The Influence of Salt Formation on Electrostatic and Compression Properties of Flurbiprofen Salts

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Abstract

Salt formation is an effective method of improving physicochemical properties of acidic and basic drugs. The selection of a salt form most suitable for drug development requires a well-designed screening strategy to ensure various issues are addressed in the early development stages. Triboelectrification of pharmaceutical powders may cause problems during processing such as segregation of components due to the effects of particle adhesion. However, very little work has been done on the effect of salt formation on triboelectrification properties. In this paper, salts of flurbiprofen were prepared by combining the drug with a selection of closely related amine counterions. The aim of the work was to investigate the impact of the counter ion on electrostatic charge of the resultant salts to inform the salt selection process. The experimental results show the magnitude of charge and polarity of the flurbiprofen salts to be highly dependent on the type of counter ion selected for the salt formation. Furthermore, particle adhesion to the stainless steel surface of the shaking container and the salts' compression properties were measured. The formed salts had lower electrostatic charges, improved tabletability, and resulted in reduced adhesion of these powders compared with the parent drug.

Keywords: triboelectrification, electrostatic, salt formation, crystal structure, compaction

1. Introduction

In many instances, physical properties of pharmaceutical powders need to be modified to attain optimal processing characteristics suitable for formulation design (Wouters and Quéré, 2012). Various strategies for modifying the physical properties of pharmaceutical materials have been attempted to address specific drug formulation problems. Crystallising acidic or basic drugs into salts is a method routinely used in the pharmaceutical industry to enhance the solubility or stability of drugs and can overcome some undesirable characteristic which exist in the parent drug. Salt formation can increase the solubility by several orders of magnitude, which has a significant effect on the dissolution rate of pharmaceutical compounds (Serajuddin, 2007). The increase in solubility and dissolution rate effectively translates into an increased rate and extent of absorption for the drug (Elder *et al.,* 2012). An estimated half of all drug molecules used in medicinal therapy are administered as salts (Stahl and Wermuth 2002). The charged groups of the parent drug and the counter ion are attracted by intermolecular coulombic force. The salt form is then precipitated and recrystallised at set conditions to minimise impurities which otherwise may have a significant effect on the strength of the resulting intermolecular bonds leading to changes in crystal habit. Consequently, salt formation is often the final stage that determines the physical properties of primary materials for formulation development. The basis for salt formation generally begins with the selection of small, compact counterions to enhance solubility (Elder *et al.,* 2012). Additions of hydrophilic groups to the counter ion can improve solubility, but the additional H-bonding capability can result in undesirable properties, e.g. polymorphism or hydrate formation (David *et al.,* 2012), which may result in differences in physicochemical properties of the material (Vranić, 2003).

However, there is often a compromise to be made between solubility and other physiochemical properties. Selection of the appropriate solid form is critical both for chemical and pharmaceutical

processing (Kumar *et al,* 2008) and therefore significant efforts are typically expended into selecting the optimum salt form for ionisable compounds. The selection process requires a well-designed screening strategy to ensure various development issues are addressed as early as possible. The selection process must therefore be rational and streamlined to aid the selection of a suitable salt as numerous salt forms are available. Alternatively, several salt forms of the drug candidate may be synthesised for preformulation testing. The selection of the most appropriate salt form does not necessarily equate to selection of the salt with the optimal solubility and dissolution rate (Waterman *et al.,* 2002), but rather a balance between best aqueous solubility, degree of crystallinity, hygroscopicity, melting point, chemical and physical stability and bulk physical properties (Gould, 1986, Serajuddin, 2007). It is well established that the salt selection strategy and formulation strategy should be fully aligned (Bastin *et al.,* 2000). The physicochemical properties of new salt forms are thoroughly characterised in the early stages of drug development and characterisation commonly includes particle size, particle habit, flow properties etc., however, very little work is reported on the characterisation of triboelectrification properties of the salt forms. Particle electrification is a common phenomenon that occurs in many powder handling industries including pharmaceutical, food and detergent industries. In the pharmaceutical industry the *triboelectrification* process refers to a method of particle electrification which can take place during powder handling operations. The triboelectric charging is regarded as a solid state electrochemistry, where there is no transport medium (electrolyte) and the reaction depends on a physical contact (Matsusaka *et al.,* 2010). Therefore, surface modifications due to salt formation are likely to affect the charge transfer process. Powder handling operations, such as pneumatic conveying, sieving, mixing and milling, cause particles to make frequent contact amongst themselves and with the walls of the processing equipment (Šupuk *et al.,* 2012). In these processes, particles are brought into contact with each other; transfer charges and remain charged upon separation (Greason, 2000). In many cases, the excessive triboelectrification of powders is problematic: in the extreme, it may lead to dust explosions, but even at more modest levels, may give rise to segregation of components

(Šupuk *et al.,* 2011) affecting the content uniformity. Furthermore, when materials become charged, their behaviour can change leading to increased inter-particle cohesion or repelling of other charged materials (Matsusaka *et al.,* 2010) which has an effect of reducing the flow and creating the resistance resulting in deposition and blockage of pipes (Matsusaka and Masuda 2003).

In this work a model acidic drug, flurbiprofen, was used. It is a hydrophobic crystalline drug known to have poor mechanical and adhesion properties, factors which are common for materials with a great propensity for triboelectrification. Flurbiprofen is a poorly soluble crystalline drug belonging to the non-steroidal anti-inflammatory (NSAID) class of drugs used to reduce inflammation and pain relief by targeting a non-selective cyclo-oxygenase (COX) inhibitor, an enzyme responsible for production of natural inflammatory substances as a reaction to an injury. It is frequently used in treatment of osteoarthritis and rheumatoid arthritis (Cushny, 2012). However, the drug does not provide immediate relief of pain due to low aqueous solubility of 0.03 mg/ml (Morimoto, 1992). It is known to have poor compaction properties (Ramirez, 2010; Chow *et al.,* 2012), flowability and adhesion properties having a tendency to adhere to the punch surfaces during compaction (Wang *et al.,* 2004, Serajuddin, 2007, Ramirez, 2010). The poor mechanical and adhesion properties may be caused by high flurbiprofen charge and diminution of this charge may lead to improvements in these properties. The drug was used to form a number of salts of varying properties, with a series of amine counter ions in an equimolar ratio using a suitable solvent. Successful salt formation was confirmed by an assessment of the salt forms following analytical characterisation. Triboelectrification properties of the formed salts were investigated using a tribo-electric device based on a shaking concept. The electric charge transferred to the particles was quantified by a Faraday cup as a function of shaking time, frequency and container material. The potential impact on the triboelectrification and compression behaviour of the salt forms was assessed.

2. Materials and Methods

2.1 Materials

Flurbiprofen, (*RS*)-2-(2-fluorobiphenyl-4-yl) propanoic acid, contains a biphenyl group and a fluorine atom at the ortho position of the second biphenyl ring (see Figure 1), has a pKa value of 4.22 (Lacoulonche *et al.* 1997), melting point of 115 °C and a molecular weight of 244.26 g/mol.

The materials used in this study are listed in Table 1. In addition to the listed materials, acetonitrile and methanol were used as solvents. The partition coefficient, CLogP, and the acid dissociation constants, pKa, were obtained from the literature.

2.2 Methods

2.2.1 Salt formation

Flurbiprofen salts were prepared by combining an equimolar ratio (0.01 moles) of the flurbiprofen with the relevant amine in 40 ml of acetonitrile. The solution was thoroughly mixed and the precipitate recovered using vacuum filtration. The precipitated salts were oven dried at 50°C and 300 mbar. The exception was the flurbiprofen tris salt which was made by dissolving the amine in a warmed solution of methanol before adding to a solution of the drug in acetonitrile. The resulting solution was kept at -20°C for 20 hours in a freezer until the flurbiprofen tris salt precipitated; then the crystals were collected by vacuum filtration.

2.2.2 Salt characterisation

The salts were characterised using a variety of analytical techniques including differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), x-ray powder diffraction (XRPD) and Fourier transform infrared spectroscopy (FT-IR) to confirm their formation. Particle size distribution and surface asperities were characterised using Malvern Mastersizer 2000 and Jeol JSM-6060CV Scanning Electron Microscope (SEM).

2.2.3 Fourier transform infra-red (FR-IR)

The powder in solid form (5-10 mg) was placed on an Attenuated Total Reflection (ATR) plate and analysed using FT-IR spectroscopy. Salt confirmation was analysed by measuring the transmittance of infrared wavelengths of the electromagnetic spectrum of the sample in the range of 400 to 4000 cm^{-1}.

2.2.4 Thermal analysis

Differential scanning calorimetry (DSC) was performed using Mettler Toledo DSC. Specimens (approx. 5 mg) were analysed in vented aluminium pans under dry nitrogen purge (at 50 mL min^{-1}) over the range 25 to 250°C at 5 °C min^{-1} heating rate. Thermogravimetric analysis (TGA) was performed using Mettler Toledo TGA using between 5 and 10 mg of sample over the temperature range 25 to 250 °C with nitrogen as a purge gas flowing at 200 ml/min.

2.2.5 *Powder x-ray diffraction (XRD)*

The XRD patterns of drug and salt samples were obtained using Bruker D2 Phaser XRD diffractometer. The samples were scanned from 5 to 100° 2θ at a rate of 1.5° min^{-1}.

2.2.6 *Particle size and shape observations*

Scanning electron microscopy (SEM) images of the sample surface were obtained using Jeol JSM-6060CV SEM. The sample surface topography, composition, particle size and other properties were obtained from the images. Samples were sputter-coated with an ultra-thin coating of gold/palladium (80:20) for 60 seconds using the Quorum SC7620 Sputter Coater. The ddescription of particle shape by Rawle (2008) was followed.

2.2.7 *Particle size distribution (PSD)*

The PSD was determined using laser light scattering technique using Malvern Mastersizer 2000 wet dispersion method. Flurbiprofen salts (0.1% w/v) were dispersed in cyclohexane using ultrasonication. Igepal CA 30 was used to aid dispersion. Particle size distribution was described using volume equivalent diameters at 10% (d_{10}), 50% (d_{50}) and 90% (d_{90}) cumulative volume.

2.2.8 *True density*

The true densities of the drug and salt powders were measured in triplicate using a Helium Pycnometer (Micrometrics, UK).

2.2.9 Tribo-electrification

A tribo-electric device based on a shaking concept, previously described by Šupuk *et al.,* (2009) and later by Asare-Addo *et al.,* (2013) was used to investigate the tribo-electrification of bulk powders by determining the charge-to-mass ratio. Charge-to-mass ratio is an important parameter that needs to be determined in order to accurately predict the behaviour of charged particles. The most common device used for charge-to-mass measurement is the Faraday cup, which works on the principle that charge induces an image of itself on a conducting surface. In this work, the charge-to-mass ratio of the bulk powders was measured following shaking using a custom made Faraday cup connected to an electrometer (Keithley Model 6514). A typical Faraday cup is shown diagrammatically in Fig. 2.

The Faraday cup consists of two conducting cups with an entrance on the top through which powder can enter. The inner cup is isolated from the outer cup by an insulating spacer. The outer cup is used to prevent external charges being measured and reduce any external noise. As demonstrated in Fig. 2, if a positively charged particle enters the Faraday cup, a negative charge (q) is induced and distributed on the inner surface of the Faraday cup, whilst a positive charge is distributed over the outer surface of the cup, setting up an electric field and a potential difference between the two cups.

The capacitance C between the inner and outer cups (Fig. 2) acquires a potential, $V = q/C$ which is measured by an electrometer connected to an inner cup. The charge-to-mass ratio is obtained by dividing the net charge measured and the mass of the sample tested. Tests were carried out under ambient temperature (22 ℃) and humidity (25-45 % RH).

2.2.10 Compression of flurbiprofen and its salts

All the powder samples were compressed using a Testometric M500 - 50 CT (Testometric Company Ltd., United Kingdom) materials testing machine equipped with 13.00 mm Atlas Evacuable Pellet Die (Specac Limited, United Kingdom). The powder was accurately weighed (300 ± 2 mg) on an analytical balance and poured into the die. Among the flat-faced punches of the materials testing machine, the lower punch was held stationary while the upper punch moved at a speed of 3 mm/min during loading and 1 mm/min on unloading. The compacts were fabricated at applied pressure range between 50 and 250 MPa. Flurbiprofen showed higher degree of capping and lamination at maximal pressure therefore only two compacts could be made at 250 MPa. After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery. Relative humidity and temperature during compaction work were in the range 25-45 % RH and 22 °C, respectively.

Tablets were then fractured diametrically using a Tablet Hardness Tester (Pharma Test PTB 311E). Maximum breaking force, diameter and thickness of compacts were used to calculate tensile strength according to Equation 1, (Fell and Newton, 1970):

$$\sigma_X = \frac{2F}{\pi DH} \qquad (1)$$

Where σ_X is tensile strength (MPa), F is the breaking force (N), D is the tablet diameter (m), and H is the thickness of tablet (m).

The tablets compressional characteristics were studied using Heckel compression model (Heckel, 1961; Heckel, 1961a), relating powder porosity (E) during compression to the applied pressure (P). The equation is written as follows:

$$ln\left(\frac{1}{E}\right) = KP + A \qquad (2)$$

Where *K and A* are constants representing particle rearrangement and slope of the linear region, respectively.

The slope of the straight line portion (*K*) is inversely related to the material's mean yield pressure (P_y):

$$\frac{1}{K} = P_y \qquad (3)$$

The yield pressure (P_y) gives an indication regarding the plasticity of the material, so it can be utilized to classify the compacts from very soft to hard, Table 2. The compression data profiles were then fitted to the linear form of Kawakita's equation, (Kawakita and Ludde, 1970-1971) given by equation 4:

$$\frac{P}{C} = \frac{1}{ab} + \frac{p}{a} \qquad (4)$$

Where *P* is the applied pressure and *C* is the engineering strain, calculated as,

$$C = V_0 - \frac{V}{V_0} \qquad (5)$$

Where V_o is the initial powder volume and *V* is the volume of the powder at pressure *P*. The Kawakita parameters *a* and b^{-1} were calculated from the linear regression of the profiles.

3. Results and Discussion

3.1 Thermal Analysis

Thermal analysis was carried out using TGA and DSC techniques. The inclusion of water within the crystal lattice is known to change the shape, symmetry and number of molecules within the unit cell (Khankari and Grant, 1995), which may influence the electrostatic behaviour. As a result, TGA analysis was carried out which showed no weight losses that would indicate hydrate/solvate formation. The results from DSC are summarised in Table 3 and are in accordance with previous publications (David *et. al.,* 2012, Schwalbe *et al*., 2010). The melting points of resultant salts increased with respect to the parent drug, with the exceptions of the F-Oct salt. Furthermore, the DSC plot of the F-Tris salt show two characteristic peaks; at 149 °C and 153 °C, suggesting the possible existence of another polymorphic form (Schwalbe *et al.,* 2010).

3.2 Powder X-ray diffraction analysis

The results from X-ray diffraction studies are shown in Figure 3. Salt formation was confirmed from differences in the X-ray diffraction patterns between 5°-40° at angle 2θ° between the parent drug and the salt forms. Additionally, the crystallinity of samples which may have a significant role on the properties of the materials including electrostatic charging due to disorders within the crystal lattice was evaluated for the salt forms. The peaks in diffraction patterns indicate crystalline character being retained for all the salts formed. Salts formed using counter ions Benz, Tris, But and AMP1 produced salts with increased crystallinity as shown by the changes in the corresponding XRD patterns in Figure 3. Furthermore, the loss of some distinct peaks was observed from diffraction patterns of F-Benz and F-AMP1 salts. The degree of crystallinity varies between the salt

forms depending on the degree of disorder in the crystal lattice induced by the counter ions during salt formation.

3.3 Fourier Transform Infra-Red (FT-IR) analysis

Salt formation was also confirmed by analysing FTIR patterns from that of the parent drug and the salt forms. Flurbiprofen molecule has a signature C=O stretching of the carboxylic acid group at 1684 cm^{-1}which was found to be absent in the salts. This was replaced by bands characteristic of carboxylic acid salts, at 1650–1550 cm^{-1} and 1440–1335 cm^{-1} (David *et. al.,* 2012). An additional band was present between 3350–3150 cm^{-1}, and is attributable to NH_3^+ stretching of solid amine salts (Socrates, 1994).

3.4 Scanning Electron Microscopy (SEM)

The particle shape and morphology of salts formed using different counter ions were analysed by SEM. As shown in Figure 4 and described in Table 3, addition of different counter ions resulted in different crystal morphologies. The results showed the salts to have recrystallised mainly with needle-like morphologies, with the exceptions of F-But, F-Oct and F-Tris which were prism, tabular and columnar, respectively. All the salts imaged show a tendency of primary particles to aggregate.

3.5 Particle Size Analysis

The particle size results from laser diffraction analysis are summarised in Table 3. The geometric particle size data indicate that generally the salt forms are noticeably larger in size than the parent drug. The exception is F-Oct salt which had smaller particle size distribution and span of 1.8 identical to the parent drug. The data also indicate differences between the salt forms with those

crystallised using Benz and Tris counter ions containing a higher proportion of fines. The results indicate that F-Chex and F-Tbut salts, as well as F-AMP1 and F-Tris salts, have similar particle size distributions. Furthermore, F-Benz, F-Chex, F-Tbut and F-AMP1 show bimodal distribution with some larger particles present possibly due to materials being needle shaped.

3.6 Triboelectrification

In the initial stage of the test procedure the initial charge of a sample was measured and indicated as time 0 in Fig. 5. The initial charge represents the charge first measured from the powder before being subjected to the tribo-electrification process. Figure 5 shows the charge measurements for flurbiprofen at the following time intervals; 0.5, 2, 5 and 10 minutes. The data points plotted on the graph are the result of at least three independent measurements. The flurbiprofen powder charged negatively against the stainless steel surface at each time interval.

It was found that the electrostatic charge increased with the shaking time and reached a maximum charge (-226 nC g^{-1}) after 5 minutes of tribo-charging. Following this stage, there was a reduction in the charge level as the tribo-charging time is increased. This is referred to as the saturated charge level and represents the amount of charge generated from particle impacts after which no further increase in charge occurs. Making assumptions centred on the current observations, it is reasonable to predict that unless the powder is neutralised, it is unlikely that the charge will ever reach a zero value beyond 10 minutes of tribo-charging, due to the powder particles interacting along the walls of the container during shaking. The frequency of shaking was kept constant as changes in frequency would affect the number of shaking cycles which, in turn, may affect the particle-wall collisions altering the charge relaxation time between successive impacts.

The charge of flurbiprofen salts was also characterised at 0.5, 2, 5 and 10 minutes. The saturated charge levels of the salt forms are shown in Fig. 6. For comparison purposes results for flurbiprofen are also added to Fig. 6. The results show that salt formed using counter ions AMP1, Benz, Tris, Oct and But resulted in samples charging negatively against the stainless steel surfaces in line with the polarity of the parent drug. In contrast, the salts formed using Tbut and Chex counter ions had electro positive charge against the stainless steel container. The level of charge on salt formed using AMP1 counter ion was considerably higher than all the samples tested including the parent drug. This level of charge was sufficient to cause processing problems i.e. increased particle adhesion to the stainless steel surfaces (Fig. 5).

The data presented in Table 3 highlight the importance of understanding the implications of forming salts using different counterions. F-Tris and F-AMP1 salts have similar saturated solubility. However, from the triboelectrification data it is evident that there is a significant difference in the chargeability of the two salts. This is likely to be due to their propensities for hydrogen bonding which significantly affects the crystal structure of the salts as revealed by structural analysis. Crystal structures (Schwalbe *et al.,* 2010) of F-Tbut, F-AMP1 and F-Tris were analysed using GDIS visualisation software (Fleming and Rohl, 2005). Hydrogen bonding functionality of the amine counterions used was varied by changing methyl groups to hydroxymethyl starting with Tbut as the initial molecule (0), and increasing the number of hydroxymethyl groups in AMP1 (1) and Tris (3). Unit cell dimensions of the resultant salts are shown in Table 4 with packing diagrams presented in Figs. 7-9. From the structural analysis the –OH groups play a significant role in determining the overall crystal structures. F-Tbut, which has no OH groups present, has an almost triclinic like crystal shape (Fig. 7) that is quite similar when the Tbut is replaced with AMP1 (Fig. 8). However with Tris as the base the crystal tends towards an orthorhombic like crystal lattice (Fig. 9). The intermolecular distances (Table 4) also reflect significant twist particularly for the O1-H1B and the F1-F2 and F1-H8 distances. The decrease in the O2-O3 distances indicates that the –OH groups are

closer to the –COO group of the flurbiprofen increasing the number of H-bonds within the crystal allowing the F-Tris salt to be a close-packed structure. The O1-H4 intermolecular distance clearly identifies significant twisting of the molecules in F-Tris than in F-Tbut. The intermolecular angles (Table 4) highlight this further where the angles obtained suggest a much more compact packing of the F-Tris molecules supporting the overall change in the crystal shape and symmetry.

The results show that varying the number of -OH groups on a counterion is sufficient to influence particle crystal habit resulting in a close-packed structure in F-Tris compared to F-AMP1 salt. Measurement of the electrostatic charge of the salts, following surface modification is expected to change the effective value of the work functions, influencing the direction of charge transfer during particle contact. The charge of F-AMP1 is ranked in the upper level of the chargeability series (Supuk *et al.* 2011). The level of charge on F-AMP1 is sufficient to cause problems during formulation processing. Furthermore, F-But and F-Tbut salts have identical physicochemical properties however, the tendency to charge against stainless steel with an opposite polarity was observed. This study demonstrates the importance of understanding triboelectrification phenomenon in an early stage development as a useful tool in the salt selection process.

3.7 Adhesion results

The corresponding adhesion values recorded at the time intervals from Fig. 5 are shown in Figs. 10 and 11. The adhesion is the mass of powder which remained on the walls and was not removed when the powder was poured into the Faraday cup. Initially the container walls were free from any adhered particles, but on shaking the particles interact with the surface walls and become highly charged. These highly charged particles then adhere to the inner walls of the container, forming a thick layer predominantly at both ends and the bottom of the shaking container. The adhesion tendency follows that of the charging trend shown in Fig. 5, whereby there is an initial increase in

adhesion up to the saturation level, after which a slight decrease is observed. As the tribo-charging time is increased post-saturation point, the free moving particles interact mainly with the concentrated wall-adhered particles instead of the surface of the container. This results in the majority of the particles interacting with each other as opposed to particle-wall interactions. This has the effect of slightly reducing the charge of the wall-adhered particles.

Figure 11 shows the mean percentage of adhesion for flurbiprofen and its salt forms corresponding to the saturated charge level given in Fig. 6. The parent drug had the highest adhesion in the stainless steel container. The salt formed using t-but counter ion had the smallest adhesion. The adhesion of particles to the walls can have a significant effect on the generated charge. The particles which adhere to the wall surfaces may change the charging process from particle-wall contacts to particle-particle contacts and this may result in the change of polarity of the overall powder sample. Particles formed following salt formation had varying shapes and surface asperities. Changing particle shape may alter the proportion of the functional groups present at the crystal surface and is likely to influence the polarity and magnitude of electrostatic charge. Furthermore, particle surface asperities affect the surface area available for charge transfer and serve as a physical separation that may also affect particle adhesion tendency.

3.8 Compression results

In the present study, different salts of flurbiprofen exhibit a monotonically increasing trend in tablet tensile strength (σ_X) with regards to pressure. All the salts show improved tabletability compared with the parent drug. Among the salts, F-AMP1 showed highest tablet tensile strength (σ_X), while F-Tbut showed the lowest (Fig. 12). The order of the tablet strength from strongest to weakest is as follows: F-AMP1 > F-Tris > F-Chex > F-Benz > F-But > F-Tbut > F-Oct > FBP.

The mean yield pressure (P_y), is inversely proportional to the ability of powder particles to deform under specific applied pressure. F-Tris has the highest P_y however having little difference with F-AMP1, while the parent drug, flurbiprofen has the lowest P_y value. On the basis of the P_y values, these materials can be classified into four categories (Table, 2). The parent drug and F-Tbut can be described as soft, F-Chex, F-Benz, F-Oct and F-But as moderately hard whilst F-Tris and F-AMP1 can be classified as hard materials. The plastic deformation trend was therefore as follows: Soft materials materials> Moderate hard materials >Hard materials.

Kawakita parameters a and b^{-1} were calculated from the linear regression of the profiles and the data fit well with having high correlation coefficients (R^2> 0.99). It has been established, b^{-1} is opposite to the plastic deformation of a material during the compression cycle (Nordström*et al.,* 2009; Odeku and Itiola, 1998). In the present study, F-Tbut and flurbiprofen showed the fastest onset of plastic deformation, which might result in lamination and capping during compression. However there are some salts (F-Chex, F-Benz, F-But and F-Oct), which plastically deform with relatively fast rate due to low b^{-1}. F-AMP1 and F-Tris salts show a high plastic deformation with slow rate (Table 3). Research is in progress to understand the crystal structure of the salt forms and the effect of orientation of molecular groups at individual surfaces will allow charge transfer mechanisms to be elucidated. Furthermore, the presence of slip planes in crystal structure may affect charge transfer which is based on a high impaction process by allowing slipping of one layer over an adjacent one. In this instance, the charging mechanism would reflect the surface charge of these planes, unless the slip planes are strengthened by hydrogen bonding or cross-linked by a high number of van der Waals forces to prevent such slippage.

4. Conclusions

The results show that the type of counter ion selected produces significant differences in the particle morphology. In turn, it is suggested that these differences influence the work function of the materials, which has been shown to greatly affect the electrostatic behaviour. Changes in the crystal habit have been shown to modify the electrostatic properties of the salt forms due to different arrangements of the atoms in the structures. In some instances, salt formation causes significant surface modification in comparison to the parent drug, affecting triboelectrification, adhesion and compaction properties. Thus, the molecular structure of the counter ion has a significant effect on the particle morphology highlighting the importance of counter ion selection as a precursor to determining electrostatic behaviour.

The electrostatic charge of the resultant salts shifted in positive direction with F-AMP1 having the highest charge in the order: F-AMP1 > F-Benz >F-Tris> F-Oct > F-But > F-Tbut > F-Chex. The parent drug had a great propensity for tribo-electric charging. The net charge of the resultant salts was shown to be lower than that of the parent drug regardless of the type of counter ion used. The exception was F-AMP1, which charged to a higher level than the parent drug and sufficiently high to cause problems during formulation and drug development. In general, the salts formed had a negative charge against the stainless steel surface. It can therefore be assumed that electrons are being transferred from the stainless steel surface to the powder particles (charging them negatively), with the exception of F-Chex and F-Tbut which had an electropositive charge.

The salts of flurbiprofen also show different mechanical behaviour during and after compression experiments. Addition of hydroxymethyl groups in F-AMP1 and F-Tris salts resulted in more compact packing with strongly hydrogen bonded layers which facilitated inter-particle adhesion producing stronger compacts.

The triboelectrification methodology used in this work is a sensitive tool able to detect magnitude of charge at the nano Coulomb level, which is an added advantage when other techniques are not able to differentiate between physical properties of the salt forms. Successfully incorporating the triboelectrification methodology, alongside other techniques may lead to a better understanding of the screening strategy to aid the selection of an optimal salt form and thereby reducing the likelihood of several salt forms of a drug candidate being manufactured for preformulation testing.

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