SEM), flow tester, tapped density tester, Vernier caliper, hardness tester, friability tester, and disintegration tester.

Methods

Coformer Screening

Sertraline and coformer structures were obtained from PubChem, converted into 3D structures using ChemOffice, and saved in PDB format. Coformers were selected based on supramolecular synthon principles (carboxylic acid, amine, and amino acid groups) and optimized using Gaussian (AM1). Molecular docking was performed in AutoDock 4.2.3 (grid box 40×40×40; LGA, 100 runs), and intermolecular interactions were analyzed using Discovery Studio Visualizer and PyMOL. Coformers were ranked based on binding energy and the count of hydrogen-bonding interactions.

Multicomponent Crystals Preparation

Sertraline multicomponent crystal were prepared using the solvent evaporation method. Sertraline and the conformer (1:1 stoichiometric) were dissolved in 10 mL methanol and allowed to evaporate by slow evaporation for up to 24 hours at 30 ^{o}C. The prepared solids were collected, dried, and placed in glass vials for further analysis (1).

Solubility Test

Equivalents of 50 mg of pure sertraline and multicomponent crystals were placed in a 10 mL container containing 0.1 N HCl. The container was stirred for 24 hours at 150 rpm at 37°C. The mixture was then filtered using Whatman filter paper (No. 42). The concentration of dissolved sertraline was determined using a spectrophotometer at a wavelength of 271 nm. The maximum absorbance was recorded, and the concentration was calculated to determine the solubility of sertraline in mg/10 mL. Drug concentrations were calculated from a calibration curve using the linear regression equation (y = bx + a), which exhibited a correlation coefficient (R) close to 1. This test was carried out in triplicate (18).

Dissolution Test

Equivalents of 50 mg of pure sertraline and multicomponent crystals were dissolution tested using a Type II apparatus, using 900 mL of 0.1 N

HCl. The test was performed at a rotation speed of 75 rpm and maintained at 37°±0.5°C. The sample was added to the medium, and 5 mL aliquots were withdrawn at predetermined intervals (5, 15, 30, 45, and 60 minutes), with the withdrawn volume replaced with fresh medium. The sample was then filtered and analyzed using a UV spectrophotometer at a wavelength of 271 nm. Drug concentrations were calculated from a calibration curve using the linear regression equation (y = bx + a), which exhibited a correlation coefficient (R) close to 1. This test was carried out in triplicate (18).

Power X-ray Diffraction (PXRD)

Samples of pure sertraline, coformers, and multicomponent crystals were finely ground using an agate mortar and pestle and prepared using the bulk powder method. The powders were packed into a static sample holder, pressed, and leveled to obtain a smooth sample surface before analysis. Powder X-ray diffraction (PXRD) patterns were recorded using an X'Pert PRO PW3040/x0 diffractometer (PANalytical B.V., The Netherlands) at room temperature with Cu-Kα radiation operated at 45 kV and 40 mA. Diffractograms were collected over a 2θ range of 5°–40° at a scanning rate of 1°/min. The diffraction patterns were compared to evaluate the crystallographic characteristics of pure sertraline, coformers, and multicomponent crystals, and the resulting data were processed using OriginPro software (21).

Differential Scanning Calorimetry (DSC)

Thermal analysis of multicomponent crystals and pure sertraline was conducted using differential scanning calorimetry. This analysis yielded thermograms for pure sertraline, coformers, and crystal multicomponent. The samples were placed in aluminum containers and subjected to testing at temperatures up to 300°C, with a heating rate of 10°C/min, under a nitrogen atmosphere at a flow rate of 40 mL/min (1).

Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) analysis was performed using an FTIR spectrometer equipped with an Attenuated Total Reflectance (ATR) accessory (Agilent Cary 630). Samples of pure sertraline, coformers, physical mixtures, and multicomponent crystals (approximately ±2 mg each) were placed directly onto the ATR crystal and compressed to ensure optimal contact with the crystal surface. Background spectra were collected before each measurement. Spectra were recorded over the wavenumber range of 4000–400 cm^{-1} (54).

Scanning Electron Microscopy (SEM)

The surface morphology of pure sertraline, coformers and multicomponent crystals was examined using a Scanning Electron Microscope (SEM; JEOL JSM-6360LA, JEOL Ltd., Tokyo, Japan). Samples were mounted on aluminum stubs using conductive carbon tape and sputter-coated with an Au–Pd layer (80:20) using a fine coater for 4 min, resulting in a coating thickness of approximately 20–40 nm. SEM observations were performed at an accelerating voltage of 15 kV under high-vacuum conditions, and micrographs were acquired at a magnification of 10,000×. The obtained images were used to compare the morphological characteristics of pure sertraline, coformers and multicomponent crystals, and the image data were processed and analyzed using OriginPro software (1).

Formulation and Evaluation of Sertraline Multicomponent Crystal Tablets

Formulation

Sertraline multicomponent crystal tablet preparation formulation using direct compression method.

Pre-Compression Evaluation

Pre-compression evaluation consists of flow properties (angle of repose and flow rate) and compressibility (51).

Flow Rate

Flow rate using a flow tester. A 30 gram sample of the mold mass is inserted into the funnel, observed based on the time required for the mold mass to flow (52).

Angle of Repose

The angle of repose was determined using the funnel method. A 15-gram sample of the molded mass was placed in the funnel, and the diameter was observed and measured using a vernier caliper, as well as the height of the molded mass

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Table 1. Formula of Sertraline Multicomponent Crystal Tablet

Composition	Formula % (mg)					
	F1	F2	F3	F4	F5	F6
Multicomponent Crystal of S-N	22.07 (61.80)	22.07 (61.80)	22.07 (61.80)	22.07 (61.80)	22.07 (61.80)	22.07 (61.80)
Sodium Starch Glycolate	5 (14)	5 (14)	4 (11.2)	4 (11.2)	6 (16.8)	5 (14)
Lactose	24.93 (69.80)	14.93 (41.8)	9.93 (27.8)	5.93 (16.6)	-	-
Avicel pH 102	40 (112)	50 (140)	56 (156.8)	60 (168)	60.93 (170.6)	61.93 (173.4)
Magnesium Stearat	3 (8.4)	3 (8.4)	3 (8.4)	3 (8.4)	3 (8.4)	3 (8.4)
Talc	5 (14)	5 (14)	5 (14)	5 (14)	8 (22.4)	8 (22.4)
Weight of Tablet	100 (280)	100 (280)	100 (280)	100 (280)	100 (280)	100 (280)

stack using a ruler to determine the angle of repose, calculated using the formula tan = height/radius of the stack (51).

Compressibility Index

Compressibility using a tapped density tester using the printed mass sample is inserted into the Nessler tube, the initial volume is observed, tapping is performed 250 times, the final volume is observed and the printed mass sample is weighed using an analytical balance, the results are recorded and the compressibility is calculated (45).

Post Compression Evaluation

Post compression evaluation looks at several parameters of tablet preparations such as weight uniformity test, tablet hardness test, tablet friability test, disintegration test, and dissolution tests.

Weight Uniformity Test

The weight uniformity test used 20 tablets, then the weight of the tablets was measured one by one using an analytical scale (49).

Tablet Hardness Test

Test the hardness of the tablet using a hardness tester YD-1 (LABOAO Instrument Equipment Co., Ltd., Zhengzhou, China) with 10 tablets selected at random and measure the hardness (kg/cm^2) of each tablet (53).

Tablet Friability Test

A total of 23 tablets were subjected to friability testing using a friability tester CS-2 (Faithful Instrument (Hebei) Co., Ltd., Hebei, China) for 4 minutes at a speed of 25 rpm (50).

Disintegration Test

Disintegration time test using a disintegration tester (Guoming, BJ-2, China) using water media at a temperature of 37±2^{o}C for 6 tablets (45).

Table 2. Evaluation of Precompression

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Formula	Evaluation of Precompression		
	Compresibility Indeks (%)	Angle of Repose (°)	Flow Rate (g/Second)
1	30.05	17.69	1.91
2	19.97	24.18	2.24
3	21.69	22.93	2.68
4	21.94	26.47	3.76
5	23.19	20.15	4.12
6	23.55	28.85	6.53

Table 3. Friability of Multicomponent Crystal Tablet of Formula VI

Test	I	II	III	Average±SD
Friability (%)	0.55	0.32	0.23	0.37±0.17

Table 4. Disintegration of Multicomponent Crystal Sertraline Tablet of Formula VI

Tablet	Replication			Average ±SD
	I	II	III	
1	5.5	5.46	5.46	5.47±0.02
2	5.5	5.46	5.46	
3	5.5	5.46	5.46	
4	5.5	5.46	5.46	
5	5.5	5.46	5.46	
6	5.5	5.46	5.46	

Dissolution Test

The dissolution test used Hanson Vision G2 Dissolution Tester (Hanson Research Corporation, Chatsworth, CA, USA) a Type II apparatus at 75 RPM for 30 minutes at 37±0.5°C with six multicomponent crystalline sertraline tablets in pH 4.5 acetate buffer. A five mL volume was filtered through Whatman No. 42 filter paper (45).

Results and Discussion

An in silico analysis was done to predict how sertraline molecules might interact with other molecules before testing in the lab. This method helps find pairs that can form stable crystals. The study looked at how candidate molecules interact with sertraline. It focused on non-covalent interactions like hydrogen bonds and π-π stacked interactions, which are important for forming crystals (22). This computer method has been effective in reducing trial-and-error when choosing molecules for crystals (23). These results suggest that in silico results can predict how sertraline crystals form with other molecules and provide a strong base for lab experiments.

Sertraline is predicted to interact strongly with carboxylic acid groups, amino acids, and imide groups in forming stable heterosynthons. This aligns with the supramolecular synthon approach in the design of multicomponent crystals, wherein coformers are selected based on hydrogen bonds (23).

Twenty-nine candidate coformers were analyzed in silico, 26 of them are anticipated to form hydrogen bonds, and 13 are expected to form π-π stacked interactions. Based on the binding energy values, the three most promising coformers were identified as L-Tryptophan, Saccharin, and Nicotinic Acid, each exhibiting the lowest binding energy values, indicative of high affinity for Sertraline. The results of the interaction between sertraline and the coformers

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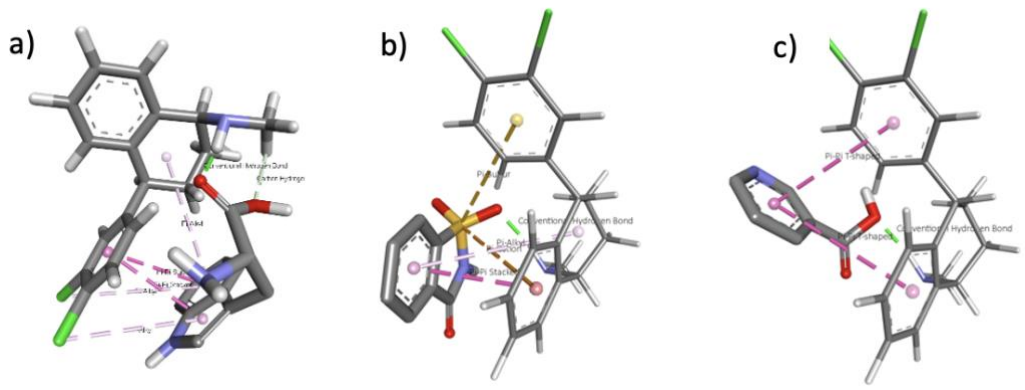

Figure 1. Interaction of Sertraline with Coformer, a) Sertraline - L-Tryptophan (S-L), b) Sertraline – Saccharin (S-S), c) Sertraline – Nicotinic Acid (S-N)

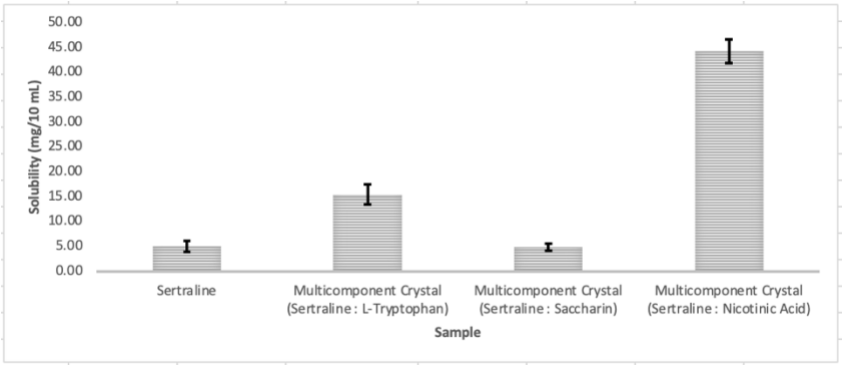

Figure 2. Solubility of Pure Sertraline and Multicomponent Crystal Sertraline

L-Tryptophan, saccharin, and nicotinic acid are illustrated in **Figure 1**.

L-Tryptophan showed a binding energy of -3.28 kcal/mol, meaning it forms a stable complex. It formed one hydrogen bond with Sertraline and had two π-π stacked interactions. Saccharin has a binding energy of -3.30 kcal/mol. In the study, a hydrogen bond was found between sertraline and saccharin, along with π-π stacking interactions. Sertraline and nicotinic acid also formed a complex with a binding energy of -3.29 kcal/mol, with a hydrogen bond between sertraline and nicotinic acid. The low bonding energies of these three coformers mean they have strong attractions, thus indicating a greater possibility of multicomponent crystals forming. Therefore, L-tryptophan, saccharin, and nicotinic acid are good candidates for making multicomponent crystal of sertraline systems to improve properties like solubility and dissolution.

The solubility test results in **Figure 2** show the differences between pure sertraline and multicomponent crystal systems. Pure sertraline dissolved at about 5.05 mg in 10 mL of HCl 0.1 N (0.505 mg/mL). The sertraline multicomponent crystal with nicotinic acid (S-N) had much higher solubility. The S-N crystal reached the highest solubility, at 44.29 mg/10 mL (4.43 mg/mL), which is 8.8 fold more than pure sertraline. The sertraline–L-tryptophan (S-L) crystal also increased solubility to 15.44 mg/10 mL (1.54 mg/mL), about 3.1 fold that of pure sertraline. The sertraline–saccharin (S-S) system did not improve as much as the other two. The solubility of S-S was only slightly higher than pure sertraline, but much lower than S-N and S-L. The big increase in solubility in multicomponent crystals, especially with nicotinic acid, shows that these crystals can change the crystal structure and improve the solubility of drugs with low solubility (24). Sertraline, as a weak base, can form specific non-covalent interactions with coformers, leading to crystals with lower lattice energy or bonding patterns that are more easily hydrated by the solvent. The DSC thermogram shows a single, distinct, and lower melting point for S-N compared to pure sertraline or nicotinic

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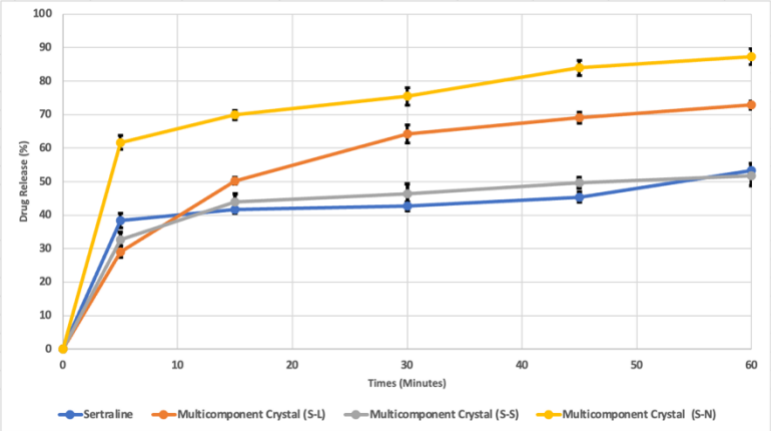

Figure 3. Dissolution of Pure Sertraline and Multicomponent Crystal Sertraline

acid, suggesting a new crystal phase with different thermal stability (25).

Changes in PXRD patterns of the multicomponent crystals show new diffraction peaks that are not present in pure sertraline or the coformer. These results indicate the formation of a new crystal structure rather than a simple physical mixture. These changes in physical properties match what Ghosh et al. (2020) found. They reported that modafinil–nicotinic acid cocrystals had different melting points and XRD patterns (25). These results show that the better solubility of S-N is due to a new solid phase with different molecular interactions.

The dissolution profiles of the four samples align with the solubility results. Pure sertraline dissolves about 52% in HCl 0.1 N in 60 minutes. The S-N multicomponent crystal dissolves the most, with over 88% in 60 minutes. S-L dissolves about 73% in 60 minutes, and S-S releases 53% of the drug. This shows that S-N can release almost 1.7 fold more drug than pure sertraline in one hour, while S-L releases 1.4 fold. This is important for medicine because it means the drug dissolves faster and more of it is available, which can improve how well oral drugs work.

The SEM results show that S-N has a different shape and smaller size compared to pure sertraline. This smaller size increases the surface area, helping the particles mix better with the liquid, which speeds up how fast they dissolve. Nicotinic acid, which is hydrophilic, enhances liquid adhesion to the particle surface compared with pure sertraline, which exhibits poor water solubility. This creates a stronger concentration difference around the S-N particles, allowing the drug to spread into the liquid faster. A study on modafinil–nicotinic acid cocrystals showed that all the modafinil dissolved in 30 minutes, much faster than pure modafinil, which only dissolved 30%. Adding water-loving polymers can keep the solution stable for longer (25).

FTIR analysis was conducted to assess the formation of multicomponent sertraline crystals with L-tryptophan, saccharin, and nicotinic acid. A comparison of the FTIR spectra of each multicomponent crystal with those of pure sertraline and pure coformer revealed changes in the characteristic peaks of the main functional groups. The shift in wavenumbers for the –OH, –NH, and C=O bands indicates the formation of new interactions, particularly hydrogen bonding between sertraline and the coformer molecules within the resulting multicomponent crystal structure (26).

Figure 4a shows the spectrum of the S-L multicomponent crystal. The N–H or O–H band at 3399 cm^{-1} is wider and sharper than in pure L-Tryptophan. This suggests a hydrogen bond forms between L-tryptophan and sertraline. A broader or slightly lower frequency in the donor hydrogen bond band often means a cocrystal or salt-cocrystal forms. The wavenumber at 1654 cm^{-1} in S-L changes in intensity and pattern compared to L-tryptophan. The COO^- band at 1576–1408 cm^{-1} also shifts. Small changes of ≤10–20 cm^{-1} suggest the carboxylic acid group forms a heterosynthon with sertraline in the cocrystal lattice. The broadening at 3399 cm^{-1} (N–H or O–H), changes in the C=O or COO^- bands at 1654 and 1576–1408 cm^{-1}, and a new pattern

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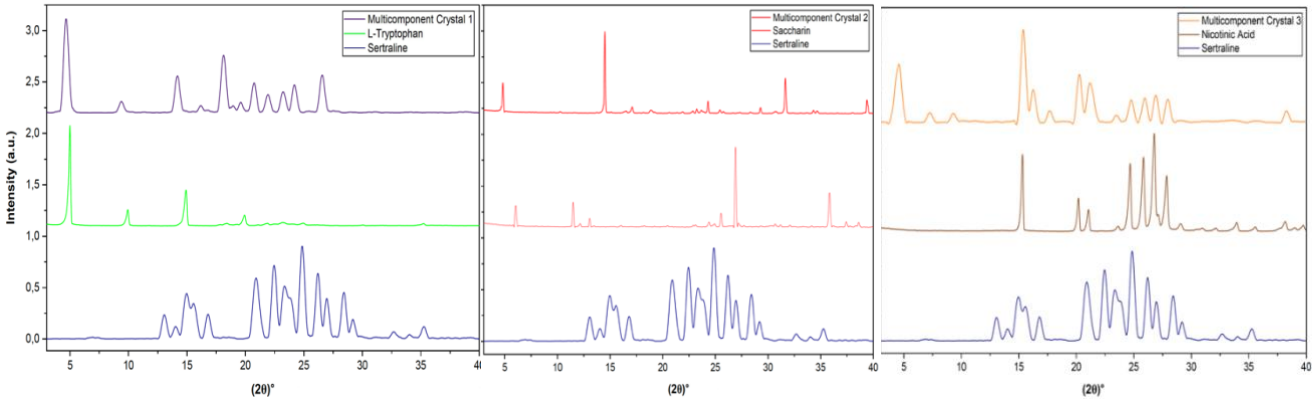

Figure 4. Spectrum FTIR a) Sertraline-L-Tryptophan (S-L), L-Tryptophan, Sertraline; b) Sertraline-Sakarin (S-S), Saccharin, and sertraline; c) Sertraline-Asam Nikotinat (S-N), Nicotinic Acid, and sertraline

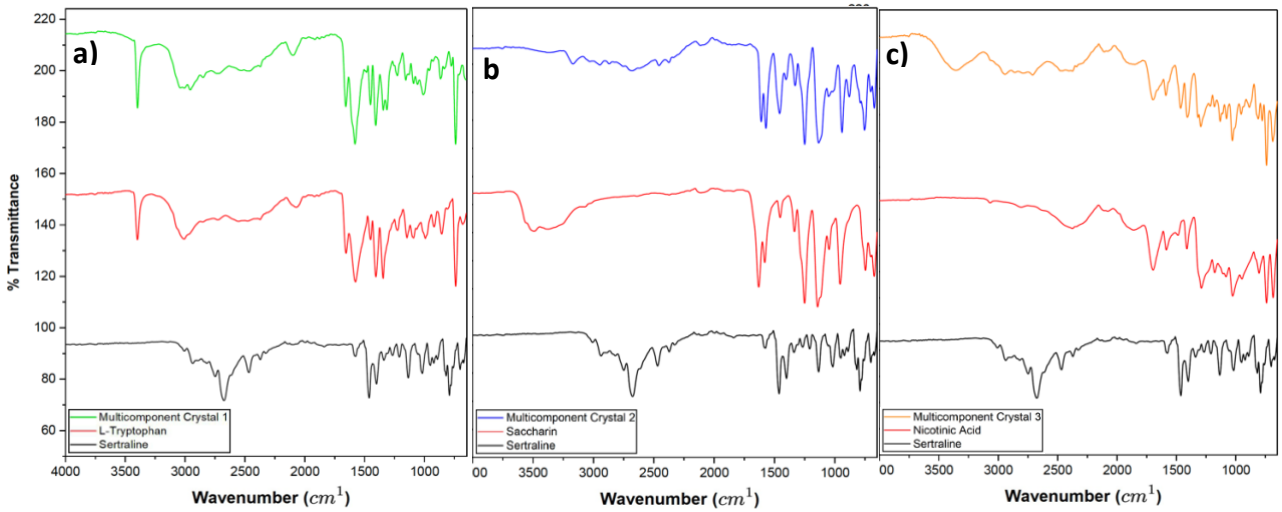

Figure 5. Thermogram DSC a) Sertraline-L-Tryptophan (S-L), L-Tryptophan, Sertraline; b) Sertraline-Sakarin (S-S), Saccharin, and sertraline; c) Sertraline-Asam Nikotinat (S-N), Nicotinic Acid, and sertraline

show sertraline and L-Tryptophan are arranged in a multicomponent crystal lattice through hydrogen bonds. **Figure 4b** shows the S-S multicomponent crystal. The N–H band of saccharin becomes broader, and the S=O band changes at 1455–1334 cm^{-1} and 1116 cm^{-1}. This indicates the N–H group and $O=SO_2$ in saccharin are involved in hydrogen bonding. This shift in the donor–acceptor band often means a cocrystal forms. Sertraline, a secondary amine, shows a weak N–H stretching vibration between 3000–3300 cm^{-1}. In the S-S crystal spectrum, this band is broad and less intense, suggesting hydrogen bonding involving N–H. The weakening of saccharin's N–H, changes in the S=O bands at 1457–1334 and 1140–1116 cm^{-1}, a band at 1612–1574 cm^{-1} in the S-S spectrum, and sertraline's N–H at 3000–3300 cm^{-1} all indicate a new multicomponent crystal phase forms, stabilized by hydrogen bonds.

In **Figure 4c**, the spectrum of nicotinic acid shows an O–H band at 3608 cm^{-1}. In the S-N crystal, this band moves to 3358 cm^{-1} and becomes wider. This change means hydrogen bonds form, with O–H donating to sertraline's nitrogen. The lower frequency and wider band show new hydrogen bonds in the cocrystal (27,28). In **Figure 4c**, the C=O band of nicotinic acid is around 1697–1700 cm^{-1}. In the S-N crystal, it stays at 1699–1695 cm^{-1}, meaning no full proton transfer happens, so a neutral cocrystal forms, not a salt (27,29). In **Figure 4c**, the S-N crystal shows new band patterns at 1464, 1411, 1295, and 1028 cm^{-1}, suggesting a new lattice structure (27–30). Sertraline has a weak N–H

band around 3007 cm^{-1}. In the S-N crystal, the N–H or O–H bands get wider because sertraline's nitrogen bonds with nicotinic acid's O–H (O–H···N) (27–29).

Figure 5 presents the DSC thermogram, which indicates the formation of three distinct sertraline multicomponent crystals, as evidenced by a single or new melting peak that does not align with the peaks of pure sertraline or the coformer. Sertraline has a melting point of 245-246 °C. The DSC testing results show sertraline's melting point at 245.94 °C, marked by an endothermic peak, indicating the presence of sertraline in the sample. The DSC thermogram of the Sertraline–L-Tryptophan (S-L) multicomponent crystal exhibited two thermal events at 258.16 °C and 278.95 °C, which were distinct from the thermal profiles of pure sertraline and L-tryptophan. The disappearance of the characteristic melting peaks of the parent compounds and the emergence of new thermal events suggest the formation of a new crystalline phase resulting from intermolecular interactions between sertraline and L-tryptophan, potentially involving hydrogen-bond formation. However, the presence of two distinct thermal events indicates that the thermal behavior of the S-L system may be more complex than that of a single homogeneous crystalline phase. These events may be associated with solid-state phase transitions, polymorphic transformations, partial decomposition, or residual crystalline domains. Therefore, the DSC data alone are insufficient to conclusively attribute these peaks solely to cocrystal formation. Nevertheless, when interpreted in conjunction with the FTIR and PXRD results, which revealed changes in intermolecular interactions and the appearance of new diffraction peaks, the DSC findings provide supporting evidence for the formation of a new multicomponent crystalline phase (31,32).

The DSC thermogram of the Sertraline–Saccharin (S-S) multicomponent crystal exhibited several thermal transitions at 93.70, 150.77, 167.00, and 186.92 °C, followed by a major endothermic event at 280.82 °C. These thermal events differed from those of the parent compounds, suggesting the formation of a new crystalline phase through intermolecular interactions between sertraline and saccharin. The high-temperature endothermic peak indicates enhanced thermal stability and stronger intermolecular interactions, which may be attributed to hydrogen bonding involving the saccharin sulfonimide group (33). However, the presence of multiple thermal events suggests a complex thermal behavior that may involve phase transitions, polymorphism, or partial decomposition. Therefore, DSC data alone are insufficient to conclusively establish cocrystal formation. Nevertheless, when considered together with the FTIR and PXRD results, the DSC findings provide supporting evidence for the formation of a new multicomponent crystalline phase. The higher melting temperature of the S-S crystal may also contribute to its lower solubility compared with the S-L and S-N systems due to increased crystal lattice stability (32).

The S-N thermogram in **Figure 5c** shows mild changes at 93.75, 177.49, and 189.13 °C, followed by strong peaks at about 242.02 and 256.25 °C. The S-N crystal melts at 242.02 °C. This is lower than S-L and S-S, leading to better solubility and dissolution rate.

In **Figure 6**, sertraline exhibits characteristic peaks at 2θ angles of 6.582°, 13.055°, 20.996°, 24.853°, 27.585°, and 31.885°. Notably, some of these peaks are absent or shifted in S-L, with the peaks at 6.582° and 13.055° not appearing. S-L displays distinct sharp peaks at 2θ angles of 4.674°, 9.404°, 14.177°, 18.193°, 22.632°, 24.853°, 28.998°, and 33.817°.

In **Figure 6a**, the absence of the peak at 4.674° in either component suggests the formation of hydrogen bonds within the crystal lattice of S-L. The peaks at 22.632°, 24.853°, and 28.998° represent new fingerprints distinct from sertraline. The emergence of new peaks, along with the disappearance or shifting of peaks from each component, serves as a primary criterion for identifying cocrystal formation. On a supramolecular level, these findings indicate the formation of a heterosynthon hydrogen-bonding system between donors or acceptors (N–H or O–H···N or O) of sertraline–L-tryptophan within the crystal lattice (34,35).

In **Figure 6b**, the S-S PXRD pattern reveals new peaks that are not identical to those of pure sertraline or pure saccharin. Peaks in the S-S

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appear at 2θ angles of 4.87°, 10.20°, 14.60°, 18.52°, 21.94°, 25.83°, 31.65°, 33.93–33.98°, and 39.39°. In the S-S diffractogram, there is a disappearance or shifting of peaks and the appearance of new peaks, particularly at angles 4.87°, 10.20°, and 14.60°, which are absent in sertraline. The appearance of new peaks, along with the disappearance or shifting of other peaks, is also a criterion indicating the formation of a new multicomponent crystal lattice distinct from sertraline (36). The disappearance or shifting of characteristic peaks from both components and the emergence of new peaks at 4.59°, 5.42°, and 7.24° suggest different unit cells and a new molecular packing due to the formation of a heterosynthon hydrogen bond O–H···N between saccharin (donor) and sertraline (acceptor).

In **Figure 6c**, the S-N multicomponent crystal produces new peaks at 2θ angles of 4.59°, 5.42°, 7.24°, 10.71°, 14.60°, 16.25°, 21.46°, 24.69°, 28.33°, and 33.42°. Conversely, the strong peaks in nicotinic acid at 15.316° and in sertraline at 24.853°, 27.56°, and 31.89° do not appear in the S-N pattern. These changes indicate a new crystal phase, not a physical mixture (30). Nicotinic acid shows strong peaks at 15.316°, 20.20°, 21.05°, 25.89°, 27.62°, 31.47°, and 33.88°. In the cocrystal, these peaks shift or disappear.

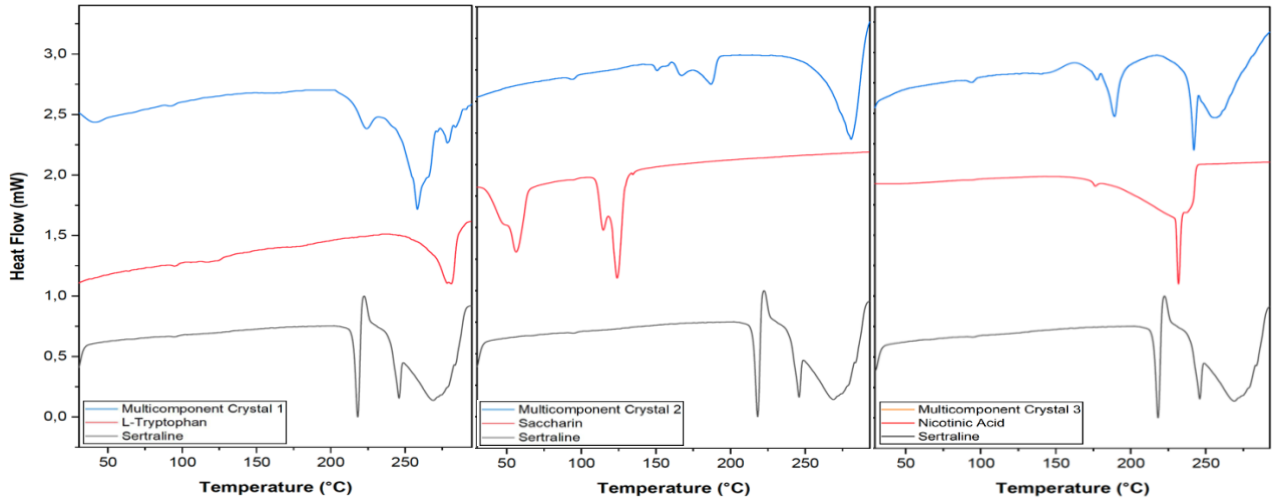

Figure 6. Diffractogram PXRD a) Sertraline-L-Tryptophan (S-L), L-Tryptophan, Sertraline; b) Sertraline-Sakarin (S-S), Saccharin, and sertraline ; c) Sertraline-Asam Nikotinat (S-N), Nicotinic Acid, and sertraline

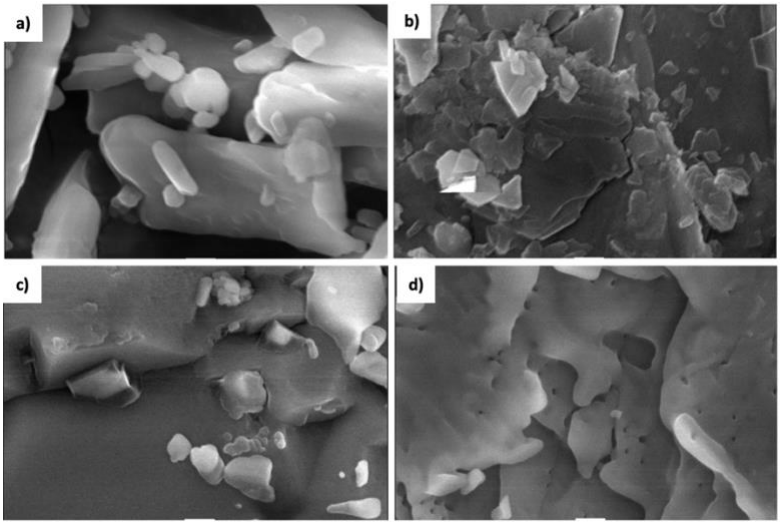

Figure 7. Morfologi SEM a) Pure Sertraline; b) Sertraline-L-Tryptophan (S-L) ; c) Sertraline-Sakarin (S-S) ; d) Sertraline-Asam Nikotinat (S-N)

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Figure 7a shows that pure sertraline has large, flat crystals with smooth surfaces and rounded edges. There are also small crystals attached to these surfaces. This shape is typical for sertraline, which usually forms in layers. **Figure 7b** shows a different crystal, called S-L, where the particles have changed into polygonal shapes with sharp edges and rough surfaces. This is different from the usual sertraline shape. In S-L, there are also groups of stacked flakes. The change from smooth to angular shapes suggests new growth patterns due to hydrogen bonds between sertraline and L-tryptophan. This is supported by PXRD, which shows new peaks, and DSC, which shows different heat patterns (6,27,29). **Figure 7c** shows the S-S crystal, which has smaller blocky shapes on a plate-like base with a more textured surface than pure sertraline. These blocky shapes have clear edges, showing a different growth pattern. This shape is typical for saccharin-based systems, where the sulfonyl oxygen forms strong bonds with N–H, changing the crystal growth and resulting in a unique shape for cocrystals (27,29). **Figure 7d** shows the S-N crystal, which is denser with a wavy surface and small pits. It also has long crystals within the mass. These features suggest that the crystals grow together differently than sertraline or nicotinic acid alone. The differences in shape between these crystals and pure sertraline show changes in the crystal structure and surface energy due to specific interactions in the cocrystal (6,27,29).

The study looked at how well six sertraline tablet formulas flowed and compressed. It found differences between them. Formulas that compressed less, had smaller angles of repose, and flowed faster were better for making tablets. Formula 6 was the best because it met all these criteria. It had a compressibility of 23.55%, which is "passable". Its angle of repose was 28.85°, making it a "Excellent". Formula 6 also had the best flow rate, meaning it moved through a funnel faster than the others. Flow rates are measured by how much powder passes through a funnel in a set time. Powders with a flow rate over 10 g/second are "Excellent," 4–10 g/second are "Good," 1.6-4 g/second are Poor and below 1.6 g/second are "Very Poor." Formula 6 is "Good". Differences in flow rates can affect tablet production. Low flow rates can cause powder build-up and uneven filling, leading to weight and ingredient inconsistencies. High flow rates, like in Formula 6, ensure smooth flow and even filling.

In the friability test, the tablets started with a weight between 6,564 and 6,585 mg. After the test, their weight was between 6,528 and 6,570 mg. This indicates that they lost 0.37% of their weight, with a Standard Deviation (SD) of 0.17%. According to the pharmacopeia (USP <1216>), tablets pass the test if they lose 1.0% or less of their weight after 100 rotations in the friabilator, and none are broken or badly cracked. Formula 6 shows great strength during later stages like coating, packaging, and shipping. In Formula 6, the proportion of Avicel pH 102 as a filler-binder undergoes plastic deformation, with the absence of lactose. Avicel pH 102 contributes to a robust, dense network through plastic deformation and the formation of extensive interfacial bonds during compression, thereby reducing friability and enhancing the abrasion resistance of the tablets during testing (37).

The weight uniformity test for Formula 6 was done on 20 tablets, repeated three times. The average weights were 287.67 mg ± 0.50, 282 mg ± 1.45, and 283 mg ± 2.19. All tests met the USP limits. According to USP <2091>, for tablets weighing 130–324 mg, no more than two tablets can be off by more than 7.5% from the average, and none can be off by more than 15%. In this test, the biggest difference from the average was about ±2 mg (±0.7%), so all tests passed the weight uniformity rules. The good weight uniformity in F6 is due to three main reasons. First, the blend flows and compacts well because it contains Avicel pH 102 (61.93%), which helps the powder fill the tablet mold evenly (38). Second, using enough magnesium stearate (3%) helps the tablets come out of the mold easily, preventing weight loss (39). Third, adding the right amount of talc helps keep the weight uniform.

The hardness test of F6 tablets showed an average hardness of 6.66 kg/cm^2, with individual tablets ranging from 6.5 to 8.3 kg/cm^2. This indicates that the tablets are very consistent. While hardness is not a regulatory requirement, it is important for the manufacturing process because it relates to how easily the tablets break.

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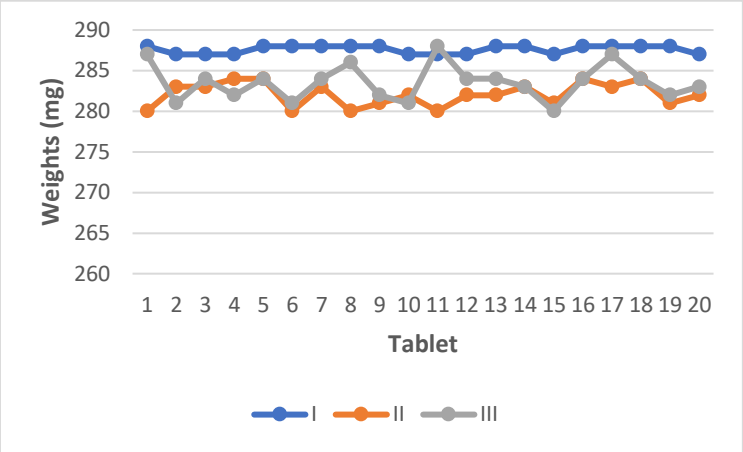

Figure 8. Weight of Variation of Multicomponent Crystal Sertraline Tablet of Formula VI

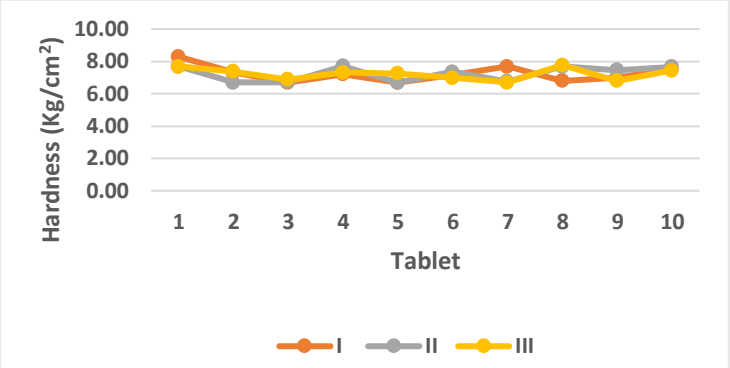

Figure 9. Hardness of Multicomponent Crystal Sertraline Tablet of Formula VI

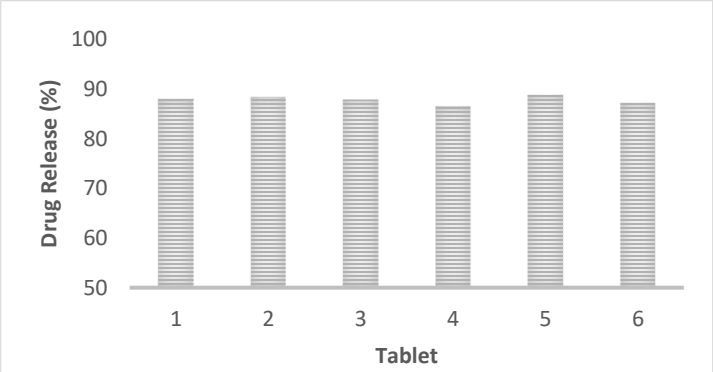

Figure 10. Dissolution of Multicomponent Crystal Sertraline Tablet of Formula VI

The hardness of F6 matches its ingredients. Avicel pH 102 makes up 61.93% of the tablets and acts as a binder-filler. It helps the tablets hold together well and stay strong without affecting how they dissolve. Avicel pH 102 is good for direct compression, which helps make strong and stable tablets (40).

The disintegration test of F6, which includes 5% Sodium Starch Glycolate (SSG), shows how SSG helps break down tablets quickly. SSG swells fast, letting water into the tablet, which helps it break into small pieces (41). Avicel pH 102 also helps by making the tablet porous, allowing water to flow through easily, which boosts SSG's effect (42,43). The right tablet hardness makes it easy to handle and store but still lets water in. Magnesium stearate, used at 3%, is controlled well, so it doesn't make the tablet water-resistant. Too much magnesium stearate can slow down

disintegration, but this doesn't happen in F6 (44). Adding active ingredients with a multicomponent crystal system improves how the tablet absorbs water and breaks down. This indicates that cocrystals have lower surface tension and break apart faster than their pure form (Karagianni et al., 2018). From a pharmaceutical perspective, a very rapid disintegration time (5–6 seconds) leads to an accelerated dissolution onset, which is associated with the capacity of multicomponent crystals to improve solubility and dissolution. The minimal variability in disintegration time across replications suggests effective mixing and compression in F6, indicating that this formulation holds promise for scale-up with relatively low batch-to-batch variation.

The dissolution test on six tablets from formulation F6 showed average dissolution rates of 87.95%, 88.33%, 87.73%, 86.45%, 88.78%, and 87.05%. Each tablet dissolved more than 85% during the test. This meets the Indonesian Pharmacopoeia VI standards for immediate-release tablets (45). Formulation F6 uses 5% Sodium Starch Glycolate (SSG) to help the tablet break down quickly. SSG helps water get into the tablet and makes it swell, which helps it dissolve faster (46). Another ingredient, Avicel pH 102, makes the tablet more porous, allowing liquid to enter quickly and aid swelling (47). The active ingredient in the tablet also helps it dissolve faster by reducing energy and improving how it mixes with water compared to pure sertraline crystals (48).

Conclusion

The modification of Sertraline through multicomponent crystal techniques can enhance its solubility and dissolution properties by utilizing L-Tryptophan and Nicotinic Acid as coformers. The formation of a new solid phase was supported by FTIR, PXRD, DSC, and SEM analyses. Among the prepared multicomponent crystals, the Sertraline–Nicotinic Acid (S-N) system demonstrated the greatest improvement in physicochemical performance, increasing solubility by 8.8-fold relative to pure sertraline and achieving drug release exceeding 88% within 60 min. Evaluations of the physical tablets indicated that all tests conformed to the requirements for both pre-compression and post-compression assessments, including weight uniformity, hardness, friability, disintegration time, and dissolution.

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Conflict of Interest

The author has no conflicts of interest in this article.

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