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CO-CRYSTALLIZATION FOR ENHANCED DISSOLUTION RATE OF FLUTAMIDE

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ABSTRACT
Flutamide is an orally active anti-androgenic agent of non-steroidal origin which is approved for treatment of prostatic carcinoma. It has low and variable oral bioavailability. This is mainly attributed to its poor dissolution behavior. Co-crystallization of drugs with inert co-former is an emerging technique for enhancing dissolution rate. Accordingly, the objective of this work was to investigate the efficacy of sucralose as a potential co-crystal co-former for enhancing the dissolution rate of flutamide. Co-crystal formation involved acetone assisted co-grinding after mixing flutamide with increasing molar ratios of sucralose (1:1, 1:2 and 1:3). The prepared formulations were subjected to physical characterization in addition to monitoring the dissolution behavior. The characterization employed Fourier transform infrared spectroscopy, differential scanning calorimetry and powder X-ray diffraction. These investigations provided evidence for co-crystal formation between the drug and sucralose. Co-crystals were formed with 1:2 drug to sucralose (molar ratio) being optimum for co-crystallization process. The dissolution studies revealed faster dissolution rate of the drug from co-crystals compared to the pure unprocessed drug or that which was subjected to wet grinding in absence of sucralose. The study also revealed dimorphic conversion of flutamide after precipitation from acetone. The study introduced sucralose as co-crystal co-former for enhanced dissolution of flutamide.

KEYWORDS: Flutamide; co-crystallization; sucralose; dissolution rate.

INTRODUCTION
Flutamide is an oral active anti-androgenic agent of non-steroidal origin. It is widely used in the treatment of prostatic carcinoma. It exerts its function via competitive inhibition of the action of testosterone and di-hydro testosterone on the prostate gland. This can subsequently inhibit the growth of cancer cell.[1] The use of flutamide can be extended to the management of hirsutism which results from elevated androgenic levels in women suffering from polycystic ovarian syndrome.[3,4] The drug undergoes rapid absorption after oral administration with subsequent rapid metabolism into the active metabolite. Unfortunately, flutamide has low and variable oral bioavailability which is mainly attributed to its poor dissolution and pre-systemic disposition.[4,5] Accordingly, enhancing the dissolution rate of flutamide is expected to eliminate the problems of variable and low bioavailability after oral administration.[6]

Authors employed different strategies to enhance the dissolution rate of flutamide. These included formulation of simple solid dispersion in hydrophilic polymers such as polyethylene glycol 6000 and polyvinyl pyrrolidone.[7] Inclusion complexation with hydroxypropyl-β-cyclodextrin was also employed with the formulation being developed by freeze drying of aqueous solution.[5,8] Co-spray drying with lactose in presence of hydrophilic excipients was also tested for dissolution enhancement.[6] The studies were even extended to utilize liquisolid system in which flutamide was solubilized in minimum amount of liquid before loading on solid surface.[9]

Co-crystallization has gained interest recently for enhancing the dissolution rate of poorly water soluble drugs. This strategy involves co-crystallization of the target drug with inert carrier (co-former). The dissolution rate of the resulting crystalline product depends on the nature of co-former with hydrophilic co-formers being able to develop co-crystals with enhanced dissolution rate of the given drug. The simplicity of the technique and the use of common pharmaceutical excipients as co-formers strengthened the use of this strategy as a promising line for dissolution enhancement.[10-13]

Sucralose is a sucrose substitute and is widely used as artificial sweetener. This sugar contains numerous

oxygen atoms making it an excellent candidate for hydrogen bond formation with nitrogenous compounds such as flutamide.[14] Accordingly, the objective of this study was to investigate sucralose as co-crystal co-former for improving the dissolution rate of flutamide.

MATERIALS AND METHODS

Materials

Flutamide was obtained from Sigma for Pharmaceutical Industries, Qwesna, Egypt. Sucralose was obtained from Egyptian International Pharmaceuticals Industries Company (EIPICO), 10th of Ramadan City, El Sharkeya, Egypt. Acetone and hydrochloric acid (HCl) were purchased from El Nasr Pharmaceutical Chemicals Company, Cairo, Egypt. Sodium lauryl sulphate (SLS) was procured from Research Lab Fine Chemical Industries, Mumbai, India.

Preparation of flutamide-sucralose co-crystals

Co-crystallization was achieved using the previously published method.[11, 15] Briefly, flutamide and sucralose were dry mixed according to the molar ratios presented in Table 1. Acetone was gradually added with mixing to just solubilize the mixture. Acetone was evaporated by continuous mixing at ambient conditions. This liberated crystalline material which was subjected to wet grinding until drying to develop flowable solid which was stored in an air-tight container. The pure drug and pure sugar were similarly treated to produce the positive controls for the drug and sugar, respectively.

Table 1: The compositions of the tested formulations presented as molar and weight ratios.

Formulation	Flutamide	Sucralose
Wet ground drug	1	0
FS 1:1	1 (1)	1 (1.439)
FS 1:2	1 (1)	2 (2.878)
FS 1:3	1 (1)	3 (4.317)

Values between brackets represent the weight ratios.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of processed and unprocessed flutamide and sucralose as well as the developed co-crystals were recorded using a FTIR spectrophotometer made by Bruker Tensor 27 (Ettlingen, Germany). The powdered sample was mixed with potassium bromide. This was compressed into thin disks which were loaded into the sample holder before scanning from 4000 to 400 cm^{-1}. This equipment employs a DLaTGS detector and is supported by Opus IR, FTIR software which was utilized in spectral data analysis.

Powder X-ray diffraction (PXRD)

The X-ray diffraction patterns of the target samples were monitored using a GNR APD 2000 pro-X-ray diffractometer with Cu Kα radiation (1.540598 A^o) (Agrate Conturbia, Italy). The diffraction pattern was detected with a position sensitive detector (VA^o NTEC-1). The diffraction pattern was collected at ambient conditions with a 2θ axis with continuous scan mode. The scanning was established in the range of 5-70^o at step size of 0.03^o.

Differential scanning calorimetry (DSC)

Thermal analysis studies utilized a differential scanning calorimeter (DSC 60, Shimadzu, Kyoto, Japan). Known weight (about 3mg) of the sample (flutamide, sucralose or the potential co-crystal) was loaded in aluminum pan. The pan was crimped and was loaded into the equipment. Empty pan was similarly crimped and was used as reference. Thermal analysis was conducted while heating the sample at constant rate (10^{o}C/minute) to cover the temperature range of 30 to 400^{o}C. Heating was conducted under steady flow of nitrogen gas. The thermal events were monitored and analyzed with the aid of thermal analysis software (TA- 60WS).

Dissolution studies

Flutamide dissolution was conducted according to the USP experimental conditions.[16] This employed 1000ml of 0.1 N HCl (pH 1.2) containing 2% w/v SLS as dissolution medium. This was equilibrated and maintained at 37 ± 0.1^{o}C and the paddle speed was adjusted to 75 rpm. Powdered samples equivalent to 250 mg of flutamide were added to the dissolution vessels. Samples (10ml) were withdrawn at appropriate time intervals (5, 10, 15, 30, 45 and 60 min) and replaced with 10 ml of fresh dissolution fluid to maintain a constant volume. The dissolution samples were filtered immediately using a 0.45 µm Millipore filter. The drug content in each sample was determined by UV spectrophotometry at 306 nm after suitable dilution. Dissolution studies were conducted in triplicates. The cumulative amount of drug dissolved was expressed as percentage of the initial amount added and was plotted as a function of time to produce the dissolution profile. This profile was used to compute the dissolution parameters which included the percentage of drug dissolved in the first 5 minutes (Q5) and the dissolution efficiency (DE). DE was calculated according to Khan (1975)[17] using the area under the dissolution profile at time (t) expressed as percentage of the area under the dissolution profile assuming immediate (100%) dissolution. These parameters were used for statistical comparison between different formulations. Further statistical manipulation was accomplished using the similarity factor test which compares the overall dissolution profiles. F2 was computed using the following equation which utilizes the number of samples (n), the percent of drug dissolved from the test formulation (R_t) and from the reference formulation (T_t) at the corresponding time points:

$$F2 = 50 \times log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]\right\}^{-0.5} \times 100.$$

RESULTS AND DISCUSSION

FTIR spectroscopy

Co-crystallization is supposed to employ non-covalent bonds between the drug and the co-former with hydrogen

bonding being shown to have a major role. Accordingly, the FTIR spectroscopy was used to monitor the potential cocrystallization. Fig. 1 shows the recorded FTIR spectra of pure and wet ground flutamide, sucralose and their wet co-ground products. The assignment of the recorded spectral pattern of the unprocessed drug and sucralose is summarized in Table 2. The recorded absorption bands of pure unprocessed flutamide reflected its chemical structure (Table 2).

This spectrum is similar to the published spectrum for the same compound.[18,19] Wet grinding of flutamide after recrystallization from its solution in acetone did not alter the spectral pattern of the drug with the recorded spectrum being similar to that of unprocessed drug (Fig. 1). This indicated that the wet processing has no effect on the chemical structure of flutamide and that any spectral alteration after wet co-grinding with sucralose can be taken as evidence for drug sugar interaction.

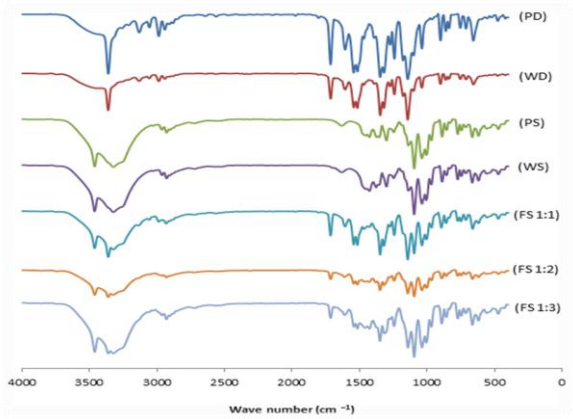

Fig. 1: FTIR spectra of pure unprocessed drug (PD), wet ground drug (WD), pure unprocessed sucralose (PS), wet ground sucralose (WS) and different co-crystal formulations. Formulation details are in Table 1.

Table 2: The characteristic absorption bands of FTIR spectra of the pure drug and sucralose.

Absorption band	Position of the peak (cm^{-1})	
	Flutamide	Sucralose
NH-stretching	3360	
CH-stretching	3132, 3056	3030
CH_2-stretching	2987, 2942	2964, 2929
C=O stretching	1715	
C=C stretching	1607	
NO_2 asymmetric stretching	1545	
NH-bending	1516	
CF_3 stretching	1349	
NO_2 symmetric stretching	1320	
CN amide stretching	1243	
CN amide torsion	902	
CN nitro	754	
Free and bonded OH stretching		3461, 3322
C-O stretching		1301, 1139, 1097, 1039, 1007, 890
C-Cl stretching		774, 667, 621

The FTIR spectrum of unprocessed sucralose correlated to its chemical structure with the principle absorption band being evident (Fig. 1, Table 2). This spectrum is similar to that recorded in other studies.[11,20] Wet grinding of the sugar after precipitation from its solution in acetone did not affect the spectral pattern of sucralose (Fig. 1).

Wet co-grinding of flutamide and sucralose after co-precipitation from their solution in acetone provided solid products with FTIR spectra which were not exactly the sum of the spectral pattern of both flutamide and sucralose. The spectral changes depended on the relative proportions of flutamide and sucralose (Fig. 1). The changes in flutamide are evident in the peaks corresponding to the NH-stretching and bending vibrations, those resulting from NO_2 symmetric and asymmetric stretching vibration as well as the peak corresponding to C-N torsion. These changes were manifested as broadening of the peaks with those of the NO_2 symmetric stretching and CN torsion shifting to lower wave number as well. The change was clearer at higher concentrations of sucralose. Along with these changes, the spectral pattern of sucralose showed broadening of the absorption bands corresponding to the hydroxyl group and CO bond. These changes are major signs for hydrogen bonding. Similar changes have been considered as indication for hydrogen bonding with authors went further to tentatively diagnose co-amorphization[21] or co-crystallization process.[11] This supposition requires confirmation by DSC and X-ray diffraction.

Differential scanning calorimetry (DSC)

DSC was employed to monitor the thermal behavior of flutamide after processing in absence and presence of sucralose. Fig. 2 shows representative thermograms of flutamide and sucralose before and after processing or co-processing. These thermograms were used to compute the thermodynamic parameters which are tabulated in

Table 3. Pure unprocessed flutamide was shown to be crystalline as indicated from the sharp endothermic peak which was seen at 110.55°C reflecting its melting transition. Flutamide decomposition was reflected as two endotherms which were noticed at 256.96 and 282.12°C. The thermal behavior is similar to that published by other investigators for flutamide.[22,23] Wet grinding of flutamide after recrystallization from acetone produced crystalline material with a melting transition at a T_m of 111.14°C. This endothermic peak was broader than that recorded with the unprocessed flutamide as indicated from the values of the onset and endset of the endothermic peak. The change in the main endotherm was associated with a change of the relative enthalpies of the degradation peaks which were shifted to 258.49 and 290.37°C (Fig. 2 and Table 3). These changes in the thermal behavior after recrystallization from acetone with wet grinding can be attributed to possible dimorphism, a phenomenon which is documented for flutamide.[24]

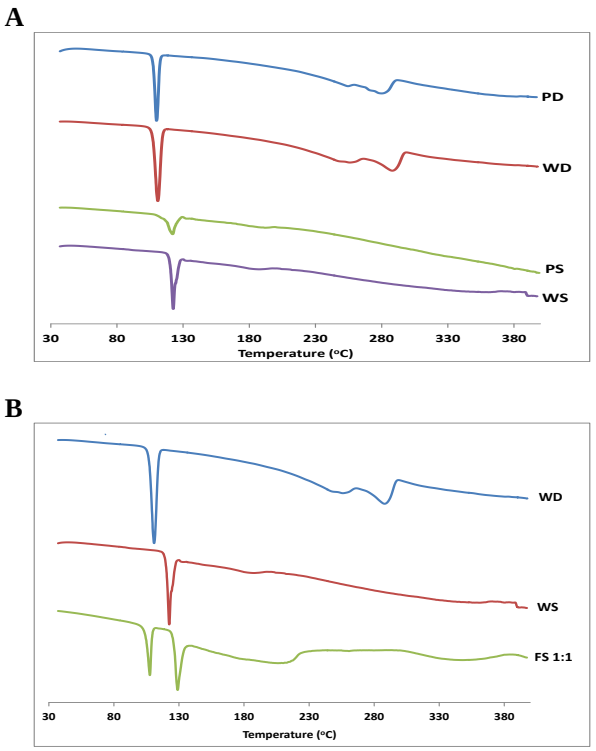

Fig. 2: DSC thermogram of pure unprocessed drug (PD), wet ground drug (WD), pure unprocessed sucralose (PS), wet ground sucralose (WS) and different co-crystal formulations. Formulation details are in Table 1.

The thermal behavior of unprocessed sucralose reflected its crystalline nature as indicated from the melting endotherm which was seen at 123.8°C (Fig. 2). This correlates with the published data on the sugar.[25,26] Recrystallization of sucralose from acetone followed by wet grinding produced crystalline powder with similar melting point but the melting transition had lower enthalpy (Fig. 2 and Table 3).

Table 3: The thermodynamic parameters of the pure drug, sucralose and the co-crystal formulations.

	Onset (°C)	Endset (°C)	T_m (°C)	Enthalpy J/g
Pure flutamide	101.81	117.98	110.55	82.74
Wet ground flutamide	100.97	119.22	111.14	106.93
Sucralose	109.9	130.98	123.8	41.67
Wet ground sucralose	120.08	130.37	123.82	25.53
FS (1:1)	97.91	116.1	109.8	36.87
	126.15	140.42	131.55	51.06
FS (1:2)	98.27	116.22	109.15	22.94
	128.86	144.8	135.74	77.82
FS (1:3)	98.82	114.78	109.33	12.88
	126.31	142.11	132	61.53

Wet co-grinding of flutamide with sucralose after recrystallization from their solution in acetone produced crystalline product with compromised thermal pattern compared with the thermal behavior of the individual components. The thermal pattern of the product of wet co-grinding depended on the relative proportions of flutamide to sucralose. For formulation containing equimolar ratio of flutamide with sucralose, the developed product had a thermal behavior showing two endothermic peaks at 109.8 and 131.55^{o}C. The relative enthalpy of those endothermic peaks was 0.72 (first peak/second peak). Those endothermic peaks do not correlate with the melting transition of either processed flutamide or sucralose. This may imply the development of new crystalline products in which dimorphs of flutamide interact separately with sucralose to develop two new crystalline species probably of co-crystal type (to be confirmed by X-ray studies, see below). This supposition is confirmed from the development of two degradation endotherms at 210.95 and 354.34 ^{o}C after wet co-grinding (Fig. 2 and Table 3). These decomposition endotherms were different from that recorded with flutamide even after wet grinding in absence of sucralose. Doubling the molar ratio of sucralose (FS 1:2) produced crystalline product showing two melting endotherms at 109.15 and 135.47^{o}C. The relative enthalpy of those transitions was 0.29 reflecting the dominance of the second peak over the first endotherm. This was associated with weakening of the decomposition endotherms which were seen in formulation containing equimolar ratio of the drug with sucralose. Further increase in the molar ratio of sucralose (FS 1:3) produced crystalline product showing two melting transitions at 109.33 and 132^{o}C with relative enthalpy of 0.2. The decomposition endotherms were too weak to be identified in this case. Overall, the DSC data suggest the formation of a mixture of co-crystalline products. Modulation in the thermal behavior after wet co-grinding has been taken as possible diagnosis for co-crystallization.[11,27,28]

Powder X-ray diffraction (PXRD)

X-ray diffraction was used to investigate the effect of processing and co-processing on the crystalline structure of flutamide. Fig. 3 shows representative diffractograms for flutamide and sucralose before and after processing and co-processing. The recorded diffraction peaks are presented in Table 4. The diffractogram of the unprocessed flutamide showed the characteristic diffraction pattern of flutamide crystals with strong diffraction peaks being noticed (Fig. 3 and Table 4). This pattern is similar to that recorded for flutamide in other studies.[24,29,30] Recrystallization of flutamide from acetone with wet grinding developed drug crystals which exhibited an X-ray diffraction pattern different from the unprocessed flutamide. The difference was shown as change in the shape and 2θ values of the diffraction peaks to reveal new diffraction peaks. The new peaks were recorded at 2 θ values of 11.09^{o}, 17.87 ^{o}, 18.14^{o}, 20.48^{o}, 21.14^{o}, 25.64^{o}, 25.97^{o}, 30.05^{o}, 35.21^{o}, 40.22^{o} and 42.8^{o}. Examples of those peaks that exhibited change in the shape include those recorded at 2θ values of 11.3^{o}, 14.75^{o}, 21.02^{o}, 21.98^{o}, 22.76^{o}, 24.74^{o}, 25.85^{o}, 28.05^{o}, 29.03^{o}, 29.96^{o} and 40.07^{o} (Fig. 3 and Table 4). These findings support the recorded change in the thermal behavior of flutamide after processing and reflect the existence of a mixture of crystalline species due to dimorphism.

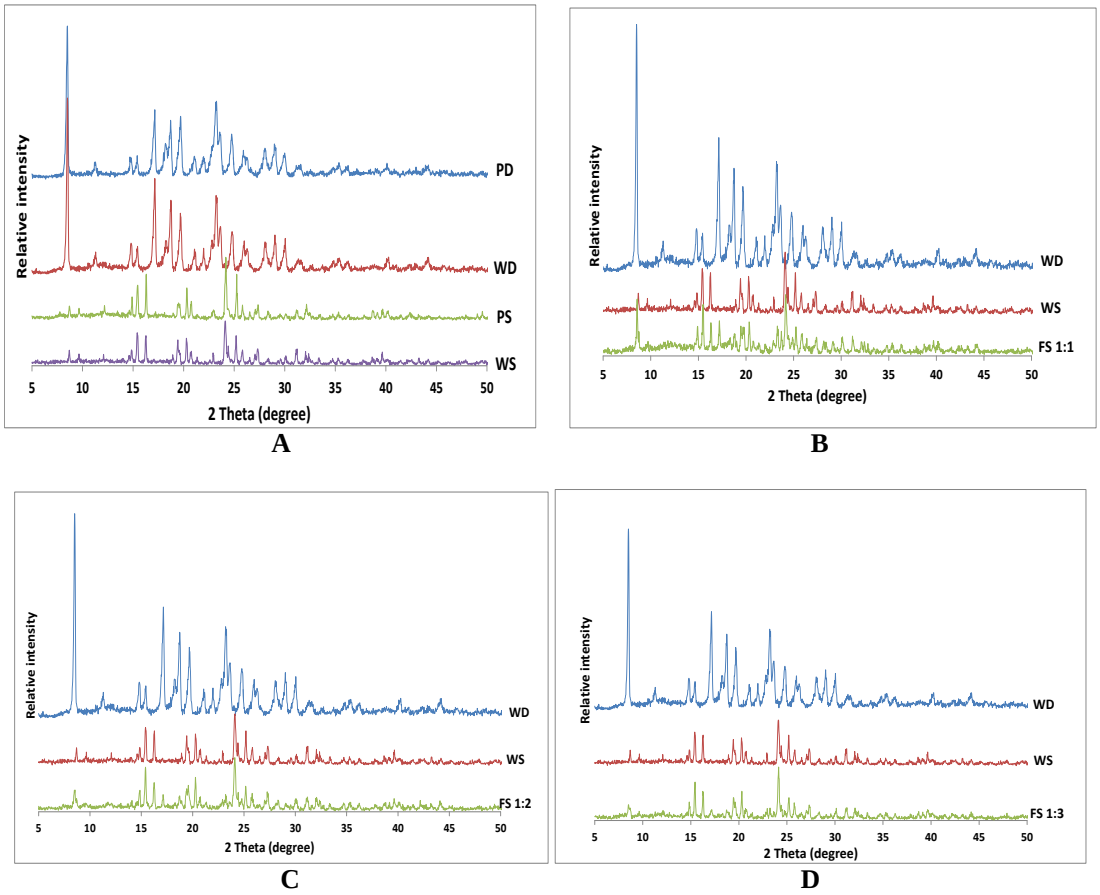

Fig. 3: X-ray diffraction pattern of pure unprocessed drug (PD), wet ground drug (WD), pure unprocessed sucralose (PS), wet ground sucralose (WS) and different co-crystal formulations. Formulation details are in Table 1.

Table 4: The characteristic diffraction peaks of pure drug, sucralose and the co-crystal formulations.

	2 Theta (degrees)
Pure flutamide	8.48, 11.18, 11.3, 11.48, 14.75, 15.41, 17.15, 18.2, 18.68, 19.52, 19.67, 20.78, 21.02, 21.98, 22.76, 23.18, 23.54, 24.74, 25.85, 26.24, 27.95, 29.06, 29.87, 29.96, 31.31, 31.55, 34.76, 35.33, 36.2, 40.07, 43.91, 44.1
Wet ground flutamide	8.51, 11.09, 11.18, 11.3, 14.75, 15.41, 17.15, 17.87, 18.14, 18.2, 18.68, 19.50, 19.67, 20.78, 21.02, 21.14, 21.98, 22.76, 23.21, 23.57, 24.74, 25.64, 25.85, 25.97, 26.24, 29.03, 29.96, 30.05, 31.31, 31.55, 34.79, 35.21, 35.33, 36.2, 40.07, 40.22, 42.8, 43.91, 44.1
Sucralose	7.76, 8.69, 9.65, 12.17, 14.6, 15.42, 16.28, 17.24, 19.4, 19.61, 20.3, 20.75, 22.79, 22.9, 24.17, 25.25, 25.82, 26.51, 27.05, 27.29, 28.34, 28.37, 28.58, 29.51, 30.1, 31.1, 31.25, 32.06, 32.12, 33.32, 34.76, 35.3, 38.63, 39.11, 39.6, 40.13, 42.32, 43.2, 49.52
Wet ground sucralose	8.69, 9.65, 12.08, 14.57, 14.91, 15.42, 16.28, 18.89, 19.4, 19.61, 20.3, 20.69, 20.75, 21.32, 22.9, 24.08, 24.41, 25.19, 25.82, 26.51, 27.05, 27.29, 28.37, 29.54, 30.02, 31.1, 32.06, 32.12, 32.36, 33.32, 34.76, 35.27, 38.63, 39.11, 39.6, 43.2, 44.15
FS (1:1)	8.54, 14.75, 15.44, 17.18, 18.71, 19.46, 19.67, 19.73, 20.36, 23.24, 23.3, 23.57, 25.22, 25.79, 26.33, 27.35, 29.03, 30.08, 31.25, 32.42, 34.76, 35.3, 36.26, 38.72, 39.68, 40.1, 40.22, 42.62, 43.19, 44.09
FS (1:2)	8.48, 8.66, 14.03, 14.78, 15.38, 16.28, 17.12, 18.68, 18.86, 19.4, 19.58, 20.69, 22.88, 23.21, 24.08, 24.41, 25.16, 25.71, 27.26, 28.31, 30.05, 31.25, 32.06, 32.33, 34.67, 35.21, 35.33, 36.2, 38.75, 39.62, 42.14, 43.25, 44.06
FS (1:3)	8.45, 8.63, 14.03, 14.81, 15.41, 16.25, 17.14, 18.67, 18.86, 19.46, 19.61, 20.66, 22.91, 23.21, 24.11, 25.16, 25.71, 25.79, 26.45, 27.26, 28.31, 30.05, 31.16, 31.22, 32.06, 32.36, 34.67, 35.21, 35.22, 36.17, 38.75, 39.56, 39.68, 43.28, 44.15

The crystalline nature of sucralose was evident from its characteristic diffraction pattern (Fig. 3 and Table 4). These results are similar to the published data on the sugar.[31] Wet grinding of sucralose after precipitation from its solution in acetone resulted in noticeable changes in the X-ray diffraction pattern of the sugar. This was shown as a change in the shape and location of the diffraction peaks compared to the unprocessed

sucralose (Fig. 3 and Table 4). Similar changes have been recorded in other studies after recrystallization from acetone and were taken as an indication for crystalline structure modification based on the solvent of crystallization.[11] Taking the changes in flutamide and sucralose after separate processing into consideration, the recrystallized materials will be adopted as positive control in assessing the diffractograms of the products of wet co-grinding.

Co-processing of flutamide with sucralose after simultaneous recrystallization from their solution in acetone developed solid product which had compromised X-ray diffraction pattern compared with that of each of the positive controls. The change depended on the relative proportions of flutamide to sucralose in the mixtures (Fig. 3 and Table 4). These changes were seen in the shape of the diffraction peaks with the development of new peaks.

For example in formulation containing 1:1 molar ratio new peaks were recorded at 2θ values of 19.73°, 20.36°, 23.3°, 25.22° and 27.35°. This was associated with a change in the shape of the peaks which were noticed at 18.71°, 23.24°, 27.35°, 29.03° and 32.42°. With respect to 1:2 molar ratio new peaks were recorded at 14.03°, 28.31°, 31.25°, 32.06° and 42.14°. Those undergoing change in the shape include the peaks at 8.48°, 17.12°, 19.4°, 38.75° and 39.62°. These changes confirm the development of new crystalline species which is of co-crystal type. For the product containing 1:3 molar ratio the X-ray diffraction pattern was a combination of that recorded in case of 1:2 molar ratio and that recorded with the processed sucralose. This was evidenced by the appearance of the peaks corresponding to sucralose in this diffractogarm. Examples of these peaks include those at 25.79°, 32.16°, 26.45° and 44.15° (Fig. 3 and table 4). This finding reflects the existence of excess sucralose in the system containing 1:3 molar ratio indicating that 1:2 molar ratio of flutamide to sucralose provides the optimum stoichiometric ratio for co-crystallization. It is important to emphasize that in all cases the recorded diffraction peaks after co-processing were of lower intensity indicating size reduction along with co-crystallization. Changes in the X-ray diffraction pattern after co-processing have been taken as indication for co-crystallization.[32-34]

Dissolution studies

To elucidate the effect of co-crystallization process, the dissolution behavior of flutamide co-crystallized products were evaluated in reference to the unprocessed (negative control) or recrystallized drug (positive control). The obtained dissolution profiles are shown in Fig. 4. These profiles were used to extract the dissolution parameters that were presented as the amount of drug dissolved in the first 5 min (Q5) and the percentage dissolution efficiency (%DE). These are presented in Table 5.

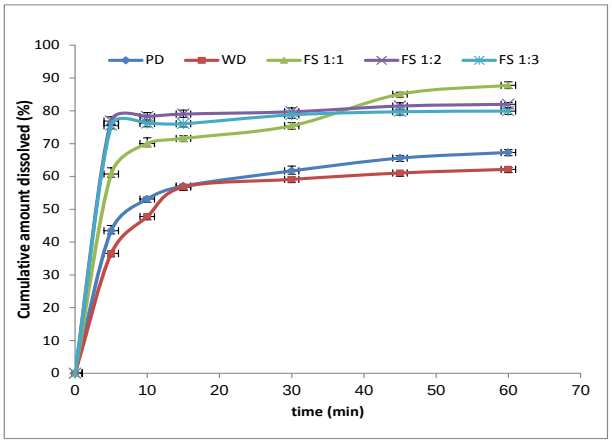

Fig. 4: The dissolution profiles of pure unprocessed drug (PD), wet ground drug (WD) and different co-crystal formulations. Formulation details are in Table 1.

Unprocessed flutamide (negative control) showed a slow dissolution with the liberation of about 43% of the loaded dose (250 mg) in the first 5 min. Poor drug solubility was further confirmed by the dissolution of only 67% of the dose within the course of the release experiment (1 h). The calculated dissolution efficiency for the unprocessed drug was 57%. Recrystallization of the drug from acetone in the absence of sucralose (positive control) released only 36% of the drug after 5 min, with the total release of 62% at the end of the dissolution time. The calculated DE for the recrystallized drug was 54% (Fig. 4 and Table 5). The reduction in dissolution parameters of the wet ground drug compared to unprocessed one indicates the formation of a new crystalline structure. This result confirms the DSC findings that indicated formation of other polymorphic form of flutamide with stronger crystalline nature, as reflected by higher melting and decomposition transitions.

Table 5: The dissolution efficiency and Q5 values of the pure unprocessed drug, wet ground drug and the prepared co-crystal formulations.

Formulation	Q5 (%)	Dissolution efficiency (%)
Pure unprocessed drug	43.4 (1.6)	57.8 (0.5)
Wet ground drug	36.5 (0.8)	54.3 (0.6)
FS 1:1	60.7 (1.9)	73.9 (0.8)
FS 1:2	76.9 (1.3)	76.6 (0.4)
FS 1:3	75.5 (0.5)	75 (0.3)

Values between brackets are SD (n = 3).

Preparation of co-crystals of drug with sucralose significantly enhanced the dissolution rate of the drug relative to that of the unprocessed drug or the positive control. The improvement of dissolution parameters largely depended on the molar ratio of sucralose to drug. The recorded Q5 values were 60.7%, 76.9% and 75.5% for co-crystals containing the drug with sucralose at molar ratios of 1:1, 1:2, and 1:3, respectively. The total amounts of drug dissolved in 60 min were 87%, 82% and 80%, respectively. Such enhancement could be attributed to the formed co-crystals with possibly weaker crystalline packing that favor rapid dissolution. This assumption is evidenced by DSC data. Particle size reduction can also be taken as another contributing factor, as suggested from the X-ray results. The same approach was previously shown to have high potential for dissolution enhancement with noticeable success being reported with a variety of drugs.[28,34-36] The calculated dissolution efficiency values were 73%, 76% and 75% for co-crystals containing the drug with sucralose at molar ratios of FS1:1, FS1:2 and FS1:3, respectively (Fig. 4 and Table 5). It worth noting that product FS1:3 with sucralose at its highest concentration did not show any enhancement in the dissolution parameters over that of FS1:2. This dissolution behavior coincides with the X-ray characterization that revealed that 1:2 molar ratio of flutamide to sucralose provides the optimum stoichiometric ratio for co-crystallization. Any further addition of sucralose will have no effect on co-crystal formation.

The similarity factor test was employed to compare between the dissolution profiles of the drug from various formulations. This comparison indicated dissimilarity between the developed co-crystals and the unprocessed drug or the recrystallized drug. This pattern was evident irrespective to the molar ratio of sucralose used with the calculated F parameter ranging from 29-38%. This indicated the superiority of co-crystals regarding flutamide dissolution rate. Regarding the effect of co-former ratio, the similarity factor test reflected that the three co-crystals prepared from the drug with sucralose at 1:1, 1:2 and 1:3 molar ratios are considered similar.

CONCLUSION

Wet grinding of flutamide after liberation from acetone solution resulted in dimorphisim with the resulting product showing comparable dissolution pattern to that of unprocessed drug. Wet co-grinding with sucralose developed co-crystalline product with faster dissolution rate compared to the pure or wet ground flutamide. Co-crystallization can be taken as a tool for enhancing the dissolution rate of flutamide.

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