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The Dynamic Study of Cocrystal Formation between Anhydrous and Monohydrate Theophylline with Sodium Saccharine Dihydrate by FTIR

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Abstract

Anhydrous theophylline and sodium saccharin have been reported can form co-crystals with many compounds as well as anhydrous theophylline and saccharin base co-crystal, but co-crystallization between teophylline monohydrate (TM) and sodium saccharin dihydrate (NSD) and its co-crystallization dynamics has not been reported yet. Usually the dynamics of the co-crystal formation was studied using PXRD and DSC. In this research FTIR instrument was tried to used. TM, TA, NSD, and the physical mixture of TM-NSD and TA-NSD were characterized by Karl Fischer titration, polarized microscopy, electrothermal, differential thermal analysis (DTA), powder X-ray diffraction (PXRD), and fourier-transform infrared spectroscopy (FTIR). To investigate the co-crystallization dynamics, a serie of physical mixtures of TM-NSD and TA-NSD were ball milled to induce co-crystal formation, in a serie of speeds and were sampled periodically along 60 minutes milling. Then these milled mixtures was analyzed by FTIR, confirmed by DTA and PXRD. Thermal contact method and phase diagram from electrothermal data early indicated the formation of co-crystals either on TM-NSD or TA-NSD. DTA thermograms of both mixture indicated the melting point of co-crystals at 121^{o}C, then the diffractograms showed a new similar crystal phase from TM-NSD and TA-NSD after milling, differ from their physical mixtures. FTIR analysis showed the spectra N-H streching shift of 3124.12 cm^{-1} (TM-NSD) and 3127.97 cm^{-1}(TA-NSD) to 3131.83 cm^{-1} after ball milling; that occured faster with the increasing of speed. TM or TA can produces a similar co-crystal after milling with NSD, proved that there are no effect of their hydrate on theophylline-saccharin co-crystallization. Then, FTIR was proved can be used to study the dynamics these co-crystals formation and showed that TM-NSD needs more energy than TA-NSD to release theophylline hydrate.

Keywords: Ball milling, Cocrystal, FTIR, Natrium saccharin dihydrate (NSD), Anhydrous theophylline (TA), Theophylline monohydrate (TM)

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Cocrystal is lattice arrangement composed of two or more components in stoichiometric compounds. Co-crystal can be composed of either atomic, molecular or ionic compound [1]. Co-crystallization has been become a development option pharmaceutical raw materials in order to get the desired physicochemical properties, such as solubility, physical stability, bioavailability, flowability and compressibility of an active compound without altering its biological activity.

Some ways of co-crystallization has been reported, such as the crystallization solution, evaporation, co-grinding, grinding with the addition of co-solvents, crystallization result of condensation, crystallization with ultrasonic, and thermal-induced crystallization [2,3,4]. Cocrystals can be evaluated by solid analysis instrument: X-ray diffractometry, thermal analysis, and polarization microscope, raman spectrophotometry, etc. [5,6,7].

It has been reported the formation of theophylline co-crystal with other compounds such as glutaric acid, oxalic acid[8] , p-hydroxybenzoic acid[9], nicotinamide[10], and saccharin[11]. Sodium saccharin has been reported to form co-crystals with quinine, haloperidol, mirtazapine, pseudoephedrine, lamifudin, risperidone, sertraline, venlafaxine, zolpidem, and amlodipine[12]. But not yet reported the formation of co-crystals of theophylline-sodium saccharin. Sodium saccharin is often used as an excipient in pharmaceutical preparations so it is very possible that a change in physical properties of the active substances in industrial processes that use excipients sodium saccharin, so that changes in the mechanical character of the mixture needs to be studied.

This research aims to study the dynamics of co-crystal formation between theophylline anhydrous (TA) - sodium saccharin dihydrate (NSD) and theophylline monohydrate (TM) - sodium saccharin dihydrate (NSD) with the co-crystallization method using ball milling and characterization of co-crystals with by observing the spectral shift of the NH strain FTIR spectrogram. Hot contact methods with the polarizing microscope, and the making of a phase diagram can be used for the early characterization study whether a combination of the two compounds can form co-crystals [13,14].

Synthone type that has been reported in co-crystals of sodium saccharin is OH --- N (-), NH --- N (-), NH --- O, NH --- O, OH --- O, NH- --N (Banerjee, 2005).

Theophylline has an amine group that can donate a proton to a hydrogen-bonded, and sodium saccharin has a group N (-) which is a good proton acceptor, so the co-crystal of theophylline-sodium saccharin formed synthone NH --- N (-).

Co-crystallized with the co-grinding method has the advantage of not using toxic solvents[15]. Co-grinding method can also cause water to hydrate the NSD out of the crystal structure [16], in this process NSD loses water hydrates so that the crystal structure changes and the easier it is to form the co-crystals with theophylline.

In organic solids, molecules fused together by intermolecular bonding, such as hydrogen bonds that restrict the mobility of a molecule. Molecules in a solid compound creates a unit called "supra-molecule". Crystal lattice structure of solids is influenced by influenced by the size, shape and functional group of the compound. Today has been to improve the physicochemical properties of a solid with a strategy based on the principles of crystal engineering, which involves understanding the properties of compounds that determine the arrangement of molecules in a solid. It is necessary to design a solid lattice in a rational and applicable to development solid organic compounds.

Anhydrous theophylline has the chemical name of 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione with the molecular structure as shown in Figure 1.A.

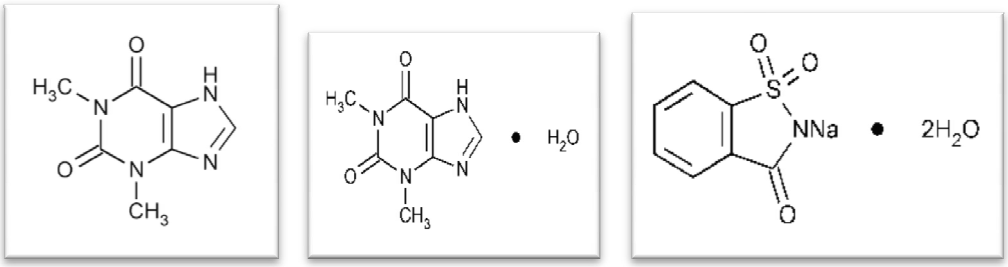


Figure 1: Molecular structure of : A. Anhydrous theophylline[17]; B. Theophylline hydrate [17] C; Sodium saccharin dihydrate[18]

The molecular formula of anhydrous theophylline is $C_7H_8N_4O_2$ with a molecular weight of 180.17 g/mol.

Organoleptic properties of theophylline anhydrous is a white, odorless, crystalline powder, and has a bitter taste. Melting point theophylline ranging from 270°C to 274°C. Theophylline is indicated for patients with asthma or COPD (chronic obstructive pulmonary disease), and used as diuretics, muscle relaxants, and cardiac stimulant. Theophylline from nature can be found in cocoa beans [17].

Theophylline monohydrate has the chemical name of 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione monohydrate with the molecular structure described in Figure 1.B. Theophylline monohydrate is pseudopolimorph or hydratomorph of theophylline. Theophylline monohydrate molecular weight is 198.18 g/mol. Organoleptic properties of theophylline anhydrous is a white powder, odorless, and has a bitter taste. Theophylline monohydrate melting point ranging from 270°C to 274°C and has biological activity similar to theophylline anhydrous [17].

Sodium saccharin dihydrate (Figure 3) has the chemical name 1,2-Benzisothiazol-3- (2H) -one-1,1-dioxide dihydrate with the formula C_7H_4 $NNaO_3$ $S.2H_2O$ and molecular weight 241.19 g / mol. Sodium saccharin dihydrate has the organoleptic properties of white crystalline powder, odorless or slightly aromatic and has a very sweet flavor with a bitter aftertaste. Melting point of sodium saccharin dihydrate is more than 300°C. In the pharmaceutical industry, sodium saccharin dihydrate is used as a sweetener [18].

Co-crystallization into a development option pharmaceutical raw materials in order to get the desired physicochemical properties, such as solubility, physical stability, bioavailability, flowability and compressibility of a compound drug without altering its biological activity. Some ways of co-crystallization has been reported, such as the crystallization solution, evaporation, co-grinding, grinding with the addition of co-solvents, crystallization result of condensation, crystallization ultrasonic, and thermal-induced crystallization.

Co-grinding method is not a new method for the formation of co-crystals, were first reported in the late 19th century In this method, the co-crystal is made by crushing or grinding of two different compounds together with a machine or by hand. Co-crystals are made by this method have been reported as co-crystals of caffeine - monocarboxylic acids.

Infrared spectrophotometry is an analytical method based on the absorption of electromagnetic radiation that lies between 1-1000 lm. Infrared spectrophotometry is the most common technique used to identify a compound. Spectrophotometric spectra in this area is divided into three areas, namely near infrared (1-2.5 m), mid infamerah (2.5 to 50 m), and the far infrared (> 25 m). Wavelengths used for identification is an area where there is a mid-infrared region of functional groups and the fingerprint region (fingerprint). The advantages of this method in addition to not destructive, it can also use a relatively small sample size, rapid analysis time, at a cost much cheaper than thermal (TG/DTA/ DSC) and PXRD analisisis method. Moreover, empirically FTIR as a method of co-crystalline solids analysis still has not been developed, so it deserves to be scrutinized. In this experiment, FTIR expected able to detect a shift from a functional group such as the formation of co-crystals of two different compounds which are affected by intermolecular hydrogen bonds are formed, resulting in FTIR spectra that will be visible as shifting of the peak of functional groups involved in the hydrogen bond formation.

Materials and Methods

Theophylline monohydrate powder, theophylline anhydrous, sodium saccharin dihydrate, anhydrous theophylline physics mixture - sodium saccharin dihydrate (TA-NSD) and theophylline monohydrate - sodium saccharin dihydrate (TM-NSD) = 1: 1.66; and the mixture after ball milling at-each characterized using polarizing microscopy, Fourier-Transform Infrared Spectroscopy (FTIR), Differential Thermal Analysis (DTA), powder X-ray diffraction (PXRD), and Karl Fischer titration. The initial orientation of co-crystal formation was done with Kofler's hot contact method using a polarization microscope and arranged the phase diagram based on melting temperature data collected from experiment by Electrothermal 9100. Dynamics of co-crystal formation was observed through experiments using a ball milling of the mixture in the ratio 1: 1.66. The ball milling speeds setted to 45, 75, and 105 rpm and samples sampling performed at minute 0, 10, 20, 30, 40, 50, and 60. Further characterization of solids to observe the formation of co-crystals with FTIR. Furthermore, to confirm the formation of co-crystals, PXRD and DTA analysis were done on a sample of sampling ball milling 105 rpm for 60 minutes of mixtures of anhydrous theophylline - sodium saccharin dihydrate (TA-NSD) and theophylline monohydrate - sodium saccharin dihydrate (TM-NSD).

Characterization of Raw Materials

Raw materials were characterized using analytical instruments solids: FTIR, DTA, and PXRD, and the determination of water content by Karl Fischer titration.

Identification by FTIR

Identification by FTIR spectroscopy performed with a sample preparation technique KBr plates. Plates are made by trituration sample with a spectral grade KBr in the ratio 1: 100 w/w. In experiments conducted with the weighing Meeler Toledo AG104 analytical balance to 100 mg of dry KBr (which has been stored in the oven 100°C) with 1 mg of the sample, and then slowly crushed by agate mortar until homogeneous and then the mixture of sample and KBr discs filled into the mold of stainless steel size of ± 13 mm. discs containing sample was then compressed with a hydraulic press pressure ± $7.5x10^{-3}$ mm Hg. The disc is then mounted on a holder, then the spectrum measured at wave numbers 4000-400 cm^{-1}. Measurement assisted with software Jasco Spectra Manager II output, which is already in the Jasco FTIR-4200 instrument. Before analyzing the samples, measurement of the background to see the influence of environmental conditions and tools. Identification by FTIR is used to confirm the identity of the compound, and also to see the shifts in the FTIR spectra during the ball milling process.

Differential Thermal Analysis

The analysis is done by using DTA: approximately 5-10 mg of sample is stored in a special aluminum cup for the preparation of the DTA. Subsequently, the sample was heated under a nitrogen gas flow with heating rate of 10°C/min, from 30°C to 350°C.

PXRD Analysis

PXRD analysis was done by using a 200 mg sample was prepared on a sample plate to test X-ray powder diffraction. Type diffractometer: PW 1710 BASED; tube anode: Cu; voltage 40 kV, current of 30 mA, 0.2 inches wide split. Data were collected at a scan speed of 0.8 seconds per step with the scanning distance at $2\theta = 5^{o}$ to 45^{o}.

Analysis of Total Hydrate Using Karl Fischer Titration

A total of 50.0 mg of sample was weighed, and the water content determined by Karl Fischer titration apparatus METLER Toledo Titrator V20, using the Karl Fischer reagent standardized.

Early Orientation Co-crystal Formation Theophylline - Sodium Saccharin dihydrate. The formation of co-crystals of theophylline with sodium saccharin dihydrate were identified by three methods: Koflers's Hot Contact Method, the manufacturing phase diagrams, and physical mixture DTA analysis.

Kofler's Hot Contact Method

A little sodium saccharin dihirat with higher point of anhydrous theophylline or theophylline monohydrate placed on a slide and covered with a glass cover. The slide is then placed on the heating plate. Following that the heating plate temperature is raised slowly, and at a temperature of 20°C below its melting temperature, heating rate 2° per minute set. After the heater is turned off entirely melted, fused sodium saccharin dihydrate allowed to cool and crystallize back. TA or TM powder placed at the edge of the cover glass and the heating plate is turned back to the TA or TM are fused, and then the heating is turned off. Fused TA or TM will move towards the contact area and rekristalit NSD. After re-crystallized TA or TM, preparations were left for about 30 minutes and then observed their melting behavior.

Phase Diagrams

Samples in the form of a single ingredient powders TA, TM, and NSD, a mixed-physics TA and TM-NSD NSD in different molar composition (0:10, 1: 9; 2: 8; ...; 9: 1; 10: 0) each inserted into the capillary tube until the height reached no more than 1 mm. Then observed when the melting point of the powder until it melts perfectly.

Analysis DTA of Physical Mixture

Theophylline monohydrate and sodium saccharin dihydrate with a molar ratio of 1: 1.66 was weighed, were then mixed until homogeneous using a mortar, and then the mixture was analyzed by DTA instrument.

FTIR Analysis of Ball Milled Mixtures

Anhydrous theophylline mixture - a mixture of sodium saccharin dihydrate and theophylline monohydrate - sodium saccharin dihydrate each weighed according to the molar ratio (1: 1.66) [13]. Mixed in with the speed-milling respectively: 45, 75, and 105 rpm. Used the ball with a measure of the weight of the ball = 6490 mg (diameter = 1.8 cm). Prepared theophylline anhydrous mixture - sodium saccharin dihydrate and theophylline monohydrate - sodium saccharin dihydrate powder mixture with a weight ratio of 1: 100 of the total weight of the ball. The data container is as follows: volume = 1120 mL; material = porcelain; inner diameter = 12.5 cm; length = 12.0 cm. Speed control (Broyeur a boulets PROLABO) has a scale speed of rotation to rotate the container at 30, 45, 60, 75, and 105 rpm. Samples were sampled at minute 10, 20, 30, 40, 50, and 60 for each of the different rotation speeds.

Confirmation by DTA and PXRD

Evaluation of the DTA and PXRD were done to the samples after 60 minutes of grinding using ball milling with a speed of 105 rpm.

Result and Discussion

Identification of the material carried by the FTIR instrument, DTA, PXRD and Karl Fischer titration. Here are the results of the identification of raw materials theophylline anhydrous theophylline monohydrate, and sodium saccharin dihydrate FTIR premises.

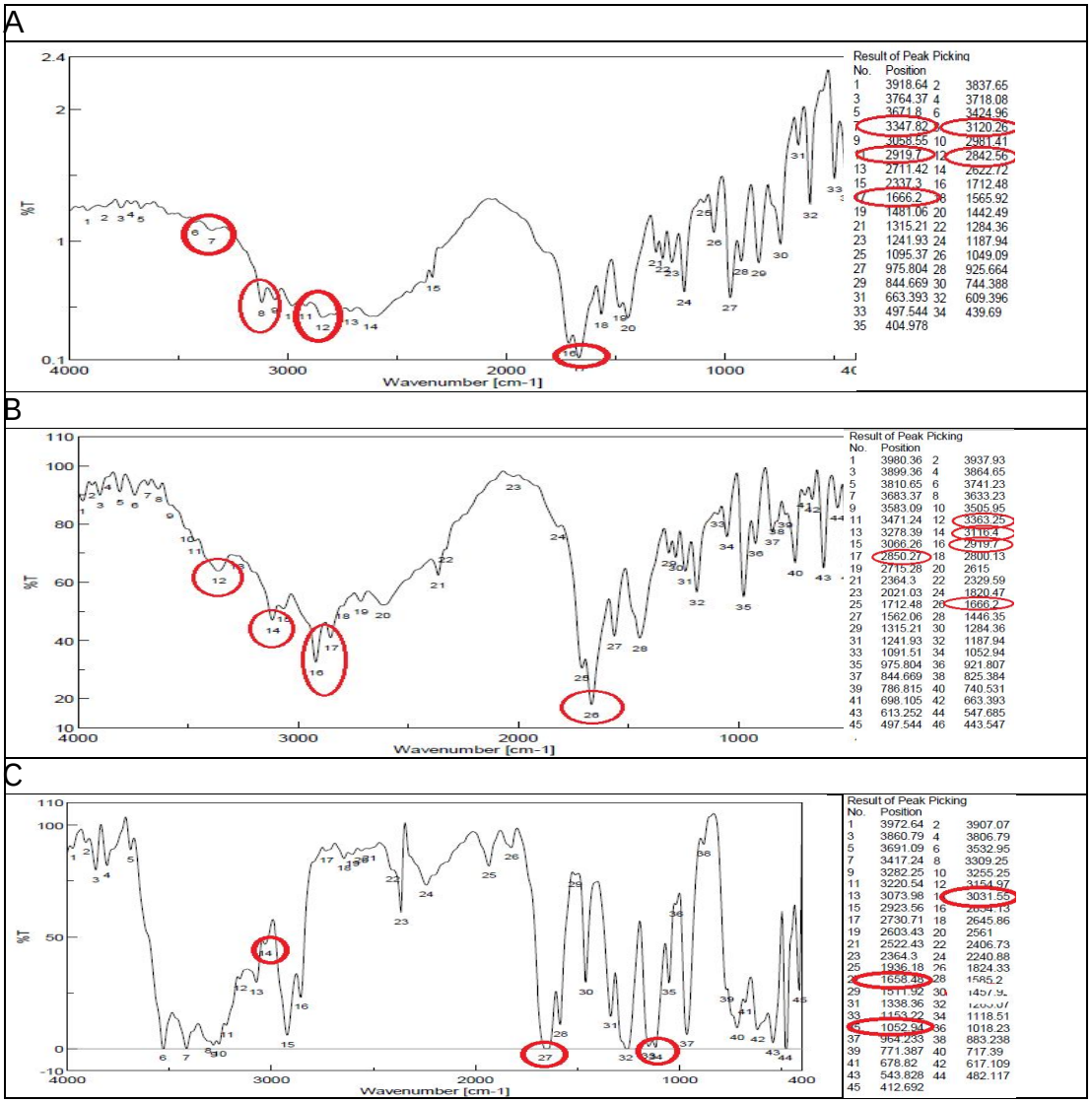


Figure 2: FTIR Spectrogram of : A. Anhydrous Theophylline; B. Theophylline Monohydrate; C. Sodium Saccharin Dihydrate

In Figure 1.4 it is shown that the FTIR spectra of sodium saccharin dihydrate have spectra at 3031.55 cm^{-1} which is an aromatic CH stretch; C = O amide spectra shown in 1658.48 cm^{-1}; and strain S = O at 1052.94 cm^{-1}.

In the spectra of anhydrous theophylline: spectra at 3347.82 cm-1 which is the spectra of the presence of hydrate molecules which are then reconfirmed by Karl Fischer titration and DTA analysis; spectra appear in pairs 2919.7 cm^{-1} and 2842.56 cm^{-1} which is characteristic of the presence of metal clusters; while the C = O amide group is indicated by the advent of 1666.2 cm^{-1}; and N-H strain detected at 3120.26 cm^{-1}. At theophylline monohydrate: spectra 3363.25 cm^{-1} which is the presence of the molecular spectra of hydrates; spectra also appear in pairs which are at 2919.7 cm^{-1} and 2850.27 cm^{-1}; which is characteristic of the presence of a methyl group, while the C = O amide group is indicated by the advent of 1666.2 cm^{-1}, NH strain detected at 3115.4 cm^{-1}.

Karl Fischer titration is used to identify and confirm the existence of hydrates in the crystal lattice on the materials used in this study. The results of the titration of the TA, TM, proved that theophylline monohidrat have one molecule of water per molecule theophylline, and sodium saccharin dihydrate bind two molecules of water for each molecule. Furthermore, the results confirmed with the DTA thermogram as shown in Figure 3 below.

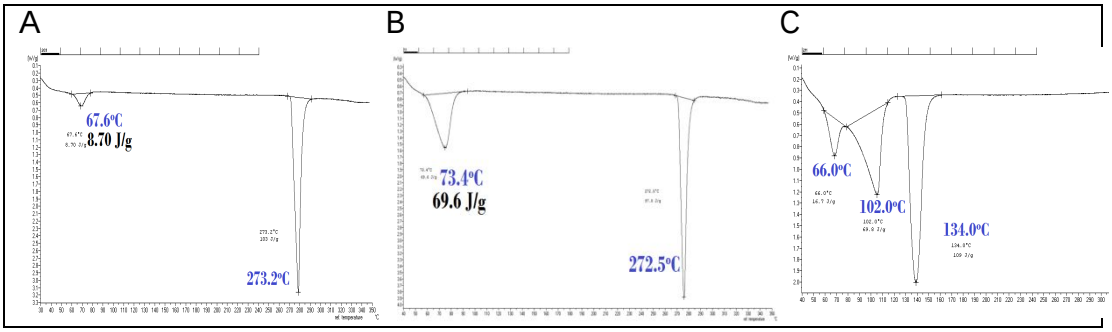


Figure 3: DTA Thermogram of: A. Theophylline Anhydrous; B. Theophylline Monohydrate; C. Sodium Saccharin Dihydrate

Further analysis of raw materials was using PXRD instrument, and obtained diffractogram as shown in Figure 4 below.

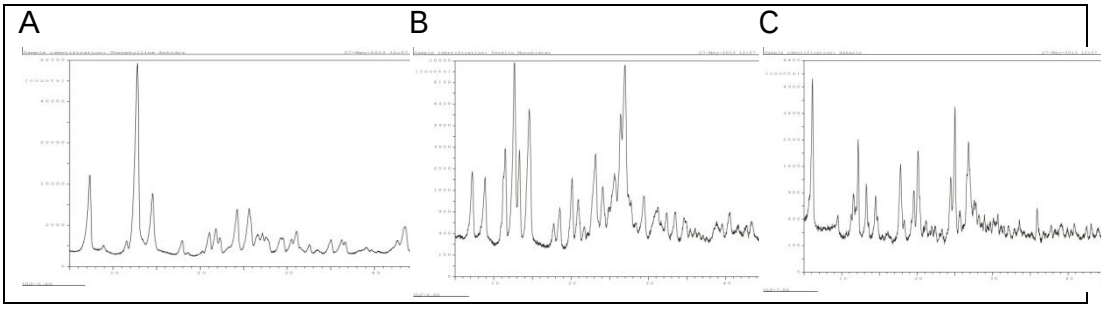


Figure 4: A.Theophylline Anhydrous Diffractogram; B.Teofilin Monohydrate; C. Sodium Saccharin Dihydrate

Early Orientation Co-crystal Formation Theophylline - Sodium Saccharin dihydrate. The formation of co-crystals of theophylline with sodium saccharin dihydrate were identified by Kofler's Hot Contact Method, the phase diagrams arrangement, and physical mixture DTA analysis.

First is to identify the possibility of the formation of co-crystals of theophylline anhydrous - sodium saccharin dihydrate and theophylline monohydrate - sodium saccharin dihydrate with Kofler's Hot Contact Method. The results are shown in Figure 5 as follows:

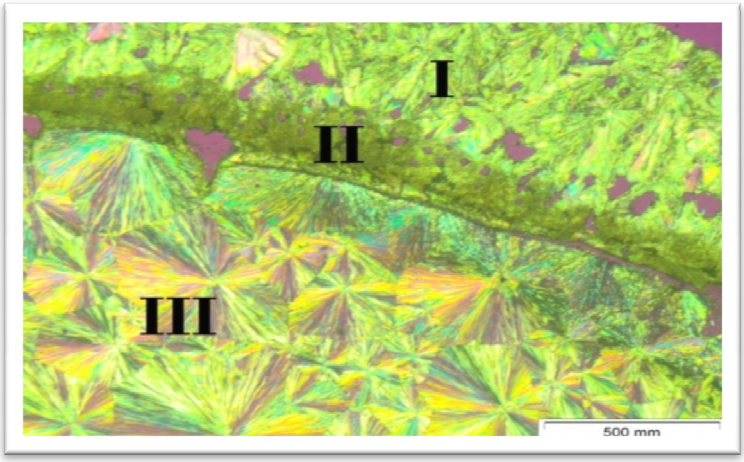


Figure 5: Hot contact method : I. Crystals of sodium saccharin dihydrate; II. Contact area; III. Theophylline crystals (magnification 40 x).

In Figure 5, Region I shows the crystal, region II is the co-crystal formation zone (contact area) and the third is a crystal of theophylline anhydrous. In the contact area indicated the growth of new crystals of different crystalline forms of the parent with the melting temperature of about 125 ºC. Both theophylline anhydrous - sodium saccharin dihydrate and theophylline monohydrate - sodium saccharin dihydrate showed the same observations.

In determining the melting point of a mixture of theophylline monohydrate - sodium saccharin dihydrate and anhydrous theophylline - sodium saccharin dihydrate performed using Electrothermal 9100 with a temperature of 260.0°C initially.

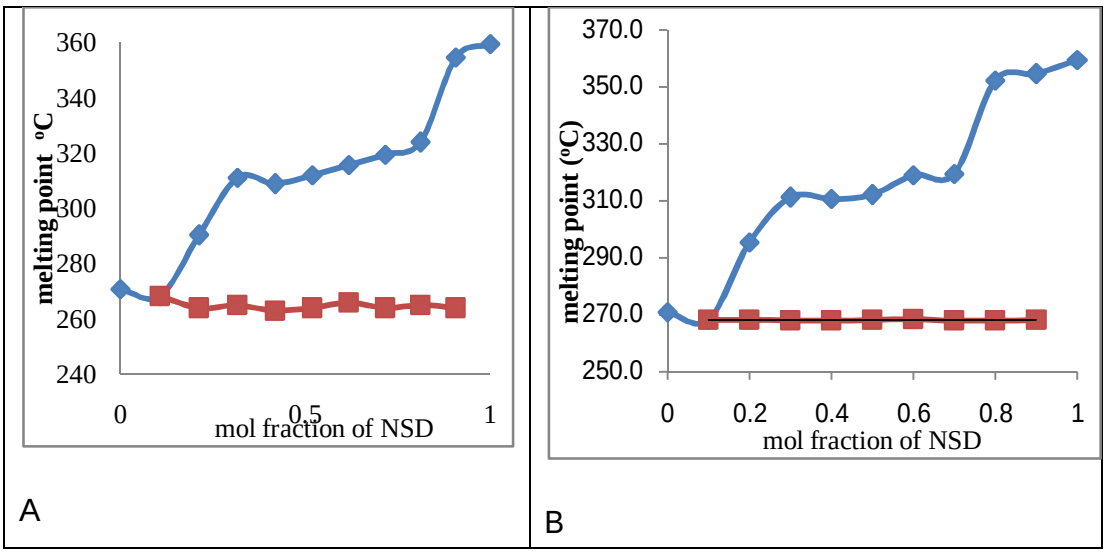


Figure 6: A. Phase diagram of : A. TM-NSD; B. TA-NSD

Figure 6 shows the phase diagram obtained a pattern that is typical for molecular compounds or co-crystal and showed the similiar pattern between two kind of mixtures.

In this experiment the DTA analysis of physical mixtures of theophylline monohydrate - sodium saccharin dihydrate, obtained thermogram as shown in the image below:

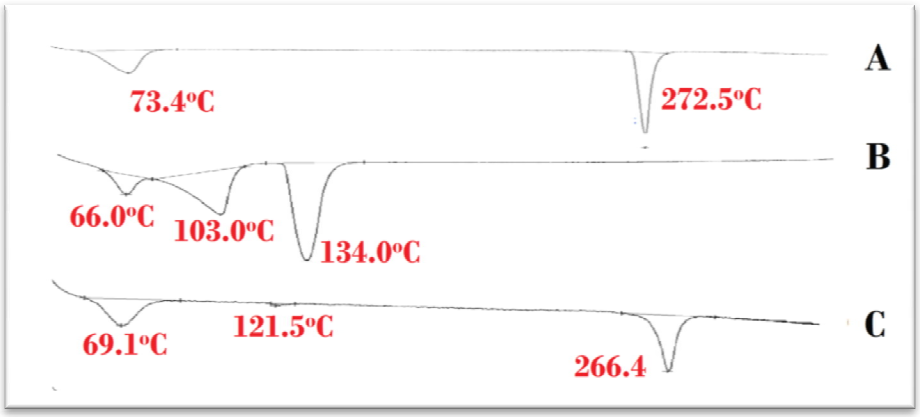
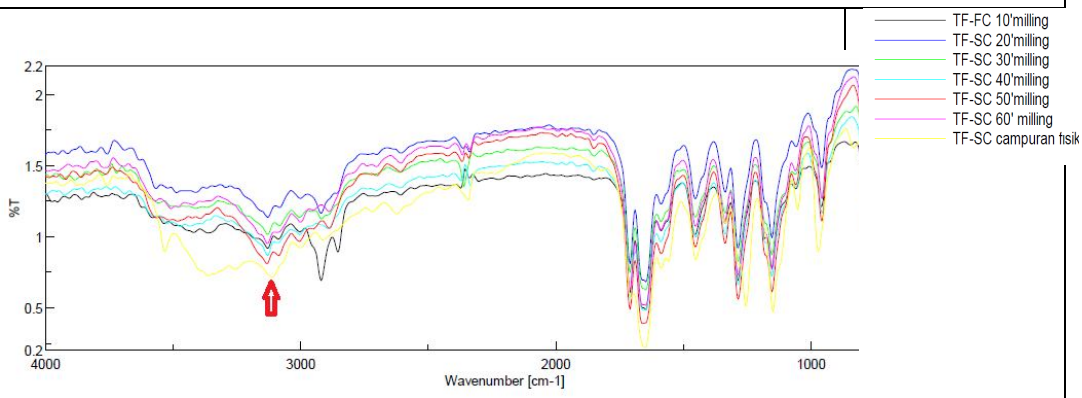


Figure 7: DTA Thermogram A. Theophylline Monohydrate; B. Sodium Saccharin Dihydrate; C. Physical Mixture of Theophylline Monohydrate - Sodium Saccharin Dihydrate

The change and appearance of a new endothermic peak in the physical mixture is one of the characteristics of co-crystal formation [20].

Data obtained from FTIR analysis of the overall results in mixed-ball mill are summarized in Figure 8 as follows:

TM-NSD (1:1,66) 45 rpm *ball milling*



10’

Result of Peak Picking

No.	Position		
1	3953.36	2	3907.07
3	3856.93	4	3779.8
5	3694.94	6	3532.95
7	3447.24	8	3363.25
9	3127.97	10	3089.4
11	2988.03	12	2919.7
13	2854.13	14	2707.57
15	2607.29	16	2372.01
17	2337.3	18	2302.59
19	2136.74	20	1851.33
21	1708.62	22	1646.91
23	1589.06	24	1454.06
25	1334.5	26	1284.36
27	1153.22	28	1060.66
29	960.377	30	844.669
31	759.816	32	674.963
33	605.539	34	536.114
35	489.831	36	455.118
37	420.406		

20’

Result of Peak Picking

No.	Position		
1	3949.5	2	3914.79
3	3837.65	4	3760.51
5	3691.09	6	3567.66
7	3486.67	8	3409.53
9	3293.82	10	3127.97
11	3081.69	12	3000.69
13	2919.7	14	2607.29
15	2364.3	16	2337.3
17	2217.74	18	1990.18
19	1851.33	20	1708.62
21	1646.91	22	1589.06
23	1454.06	24	1334.5
25	1284.36	26	1153.22
27	1060.66	28	956.52
29	763.673	30	674.963
31	644.108	32	605.539
33	532.257	34	497.544
35	447.404		

30’

Result of Peak Picking

No.	Position		
1	3980.36	2	3930.22
3	3883.93	4	3822.22
5	3775.94	6	3721.94
7	3679.51	8	3566.09
9	3409.53	10	3127.97
11	3081.69	12	3004.55
13	2919.7	14	2723
15	2611.14	16	2429.87
17	2360.44	18	2302.59
19	1959.32	20	1851.33
21	1708.62	22	1646.91
23	1589.06	24	1454.06
25	1334.5	26	1284.36
27	1153.22	28	1060.66
29	956.52	30	759.816
31	709.676	32	678.82
33	640.251	34	605.539
35	539.971	36	493.688

40’

Result of Peak Picking

No.	Position		
1	3926.36	2	3833.79
3	3745.08	4	3687.23
5	3525.24	6	3471.24
7	3436.52	8	3131.83
9	3004.55	10	2892.7
11	2703.71	12	2607.29
13	2514.72	14	2426.01
15	2372.01	16	2333.45
17	1994.03	18	1959.32
19	1851.33	20	1708.62
21	1646.91	22	1589.06
23	1450.21	24	1338.36
25	1284.36	26	1153.22
27	1060.66	28	956.52
29	763.673	30	709.676
31	674.963	32	647.965
33	605.539	34	512.972
35	439.69		

50’

Result of Peak Picking

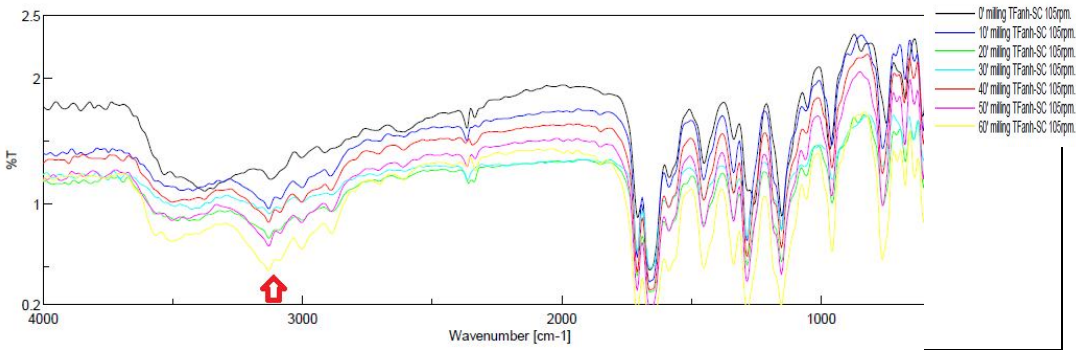
No.	Position		
1	3922.5	2	3860.79
3	3764.37	4	3482.81
5	3394.1	6	3131.83
7	3085.55	8	3004.55
9	2888.84	10	2703.71
11	2607.29	12	2422.15
13	2368.16	14	2341.16
15	2302.59	16	1994.03
17	1959.32	18	1851.33
19	1708.62	20	1662.34
21	1585.2	22	1454.06
23	1338.36	24	1284.36
25	1153.22	26	1060.66
27	956.52	28	763.673
29	678.82	30	640.251
31	605.539	32	539.971
33	412.692		

60’

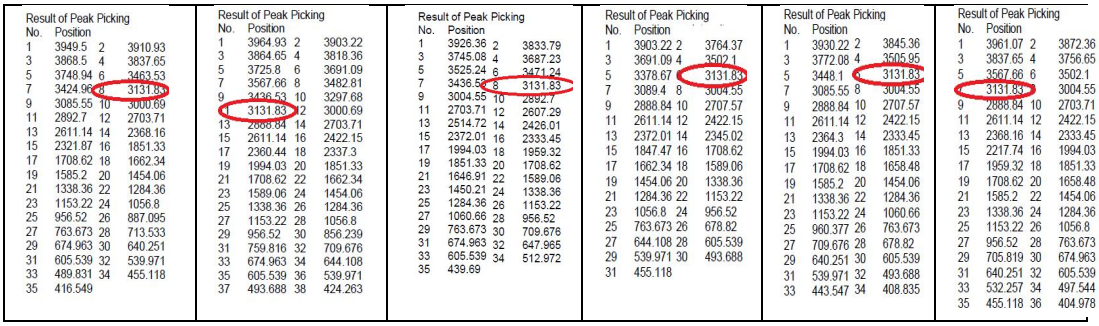
Result of Peak Picking

No.	Position		
1	3849.22	2	3772.08
3	3694.94	4	3567.66
5	3509.81	6	3421.1
7	3131.83	8	3000.69
9	2960.55	10	2888.84
11	2738.42	12	2703.71
13	2607.29	14	2426.01
15	2364.3	16	2337.3
17	2283.3	18	1990.18
19	1959.32	20	1851.33
21	1708.62	22	1646.91
23	1589.06	24	1454.06
25	1338.36	26	1284.36
27	1153.22	28	1060.66
29	956.52	30	763.673
31	678.82	32	644.108
33	601.682	34	539.971
35	501.401	36	455.118
37	424.263		

TFA-NSD (1:1,66) 105 rpm *ball milling*



10’ | 20’ | 30’ | 40’ | 50’ | 60’



Result of Peak Picking

No.	Position		
1	3949.5	2	3910.93
3	3868.5	4	3837.65
5	3748.94	6	3463.53
7	3424.96	8	3131.83
9	3085.55	10	3000.69
11	2892.7	12	2703.71
13	2611.14	14	2368.16
15	2321.87	16	1851.33
17	1708.62	18	1662.34
19	1585.2	20	1454.06
21	1338.36	22	1284.36
23	1153.22	24	1056.8
25	956.52	26	867.095
27	763.673	28	713.533
29	674.963	30	640.251
31	605.539	32	539.971
33	489.831	34	455.118
35	416.549		

Result of Peak Picking

No.	Position		
1	3964.93	2	3903.22
3	3864.65	4	3818.36
5	3725.8	6	3691.09
7	3567.66	8	3482.81
9	3436.53	10	3297.68
11	3131.83	12	3000.69
13	2868.84	14	2703.71
15	2611.14	16	2422.15
17	2360.44	18	2337.3
19	1994.03	20	1851.33
21	1708.62	22	1662.34
23	1589.06	24	1454.06
25	1338.36	26	1284.36
27	1153.22	28	1056.8
29	956.52	30	856.239
31	759.816	32	709.676
33	674.963	34	644.108
35	605.539	36	539.971
37	493.688	38	424.263

Result of Peak Picking

No.	Position		
1	3926.36	2	3833.79
3	3745.08	4	3687.23
5	3525.24	6	3471.24
7	3436.53	8	3131.83
9	3004.55	10	2892.7
11	2703.71	12	2607.29
13	2514.72	14	2426.01
15	2372.01	16	2333.45
17	1994.03	18	1959.32
19	1851.33	20	1708.62
21	1646.91	22	1589.06
23	1450.21	24	1338.36
25	1284.36	26	1153.22
27	1060.66	28	956.52
29	763.673	30	709.676
31	674.963	32	647.965
33	605.539	34	512.972
35	439.69		

Result of Peak Picking

No.	Position		
1	3903.22	2	3764.37
3	3691.09	4	3502.1
5	3378.67	6	3131.83
7	3089.4	8	3004.55
9	2888.84	10	2707.57
11	2611.14	12	2422.15
13	2372.01	14	2345.02
15	1847.47	16	1708.62
17	1662.34	18	1589.06
19	1454.06	20	1338.36
21	1284.36	22	1153.22
23	1056.8	24	956.52
25	763.673	26	678.82
27	644.108	28	605.539
29	539.971	30	493.688
31	455.118		

Result of Peak Picking

No.	Position		
1	3930.22	2	3845.36
3	3772.08	4	3505.95
5	3448.1	6	3131.83
7	3085.55	8	3004.55
9	2888.84	10	2707.57
11	2611.14	12	2422.15
13	2364.3	14	2333.45
15	1994.03	16	1851.33
17	1708.62	18	1658.48
19	1585.2	20	1454.06
21	1338.36	22	1284.36
23	1153.22	24	1060.66
25	960.377	26	763.673
27	709.676	28	678.82
29	640.251	30	605.539
31	539.971	32	493.688
33	443.547	34	408.835

Result of Peak Picking

No.	Position		
1	3961.07	2	3872.36
3	3837.65	4	3756.65
5	3567.66	6	3502.1
7	3131.83	8	3004.55
9	2888.84	10	2703.71
11	2611.14	12	2422.15
13	2368.16	14	2333.45
15	2217.74	16	1994.03
17	1959.32	18	1851.33
19	1708.62	20	1658.48
21	1585.2	22	1454.06
23	1338.36	24	1284.36
25	1153.22	26	1056.8
27	956.52	28	763.673
29	705.819	30	674.963
31	640.251	32	605.539
33	532.257	34	497.544
35	455.118	36	404.978

Figure 8: FTIR Spectrogram Data of Ball Milled TM-NSD and TA-NSD.

Crystal engineering is used to design the chemical composition and structure of a new, non-covalent bonds are exploited in order to design supramolecular structures. And the most commonly studied are hydrogen-bonded network is referring to the donor-acceptor interaction. Co-crystals significantly change the association between molecular and crystal clusters that modify the physical and pharmaceutical properties can be affected. Multi-component networks can be assembled using supramolecular heterosynthone (*synthone* = connector between molecules) through hydrogen bonding pattern-based approach [12].

In the FTIR spectra of streching NH will look at the frequency of 3350 and 3180 cm^{-1}. From FTIR analysis of the mixtures looks milling shift spectra observed in each treatment. To a mixture of physics TM-NSD, the peak observed at a frequency of 3108.09 cm^{-1}, whereas for a mixed physical-NSD TA spectra observed at 3124.12 cm^{-1}. After milling spectra of the NH strain TM-NSD will be shifted to 3127.97 cm^{-1}, and then continues shifted to 3131.83 cm^{-1}. At a speed of 45 rpm, in the 10th minute spectra shifted from 3108.09 cm^{-1} to 3127.97 cm^{-1}, then in the 40th minute spectra shifted to 3131.83cm^{-1}. At a speed of 75 and 105 rpm, shifted spectra of 3108.09 cm^{-1} to 3127.97 cm^{-1} in the 10th minute, then in the 20th minute shifts to 3131.83 cm^{-1}. While the TA-NSD, spectra at 3124.12 cm^{-1} at a speed of 45 rpm milling shifted to 3131.83 cm^{-1} in the 20th minute, while at speeds of 75 and 105 rpm shifts to 3131.83 cm^{-1} since the minute 10th. From these data it is seen that the spectra increasingly shifted to higher frequency yag. This illustrates the formation of hydrogen bonds between the NH of theophylline with the saccharine N- (hydrogen bonding occurs between the NH --- N (-)). As a result of the formation of hydrogen bonds, the NH bond becomes increasingly rigid and relatively shorter so that the stretch frequency increases.

The formation of co-crystals is proportional to the amount of mechanical energy that is used during the co-ginding, evidenced by the formation of co-crystals faster at higher milling speeds. TA is easier to form co-crystals compared to TM, due to requiring more energy to break the hydrogen bonds with the crystal water.

Saccharin as co-former, has two different mechanisms to form co-crystals. namely the mechanism of "acid-base" with saccharin as an acid, and the mechanism of formation of hydrogen bonds. The formation of co-crystals can be estimated from the bathochromic shift saccharinate in the C = O group is the wavelength of 1720 to 1690 cm^{-1} [21]. While the co-crystal results of this study do not indicate a shift in the spectra of 1708 cm^{-1}, both in the FTIR spectrum of the physical mixture and after milling, so it can be concluded that the carbonyl groups in saccharin does not have a role in the formation of co-crystals of theophylline-sodium saccharin.

From the data in Table 1 below, it can be taken illustrates that the formation of co-crystals TM-NSD requires higher energy than the TA-NSD. This is due to the TM requires more energy to remove the water hydrates to form a new hydrogen bond with the NSD. Termination of hydrate hydrogen bonds with water comes from changes in the spectra of 3108.69 cm^{-1} to 3127.97 cm^{-1}. While the TA spectra directly shifted from 3124 cm^{-1} to 3131.83 cm^{-1}.

Table 1. Data of FTIR specific spectra of TA-NSD and TM-NSD co-crystal

Time of milling (minutes)	Spectra position (cm^{-1}) after grinding in various speeds					
	TM-NSD			TA-NSD		
	45 rpm	75 rpm	105 rpm	45 rpm	75 rpm	105 rpm
0	3108.69	3108.69	3108.69	3124.12	3124.12	3124.12
10	3127.97	3127.97	3127.97	3124.12	3131.83	3131.83
20	3127.97	3131.83	3131.83	3131.83	3131.83	3131.83
30	3127.97	3131.83	3131.83	3131.83	3131.83	3131.83
40	3131.83	3131.83	3131.83	3131.83	3131.83	3131.83
50	3131.83	3131.83	3131.83	3131.83	3131.83	3131.83
60	3131.83	3131.83	3131.83	3131.83	3131.83	3131.83

Thermogram of TM (Figure 9A) indicated that the water will come out of the hydrate crystal structure at a temperature of 73.4°C and melt at temperatures 272.5°C.

In FY thermogram, there is a small endothermic curve at temperatures 67.7°C so in accordance with the results of the Karl Fischer, an estimated 1/6 of the crystal water molecules at each lattice.

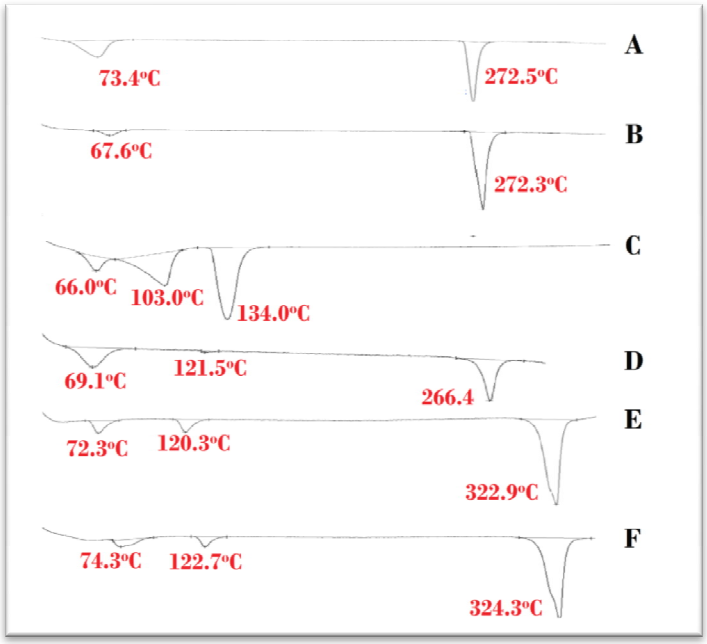


Figure 9: A. Thermogram TM; B. TA; C. NSD; D. Physical Mixture TM-NSD; E. TM-NSD ball milled 60 min 105 rpm; F.TA-NSD ball milled 60 min 105 rpm.

In Figure 9B is shown that TA crystals will melt at a temperature 273.2°C, are not much different from the melting point TM 272.5°C. At NSD thermogram (Figure 9C) shown dehidratation curve at a temperature of 102.0°C and 66.0°C. Hydrate is released, causing NSD melt at a temperature of 134.0°C, much lower than the melting point of sodium saccharin which is at a temperature of more than 300°C and are shown in the third endothermic curve of sample TM-TA-NSD and NSD in Table 2.

The results of DTA analysis of physical mixtures with mixture after-ball milling show the difference in temperature endothermic shown in Figure 9 and Table 2. It is clear that a change in the physics of crystal structure after milling. In the physical mixtures endothermic peak lay at 266.4°C which is the melting point of theophylline while the sample after milling formed a new endothermic peak in the area around 121°C.

Endothermic peak at 322.9°C point is the melting point of sodium saccharin. sodium saccharin in this case insoluble hydrate with water coming out of the crystal lattice. because hydrate water was out at the time of milling[16]. While the melting endothermic peak of theophylline at a temperature of about 270°C is no longer found in the mixture after in-milling, so it can be concluded that all of theophylline have formed co-crystals with sodium saccharin.

Table 2. Melting point (endotermic curve) from DTA

Sample	Melting point (°C)		
	1	2	3
TM	73.4	272.5	-
TA	67.7	272.3	-
NSD	66.0	103.0	134.0
Physical mixture TM-NSD	69.1	121.5	266.4
TM-NSD *ball milled* 60' 105 rpm	72.3	120.3	322.9
TA-NSD *ball milled* 60' 105 rpm	74.3	122.7	324.3

Hydrates are trapped in the crystal lattice NSD will be out along the length of milling on the solid NSD. The longer the milling time and the higher the speed milling will affect the amount of water coming out of the hydrate crystal structure of NSD, after hydrate out of NSD crystal structure, theophylline would be easier to interact with sodium saccharin so that the co-crystallization can occur. The initiation of co-crystal formation can be observed in accordance with Table 1 that the advent of the typical FTIR spectra at 3131.83 cm^{-1}.

Then the diffractogram in Figure 10 describes the crystal lattice. different diffractogram pattern showed differences in the character of the crystal lattice. The formation of co-crystals can be observed on the diffractogram pattern changes into a 10D 10E and 10F diffractogram be 10G. Diffractogram milling results TA-NSD (10E) with TM-NSD (10G) showed the same pattern. This illustrates that the co-crystal and TM-TA-NSD NSD has the same crystal structure. They differ only in the energy required for the formation of co-crystals. because the TM takes more energy to remove water from the hydrate crystal lattice of the TA.

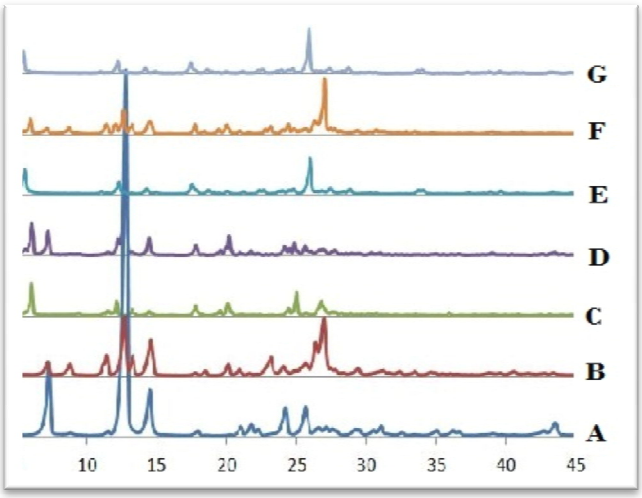


Figure 10: X-ray powder diffractogram A. TA; B. TM; C. NSD; D. Mixed-NSD physical TA; E. TA-NSD ball mill 60 min 105 rpm; F. Physical mixture TM-NSD; G. TA-NSD ball mill 60 minutes 105 rpm.

Furthermore in Figure 11, the co-crystal diffractogram TM-TA-NSD and NSD compared with the diffractogram of co-crystals of theophylline-saccharin base ever reported by Ronco, et al. (2011).[11]

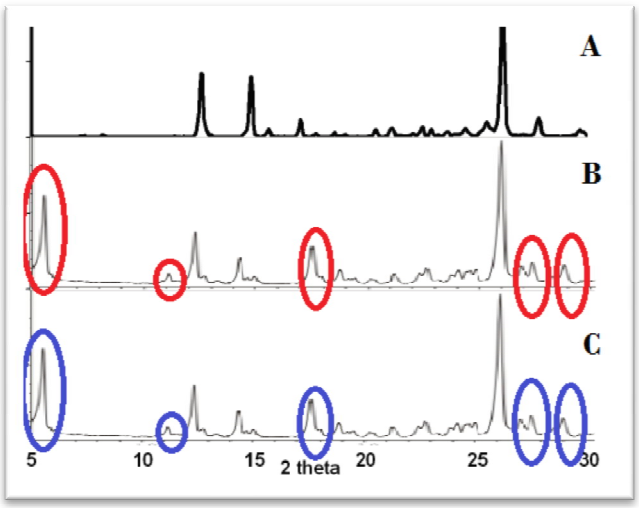


Figure 11: Diffractogram (2θ from 5° to 30°) : A. The co**-crystal of theophylline-saccharin base; B. Co-crystal TM-NSD; C. Co-crystal TA-NSD.**

In Figure 11, it is shown that the co-crystal diffractogram TM-TA-NSD NSD and has a typical peaks $2\theta = 5.58^{o}$; 12.32^{o}; 17.48^{o}; 26.86^{o}; 27.4^{o}; and 28.84^{o} which is absent in the diffractogram of co-crystals of theophylline-saccharin base. It can be concluded that the crystal lattice of co-crystals of theophylline-saccharin co-crystal base with TA-NSD / TM-NSD obtained from this experiment has a different crystal structure.

Conclusion

The dynamics of the formation of co-crystals of theophylline anhydrous - sodium saccharin dihydrate and theophylline monohydrate-sodium saccharin dihydrate can be observed through FTIR spectrogram. In a mixture of theophylline monohydrate - sodium saccharin dihydrate spectra of strain NH wavenumber shifts from 3108.69 cm^{-1} to 3127.97 cm^{-1} and then to 3131.83 cm^{-1}. whereas the anhydrous theophylline - sodium saccharin dihydrate spectral shift observed at 3124.12 cm^{-1} to 3131.83 cm^{-1}. The formation of co-crystals is proportional to the mechanical energy is given. and shown that the formation of co-crystals of theophylline monohydrate - sodium saccharin dihydrate require higher energy compared with theophylline anhydrous - sodium saccharin dihydrate. DTA thermogram of a co-crystal of theophylline anhydrous - sodium saccharin dihydrate and theophylline monohydrate - sodium saccharin dihydrate showed endothermic curve / co-crystal melting temperature of the same characteristic in 121ºC. PXRD analysis results also showed the same pattern of co-crystals of theophylline anhydrous - sodium saccharin dihydrate and theophylline monohydrate - sodium saccharin dihydrate with characteristic peaks at an angle 2 theta = 5.58^{o}; 12.32^{o}; 17.48^{o}; 26.86^{o}; 27.4^{o}; and 28.84^{o}. It is proved that the co-crystal of theophylline anhydrous - sodium saccharin dihydrate and theophylline monohydrate - sodium saccharin dihydrate solids have the same character that indicates the same crystal structure. It can be concluded that the difference in the amount of hydrate from anhydrous theophylline and theophylline monohydrate does not affect the character and structure of co-crystals produced, but require co-crystal formation energies are different. The more water theophylline crystals. the higher the energy required for the formation of co-crystal. Furthermore. it is also advisable to test the DSC/DTA further on some molar ratio to determine the composition of the stoichiometric formation of co-crystals of anhydrous theophylline and theophylline monohydrate with sodium saccharin dihydrate.

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