Volume 1, Number 1, June 2017

SCIENCE & DEVELOPMENT

CBAS
College of Basic and Applied Science

A Journal of the College of Basic and Applied Science (CBAS), University of Ghana

Mechano synthesis of co-crystals of Sulfamethoxazole and 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid based on Green Chemistry principles

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Abstract

Co-crystals have been used to produce new drugs and to improve the physical properties of drugs. Some disease causing germs have developed resistance to newer drugs, hence there is a general trend to take 'old' but efficacious drugs, improve their properties and use them to treat the conditions. This study used mechano-synthesis to produce a co-crystal of two active pharmaceutical ingredients (API), Sulfamethoxazole and 8-hdroxy-7-iodoquinoline-5-sulfonic acid (Ferron), based on Green Chemistry principles. The two APIs were combined by mixing, grinding and kneading. The resulting co-crystals were characterized using analytical methods such as spectroscopy, thermal analysis and diffractometry. *In-Silico* techniques based on computer modelling using Gaussian 09 and VEDA 4 software were used to interpret the vibrational spectrum of the co-crystals. The study found that kneading gave the highest yield compared to mixing and grinding. The study also confirmed that a combination of the analytical methods was necessary to characterize a co-crystal. Co-crystals of Sulfamethoxazole and 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid can therefore be formed by kneading, implying that the production of the co-crystals can be done using a process that reduces pollution by the minimal use of solvents. Another implication is that Sulfamethoxazole, whose use has been minimised because of problems such as allergic reactions from patients, can be looked at again and used to produce 'polydrugs' which can be used to manage conditions at relatively cheaper costs.

Keywords: Mechano-synthesis, co-crystallization, DSC, VEDA 4, Green Chemistry, Sulfamethoxazole, 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid

Introduction

Co-crystals have been defined differently by several authors, but in all these definitions, a common theme is that a co-crystal consists of two or more non-ionic compounds in a single crystalline phase in a given stoichiometric ratio held together by hydrogen bonds or other non-covalent bonds (Dunitz, 2003 ; Rodríguez-Hornedo, *et al.*, 2007).The components in a co-crystal maintain their chemical properties even after the process since no covalent bonds are broken or formed.

Crystalline salts on the other hand interact electrostatically and the components are ionized (Stahly, 2007). Co-crystals are useful especially in the pharmaceutical industry in the design and preparation of drug forms in which one or more of active pharmaceutical ingredients or components are non-ionic.

This usefulness stems from the possibility of improving the properties of drugs by forming co-crystals of the APIs. Some of the documented properties of drugs which have been improved are bioavailability and/or dissolution of drugs which have poor solubility; chemical stability and melting point (Blagden *et al.*, 2007; Kotak *et al.*, 2015).

Old drugs whose use has been discontinued either due to the discovery of newer drugs or because of some unfavourable properties discovered in their use have recently attracted renewed attention. This is because of the emergence of drug-resistant strains of the disease causing agents. Antibiotics and antibacterials fall in this category (Falagas *et al.*, 2008; Maviglia *et al.,* 2009; Falagas & Kasiakou, 2005; Giamarellou & Poulakou, 2009).

An additional advantage that drugs formed using co-crystals have over crystalline salts is that many more numerous neutral compounds (mainly GRAS[1]) can be used in drug formulations, rather than the relatively fewer counterions which are used in crystalline salts (Halden, 2014).

The use of co-crystallization in the design and production of drugs is one of the ways that scientists can protect people and the environment at the same time since it promotes the use of Green Chemistry principles. Green Chemistry uses methods and conducts reactions at low or ambient temperatures; reduces the use of chemicals, which in turn reduces the generation of hazardous wastes or substances that must be safely disposed of (Anastas & Warner, 1998).

Though the production of co-crystals by the slow evaporation of a solvent in which the components are dissolved is very common, solid grinding of the components has also been used and is still being used to produce co-crystals. In some instances, co-crystals produced by solid-grinding exhibit different characteristics from those produced using solvent evaporation (Bruni *et al.*, 1999).

Mechano-synthesis is defined as co-crystal formation in the solid state based on mechanical activation of materials by processes such as grinding or milling (Rodríguez-Hornedo *et al.*, 2007). Here the components are ground together with a mortar and pestle or in a mixer mill to induce co-crystal formation. This method uses at least two of the Green Chemistry principles: low temperature and very little or no crystallization solvent (Alatas, *et al.*, 2013).

A complex set of reactions take place when two solid substances are ground together, from the breaking of the crystalline structure to the production of cracks and the development of new surfaces (Fernández-Bertran, 1999). This method of synthesis is already in use in the local pharmaceutical industry since it does not require sophisticated machinery and/or solvents which may be needed when using solvent evaporation methods.

This study is, therefore, aimed at co-crystallizing Sulfamethoxazole, a well-known Active Pharmaceutical Ingredient (API), used as an antibiotic, with a lesser known but old API, 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid, which has anti-protozoan properties, using Green Chemistry principles.

Experimentals

Sulfamethoxazole (SMX), 98% purity Analar grade, was purchased from Central Drug House (CDH), New Delhi, India, and was used without further purification. 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid (8H7QS), Spot-Test reagent grade, was purchased from BDH Chemicals Ltd., Poole, England, and was used without further purification. Ethanol, 99.7 – 100%, Analar grade, was purchased from Pharmacos Banbury, United Kingdom, and was used without further purification. Distilled water was prepared using an Accumax (India) stainless steel water distillation unit.

A solvent system consisting of Ethanol and distilled Water in a 1:1 volume ratio was prepared and used in the study.

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[1] Generally Recognised as Safe

Mechano-Synthesis

A Fritsch 'Pulverisette 2' Mortar Grinder was used for both grinding and kneading. The ground sample was prepared by weighing 0.5020 g of SMX and 0.6978 g of 8H7QS into the mortar bowl and grinding for 30 minutes. The kneaded sample was prepared by weighing 0.5020 g of SMX and 0.6978 g of 8H7QS into the mortar bowl, adding 5 drops of the solvent system and kneading for 30 minutes. The 'mixed' sample was prepared by weighing 0.5020 g of SMX and 0.6978 g of 8H7QS into the mortar bowl and mixing with a spatula for 10 minutes. The powdered products were then analysed.

Infra-Red Spectroscopy

The infra-red spectra of a suitable quantity of crystalline Sulfamethoxazole (SMX), crystalline 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid (8H7QS) and co-crystals (of 8H7QS and SMX) were measured in the 4000 – 400 cm^{-1} region at 4 cm^{-1} resolution and an average of 23 scans on a Perkin Elmer Spectrum Two FT-IR Spectrophotometer. The spectra were elaborated using the Spekwin 32 (Menges, 2015) software to convert the transmittance to absorbance.

Ultraviolet Spectroscopy

A 0.0128M solution of each of the pure compounds and the co-crystals was prepared by dissolving the compound/powdered co-crystal in a mixed solvent system of Ethanol:Water (1:1 by vol.). The solution was used subsequently for the Ultraviolet spectroscopy. The UV spectra of Sulfamethoxazole, 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid and the co-crystal were determined using a Spectroquant Pharo 300 UV-Vis Spectrophotometer in the region 190 nm – 1100 nm. The spectra were elaborated using the Spekwin 32(Menges, 2015) software.

Powder X-ray Diffraction:

Suitable quantities of Sulfamethoxazole (SMX), 8-Hydroxy-7-Iodoquinoline-5-Sulfonicacid (8H7QS) and the powdered co-crystals of 8H7QS and SMX were introduced into a PANalytical Empyrean X-ray Diffractometer with a copper anode. The K –alpha1 wavelength was 1.54060Å and the K-alpha2 wavelength was 1.39225Å.

Each sample was scanned continuously in steps of .08° in 3 seconds with 2θ from 5.04° to 80° while spinning to acquire the Powder X-ray Diffractograms. Spekwin 32 (Menges, 2015) software was used to sketch the diffractograms.

Thermal Analysis

An appropriate quantity of crystalline Sulfamethoxazole (SMX), 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid (8H7QS), and the co-crystals of 8H7QS and SMX were analysed using the thermal analytical methods of Thermo Gravimetry, TGA, and Thermal Calorimetry, DSC. The equipment used was TA Instruments SDT-Q600 V20.9 Build 20 (Bernstein, 2002).

The DSC results were collected on a Mettler DSC 822e under an inert atmosphere (nitrogen at 20 ml/Min) at a heating rate of 10 deg C per minute (Lu *et al.*, 2008).

Crystal Structure

The crystal structure for Sulfamethoxazole was acquired from Crystallography Open Database (Gražulis *et al.*, 2012; Grazulis *et al.*, 2009; Downs & Hall-Wallace, 2003) as determined and published by Perlovich G. L. *et al.*, 2013), was visualized using OLEX 2 software (Dolomanov, Bourhis, Gildea, Howard, & Puschmann, 2009) and plotted using ORTEP-plot in PLATON version 271014.

X-ray crystal structure data on 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid was obtained from Crystal Open Database (COD) (Information card for 2005313) as published by Balasubramanian and Muthiah (1996), was visualized using OLEX 2 software (Dolomanov *et al.*, 2009) and plotted using ORTEP-plot in PLATON version 271014.

Results and Discussions

Infra-Red Spectroscopy

The experimentally determined infra-red spectrum of 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid showed no distinct peaks above the 3000 cm^{-1} wavenumber. This confirms the IR spectrum as reported in the data base of NIST (*8-Hydroxy-7-iodo-5-quinoline sulfonic acid*, 2011)

Using IR spectroscopy, the structural consequences of combining the two compounds using mechano-synthesis were shown using the vibrational modes of the bonds maintained or newly formed in the process (Thanigaimani *et al.*, 2015).

The number of atoms in 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid, 8H7QS, is 22 and that of Sulfamethoxazole, SMX is 28. The degrees of freedom which constitute vibrational motion for each of the compounds are therefore 60 and 78 respectively (Banks *et al.*, 2010).

The Total Energy Distribution, TED data generated from the Potential Energy Distribution, PED, was used in discussing the IR spectrum of the two starting compounds. The PED analysis is more accurate than the visualization of an atom movement to interpret a theoretical vibrational spectrum of a molecule. It also quantitatively describes the contribution to movement of a given group of atoms in a normal mode (Jamróz, 2013). The PED analysis is indispensible tool in serious analysis of the vibrational spectra. To perform the PED analysis it is necessary to define 3N-6 linearly independent local mode coordinates. Already for 20-atomic molecules it is a difficult task. The VEDA program reads the input data automatically from the Gaussian program output files. Then, VEDA automatically proposes an introductory set of local mode coordinates. Next, the more adequate coordinates are proposed by the program and optimized to obtain maximal elements of each column (internal coordinate.

Figure 1 is a labelled molecule of 8H7QS based on its crystal structure. The highest peak from the experimental data for 8H7QS was at 598 cm^{-1} and this was shown in the calculated data at 600.82 cm^{-1}. This was attributed to the stretching of the bond between C6 and H6. There was also a contribution from the torsion involving H2, C2, C3 and C4.

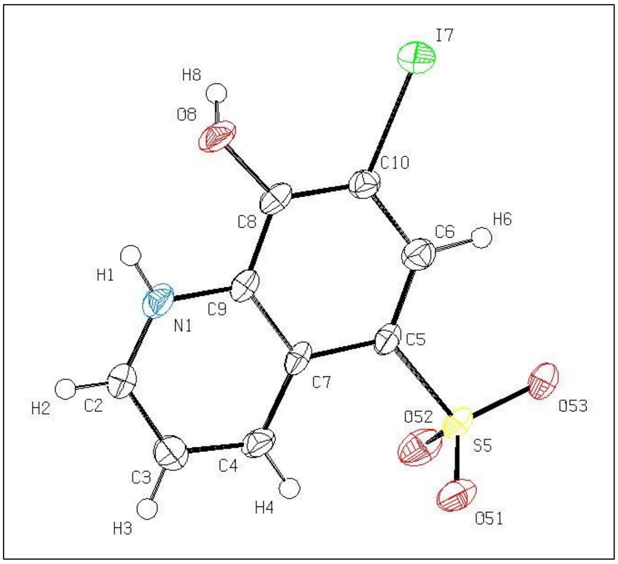

Fig. 1: Labelled molecule of 8-hydroxy-7-iodoquinoline5-sulfonic acid (8H7QS)

A C - C pure mode was determined at 1401 cm^{-1} to be due to stretching between C4 and C7. This was shown experimentally at 1383 cm^{-1}. Most of the C – C bonds gave peaks theoretically varying from 850 cm^{-1} to 1500 cm^{-1}, but these were mixed with other modes.

C – H had a pure stretching mode at a calculated wavelength of 1037.18 cm^{-1}; experimentally it was shown at 1042 cm^{-1}. At a wavelength of 707.52 cm^{-1} (experimentally at 726 cm^{-1}), the stretching of both C-H and N-H were mixed, though the N-H contributed more to the absorbance.

The stretching of the O8-H8 bond was assigned the wavelengths 3254, 1710, 237 and 209 cm^{-1}, but these were not shown clearly experimentally. This may be due to the location of the lone pair of electrons in the antibonding orbital of H8 as determined with the NBO analysis.

The stretching of the S –O bond gave a pure mode at 397.3 cm^{-1} (experimentally at 403 cm^{-1}).

Figure 2 below is a labelled molecule of SMX based on its crystal structure. The highest peak in the calculated spectrum of Sulphamethoxazole is at a frequency of 507.75 cm^{-1} corresponds to the peak at 561.84 cm^{-1} in the experimental spectrum. This is attributed to the torsion of the planes which pass through H2-C2-C3-C4 and H3-C3-C4-S1. The peaks around 3000 cm-1 frequency are due mainly to torsion of some planes in the molecule. For example, the peaks at 3377 cm^{-1} and 3298 cm^{-1}, calculated to be at 3354.13 cm^{-1} and 3262.24 cm^{-1} respectively, are due in part to torsion in the plane through H1B-N1-C1-C2. However, the peaks at calculated frequencies of 3171.04 cm^{-1} and 3088.09 cm^{-1} are due to pure bending modes between O3-N3-C7 and H2A-N2-O2 respectively.

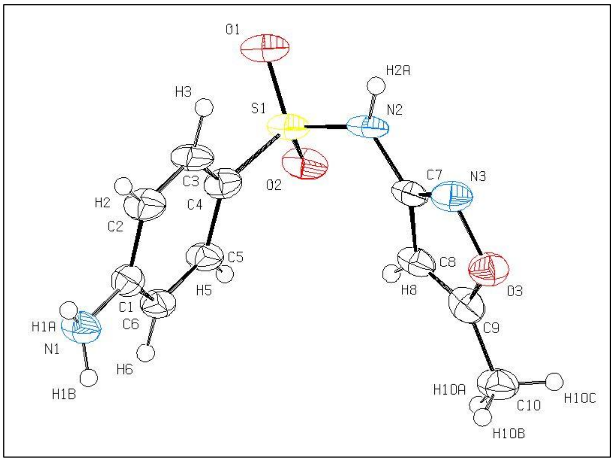

Fig. 2: Labelled molecule of Sulfamethoxazole (SMX)

The peak at 1509.14 cm^{-1} in the calculated spectrum, corresponding to the peak at 1501 cm^{-1} in the experimental spectrum, is also due to a pure mode of torsion in the plane C1-C6-C5-C8. The stretching modes between atoms in the group frequency region are mainly mixed with other modes except for the calculated modes at 1053.32 cm^{-1} and 1038.59 cm^{-1} which are single modes attributed to the stretching of the C3-H3 bond and the O2-N2 bonds respectively. These bonds are seen around the 1000 cm^{-1} in the experimental spectrum. The pure bending mode between atoms H10A-C10-C9 gives a peak at a calculated frequency of 1300.24 cm^{-1} which corresponds the peak at 1303 cm^{-1} determined experimentally. The is a pure bending modes between the atoms H6-C6-C1 and N1-C1-C6 give peaks at calculated frequencies of 1361.9 cm^{-1} and 1358.44 cm^{-1} respectively. These peaks correspond to the peak at the frequency of 1363 cm^{-1} determined experimentally.

Vibrational modes from bonds in 8H7QS, especially in the 'fingerprint' zone, which were not available when the co-crystal was formed by Grinding, Kneading and 'Mixing' have been given in Tables 1 to 3 respectively below. Also shown are the assignments as determined from PED calculations using the VEDA 4 software (Jamróz, 2015).

Table 1: Vibrational modes of absorptions of 8H7QS remaining after Grinding

No.	Calculated		Experimental		Assignment
	IR Absorbance	Wavenumber (cm^{-1})	IR Absorbance	Wavenumber (cm^{-1})	
1	53.1	1449.47	0.816	1459	13δHNC
2	18.56	1342.05	0.8246	1348	11τCCCS+11τCNCC
3	141.36	1291.64	0.8529	1298	
4	55.53	1181.96	0.9561	1174	12vCC+11vCC+11δHCC
5	8.69	950.05	0.8817	956	78δOOS
6	40.33	867.54	0.857	936	11δHCC+22δHCC
7	3.87	856.15	0.8839	917	11vCC+10δHCC+16δICC
8	11.25	801.96	0.8565	847	11δHCC+16τHOCC+18τHCCC+18τHCCN

Table 2: Vibrational modes of absorptions of 8H7QS remaining after Kneading

No.	Calculated		Experimental		Assignment
	IR Absorbance	Wavenumber (cm^{-1})	IR Absorbance	Wavenumber (cm^{-1})	
1	53.1	1449.47	0.816	1459	13δHNC
2	18.56	1342.05	0.8246	1348	11τCCCS+11τCNCC
3	141.36	1291.64	0.8529	1298	
4	55.53	1181.96	0.9561	1174	12νCC+11νCC+11δHCC
5	40.33	867.54	0.857	936	11δHCC+22δHCC
6	3.87	856.15	0.8839	917	11νCC+10δHCC+16δICC
7	11.25	801.96	0.8565	847	11δHCC+16τHOCC+18τHCCC+18τHCCN

Table 3: Vibrational modes of absorptions of 8H7QS remaining after 'Mixing'

No.	Calculated		Experimental		Assignment
	IR Absorbance	Wavenumber (cm^{-1})	IR Absorbance	Wavenumber (cm^{-1})	
1	127.36	1616.22	0.8461	1621	12δHOC
2	53.1	1449.47	0.816	1459	13δHNC
3	18.56	1342.05	0.8246	1348	11τCCCS+11τCNCC
4	40.33	867.54	0.857	936	11δHCC+22δHCC
5	3.87	856.15	0.8839	917	11νCC+10δHCC+16δICC
6	11.25	801.96	0.8565	847	11δHCC+16τHOCC+18τHCCC+18τHCCN
7	29.99	707.52	0.8658	726	10νCH+18νNH
8	23.56	620.03	0.8954	624	16τHNCC
9	182.25	600.82	1	598	10νCH+13τHCCC

Co-crystals from all mechano-synthesis methods used have similar IR spectra, especially in the 'finger print' region.

The wavenumbers at which the co-crystals absorbed which are not in the starting compounds are highest for the kneading method; these were at 3105 cm^{-1}, 1502 cm^{-1}, and 571 cm^{-1}. In the case of grinding, there was an absorption at only one new wavenumber, 3070 cm^{-1}. Similarly, when the compounds were mixed, there was only one new wavenumber with absorption at 3104 cm-1.

This implies that new bonds are formed by kneading whose vibrational modes are at those wavenumbers.

Under all three syntheses, the 8H7QS bonds which were de-emphasised in the co-crystallization process were the bending of HNC, HCC, ICC, the twisting of CCCS, CNCC, HOCC, HCCC, and HCCN; and the stretching of CC.

Similar vibrational modes of both 8H7QS and SMX were not available in the co-crystals formed through either grinding or kneading. For example, the vibrational modes which absorbed between wavenumbers 1830 cm^{-1} and 2170 cm^{-1} in the spectrum of 8H7QS were all absent in the co-crystals, no matter the method of production. This is shown in Figure 3.

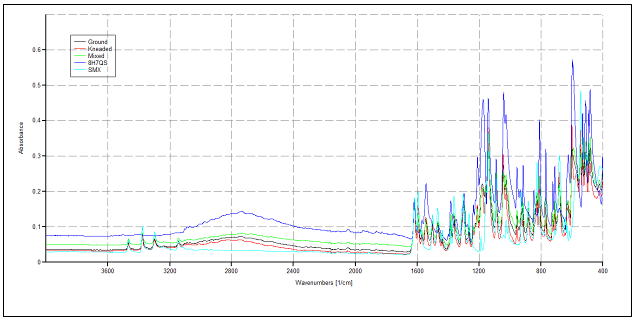

Fig. 3: IR spectra of both compounds and Co-crystals

At wavenumbers common to all products of the mechano synthesis, the lowest absorption were from the kneaded products as shown in Figure 4. This supports the conclusion that the kneading process produces the most co-crystals since the formation of the co-crystals has the effect of reducing the amount of starting compounds available which could have absorbed at those wavenumbers.

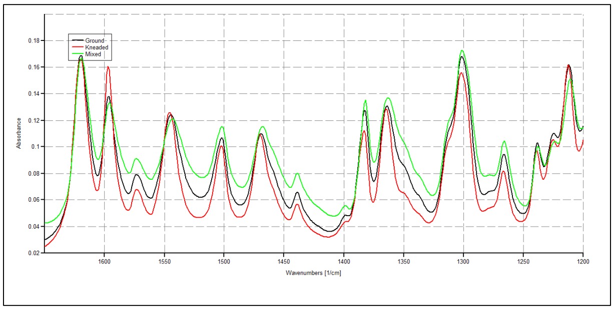

Fig. 4: IR spectra of both compounds and Co-crystals

UV Spectra

The 8H7QS had a peak at 297 nm and a shoulder between 325 nm and 345 nm while the SMX had a single peak at 300 nm.

When the two compounds were ground together for 30 minutes, the peak was at 292 nm and a shoulder between 320 nm and 350 nm.

When the compounds were kneaded together, the peak was at 297 nm and a shoulder between 315 nm and 345 nm.

When the compounds were 'mixed' together, the peak was at 296 nm and the shoulder between 315 nm and 350 nm. The UV spectra is given in Figure 5.

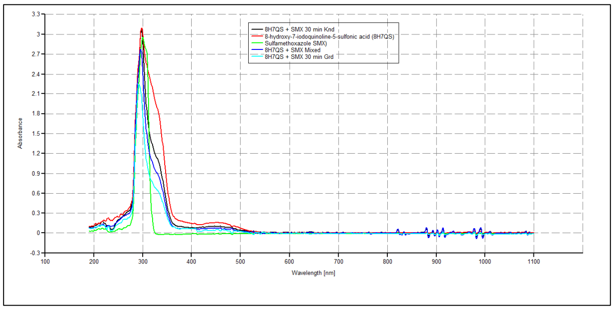

Fig. 5: UV spectra of Compounds and Co-crystals

Differential Scanning Calorimetry

The melting point of 8H7QS was found to be 269.25°C, while the decomposition temperature of the 8H7QS was determined to be 283.07°C. The literature value for the melting point of 8H7QS is 269-270°C. The literature value is close to the laboratory determined value of 268-270°C using the capillary method.

The melting point of SMX on the other hand is 168.30°C which is close to the literature value of 166-171.5°C and to that determined in the laboratory which was 170°C. The decomposition temperature was determined to be 250.07°C.

The melting point of the co-crystal produced is lower than the melting points of the starting materials and decreases in the order 'Mixed'> Ground>Kneaded as given in Table 4.

The latent heat of the co-crystals formed using the different synthesis methods is approximately the same, though it decreases slightly in the order 'Mixed'> Ground>Kneaded. This implies that the products are the same, but with different impurities which may be remnants of the starting compounds.

Table 4: Melting point and Latent Heat of compounds and co-crystals

Sample	Melting point (°C)	Latent Heat (J/g)
8H7QS	269.25	
SMX	168.30	-112.34
8H7QS + SMX 'Mixed'	167.50	-38.85
8H7QS + SMX Ground	166.32	-38.96
8H7QS + SMX Kneaded	156.92	-40.25

Co-crystals were formed under the various synthesis conditions with the highest yield being when the powders were kneaded. The different forms of co-crystals all decomposed at temperatures (between 193-196°C) far lower than the decomposition temperatures of the starting compounds. Table 5 below gives the latent heat of decomposition of the co-crystals.

Table 5: Decomposition point of compounds and co-crystals

Sample	Onset Decomposition Point (°C)	Latent Heat of Decomposition (J/g)
8H7QS	283.07	-375.87*
SMX	250.07	471.65
8H7QS + SMX 'Mixed'	195.81	159.01
8H7QS + SMX Ground	193.16	230.91
8H7QS + SMX Kneaded	194.66	298.60

* Latent heat of melting and decomposition

Powder X-Ray Diffractometry

Generally, the intensities of the peaks were lowered when the co-crystals were formed.

All the major peaks in the diffractogram of the co-crystal formed by 'mixing' of 8H7QS and SMX are found as peaks at the same angles, 2θ, in the diffractograms of 8H7QS and/or SMX except for the peak at 2θ = 6.88°. Peaks at 2θ = 11.76° and 20.56° found in the diffractogram of 8H7QS however did not appear in the diffractogram of the co-crystal. Likewise, peaks at 2θ = 42°, 7.36° and 35.20° in the diffractogram of SMX did not appear in the diffractogram of the co-crystal.

In the case of the co-crystal formed by grinding, the diffractograms showed fewer peaks at angles common to both 8H7QS and SMX on one hand and the co-crystal on the other. For example, the peaks at 2θ = 28.80°, 17.76° and 21.52° of the diffractogram of the co-crystal had no corresponding peaks at the same angles for either 8H7QS or SMX. Conversely, most of the major peaks in the diffractogram of either 8H7QS or SMX did not appear in the diffractogram of the co-crystal.

In the case of the co-crystal from kneading, the five peaks with the highest intensities of 8H7QS were not found in the diffractogram of the co-crystal, though three of the highest peaks of SMX were visible. The co-crystal had characteristic peaks at 2θ = 17.52° and 22.56°. The characteristic intense peak of SMX at 2θ = 24.08° was also not visible in the diffractogram of the co-crystal.

When the diffractogram of the co-crystals from the different synthesis were compared, characteristic peaks were found at 2θ = 9.92°, 17.52°, 27.60°, 28.60° and 40.30°.

This indicates the formation of a product, in this case, a co-crystal, when the two compounds are brought together, with the best method of synthesis being kneading.

Conclusion

Co-crystals of 8-Hydroxy-7-Iodoquinoline-5-Sulfonic acid and Sulfamethoxazole were successfully produced using Green Chemistry principles by applying mechano-synthesis methods.

Kneading of the compounds together gives the highest yield of the co-crystals compared to mixing which gave the least.

Using UV spectroscopy alone does not show clearly the formation of the co-crystals.

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